Kinetics and mechanism of the reaction of iodine with isonicotinoylhydrazide

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The title reaction proceeds through two parallel pathways involving attack by IOH ($k_{14} = (5.69 \pm 0.97) \times 10^8 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$) and by I₂ ($k_{13} = 0.31 \pm 0.11$) mol⁻¹ dm³ s⁻¹) on ⁺HNC₅H₄C(O)NHNH₂ (INAH). These results are similar to those of Hasty on the system N₂H₄ + I₂, but differ from the mechanisms proposed by Cooper and Bah and Yew for similar systems. Because k_{14} is close enough to (though significantly less than) the diffusion limit, our data permit us to estimate the first-order rate constant for I₂ hydrolysis, obtaining in reasonable agreement with previous data $k_5 = 0.33 \text{ s}^{-1}$ at pH = 1.66. The general kinetic law is shown to give rise to an [R-NH-NH₂] independent pathway of oxidation at sufficiently high pH. A mechanism is proposed to explain the much higher reactivity of IOH (as compared to I₂) towards R-NH-NH₂.

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La réaction mentionnée dans le titre peut se produire par le biais de deux voies parallèles impliquant des attaques soit du IOH $(k_{14} = (5,69 \pm 0.97) \times 10^8 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1})$ ou du $I_2 (k_{13} = 0.31 \pm 0.11) \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1})$ sur la ⁺HNC₅H₄C(O)NHNH₂ (INAH). Ces résultats sont semblables à ceux obtenus par Hasty sur le système N₂H₄ + I₂; ils diffèrent toutefois des mécanismes proposés par Cooper et Bah et Yew pour des systèmes similaires. La valeur de k_{14} étant proche (quoique plus basse d'une façon significative) de la limite de diffusion, nos données nous permettent d'évaluer la constante de vitesse du premier ordre pour l'hydrolyse du I₂ et d'obtenir une valeur en bon accord avec la constante $k_5 = 0.33 \text{ s}^{-1}$ (à un pH de 1,66) rapportée antérieurement. On montre que la loi cinétique générale donne lieu, à des pH suffisamment élevés, à des voies d'oxydation qui ne dépendent pas de la concentration en R-NH-NH₂. On propose un mécanisme pour expliquer la réactivité beaucoup plus grande du IOH (comparée à celle du I₂) vis-à-vis le R-NH-NH₂.

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Introduction

It is well known that iodine quantitatively oxidizes substances containing the $-NH-NH_2$ group. This reaction is the basis of one of the standard analytical procedures to titrate hydrazine and related substances, in particular isonicotinoylhydrazide (isoniazid, INAH),



which is widely used in the pharmaceutical industry because of its bacteriostatic properties against *Mycobacterium tuberculosis*. The rate of the oxidation reaction is very sensitive to all variables which affect the speciation of both reagents in solution, and thus the rate may vary widely according to the chemistry of the solution. In the present paper we report the results of a kinetic study of the oxidation of INAH by iodine, which is important per se and also helps to shed light on the general mechanisms of oxidation of the ---NH----NH₂ function by iodine.

The mechanism of oxidation of hydrazine itself by iodine has been the subject of several studies, among which no complete agreement is found. Thus, Hasty (1) reports the rate law

$$[1] \quad R = k_{a} [N_{2}H_{5}^{+}][I_{2}] + k_{b} [N_{2}H_{5}^{+}][HIO]$$

the second term accounting for the largest fraction of reaction under experimental conditions (large excess of iodide and pH values in the range 1–2). The values for k_a and k_b are found to be ca. 1.0 dm³ mol⁻¹ s⁻¹ and 2 × 10⁹ dm³ mol⁻¹ s⁻¹ which are interpreted as indicative of IOH being the most active among the various oxidized iodine species (HIO, I₂, I₃⁻, I₅⁻). According to this study, iodine itself also reacts with $N_2H_5^+$, and because $[I_2] \gg [IOH]$, the contribution to the overall rate of the first term in eq. [1] is not negligible.

On the other hand, Cooper and co-workers (2) propose a different mechanism, involving only I^+ and N_2H_4 in the activated state. This is reached from a pre-equilibrated $N_2H_4I^+$ species, the concentration of which is sensitive to I^- :

- $[2] \qquad N_2H_4 + I_2 \rightleftharpoons N_2H_4I^+ + I^-$
- $[3] N_2H_4I^+ \rightarrow \text{products}$

[4]
$$R = \frac{k_3 k_2 [N_2 H_4] [I_2]}{k_{-2} [I^-] + k_3}$$

Because of the relationship between [IOH] and $[I_2]$ (eq. [5], $Q_5 = 4.83 \times 10^{-13}$) (ref. 3),

$$[5] \quad I_2 + H_2 O \rightleftharpoons IOH + I^- + H^+$$

and between $[N_2H_4]$ and $[N_2H_5^+]$ (eq. [6], $K_6 = 10^{-7.98}$) (ref. 4),

 $[6] \qquad N_2H_5^+ \rightleftharpoons N_2H_4 + H^+$

both mechanisms are in fact compatible with the same set of experimental data; part of the difficulty is due to the similar pH dependency of [5] and [6] in the pH range of the kinetic studies, where $[IOH] \propto [H^+]^{-1}$ and $[N_2H_4] \propto [H^+]^{-1}$ (furthermore, the proportionality constants are not very different). Kinetic data indicate only a deprotonation equilibrium generating a reactive species at high pH values.

References I and 2 both agree in the existence of pathways which at high enough $[I^-]$ become proportional to $[I^-]^{-2}$, although the origin of this dependency is variously attributed to equilibrium [2] (2) or to equilibrium [5] (1), which together with

$$[7] \quad \mathfrak{l}_3^- \rightleftharpoons \mathfrak{l}_2 + \mathfrak{l}^- \qquad Q_7 = (736)^{-1}$$

explains the observed partial order. Other authors (5) in turn

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find a dependence on $[I^-]^{-1}$, giving rise to a third proposed rate law

[8]
$$R = k_8 [N_2H_4][I_2]$$

attributed to the direct attack of I_2 on N_2H_4 as the ratedetermining step. According to Hasty (1), the overall mechanism includes both the attack by IOH and by I_2 on hydrazine, although the $[H^+]$ dependency of this latter pathway, is diversely reported to be of order -1 (5) or zero (1); the difference can be traced back to different assumptions as to the relative reactivities of $N_2H_5^+$ and N_2H_4 .

Experimental

Analytical reagents were employed without further purification. INAH was a gift from G. Ramón Laboratories, Buenos Aires, and was recrystallized several times from doubly distilled ethanol in the presence of activated charcoal. All solutions were prepared with doubly distilled water. Iodine solutions were standardized with sodium thiosulfate.

Spectrophotometric measurements were carried out in a Hitachi– Perkin–Elmer 139 spectrophotometer fitted with thermostated cell compartments.

The kinetics of the reaction were followed by measuring the decrease in absorbance at 390 nm, 24.9°C, and $I = 1 \mod \text{dm}^{-3}$ (NaCl). The measurements were not made at 352 nm (λ_{max} of I_3^-) because, at this wavelength, background absorbance was inconveniently high.

A typical kinetic experiment was performed as follows: HCl and NaCl solution (Reagent A) and KI, I₂, and NaCl solution (Reagent B) were prepared. Solid INAH was dissolved in Reagent A and Reagent B was poured over it. The initial (analytical) concentration of iodine (F_{12}^0) was ca. 1.1×10^{-4} mol dm⁻³. INAH and KI were in high excess over I₂. F_{INAH} and F_{I^-} were in the ranges $5 \times 10^{-3} - 5 \times 10^{-2}$ mol dm⁻³ and $1 \times 10^{-2} - 4 \times 10^{-2}$ mol dm⁻³ respectively, and were constant during each experiment. The pH was also constant during those runs without need of buffers because of the high acidities. In different experiments, pH varied in the range 1.3-2.0.

From the absorbance – time data, very good pseudo-first-order plots were obtained: $\log [(A_0 - A)/(A - A_{\infty})]$ was a linear function of time for up to 5 half-lives. The reported k_{obsd} values were obtained from the slopes of the plots of duplicate experiments. No complications due to the formation of ⁺HNC₅H₄C(O)HNNH(O)CC₅H₄NH⁺ were detected because, in the presence of a large excess of INAH, I₂ reacts quantitatively with the original reagent.

Results

The experimental rate constants k_{obsd} (eq. [9])

[9]
$$k_{obsd} = [I_3^-]^{-1} (-d[I_3^-]/dt) = F_{I_2}^{-1} (-d[I_3^-]/dt)$$

are shown in Tables 1–3. Because of the large excess of I^- , the total analytical iodine concentration is identical to the actual I_3^- concentration in all the experiments.

The data in Table 1 show that the reaction is first order in INAH at pH = 1.66; similar results are found at other pH values, the rate increasing with increasing pH in the pH range 1.3-2.0 (see Table 2). The high sensitivity to pH is similar to that observed for N₂H₄. Table 3 gives the relationship between rate and F_{1^-} .

Discussion

In the presence of large excess of INAH, I_2 is quantitatively reduced according to eq. [10] (6).

[10] R-C(O)NH-NH₂ +
$$2I_3^-$$
 + $H_2O \rightarrow R$ -C(O)OH

$$+ N_2 + 6I^- + 4H^+$$

Benzoic acid may further react with excess isoniazid, eq. [11] (6).

TABLE 1. Dependency of k_{obsd} on F_{INAH} ; $F_{I^-} = 2 \times 10^{-2}$ mol dm⁻³; pH = 1.66; $t = 24.9^{\circ}$ C; I = 1 mol dm⁻³ (NaCl). The data fit the equation $k_{obsd} = 4.52 \times 10^{-2}$ mol⁻¹ dm³ s⁻¹ F_{INAH} with $\rho = 0.9868$

$\frac{k_{\text{obsd}} \times 10^4}{(\text{s}^{-1})}$	F_{INAH} (mol dm ⁻³)	
2.33	0.005	
5.36	0.010	
7.36	0.015	
8.69	0.020	
12.0	0.030	
16.8	0.040	
24.5	0.050	

TABLE 2. Dependency on [H ⁺]; $F_{INAH} = 2 \times$ dm ⁻³ ; $F_{I^-} = 3.5 \times$ dm ⁻³ ; $t = 24.9^{\circ}$ C; I dm ⁻³ (NaCl)	of k_{obsd} 10^{-2} mol 10^{-2} mol = 1 mol
$k_{\text{obsd}} \times 10^4$ (s ⁻¹)	рH
1.03	1.297
1.31	1.418
2.47	1.531
2.96	1.591
4.33	1.713
8.61	1.954

$$\begin{bmatrix} 11 \end{bmatrix} R - C(O)NH - NH_2 + HO(O)C - R$$

 \rightarrow R-C(O)NH-NH(O)C-R + H₂O

 $+ H^+$

but this reaction is irrelevant for our study. The stoichiometry of the reaction is therefore similar to that of $I_2 + N_2H_4$.

In view of the proposed mechanisms for the $I_2 + N_2H_4$ reaction, our data will be analyzed in terms of a general set of elementary equations, involving attack by both I_2 and IOH. I_3^- and I_5^- can safely be disregarded because of the inhibitory effect of iodide (Table 3).

 $[5a] I_2 + H_2O \xrightarrow{k_5} IOH + I^- + H^+$

$$[5b] IOH + I^- + H^+ \xrightarrow{\sim} I_2 + H_2O$$

[7]
$$I_3^- \rightleftharpoons I_2 + I^ Q_7 = (736)^{-1}$$
 (ref. 3)

$$[12] H^{\dagger} \bigcirc -C^{\circ}_{NH \to NH_{3}^{\dagger}} \rightleftharpoons H^{\dagger} \bigcirc -C^{\circ}_{NH \to NH_{2}}$$

$$INAH_{2}^{\dagger} INAH$$

$$pK_{a}$$
 (INAH) = 1.85 (ref. 7)

[13] INAH + $I_2 \xrightarrow{k_{13}}$ products

[14] INAH + IOH
$$\xrightarrow{^{14}}$$
 products

Thus,

$$\begin{bmatrix} 15 \\ -1/2dF_{I_2}/dt = -1/2 d [I_3]/dt = -d [INAH]/dt = \\ \{k_{I_3} [I_2] [INAH] + k_{I_4} [IOH] [INAH] \}$$

The general expression for k_{obsd} under this mechanism is [16]

$$\begin{bmatrix} I6 \end{bmatrix} \quad k_{obsd} = 2 \left\{ k_{13} + \frac{k_{14}}{\left(\frac{F_{1^{-}} [H^{+}]}{Q_{5}} + \frac{k_{14} [INAH]}{k_{5}}\right)} \right\} \frac{\begin{bmatrix} INAH \end{bmatrix}}{\left\{F_{1^{-}}Q_{7}^{-1} + 1 + \frac{1}{\left[\frac{F_{1^{-}} [H^{+}]}{Q_{5}} + \frac{k_{14} [INAH]}{k_{5}}\right)}\right\}}$$

where

[17] [INAH] = $F_{\text{INAH}} K_a (K_a + [\text{H}^+])^{-1}$

Two limiting assumptions can be identified by inspection of the terms in eq. [16]:

[18]
$$k_{13} \ll k_{14} k_5 (k_{-5} F_{1} [H^+] + k_{14} [INAH])^{-1}$$

$$[19] \quad k_{14} [\text{INAH}] \ll k_{-5} F_{1^-} [\text{H}^+]$$

Previous work on $I_2 + N_2H_4$ has accepted [19] as a general assumption, while the ratio of the I_2 to the IOH-pathway is a matter of controversy. It must be noted, however, that the second assumption is incorrect at high pH values, and even in the pH range 1-2 the error involved may be significant if k_{14} approaches diffusion control.

Our set of data was fitted to eq. [16] by a nonlinear leastsquares fitting method. According to ref. 8, for the hydrolysis of I_2 the following scheme and rate constants apply:

[20]
$$I_2 + H_2O \xrightarrow[1.6]{2.1 \text{ s}^{-1}} I_2OH^- + H^-$$

[21]
$$I_2OH^- \xrightarrow{3 \times 10^7 \text{ s}^{-1}}{5 \times 10^9 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}} IOH + H^+$$

whence

[22]
$$k_5^{\text{in}} = \frac{2.1 \times 3 \times 10^7}{(1.6 \times 10^{10} \,[\text{H}^+] + 3 \times 10^7)} \,\text{s}^{-1}$$

$$\begin{bmatrix} 23 \end{bmatrix} \quad \frac{1}{k_{obsd}} = \frac{1}{F_{INAH}} \left\{ \frac{[H^+] \{K_a + [H^+]\}F_{I^-} (Q_7^{-1}F_{I^-} + 1)}{2k_{14} K_a Q_5} \right\} + \frac{(Q_7^{-1}F_{I^-} + 1)}{2k_5} \\ \begin{bmatrix} 24 \end{bmatrix} \quad \frac{1}{k_{obsd}(Q_7^{-1}F_{I^-} + 1)} = F_{I^-} \left\{ \frac{[H^+] \{K_a + [H^+]\}}{2k_{14} K_a Q_5 F_{INAH}} \right\} + \frac{1}{2k_5} \\ \begin{bmatrix} 25 \end{bmatrix} \quad \frac{1}{k_{obsd}} = [H^+] \{K_a + [H^+]\} \left\{ \frac{F_{I^-} (Q_7^{-1}F_{I^-} + 1)}{2k_{14} K_a Q_5 F_{INAH}} \right\} + \frac{(Q_7^{-1}F_{I^-} + 1)}{2k_5} \\ \end{bmatrix}$$

Values of k_{14} and k_5 from the slopes and intercepts are given in Table 5 as a check for internal consistency. The differences are related to the use of approximation [18]. Note in [25] that k_5 should in fact be pH dependent; however, a good straight line

$$\begin{bmatrix} 26 \end{bmatrix} \quad k_{\text{obsd}} \left(Q_7^{-1} F_{1^-} + 1 \right) = \frac{1}{F_{1^-}} \left\{ \frac{2k_{14} K_a Q_5 F_{\text{INAH}}}{[\text{H}^+] \{K_a + [\text{H}^+]\}} \right\} + \frac{2k_{13} K_a F_{\text{INAH}}}{\{K_a + [\text{H}^+]\}} \\ \begin{bmatrix} 27 \end{bmatrix} \quad k_{\text{obsd}} \left\{ K_a + [\text{H}^+] \right\} = \frac{1}{[\text{H}^+]} \left\{ \frac{2k_{14} K_a Q_5 F_{\text{INAH}}}{F_{1^-} (Q_7^{-1} F_{1^-} + 1)} \right\} + \frac{2k_{13} K_a F_{\text{INAH}}}{(Q_7^{-1} F_{1^-} + 1)} \\ \end{bmatrix}$$

Our data indicate that both IOH and I_2 are capable of oxidizing INAH. The relative importance of both reagents is essentially dominated by the low concentrations of IOH in the pH range studied, as k_{14} approaches the diffusion controlled limit.

Rather than using this expression for k_5 , taken from the work of Eigen and Kustin (8), k_5 was left as another adjustable parameter and the obtained values used as a check of the procedure by comparison with literature data. Our result agrees within a factor of 2 with the Eigen and Kustin data. These in fact refer to 20°C, and kinetic $Q_5 = k_5/k_{-5}$ does not agree with equilibrium measurements at 25°C. In terms containing (k_5/k_{-5}) we have used the equilibrium value; otherwise, kinetic k_5 values were used. These results are summarized in Table 4, which gives the values of k_{13} and k_{14} obtained for various n = $(k_5^{\text{fitted}}/k_5^{\text{lit}})$, together with the corresponding standard deviations. The best fit is achieved with large n values; improvement by increasing n beyond 2 is only marginal, and therefore we have selected from our data: $k_5 = 0.33 \text{ s}^{-1}$ at pH = 1.66 (cf. $k_5^{\text{lit}} =$ 0.17 s⁻¹ as calculated from eq. [22]); $k_{13} = (0.31 \pm 0.11)$ $mol^{-1} dm^3 s^{-1}$; $k_{14} = (5.69 \pm 0.97) \times 10^8 mol^{-1} dm^3 s^{-1}$. The calculated standard deviations for k_{13} and k_{14} demonstrate that the rate is not overly sensitive to k_{13} , so that this parameter is affected by rather large error brackets.

In order to demonstrate that deviations from the assumed dependency on a given variable (F_{INAH} , F_{I^-} , or pH) are not blurred by the fitting to the given reaction scheme, we have taken advantage of the approximate validity of assumption [18] to plot k_{obsd}^{-1} vs. F_{INAH}^{-1} (at constant F_{I^-} and pH), k_{obsd}^{-1} ($Q_7^{-1}F_{I^-} + 1)^{-1}$ vs. F_{I^-} (at constant F_{INAH} and pH), and k_{obsd}^{-1} vs. [H⁺] ($K_a + [H^+]$) (at constant F_{INAH} and F_{I^-}) to show the validity of eq. [23]–[25] which are obtained from [16], [17], and [18] by appropriate rearrangements, see Figs. 1–3.

is found for a limited range in [H⁺] (Fig. 3).

Conversely, accepting [19], eq. [16] leads to [26] and [27]. From the intercepts and slopes of the corresponding linear plots, values of k_{14} and k_{13} are obtained (Table 6), which illustrate the errors involved in [19].

The ratio $[k_{13}/(k_{13} + k_{14}k_5 (k_{-5}F_{1} [H^+] + k_{14} [INAH])^{-1})]$ gives the fractions of INAH which is oxidized by I₂; this value is in the range 0.22-0.67, the highest value corresponding to the highest $[H^+][1^-]$ value used in this study.



TABLE 3. Dependency of k_{obsd} on F_{1^-} ;

FIG. 1. k_{obsd}^{-1} as function of F_{INAH}^{-1} ; $F_{I^-} = 2 \times 10^{-2}$ mol dm⁻³; pH = 1.66; $t = 24.9^{\circ}$ C; I = 1 mol dm⁻³ (NaCl).

The value obtained for k_{14} is of the same order of magnitude as that calculated from Hasty's data (1) for:³

[28] IOH + $N_2H_4 \rightarrow$ products

This is reasonable in view of the high reactivity; it should be noted, however, that k_{14} , although close to the diffusion limit, is significantly below it. IOH discriminates between reacting with I⁻ (+H⁺) and with R—NH—NH₂ in favour of the former for all our experimental conditions, where $[k_{-5} F_{1^-} [H^+]/k_{14} \times$ [INAH]] > 1. On the other hand, it is interesting to note that under the conditions of the usual INAH titration procedure k_{14} [INAH] > $k_{-5} F_{1^-} [H^+]$, and thus the value of k_{obsd} (eq. [16]) would reduce to

[29]
$$k_{obsd} = 2[k_5 + k_{13} K_a F_{INAH} (K_a + [H^+])] (Q_7^{-1} F_{1^-} + 1)^{-1}$$

the IOH pathway being thus controlled by the hydrolysis of I₂ (eq. [5a]), and becoming zero order in INAH. It should also be noted that the values of the equilibrium quotients $Q_7 = (736)^{-1}$ and $Q_5 = 4.83 \times 10^{-13}$ are obtained from ref. 3, while $(k_7/k_{-7}) = (539)^{-1}$ and $(k_5/k_{-5}) = 6.82 \times 10^{-13}$ result from the



FIG. 2. $k_{obsd}^{-1} (Q_7^{-1} F_{I^-} + 1)^{-1}$ as function of F_{I^-} ; $F_{INAH} = 2 \times 10^{-2} \text{ mol dm}^{-3}$; pH = 1.61; $t = 24.9^{\circ}\text{C}$; $I = 1 \text{ mol dm}^{-3}$ (NaCl).

kinetic study of these reactions (8, 9). Furthermore, it has been suggested (3) that k_5 (and consequently k_5/k_{-5}) may be substantially larger. These errors are reflected directly in the value of k_{14} ; we have chosen to use equilibrium data for Q_7 and Q_5 which are perhaps less uncertain, although sensitive to medium effects.

In part, the ambiguities in the interpretation of the data of the $I_2 + N_2H_4$ reaction arise from the pH dependency, which is consistent with either equilibrium [5] or [6].

In our system, replacement of one H by a nicotinoyl group allows us to avoid equilibrium [6] as a possible source of rate change with pH (protonation of the pyridine end is not likely to be of much influence); once the relevance of the $R-NH-HN_3^+/R-NH-NH_2$ equilibrium has been taken into account, it is still necessary to resort to a second pH-dependent equilibrium to explain our data, thus confirming the importance of IOH as oxidizer.

All the studies discussed thus far (including ours) yield information only on the composition of the activated state, in contrast with the information available for the oxidation of hydrazine with one-electron oxidants (known to take place via N₂H₃ radicals or their organic analogs (10)). The nature of the species leading from R—NH—NH₂ to N₂ by reaction with I₂ is not known, but the very high ratios k_{14}/k_{13} (1.84 × 10⁹ in our system, 2 × 10⁹ in ref. 1) can be rationalized in terms of the following mechanism:

$$\begin{bmatrix} 30 \end{bmatrix} R - NH - N: + 1OH \rightarrow R - NH - N: IOH \quad (diffusion \\ | \\ H \\ \end{bmatrix} = \begin{bmatrix} 31 \end{bmatrix} R - NH - N: IOH \rightarrow R - NH - NHI + H_2O \quad (fast) \\ | \\ H \\ \end{bmatrix} = \begin{bmatrix} 31 \end{bmatrix} R - NH - NHI \rightarrow R - NH - NHI + H_2O \quad (fast) \\ | \\ H \\ \end{bmatrix}$$

³From the data in Table 4 of ref. 1, the value $k_{28} = 2 \times 10^9$ mol dm⁻³ s⁻¹ is obtained; this seems to be the correct value rather than that of 7 × 10⁷ mol dm⁻³ s⁻¹ later quoted in the same paper for $2k_{28}$.

TABLE 4. Values of k_5 , k_{13} , and k_{14} and their standard deviations from our experimental data

	$\sigma \times 10^4$	k_{13} mol ⁻¹ dm ³ s ⁻¹	$\frac{\sigma_{k_{13}}}{\text{mol}^{-1} \text{dm}^3 \text{ s}^{-1}}$	$k_{14} \times 10^{-8}$ mol ⁻¹ dm ³ s ⁻¹	$\sigma_{k_{14}} \times 10^{-8}$ mol ⁻¹ dm ³ s ⁻¹
0.1	0.941	0.517	0.134	5.64	2.44
0.25	0.807	0.383	0.124	6.00	1.52
0.5	0.754	0.338	0.117	5.90	1.19
1	0.729	0.320	0.113	5.77	1.04
1.5	0.721	0.315	0.111	5.72	0.99
2	0.717	0.313	0.110	5.69	0.97
*n =	$= (k_5^{\text{fitted}} / \overline{k}_5^{\text{lit}}).$				



FIG. 3. k_{obsd}^{-1} as function of [H⁺] ($K_a + [H^+]$); $F_{INAH} = 2 \times 10^{-2} \text{ mol dm}^3$; $F_{1^-} = 3.5 \times 10^{-2} \text{ mol dm}^3$; $t = 24.9^{\circ}$ C; $I = 1 \text{ mol dm}^{-3}$ (NaCl).

TABLE 5. Estimations of k_{14} and k_5 from different sets of data, accepting approximation [18]

Equation	Variable	ρ	$k_{14} \times 10^{-8}$ mol ⁻¹ dm ³ s ⁻¹	<i>k</i> s s ⁻¹
[23]	$\begin{bmatrix} F_{\text{INAH}} \\ F_{\text{I}}^{-} \\ [\text{H}^+] \end{bmatrix}$	0.9954	8.75	0.25
[24]		0.9991	11.6	0.025
[25]		0.9835	11.5	0.025*

*See text. The nonlinear least-squares fitting method gives $k_{14} = (5.69 \pm 0.97) \times 10^8 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$.



TABLE 6. Estimation of k_{14} and k_{13} from different sets of data, accepting approximation [19]*

Equation	Variable		$k_{14} \times 10^{-8}$ mol ⁻¹ dm ³ s ⁻¹	$\frac{k_{13}}{\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}}$
[26]	$\begin{bmatrix} F_{t-} \\ [H^+] \end{bmatrix}$	0.9977	5.85	0.22
[27]		0.9879	7.50	0.12

*The nonlinear least-squares fitting method gives $k_{14} = (5.69 \pm 0.97) \times 10^8 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ and $k_{13} = (0.31 \pm 0.11) \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$.

The slower rate of I_2 could be due either to (*a*) the lower electrophilicity of I_2 as compared to IOH, which would make [34] reversible, as compared to irreversible [30]: or (*b*) the more difficult evolution of the possible

$$R - NH - N: I_{2} \text{ adduct (eq. [35]) as compared to} \\ H \\ R - NH - N: IOH, \\ H \\ R - NH - N: IOH, \\ H \\ H$$

making more likely the reverse reaction [35].

In conditions of excess iodine, the stoichiometry of the initial reaction is described by eqs. [10] and [11]; thus, the analytical procedure for dosing INAH by I_2 according to ref. 6 prescribes a stoichiometry ratio $[I_2]/[INAH] = 1:1$ at 15-min reaction. By waiting longer, reaction [37] takes place:

[37] R-C(O)NH-NH(O)C-R +
$$2I_2$$
 + $2H_2O$
 $\rightarrow 2R$ -C(O)OH + N_2 + $4I^-$ + $4H^+$

and therefore the ratio $[I_2]/[INAH] = 2:1$, as indicated for 90-min reaction in the U.S. Pharmacopaea (11). The kinetics of reaction [37] are currently being studied in our laboratories.

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