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Kinetics and mechanism of the cleavage of *N*-phthaloylglycine in buffers of some primary amines

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Kinetic studies on the nucleophilic cleavage of *N*-phthaloylglycine (NPG) in buffers of 2-methoxyethylamine, and 2-hydroxyethylamine reveal the relationship: $k_n^{app} = A_1\,[Am]_T/(1 + A_2\,[Am]_T)$ where A_1 and A_2 are constants (kinetic parameters) and k_n^{app} and $[Am]_T$ represent apparent nucleophilic second-order rate constant and total amine buffer concentration, respectively.

Keywords: *N*-phthaloylglycine, 2-methoxyethylamine, 2-hydroxyethylamine, tris-(hydroxymethyl)aminomethane, hydrazine, aminolysis, general base catalysis

There appears to be no general or specific rule to predict the occurrence of general base (GB) catalysis. For example, GB catalysis was detected in the reactions of hydrazine[6] and morpholine[7] with phthalimide while such catalysis was not detected in the reaction of morpholine with NPG[2] and *N*-ethoxycarbonylphthalimide.[8] The recent apparent unusual observations[2] in the hydrazinolysis of NPG encouraged us to extend this study to include some other amines. Thus, in continuation of such study, we have carried out rate studies on the reactions of NPG with 2-methoxyethylamine and 2-hydroxyethylamine because GB catalysis was observed in the reactions of these amines with phthalimide.[9] The observed results and their probable explanation(s) are described in this manuscript.

Experimental

Reagent grade chemicals such as *N*-phthaloylglycine (NPG), 2-methoxyethylamine, 2-hydroxyethylamine, tris-(hydroxymethyl) aminomethane (Tris) and hydrazine were obtained from commercial sources. The stock solutions of NPG were prepared in acetonitrile and amine buffers of desired pH were freshly prepared just before the start of kinetic runs.

Rates of aminolysis of NPG were studied spectrophotometrically by monitoring the disappearance of NPG as a function of reaction time at 300 nm and 30°C. Details of the kinetic procedure and data analysis have been described elsewhere.[10]

Results and discussion

Effect of [Tris buffer] on rate of hydrazinolysis of NPG: A few kinetic runs have been carried out to study the rate of cleavage of NPG within the total Tris buffer concentration ($[Am]_T$) range of 0.2 to 0.75 mol/dm^3 at pH 8.12 ± 0.01 in the presence of 0.01 mol/dm^3 NH_2NH_2. Pseudo-first-order rate constants (k_{obs}) are almost independent of $[Am]_T$. The ionic strength of the reaction medium was kept constant at 1.0 mol/dm^3 using NaCl. Similar results were obtained at 0.05 mol/dm^3 NH_2NH_2. These observations show the absence of nucleophilic reactivity of Tris toward NPG which is most likely due to steric factors. However, a single kinetic run, carried out at $[Am]_T = 0.8$ mol dm^{-3}, pH 8.14, $[NH_2NH_2] = 0$ and 30°C, gave $k_{obs} = (4.49 \pm 0.03) \times 10^{-5}$ s^{-1} which yielded an approximate value of k_n as 6.8×10^{-5} dm^{-3}/mol/s (nucleophilic second-order rate constant, $k_n = (k_{obs}–k_0)/(f_b\ [Am]_T)$ with $k_0 = k_{OH}[HO^-]$, $k_{OH} = 6.2$ dm^{-3}/mol/s[11], $[HO^-] = 10^{pH-pKw}/\gamma$ where pK_w = 13.84[12], activity coefficient $\gamma = 0.7$ at 1 mol/dm^3 ionic strength[13] and $f_b = K_a/(a_H + K_a)$ with K_a representing ionisation constant of the conjugate acid of Tris free base, pK_a = 8.14[14]).

The rate of reaction of hydrazine with NPG in the presence of Tris buffer is concluded to involve both uncatalysed and general base-catalysed reaction steps. The previously reported specific base-catalysed term ($k_{sb}[NH_2NH_2][HO^-][NPG]$) in the rate law for hydrazinolysis of NPG[2] is shown to be actually a general base-catalysed term.

Effects of amine buffer concentrations on the rate of conversion of NPG into P_1: The effects of total buffer concentrations of amines (2-methoxyethylamine and 2-hydroxyethylamine), $[Am]_T$, were studied by carrying out kinetic runs at different $[Am]_T$ within its range of

Table 2 Values of empirical constants, A_1 and A_2, calculated from Equation (5)[a]

Amine	pH	10^2 A_1 /dm^6/mol^2/s	A_2 /dm^3/mol	$[Am]_T$ range[b] /mol/dm^3
$CH_3OCH_2CH_2NH_2$	9.12 ± 0.04[c]	0.8 ± 0.1[c]	1.7 ± 0.2[c]	0.1 – 0.9
	9.33 ± 0.01	1.7 ± 0.3	2.3 ± 0.6	0.2 – 0.8
	9.56 ± 0.02	3.3 ± 0.2	2.5 ± 0.2	0.1 – 0.85
	9.71 ± 0.03	2.9 ± 0.4	1.1 ± 0.4	0.1 – 0.8
	9.86 ± 0.01	3.4 ± 0.3	0.7 ± 0.2	0.1 – 0.8
	0.20 ± 0.02	4.1 ± 0.4	0.3 ± 0.2	0.2 – 0.8
$HOCH_2CH_2NH_2$	9.09 ± 0.02	1.5 ± 0.2	1.8 ± 0.4	0.1 – 0.8
	9.34 ± 0.01	2.7 ± 0.2	1.8 ± 0.2	0.1 – 0.8
	9.63 ± 0.01	5.1 ± 0.2	1.5 ± 0.1	0.1 – 0.8
	9.73 ± 0.01	4.4 ± 0.2	1.1 ± 0.1	0.1 – 0.8
	9.97 ± 0.01	6.9 ± 0.2	0.9 ± 0.1	0.1 – 0.8
	10.37 ± 0.02	8.6 ± 0.4	0.3 ± 0.1	0.2 – 0.8

[a]Conditions: $[NPG]_0 = 2 \times 10^{-4}$ mol/dm^3, 30°C, ionic strength 1.0 mol/dm^3 (maintained by NaCl), $\lambda = 300$ nm, 2% v/v CH_3CN in the aqueous reaction mixture of each kinetic run. [b]Total amine buffer concentration range, [c]Error limits are standard deviations.

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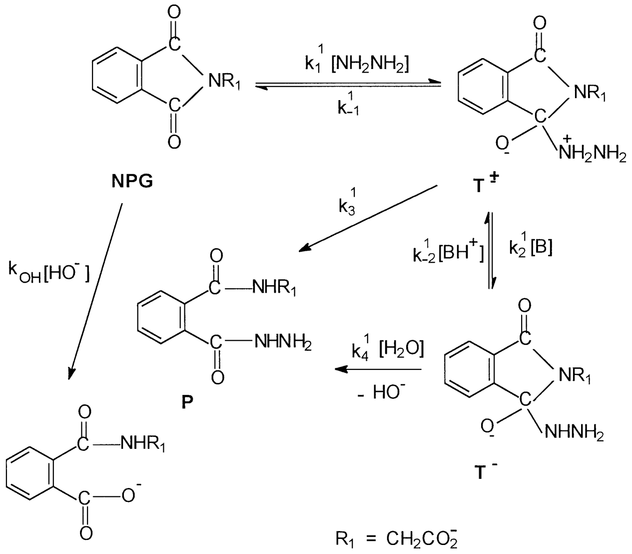
$0.1 - \leq 0.9$ mol/dm^3 at a constant pH, 1.0 mol/dm^3 ionic strength (by NaCl) and 30°C. Similar results were obtained at different pH values. First-order rate constants, k_{obs}, at a constant pH, were found to follow the following empirical equation

$$k_n^{app} = \frac{A_1 [Am]_T}{1 + A_2 [Am]_T} \tag{5}$$

where $k_n^{app} = (k_{obs} - k_{OH} [HO^-]) / [Am]_T$. The empirical constants, A_1 and A_2, were calculated from Equation (5) and these results are summarised in Table 2.

The distinct non-linear plots of k_n^{app} versus $[Am]_T$ for $CH_3OCH_2CH_2NH_2$ and $HOCH_2CH_2NH_2$ reveal a change in the rate-determining step with change in the catalyst concentration which in turn implies the formation of an intermediate on the reaction path.[1a] The other possible reasons for the non-linear dependence of k_n^{app} on $[Am]_T$ may be ruled out as discussed elsewhere in the related reacting system.[9] The simplest mechanism which could explain the observed data is shown in Scheme 1 with replacement of NH_2NH_2 by RNH_2 as well as B and BH^+ by RNH_2 and RNH_3^+, respectively, where $R = CH_3OCH_2CH_2$ or $HOCH_2CH_2$. The observed rate law:



Scheme 1

rate = k_{obs} [NPG]$_T$ and Scheme 1 lead to Equation (6)

$$k_n^{app} = \frac{K_1^1 k_4^{1'} k_2^1 f_b^2 [Am]_T}{k_4^{1'} + k_{-2}^1 f_a [Am]_T} \tag{6}$$

where $k_4^{1'} = k_4^1 [H_2O]$, $f_b = K_a^{Am} / (a_H + K_a^{Am})$, $f_a = 1 - f_b$ and $K_a^{Am} = a_H [RNH_2] / [RNH_3^+]$. Equation (6) is similar to Equation (5) with

$$A_1 = K_1^1 k_2^1 f_b^2 \tag{7}$$

and

$$A_2 = f_a k_{-2}^1 / k_4^{1'} \tag{8}$$

Equations (7) and (8) predict that the plots of $A_1 (a_H + K_a^{Am})^2 a_H$ and $A_2 (a_H + K_a^{Am})$ versus a_H should be linear. Such plots appear to be linear. But the observed data points are significantly scattered from the linear plots of $A_2 (a_H + K_a^{Am})$ versus a_H. The standard deviations associated with most of the A_2 values are significantly high (Table 2) and this could be the cause for significant scattering of the observed data points in the linear plots.

The calculated values of $K_1^1 k_2^1$ and $k_{-2}^1 / k_4^{1'}$ from respective equations (7) and (8) are $(7.80 \pm 1.78) \times 10^{-2}$ dm^6/mol^2/s^1 and 3.3 ± 1.4 dm^3/mol^1 for $CH_3OCH_2CH_2NH_2$ with $pK_a^{Am} = 9.45$[26] and $(17.6 \pm 5.4) \times 10^{-2}$ dm^6/mol^2 s^1 and 2.7 ± 0.3 dm^3/mol for $HOCH_2CH_2NH_2$ with $pK_a^{Am} = 9.60$.[27] The value of $K_1^1 k_2^1$ (= 0.078 dm^6/mol^2/s) for $CH_3OCH_2CH_2NH_2$ may be compared with the general base-catalysed third-order rate constant (k_2^b) for the reactions of $CH_3OCH_2CH_2NH_2$ with *N*-bromopropylphthalimide ($k_2^b = 0.052$ dm^6/mol^2/s) and anionic *N*-hydroxyphthalimide ($k_2^b = 0.049$ dm^6/mol^2/s) where the observed data obeyed the relationship: $k_{obs} - k_{OH} [HO^-] = k_n [Am]_T + k_{gb} [Am]_T^2$.[10] However, the observed data for the reactions of $CH_3OCH_2CH_2NH_2$ and $HOCH_2CH_2NH_2$ with phthalimide obeyed a kinetic equation similar to Equation (5). The respective values of $K_1^1 k_2^1$ for the reactions of $CH_3OCH_2CH_2NH_2$ and $HOCH_2CH_2NH_2$ with phthalimide[9] are nearly 30- and 50-fold larger than those with NPG which could be explained in terms of polar effects within the limits of standard deviations of the calculated values of $K_1^1 k_2^1$.

Addendum: General base catalysis could be detected kinetically in the cleavages of NPG and phthalimide (PTH) in the buffer solutions of 2-methoxyethylamine, 2-hydroxyethylamine and hydrazine. Uncatalyzed nucleophilic reactions of these amines with PTH and 2-methoxyethylamine and 2-hydroxyethylamine with NPG were not detected while such reaction was detected in the reactions of hydrazine with NPG and 2-methoxyethylamine with *N*-bromopropylphthalimide (NBPT) and anionic *N*-hydroxyphthalimide (NHPT). But the observed rate law for the cleavage of NBPT and NHPT was different from that for the cleavage of NPG and PTH in the presence of the 2-methoxyethylamine buffer.

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Techniques used: Absorption spectroscopy. pH measurements, Nonlinear least squares analysis

Table 1 Values of k_{obs}, E_{app}^a and A_∞^b for the cleavage of NPG in the presence of hydrazine and Tris at different pH^c

Scheme 2, **P_3**, **P_4**

Fig. 1 Effects of the total buffer concentration of 2-methoxyethylamine ($[Am]_T$) on apparent nucleophilic second-order rate constant (k_n^{app}) for the cleavage of NPG at pH 9.12 (▷), 9.33 (●), 9.56 (∇), 9.71 (□), 9.86 (Δ), and 10.20 (O). The solid lines are drawn through the least squares calculated points using equation (5) and the parameters listed in Table 2.

Fig. 2 Effects of the total buffer concentration of 2-hydroxyethylamine ($[Am]_T$) on apparent nucleophilic second-order rate constant (k_n^{app}) for the cleavage of NPG at pH 9.09 (▷), 9.34 (●), 9.63 (∇), 9.73 (□), 9.97 (Δ), and 10.37 (O). The solid lines are drawn through the least squares calculated points using equation (5) and the parameters listed in Table 2.

Fig. 3 Plots of $A_1 Q_1$ (O,∇) and $A_2 Q_2$ (Δ, □) versus a_H for the cleavage of NPG under the buffers of 2-methoxyethylamine (O, Δ) and 2-hydroxyethylamine (∇, □). The solid lines are drawn through the calculated points. $Q_1 = (a_H + K_a)^2 a_H$ and $Q_2 = (a_H + K_a)$.

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Scheme : 2, P_3, P_4
Figures : 1,2,3

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