SHORT PAPER

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Kinetic studies on the cleavage of *N*-phthaloylglycine in the buffers of hydrazine and morpholine†

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Specific base-catalysed and unatalysed nucleophilic reactions of hydrazine with *N*-phthaloyl-glycine (NPG) have been observed in hydrazine buffers of pH 7.39–8.45. Cleavage of NPG in morpholine buffers of pH 8.25-9.16 shows only uncatalysed reaction between morpholine and NPG.

Keywords: *N*-phthaloylglycine, hydrazine, morpholine, aminolysis, hydrolysis, kinetics

Intra- and intermolecular general acid–base (GA – GB) catalysis occur in many enzyme-catalysed reactions.[1] Despite the accumulation of a huge amount of kinetic data on such catalyses, the actual cause that originates such catalyses still remains mysterious.[2] For example, GB catalysis was detected in the reaction of hydrazine with phthalimide[3] while such catalysis was absent in its reaction with maleimide[4] under similar experimental conditions. Similarly, morpholine exhibited GB catalysis in its reaction with both phthalimide[5] and maleimide[6] while such catalysis could not be detected in its reaction with *N*-ethoxycarbonylphthalimide.[7] However, a rationalisation of when GA – GB catalysis will occur in a reaction might be made (if ever possible) only when a large amount of kinetic data on such catalysed reactions involving reactants and catalysts of diverse structural nature are available. The major part of the huge amount of kinetic data on GA–GB catalysis is concerned with the reaction systems where the leaving groups maintain free rotation around the bond being cleaved during the course of the reaction. We have been studying the kinetics and mechanism of aminolysis of imides where the leaving groups are not free to rotate around the bond being cleaved during the course of reaction. In the continuation of this study, we examined the reactions of N-phthaloylglycine with hydrazine and morpholine. The observed results and their probable explanation(s) are described in this article.

Experimental

Rates of aminolysis of NPG were studied spectrophotometrically by monitoring the disappearance of NPG as a function of reaction time at 300 nm and at 30°C. Details of the kinetic procedure and data analysis have been described elsewhere.[8] Based upon the detailed product characterisation studies on hydrazinolysis,[3] methylaminolysis[9] of phthalimide and aminolysis of *N* – substituted phthalimides[8], the immediate stable products in hydrazinolysis and morpholinolysis of NPG are expected to be *N*–(*o*-*N*-hydrazinylcarbamoylbenzoyl) glycine and *N*–(*o*-*N*-morpholinylcarbamoylbenzoyl)glycine, respectively.

Results

Five kinetic runs were carried out on hydrazinolysis of NPG within the total hydrazine buffer concentration ($[Am]_T$) range of 0.06 to ≤ 0.30 mol/dm^3 at pH 7.39 ± 0.01 and 30°C. The ionic strength of the reaction mixture was kept constant at 0.5 mol/dm^3 by NaCl. Similar observations were obtained at different pH. Pseudo-first-order rate constants (k_{obs}), obtained at a constant pH, obeyed eqn (1)

$$k_{obs} = k_0 + k_n^{app}[Am]_T \quad (1)$$

where k_0 and k_n represent buffer-independent first-order rate constant for hydrolysis and apparent nucleophilic second-order rate constant for hydrazinolysis of NPG, respectively, and $[Am]_T = [Am] + [AmH^+]$. The values of k_0 and k_n^{app} were calculated from eqn (1) using the linear least squares technique and these calculated values of k_0 and k_n^{app} at different pH are summarised in Table 1. The nature of fitting of observed data to eqn (1) is evident from the standard deviations associated with the parameters k_0 and k_n^{app} (Table 1) and from the plots of Fig. 1 where the solid lines are drawn

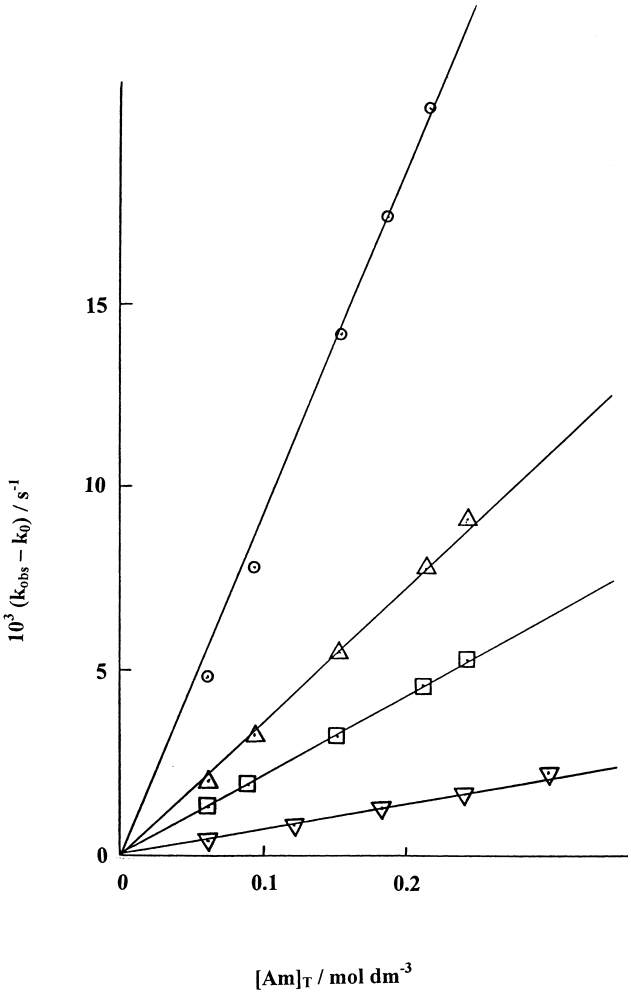

Fig. 1 Plots showing the dependence of (k_{obs} – k_o) versus $[Am]_T$ for hydrazinolysis of NPG at pH 7.39 (▽), 7.77 (□), 7.92 (△) and 8.45 (○). Solid lines are drawn through the least squares calculated data points.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Rate constants, k_0 and k_n^{app}, calculated from eqn (1)[a]

Amine	pH	$10^5\ k_0$ (s^{-1})	$10^4\ k_n^{app}$ (dm^3/mol/s)	$10^4\ k_n^{app}{}_{calcd}$ (dm^3/mol/s)
Hydrazine	7.39 ± 0.01[b]	–5.0 ± 9.0[b]	73.0 ± 4.5[b]	
		(0.60)[c]	69.6 ± 3.6	97.5[d]
	7.77 ± 0.01	–16.0 ± 4.0	227 ± 2	
		(1.43)	212 ± 8	210
	7.92 ± 0.00	–34.0 ± 9.0	389 ± 6	
		(2.03)	358 ± 18	360
	8.45 ± 0.03	–140 ± 12	1040 ± 10	
		(6.87)	908 ± 71	935
Morpholine	8.25 ± 0.02	1.90 ± 0.23	1.91 ± 0.05	1.80[e]
	8.64 ± 0.02	7.18 ± 0.13	2.81 ± 0.08	3.05
	9.16 ± 0.01	20.1 ± 0.8	4.68 ± 0.19	4.60

[a] [*N*-phthaloylglycine]$_0$ = 2 x 10^{-4} mol dm^{-3}, 30°C, λ = 300 nm, ionic strength 0.5 mol/dm^3, aqueous reaction mixture for each kinetic run contained 2 vol % MeCN. [b] Error limits are standard deviations.

[c] Parenthesised k_0 were obtained from the relationship: $k_0 = k_{OH}[HO^-]$ as described in the text.

[d] Calculated from eqn (4) with calculated values of k_n and k_{sb} as mentioned in the text.

[e] Calculated from eqn (7) with calculated value of k_n as mentioned in the text.

through the calculated data points. The values of k_0 at different pH are either negative or positive with association of considerably high standard deviations. These values of k_0 are statistically unreliable which could be due to insignificant contribution of k_0 term compared with $k_n^{app}[Am]_T$ in eqn (1). However, relatively more reliable values of k_0 were calculated from the relationship: $k_0 = k_{OH}[HO^-]$ where k_{OH} = 11.8 dm^3/mol/s[10] and $[HO^-] = (10^{pH\ -\ pKw})/\gamma$ with pK_w = 13.84[11] and activity coefficient γ (= 0.7) was calculated from the Davies equation.[12] These calculated values of k_0 as shown in Table 1 were also used to calculate k_n^{app} from the relationship: $k_{obs} - k_0 = k_n^{app}\ [Am]_T$ and the values of k_n^{app}, obtained at different pH, are shown in Table 1.

Morpholine buffer effect on rate of morpholinolysis of NPG was studied by carrying out five kinetic runs within the morpholine buffer concentration range of ≥ 0.06 to ≤ 0.60 mol/dm^3 at pH 8.25 ± 0.02, 0.5 mol/dm^3 ionic strength (by NaCl) and 30°C. Similar observations were obtained at pH 8.64 ± 0.02 and 9.16 ± 0.01. Pseudo-first-order rate constants (k_{obs}), at a constant pH, obeyed eqn (1) as evident from the plots of Fig. 2 where the solid lines are drawn through the calculated data points. The linear least squares calculated values of k_0 and k_n^{app} at different pH are summarised in Table 1. The calculated values of k_0 yielded k_{OH} = 6.6 ± 1.4 dm^3/mol/s from the relationship: $k_0 = k_{OH}[HO^-]$ with $[HO^-] = (10^{pH\ -\ pKw})/\gamma$ where pK_w = 13.84 and γ = 0.7. The value of k_{OH} (= 6.6 dm^3/mol/s) may be compared with the reported values of 11.8 dm^3/mol/s[10] and 6.2 dm^3/mol/s[13].

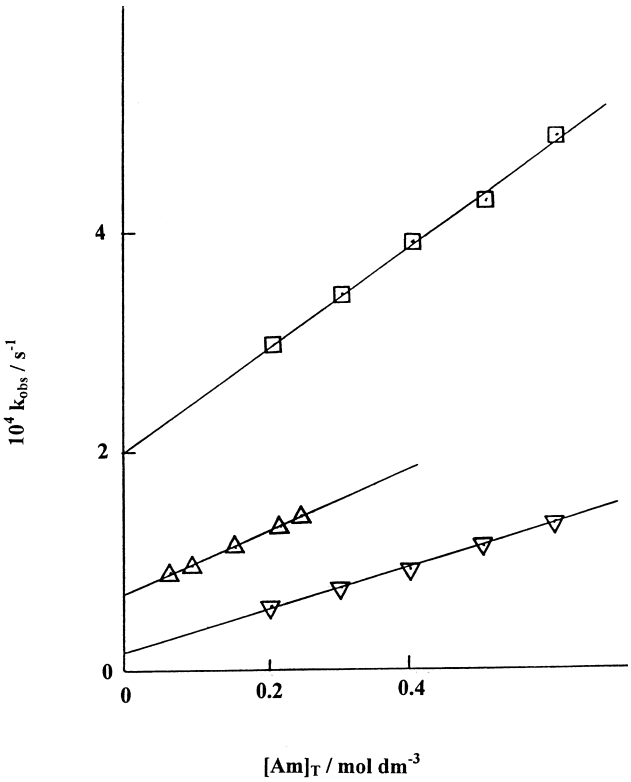
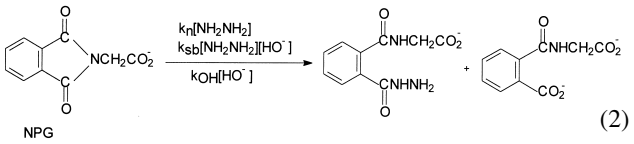


Fig. 2 Plots showing the dependence of k_{obs} versus $[Am]_T$ for morpholinolysis of NPG at pH 8.27 (▽), 8.64 (△) and 9.16 (□). Solid lines are drawn through the least squares calculated data points.

DISCUSSION

General base catalysis was observed in the nucleophilic reactions of monoprotonated ethane-1,2-diamine, $EDAH^+$[14], and methylamine[9] with phthalimide, but such catalysis was not observed in the reactions of these amines with maleimide[4] and $EDAH^+$ with *N*-ethoxycarbonylphthalimide.[7] The values of k_n^{app} at different pH show the presence and absence of specific base catalysis in the reaction of NPG with hydrazine and morpholine, respectively. It is unusual and surprising to observe the presence of and absence of specific base catalysis and GB catalysis, respectively, in the hydrazinolysis of NPG because, to the best of our literature search, specific base catalysis could be detected only in those nucleophilic reactions which involved GB catalysis.

The general reaction scheme for the cleavage of NPG in the buffers of hydrazine may be given by eqn (2)



(2)

The observed rate law (rate = $k_{obs}[NPG]$), and the rate law derived from eqn (2) lead to eqn (3)

$$k_{obs} = k_0 + \{(k_n K_a + k_{sb} K_a [HO^-])[Am]_T/(a_H + K_a)\} \quad (3)$$

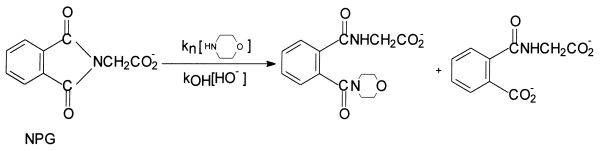
where $k_0 = k_{OH}[HO^-]$, $K_a = a_H\ [NH_2NH_2]/[NH_2NH_3^+]$ and $[Am]_T = [NH_2NH_2] + [NH_2NH_3^+]$. Comparison of eqns (1) and (3) gives eqn (4)

$$k_n^{app}(a_H + K_a) = k_nK_a + k_{sb}K_a[HO^-] \quad (4)$$

The plot of $k_n^{app}(a_H + K_a)$ versus $[HO^-]$ appeared to be linear with least squares calculated values of k_nK_a and $k_{sb}K_a$ as (3.78 ± 0.85) x 10^{-10}/s and (1.06 ± 0.28) 10^{-4}/dm^3/mol/s, respectively. The calculated values of k_nK_a and $k_{sb}K_a$ yielded 10^3 k_n = 53.3 ± 12.0 dm^3/mol/s and 10^{-4} k_{sb} = 1.50 ± 0.40 dm^6/mol^2/s, respectively, with pK_a = 8.15.

The unimportance of GB catalysis and importance of specific base catalysis in hydrazinolysis of NPG are surprising within the domain of the existing knowledge of such catalyses. However, the occurrence and nonoccurrence of these catalyses in the most extensively studied reactions (aminolysis of esters and amides) are not yet fully understood.[15] The qualitative explanation for the absence of GB catalysis may be found in terms of the probable high sensitivity of GB catalysis (*i.e.* high Bronsted slope β_{gb}) towards the basicity of the general base.

The general reaction scheme for the cleavage of NPG in morpholine buffers may be given by eqn (5)



(5)

The observed rate law (rate = k_{obs} [NPG]) and eqn (5) lead to eqn (6)

$$k_{obs} = k_0 + (k_n\ K_a/(a_H + K_a))\ [Am]_T \quad (6)$$

where $[Am]_T$ = [morpholine] + [morpholineH$^+$], $k_0 = k_{OH}$ $[HO^-]$ and $K_a = a_H$[morpholine]/[morpholineH$^+$]. Comparison of eqns (1) and (6) gives eqn (7)

$$k_n^{app} = k_n\ K_a/(a_H + K_a) \quad (7)$$

The plot of k_n^{app} versus $K_a/(a_H + K_a)$ turned out to be linear with the slope (k_n) = (5.84 ± 0.42) × 10^{-4} dm^3/mol/s. Nucleophilic second-order rate constants (k_n) for morpholinolysis of phthalimide [4], *N*-ethoxycarbonylphthalimide [6] and NPG yielded a Taft plot of intercept and slope (ρ*) of –2.49 ± 0.03 and 0.70 ± 0.00, respectively. Although a three data point Taft plot cannot be considered very reliable, the value of ρ* (0.70) is not significantly different from the ρ* value (1.0) obtained for nucleophilic second-order rate constants (k_{OH}) for hydroxide ion-catalysed hydrolysis of *N*-substituted phthalimides.[16]

Addendum

General base (GB) catalysis could not be detected in the hydrazinolysis of NPG under hydrazine buffers while, under similar experimental conditions, GB catalysis was so effective that the uncatalyzed nucleophilic second-order rate constant (k_n) was not obtained in the hydrazinolysis of phthalimide (PTH). Similarly, specific base catalysis has been observed in the reaction of hydrazine with NPG under hydrazine buffers, but such catalysis was not detected in the hydrazinolysis of PTH under similar experimental conditions. The nucleophilic reaction of morpholine with PTH exhibited GB catalysis while such catalysis was not observed in the morpholinolysis of NPG under similar experimental conditions. Hydroxide ion – catalysed second-order rate constants (k_{OH}) for hydrolysis and k_n for morpholinolysis of PTH and *N*-substituted phthalimides constitute good Taft plots. The characteristic difference in the reactivity of hydrazine and morpholine towards NPG and PTH are difficult to explain in terms of pK_a, structural features, and intrinsic nucleophilicity and electrophilicity of these amines and phthalimides, respectively.

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