Suggested Improvement in the Ing−Manske Procedure and Gabriel Synthesis of Primary Amines: Kinetic Study on Alkaline Hydrolysis of *N*-Phthaloylglycine and Acid Hydrolysis of *N*-(*o*-Carboxybenzoyl)glycine in Aqueous Organic Solvents

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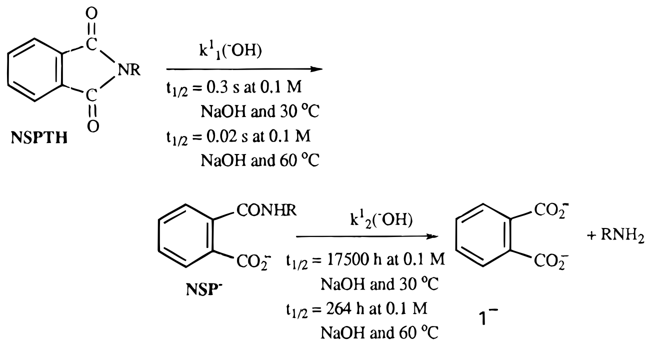
A slight modification of the Gabriel synthesis of primary amines is suggested on the basis of the observed and reported values of rate constants for the alkaline and acid hydrolyses of phthalimide, phthalamic acid, benzamide, and their *N*-substituted derivatives. The suggested procedure requires shorter reactions time and milder acid−base reaction conditions compared with the conventional acid−base hydrolysis in the Gabriel synthesis. A slight modification in the *Ing−Manske procedure* is also suggested. Pseudo-first-order rate constants, k_{obs}, for hydrolysis of *N*-phthaloylglycine, NPG, decrease from 24.1×10^{-3} to 7.72×10^{-3} and 6.12×10^{-3} s^{-1} with increasing acetonitrile and 1,4-dioxan contents, respectively, from 2 to 50% v/v (all the percentages given in the paper are vol %), while increasing the organic cosolvents content from 50 to 80% increases k_{obs} from 7.72×10^{-3} to 19.7×10^{-3} s^{-1} for acetonitrile and from 6.12×10^{-3} to 52.8×10^{-3} s^{-1} for 1,4-dioxan, in aqueous organic solvents containing 0.004 M NaOH at 35 °C. The rate constants for NPG hydrolysis decrease from 2.11×10^{-2} to 1.19×10^{-4} s^{-1} with increasing MeOH content from 2 to 84%, in aqueous organic solvents containing 2% MeCN and 0.004 M NaOH at 35 °C.

Introduction

The Gabriel synthesis, for converting halides to primary amines, involves two major steps: (i) the synthesis of *N*-substituted phthalimides from halides and (ii) the synthesis of primary amines from *N*-substituted phthalimides.[1] The formation of a primary amine from the *N*-substituted phthalimide involves either hydrolysis, whether acid- or base-catalyzed, or hydrazinolysis (the *Ing−Manske procedure*).[2] In an effort to improve the Gabriel synthesis, Osby and co-workers[3] have reported the conversion of phthalimides to primary amines in an efficient, two-stage operation using $NaBH_4$/2-propanol and then acetic acid. Several alternatives to the Gabriel synthesis have been recently reported.[2] None of the reports on improving the Gabriel synthesis appear to be based on the mechanistic details of the reactions involved. We wish to report an improvement in the second step of the Gabriel synthesis based on the detailed mechanisms of the reactions. The suggested improvement in the second step of the Gabriel synthesis is supported by the results of a kinetic study on the alkaline hydrolysis of NPG and the acid hydrolysis of *N*-(*o*-carboxybenzoyl)glycine in water−organic solvents. The kinetic results obtained and their probable explanations are described in this paper.

The complete degradation of phthalimide (PTH) and its *N*-substituted derivatives (NSPTH) under basic and acidic conditions may be represented by Schemes 1 and 2, respectively. The values of the hydroxide ion-catalyzed second-order rate constants, k^1_{1OH} (= $k^1_1/[^-OH]$, where k^1_1 represents the pseudo-first-order rate constant), for the conversion of NSPTH to NSP^- are summarized in Table 1. The literature values of the second-order rate constants, k^1_{2OH} (= $k^1_2/[^-OH]$) for the hydroxide ion-catalyzed cleavage of benzamide, *N*-methylbenzamide, and *o*-methoxybenzamide are also listed in Table 1. The value of k^1_{2OH} (= $k^1_2/[^-OH]$) for the conversion of NSP^- to phthalate ion ($\mathbf{1}^-$) may be slightly smaller than k^1_{2OH} for benzamide because of steric and electrostatic effects. The literature values of the pseudo-first-order rate constants, k^2_1 (= $k^2_{1H}[H^+]$), for the H^+-catalyzed conversion of PTH to phthalamic acid under different conditions are listed in Table 1. The values of k^2_1 for NSPTH, where

Scheme 1



Scheme 2

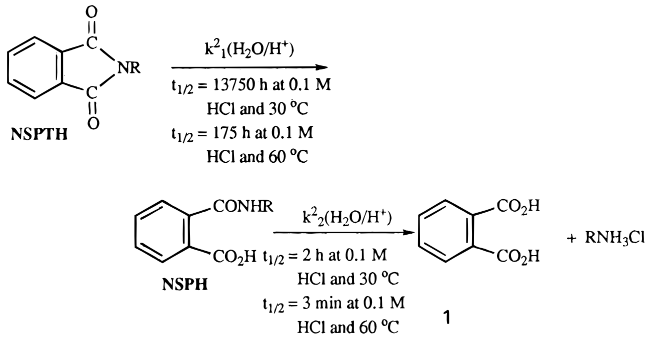


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Table 1. Pseudo-First-Order Rate Constants (k) and $^-$OH- and H$^+$-Catalyzed Second-Order Rate Constants (k_{OH} and k_H) for the Cleavage of Substrates (Amides and Imides)[a]

substrate	rate constant	pH, [H$^+$], or [$^-$OH]	T (°C)
phthalimide	$10^5k_H = 9.8\ M^{-1}\ s^{-1}$		100[26]
	$10^{-3}k_{OH} = 4.1\ M^{-1}\ s^{-1}$		100[26]
	$k_{OH} = 26.3\ M^{-1}\ s^{-1}$		30[27]
N-(2-bromoethyl)phthalimide	$k_{OH} = 31.3\ M^{-1}\ s^{-1}$		25[28]
N-(3-bromopropyl)phthalimide	$k_{OH} = 33.5\ M^{-1}\ s^{-1}$		30[28]
N-(ethoxycarbonyl)phthalimide	$k_{OH} = 2196\ M^{-1}\ s^{-1}$		30[28]
N-hydroxyphthalimide anion	$k_{OH} = 1.3\ M^{-1}\ s^{-1}$		30[29]
N-hydroxyphthalimide	$k_{OH} = 177\ M^{-1}\ s^{-1}$		30[29]
benzamide	$10^9k = 3.1\ s^{-1}$	0.001 M HCl	48[10]
	$10^4k = 3.5\ s^{-1}$	1.0 M HCl	100[10]
	$10^5k = 1.0\ s^{-1}$	4.0 M HCl	48[10]
	$10^4k_{OH} = 15.8\ M^{-1}\ s^{-1}$		100.4[30]
N-methylbenzamide	$10^4k_{OH} = 7.2\ M^{-1}\ s^{-1}$		100.4[30]
o-methoxybenzamide	$10^4k_{OH} = 11.0\ M^{-1}\ s^{-1}$		100[31]
phthalamic acid	$10^4k = 2.4\ s^{-1}$	pH 1.3−1.8	47.3[32]
	$10^4k = 2.4\ s^{-1}$	0.001 M HCl	47.3[10]
	$10^4k = 20.0\ s^{-1}$	pH ≤ 2.0	48[11]
N,*N*-dimethylphthalamic acid	$10^4k = 10.0\ s^{-1}$	≥0.002 M HCl	35[14]
o-HOOCC$_6$H$_4$CONHC$_6$H$_4$X	$10^k \approx 70.0\ s^{-1}$	pH ≈ 2	65.8[15a]
with X = H	$10^4k = 1.9\ s^{-1}$	0.1 M HCl	24.6[15a]
	$10^4k = 28.2\ s^{-1}$	0.01 M HCl	50.15[11]
X = 4′-OMe	$10^4k \approx 117.0\ s^{-1}$	pH ≈ 2	65.8[15a]
= 3′-OMe	$10^4k = 24.1\ s^{-1}$	0.01 M HCl	50.15[11]
= 3′-Me	$10^4k = 36.2\ s^{-1}$	0.01 M HCl	50.15[11]
X = 3′-Cl	$10^4k \approx 25.0\ s^{-1}$	pH ≈ 2	65.8[15a]
	$10^4k = 10.4\ s^{-1}$	0.01 M HCl	50.15[11]

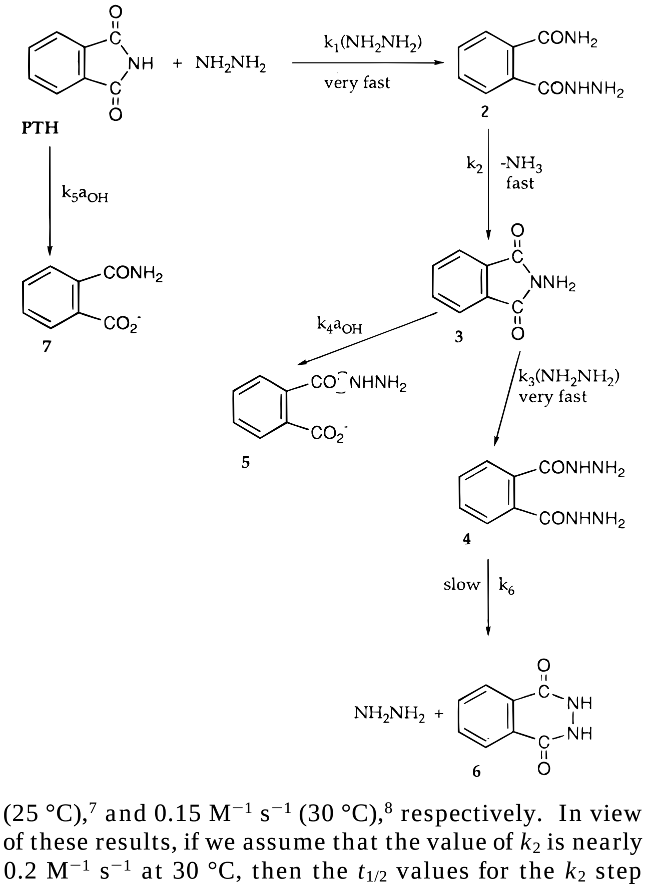
[a] Reaction solvent is water.

R represents alkyl groups, may not be significantly different from $k^2{}_1$ for PTH under essentially similar conditions. The literature values of the first-order rate constants, $k^2{}_2$, for conversion of phthalamic and a few *N*-substituted phthalamic acids (NSPH) to phthalic acid (**1**) are also summarized in Table 1.

In view of the reported values of $k^1{}_1$, $k^1{}_2$, $k^2{}_1$, and $k^2{}_2$, it is apparent that for the least reactive NSPTH, the half-life period, $t_{1/2}$, for the $k^1{}_1$ step is nearly 0.3 s at 30 °C (0.02 s at 60 °C) and 0.1 M NaOH, while $t_{1/2}$ for $k^2{}_1$ is nearly 13 750 h at 30 °C (175 h, at 60 °C) and 0.1 M HCl under similar experimental conditions. Similarly, $t_{1/2}$ for the $k^1{}_2$ step is nearly 17 500 h at 30 °C (260 h at 60 °C) and 0.1 M NaOH, while $t_{1/2}$ for the $k^2{}_2$ step is nearly 2 h at 30 °C (3 min at 60 °C) and 0.1 M HCl under essentially similar other experimental conditions.

Because of the significantly large values of $t_{1/2}$ for the $k^1{}_2$ step in alkaline medium and for the $k^2{}_1$ step in acidic medium in the complete degradation of NSPTH, the use of both basic and acidic hydrolysis of NSPTH turned out to be an inefficient experimental procedure to prepare primary amines in the Gabriel synthesis. A more useful and widely used modified procedure of the Gabriel synthesis is the Inge−Manske procedure, which involves the hydrazinolysis of NSPTH to generate the desired primary amines.[2] The detailed reaction mechanism for hydrazinolysis of PTH is shown in Scheme 3.[4]

Scheme 3



The reported value of k_1 is 22.4 $M^{-2}\ s^{-1}$ at 30 °C,[4] which shows that $t_{1/2}$ for the k_1 step is nearly 3 s at 30 °C and 0.1 M NH$_2$NH$_2$. The cyclization of **2** to **3** is expected to be catalyzed by hydroxide ion. The values of the second-order rate constants for the hydroxide ion-catalyzed cyclization of phthalamide,[5] *N*′-dimethylphthalamide,[5] *o*-(aminomethyl)benzamide,[6] and *o*-(hydroxymethyl)benzamide[7,8] are 4.9 (25.9 °C), 7.6 (25.9 °C), 0.16 (30 °C), 0.04 (25 °C),[7] and 0.15 $M^{-1}\ s^{-1}$ (30 °C),[8] respectively. In view of these results, if we assume that the value of k_2 is nearly 0.2 $M^{-1}\ s^{-1}$ at 30 °C, then the $t_{1/2}$ values for the k_2 step at pH 10 are nearly 10 h at 30 °C and 30 min at 60 °C. It is to be noted that these conclusions are valid for the reactions carried out in 100% water solvent. The change in reaction solvent from 100% water to organic or mixed aqueous organic solvents is expected to reduce the values of both rate constants, k_1 and k_2. It is now evident that

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the significantly lower value of $t_{1/2}$ for the k_2 step compared to that for the $k^1{}_2$ step or $k^2{}_1$ step makes the Inge−Manske procedure superior to the usual basic and acidic hydrolysis of NSPTH (Schemes 1 and 2) involved in the Gabriel synthesis.

Note: The Inge−Manske procedure may be expected to be significantly improved in terms of reducing the time period for generating the primary amine from NSPTH if the pH of the reaction mixture is increased by adding NaOH solution to it after completion of the k_1 *step. The significant increase in the pH of the reaction mixture at the start of the* k_1 *step is bound to convert a significant amount of NSPTH to* NSP^-*, which is relatively much less reactive toward both* ^-OH *and* NH_2NH_2.

Experimental Section

Materials. Reagent-grade *N*-phthaloylglycine, NPG, and phthalimide, PTH, were obtained from Fluka and BDH. All other chemicals used were also reagent-grade commercial products. The stock solutions of NPG and PTH were prepared in acetonitrile.

Kinetic Measurements. (a) Alkaline Hydrolysis of NPG. Under aqueous alkaline and acidic pH conditions, NPG absorbs strongly (molar absorption coefficient at 300 nm is nearly 2×10^3 M^{-1} cm^{-1}) while the hydrolysis product of NPG, *N*-(*o*-carboxybenzoyl)glycine, absorbs weakly at 300 nm (molar absorption coefficient is < 50 M^{-1} cm^{-1}). When the water content was changed from 98 to 15% (all percentages given in the paper are vol %), mixed aqueous−organic solvents did not reveal a significant change in the molar absorption coefficients of NPG and its hydrolysis product at 300 nm. Thus, the rates of alkaline hydrolysis of NPG were studied spectrophotometrically by monitoring the disappearance of the reactant (NPG) at 300 nm. The details of the kinetic procedure are described elsewhere.[9]

All the kinetic runs were carried out under experimental conditions in which the reaction rate obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants, k_{obs}, were calculated from eq 1

$$AU = \delta_{app}[X]_0 \exp(-k_{obs}t) + AU_\infty \qquad (1)$$

using a nonlinear least-squares technique considering δ_{app} (apparent molar absorption coefficient) and AU_∞ (the absorbance at $t = \infty$) as unknown parameters. In eq 1, AU is the absorbance at any reaction time, t, and $[X]_0$ is the initial concentration of NPG. The reactions were carried out for up to 4−9 half-lives, and the observed data fitted eq 1 well.

(b) Aqueous Cleavage of *N*-(*o*-Carboxybenzoyl)glycine and Phthalamic Acid in Acidic Medium. The aqueous cleavage of phthalamic acid and *N*-substituted phthalamic acids (NSPH) at pH ≤ 3 is known to follow an irreversible consecutive reaction path (eq 2)

$$A \xrightarrow{k_1} PAn \xrightarrow{k_2} C \qquad (2)$$

where A, PAn, and C represent phthalamic acid or NSPH, phthalic anhydride, and phthalic acid, respectively. It is interesting to note that in the classic paper on hydrolysis of phthalamic acid, Bender *et al.* used an ingenious technique to affirm indirectly the formation of PAn.[10] In 1977, Blackburn *et al.*[11] showed spectrophotometrically the formation and decay of PAn in the hydrolysis of phthalamic acid in the presence of high concentrations of sodium perchlorate, where the rate of hydrolysis of PAn was greatly retarded.[12] We found that the respective values of k_2 and k_2/k_1 (when A = *N,N*-dimethylphthalamic acid) changed from 1.19×10^{-2} to 1.48×10^{-4} s^{-1} and 22.5 to 0.1 with increasing MeCN content from 2 to 70% in mixed aqueous solvents containing 0.005 M HCl at 25 °C.[13,14] These results show that the presence of PAn in the hydrolysis of A can be easily detected spectrophotometrically by using water−acetonitrile or water−aprotic organic solvents with high contents of organic cosolvent. Phthalic acid and A do not absorb significantly, while PAn absorbs strongly at 310 nm. Thus, the rates of formation and decay of PAn were studied spectrophotometrically at 310 nm in H_2O−MeCN solvents containing >60% MeCN.

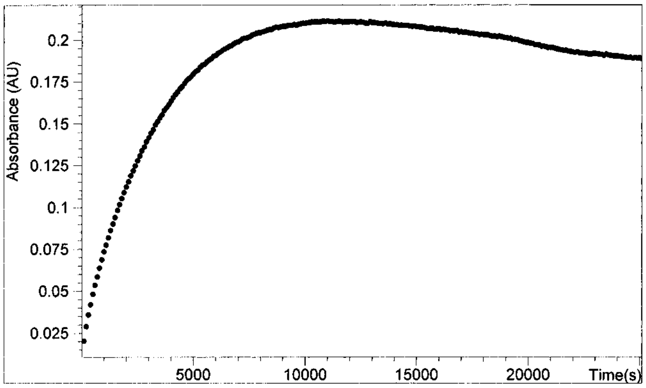

Figure 1. Plot of absorbance (AU) at 310 nm against time for a mixed aqueous solution of *N*-(*o*-carboxybenzoyl)glycine (3.57×10^{-3} M) in 71.4% MeCN, 0.108 M HCl at 35 °C.

In a typical kinetic run with a total volume of 5 mL of the reaction mixture containing 0.004 M NPG, 0.02 M NaOH, and 80% MeCN, the reaction was allowed to complete a period of more than 50 half-lives (i.e. > 600 s) at 35 °C. The hydrolysis of the hydrolytic product of NPG (i.e., A in eq 2) was then initiated by adding 0.6 mL of 1.18 M HCl to the reaction mixture. The resulting reaction mixture, having a total volume of 5.6 mL, contained 3.57×10^{-3} M A, 0.108 M HCl, and 71.4% MeCN. The change in the absorbance, AU, at 310 nm was monitored as a function of time (t) using a diode-array spectrophotometer. The observed data (for a typical kinetic run) are shown in Figure 1.

The hydrolysis of phthalamic acid was carried out as follows. The alkaline hydrolysis of PTH in a reaction mixture (15 mL) containing 4.4×10^{-3} M PTH, 0.02 M NaOH, and 70% MeCN was allowed to complete a period of nearly 7 half-lives (i.e., nearly 21.5 h) at ambient temperature (≈28 °C). The hydrolysis of phthalamic acid was then initiated by adding 0.8 mL of 1.18 M HCl to 5.0 mL of the reaction mixture. The resulting reaction mixture contained 3.79×10^{-3} M phthalamic acid, 0.146 M HCl, and 60.3% MeCN. The change in absorbance at 310 nm was monitored as a function of time using a diode-array spectrophotometer. The observed data (AU versus t) is shown in Figure 2.

Results and Discussion

(a) Effects of Mixed Aqueous-Organic Solvents on the Rate of Alkaline Hydrolysis of NPG. A series of kinetic runs was carried out at 0.004 M NaOH and 35 °C in mixed aqueous solvents containing different contents of MeCN (2−84%), 1,4-dioxan (2−83%), and MeOH (2−84%). A few kinetic runs were also carried out within the 1,4-dioxan content range 10−80% at 0.008 M NaOH, 2% MeCN, and 35 °C. Pseudo-first-order rate contents, k_{obs}, are shown graphically in Figure 3. Increasing MeCN from 2 to 50% decreased k_{obs} from 2.41×10^{-2} to 7.72×10^{-3} s^{-1}, while a further increase from 50 to 84% increased k_{obs} from 7.72×10^{-3} to 2.63×10^{-2} s^{-1}.

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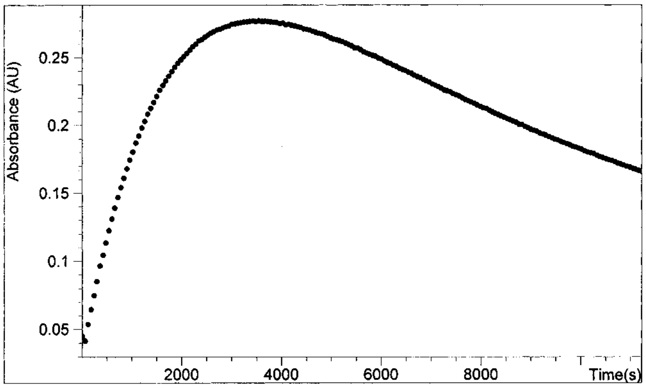


Figure 2. Plot of absorbance (AU) at 310 nm against time for a mixed aqueous solution of phthalamic acid (3.79×10^{-3} M) in 60.3% MeCN, 0.146 M HCl at 35 °C.

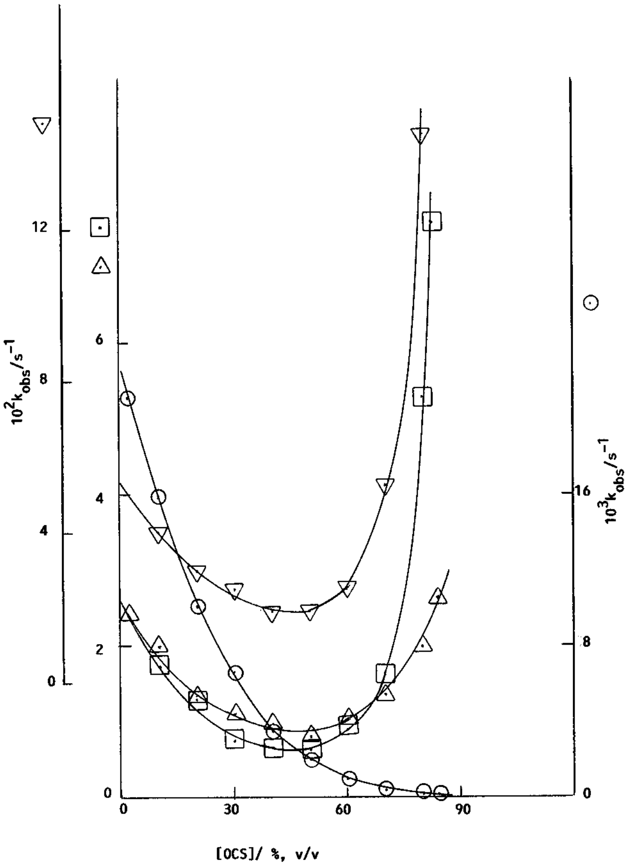
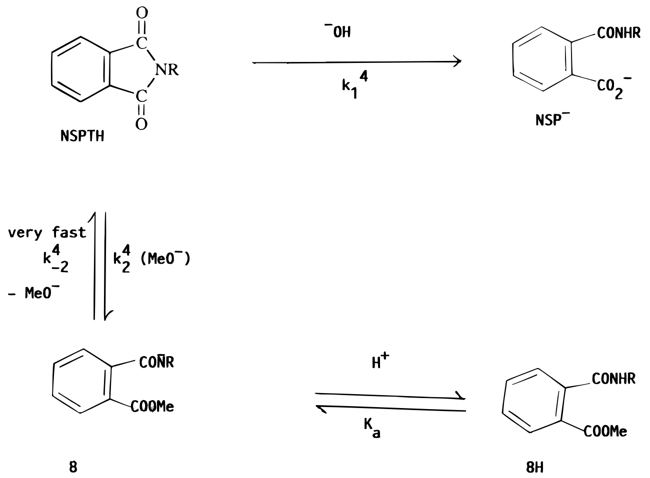


Figure 3. Plots of k_{obs} at 35 °C (for alkaline hydrolysis of *N*-phthaloylglycine, NPG) against the percentage contents of organic cosolvent (OCS) of reaction mixtures containing 4×10^{-4} M NPG, 0.004 M NaOH, and mixed solvents, H_2O−MeCN (△), H_2O−1,4-dioxan (⊡) with 2% MeCN, and (▽) with 2% MeCN and 0.008 M NaOH, and H_2O−MeOH (⊙) with 2% MeCN.

Similarly, increasing 1,4-dioxan from 10 to 50% decreased k_{obs} from 1.71×10^{-2} to 6.12×10^{-3} s^{-1} at 0.004 M NaOH and from 4.00×10^{-2} to 1.93×10^{-2} s^{-1} at 0.008 M NaOH. But increasing 1,4-dioxan from 50 to 83 (at 0.004 M NaOH) and 80% (at 0.008 M NaOH) increased k_{obs} from 6.12×10^{-3} to 7.57×10^{-2} s^{-1} and 1.93×10^{-2} to 0.145 s^{-1}, respectively. Similar observations have been reported in several related reactions.[15] The rate constants decreased from 2.11×10^{-2} to 1.19×10^{-4} s^{-1} with increasing MeOH content from 2 to 84% at 0.004 M NaOH and 2% MeCN.

Scheme 4



The hydroxide ion catalyzed cleavage of NPG involves $^-$OH and ionized NPG as the reactants. The rate of reaction of H_2O with ionized NPG is negligible compared with the rate of reaction of $^-$OH with ionized NPG at $[^-OH] \geq 0.002$ M.

It is interesting to note that MeO$^-$ reacts with acetyl salicylate ion,[16] AS$^-$, and phenyl acetate[17] nearly 60 times faster than $^-$OH in aqueous methanol solvents. Pseudo-first-order rate constants for the cleavage of AS$^-$ revealed an increase with increasing MeOH content (within the range 2−18%) in MeOH−H_2O solvents containing 2% MeCN and 0.01 M NaOH.[16] Such an increase could not be detected in the cleavage of ionized NPG under essentially similar experimental conditions. This may be explained by the simplified reaction mechanism as shown in Scheme 4 for the alkaline cleavage of NPG in MeOH−H_2O mixtures.

The value of k_1^4 is 5 M^{-1} s^{-1} at 30 °C in an aqueous solvent containing 2% MeCN. If $k_2^4/k_1^4 \approx 60$, then $k_2^4 \approx$ 300 M^{-1} s^{-1} at 30 °C. The values of the rate constants, k_{OH}, for $^-$OH-catalyzed cyclization of methyl *o*-carbamoylbenzoate, methyl *o*-(aminomethyl)benzoate, and ethyl *o*-(hydroxymethyl)benzoate are 3.1×10^3 (25.9 °C),[5] 7×10^3 (30 °C),[18] and 10^4 M^{-1} s^{-1} (30 °C),[19] respectively. These values of k_{OH} predict a value of k_{-2}^4 as $\approx 10^3$ s^{-1}, provided $K_a/K_w \approx 1$ M^{-1}, where K_a is the ionization constants of **8H**. This analysis indicates that at $[MeO^-] \leq 0.004$ M, the value of $k_{-2}^4/k_2^4[MeO^-] \geq 800$. Thus, under the experimental conditions imposed, the ratio [**8**]/[NPG] $\leq$ 1/800 and hence insignificant amounts of **8** or **8H** are expected to exist during the course of the cleavage of NPG.

The decrease in k_{obs} with increasing organic cosolvent content (i.e., decreasing dielectric constant, ϵ, of the reaction medium) may be explained in terms of simple electrostatic theory.[20] But in the electrostatic treatment of the effects of ϵ on reaction rates, the charges on the reactants are presumed to be at the reaction site, while in the present system the negative charge on the reactant NPG is not entirely at the specific reaction site. Thus,

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Table 2. Calculated Parameters from Eq 3[a]

sub	$10^3[X]_0$[b]	MeCN (%, v/v)	[HCl] (M)	δ_{PAn}[c] (M^{-1} cm^{-1})	10^5k_1 (s^{-1})	10^4k_2 (s^{-1})	AU_0	t_{fin}[d] (s)
NCG	3.85	67.3	0.026	230	8.47 ± 0.23[e]	3.20 ± 0.13[e]	0.021 ± 0.001[e]	4353
	3.57	71.4	0.108	210	5.72 ± 0.29	1.14 ± 0.04	0.034 ± 0.004	25 103
	5.36	71.4	0.108	210	8.22 ± 0.20	1.62 ± 0.06	0.025 ± 0.002	6573
	3.70	74.1	0.069	200	6.70 ± 0.23	1.02 ± 0.02	0.043 ± 0.004	21 503
	5.56	74.1	0.069	200	7.57 ± 0.18	1.37 ± 0.06	0.032 ± 0.002	7173
PHA[f]	3.79	60.3	0.146	255	17.8 ± 0.4	3.70 ± 0.08 (4.85)[g]	0.044 ± 0.004	11 223
	3.86	70.2	0.024	216	20.2 ± 0.2	1.76 ± 0.02 (1.79)[h]	0.082 ± 0.002	14 343

[a] Conditions: Mixed H_2O−MeCN solvent, 35 °C, $\lambda = 310$ nm. [b] Initial concentration of substrate (sub). [c] Molar absorption coefficient of PAn at 310 nm from ref 13. [d] Final time attained in the kinetic run. [e] Error limits are standard deviations. [f] Phthalamic acid. [g] k_2 value at 60% MeCN from ref 13. [h] k_2 value at 70% MeCN from ref 13.

the use of the simple electrostatic theory to predict quantitatively the effects of ϵ on the reaction rates of such reacting systems is rather hazardous.

The increase in k_{obs} with increasing MeCN and 1,4-dioxan in mixed aqueous solvents containing water ≤ 50−60% indicates that the effects of ϵ on k_{obs} become unimportant under such experimental conditions. It is interesting to note that although ϵ of MeCN is not significantly different from ϵ of MeOH,[21−23] the k_{obs} versus percent organic cosolvent profile for MeCN is different from that for MeOH at ≥50% (Figure 3). Although several explanations may be given to explain such observations, we prefer the specific medium effect, which is the consequence of the preferential solvation of a specific type of ion (either cation or anion) by the organic cosolvent in the mixed aqueous solvent as the most effective solvent effect on the rates of reaction described in this paper. However, in the mixed aqueous−organic solvents where the organic cosolvent is worse than water in solvating ionic solutes, solutes of high charge density are preferentially solvated only by water molecules, and therefore, differential solvation effects on reaction rates may be realized only at very high contents of the poor solvating component of mixed aqueous solvents. Aprotic organic cosolvents (such as acetonitrile and 1,4-dioxan) solvate anionic reactant and transition state very poorly compared with protic organic cosolvents (such as methanol) in mixed aqueous solvents of similar ϵ. The cations are apparently more strongly solvated compared to anions by aprotic organic cosolvents. Such differential solvation effects on anions and cations are expected to either increase the stability of the ion-pair formed between anion and cation or increase the nucleophilicity of the anionic nucleophile if ion-pair formation is prevented by geometric constraints.

The charge density of ^-OH is apparently larger than that of anionic NPG. Thus, the solvation shell of anionic NPG is expected to contain larger number of aprotic organic cosolvent molecules compared to the solvation shell of ^-OH in mixed aqueous−aprotic organic cosolvent with low water content. This characteristic will cause stronger ion-pair formation between anionic NPG and Na^+ than that between ^-OH and Na^+, and this in turn will cause a stronger increase in the electrophilicity of the carbonyl carbon of anionic NPG and a weaker decrease in the nucleophilicity of ^-OH with increasing MeCN or 1,4-dioxan content. This explains qualitatively the observed increase in k_{obs} with increasing MeCN and 1,4-dioxan contents (Figure 3).

An alternative possibility, that the reactant ions (anionic NPG and ^-OH) will, on average, be surrounded by water molecules to a larger extent in water−acetonitrile and water−1,4-dioxan than in water−methanol mixtures, thus increasing the reaction rates in the former mixed solvents because of a higher dielectric constant in the immediate environment of the reacting ions, cannot be ruled out completely. But under such circumstances, the maximum value of ϵ in the immediate neighborhood of the reacting ions cannot be larger than ϵ of pure water solvent. Thus, the k_{obs} at 98% H_2O must be larger than k_{obs} obtained at any content of MeCN or 1,4-dioxan. The larger values of k_{obs} at 84% MeCN ($k_{obs} = 2.63 \times 10^{-2}$ s^{-1}) and 83% 1,4-dioxan ($k_{obs} = 7.57 \times 10^{-2}$ s^{-1}) than in 98% H_2O ($k_{obs} = 2.41 \times 10^{-2}$ s^{-1}) under similar experimental conditions make this alternative possibility less attractive.

(b) Acidic Aqueous Cleavage of *N*-(*o*-Carboxybenzoyl)glycine (NCG) and Phthalamic Acid in Mixed H_2O−MeCN Solvents. The observed data (absorbance versus time) shown in Figures 1 and 2 reveal the formation and decay of an intermediate with the progress of the reaction. This shows that the rates of hydrolysis of NCG and phthalamic acid follow the reaction scheme shown by eq 2. The observed data were treated using eq 3

$$AU = AU_0 + \frac{\delta'[X]_0 k_1}{(k_2 - k_1)}[\exp(-k_1 t) - \exp(-k_2 t)] \qquad (3)$$

where $[X]_0$ is the initial concentration of the reactant (NCG or phthalamic acid), $\delta' = \delta_{PAn} - \delta$, and $AU_0 = \delta[X]_0$ with $\delta = \delta_A \approx \delta_C$. The notations δ_A, δ_{PAn}, and δ_C represent the molar absorption coefficients of A, phthalic anhydride, and phthalic acid, respectively. The assumption that $\delta_A \approx \delta_C$ at 310 nm is supported by the spectra of phthalamic acid and phthalic acid.[11] The unknown parameters k_1, k_2, and AU_0 were calculated from eq 3 using a nonlinear least-squares technique with known values of δ' and $[X]_0$. Since the molar absorption coefficients of *N*,*N*-dimethylphthalamic acid[14] and phthalic acid[13] turned out to be nearly zero at 310 nm within 1−80% MeCN content range, we consider $\delta' = \delta_{PAn}$ and the values of δ_{PAn} at different % MeCN were obtained from ref 13.

The nonlinear least-squares calculated values of k_1, k_2, and AU_0 under different reaction conditions are summarized in Table 2. The values of k_2 obtained for the hydrolysis of NCG and phthalamic acid are comparable with the first-order rate constants for hydrolysis of authentic PAn under similar experimental conditions. The vaules of k_1 for phthalamic acid at 60.3 and 70.2% MeCN and 35 °C may be compared with the reported values of k_1 at 100% H_2O and 48 °C (Table 1). The value

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of k_1 (= 7.5×10^{-5} s^{-1}) for NCG is nearly 2.5 times smaller than k_1 for phthalamic acid. This is reasonable, since the reported ρ values for *N*-arylphthalamic acids are −1.23[11] and −1.05 in pure water solvent and $\sigma^*_{\mathrm{CH2COOH}}$ is larger than σ^*_{H}, $\sigma^*_{\mathrm{CH2COOMe}} = 0.7$ and $\sigma^*_{\mathrm{H}} = 0.49$.[24]

Suggested Experimental Procedure for the Second Step in the Gabriel Synthesis. The reaction mixture containing x mol of NSPTH and (x + 0.01) mol of NaOH dissolved in an appropriate solvent should be allowed to reflux until all the NSPTH is converted to the corresponding anionic phthalamic acid (NSP$^-$). The reflux period is expected to be dependent on the solvent, the nature of the NSPTH, and the temperature of the reaction medium. It may vary from a few seconds to a few minutes with the change in the solvent from pure water to the mixed aqueous−organic solvent with organic cosolvent content of ≤70%. It may be noted that the increase in the content of MeCN from 1 to 70% in mixed H_2O−MeCN solvent caused nearly a 12-fold decrease in the rate of hydrolysis of PTH at 55 °C and 0.01 M KOH.[25] But the rate of hydrolysis of NPG increased by nearly 2.5- and 9.0-fold, respectively, with increasing MeCN and 1,4-dioxan contents from 50 to 80% at 35 °C and 0.004 M NaOH. After the completion of the $k^1{}_1$ step (Scheme 1), (x + 0.02) mol of HCl should be added to the reaction mixture so that the pH of the reaction mixture becomes ≤2. The reaction mixture is refluxed again until the $k^2{}_1$ step (Scheme 2) is completed. The reflux period may vary from a few minutes (in pure water solvent) to 1 h or less (in mixed H_2O−MeCN solvent). Pseudo-first-order rate constants for the conversion of *N*,*N*-dimethylphthalamic acid to phthalic acid at 25 °C and 0.005 M HCl were found to be unchanged with changing MeCN content from 10 to 90% in mixed H_2O−MeCN solvent.[14]

Choice of the Solvents. The most suitable solvent is water. But most NSPTH compounds may be sparingly soluble in pure water. Mixed aqueous−organic solvents may be used in order to achieve better solubility of NSPTH. But the organic cosolvent must be an aprotic solvent such as acetonitrile, 1,4-dioxan, or tetrahydrofuran. Protic organic solvents such as methanol, ethanol, etc., should be avoided because of the relatively slow alkaline hydrolysis of NSPTH in these solvents. If NSPTH carries an easily ionizable proton that is not attached to nitrogen, then mixed water−aprotic organic solvents are even better than water.

Note: At the end of the reaction in the $k^2{}_2$ step (Scheme 2), the organic cosolvent may be separated from the aqueous layer by salting out.

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