

Solvent effects on alkaline hydrolysis of N-benzylphthalimide in mixed water-acetonitrile and mixed water-N,N-dimethylformamide

Cheong May Ye, Azhar Ariffin &
Mohammad Niyaz Khan*

Department of Chemistry, Faculty of Science,
University of Malaya, 50603 Kuala Lumpur, Malaysia

Email: azhar70@um.edu.my

Received 13 April 2005; revised 30 June 2005

The nucleophilic second-order rate constant (k_{OH}) for the reaction of OH^- with N-benzylphthalimide appears to follow a reaction mechanism similar to that for reactions of OH^- with phthalimide and its N-alkylphthalimides. The rate of hydrolysis reveals an insignificant contribution of water-catalysed cleavage of NBPT compared with its hydroxide ion catalysed reaction. The observed pseudo first-order rate constant, k_{obs} , for alkaline hydrolysis of NBPT decreases with increase in the content of organic cosolvents (up to 70%, v/v) in mixed water- CH_3CN and water-DMF solvents.

IPC Code: Int. Cl.⁷ C07B41/00

Imides are widely spread among biologically and pharmaceutically important natural products and consequently extensive research carried out in this area¹. Studies on the effects of mixed aqueous-organic solvents on the rates of inter- and intra-molecular reactions are gaining importance for understanding the complexity of some biological and non-biological reactions including micellar-mediated reaction². The observed pseudo first-order rate constants for alkaline hydrolysis of phthalimide, maleimide, methyl, ethyl and phenyl salicylates, dimethyl phthalate and methyl 4-hydroxybenzoate were found to decrease with increase in the contents of organic co-solvents (up to $\geq 65\%$, v/v) in mixed aqueous-organic solvents³. Similar results have been reported for the reaction of *p*-nitrophenyl acetate with hydroxide ion⁴, *m*-chlorophenoxide and benzohydroxamates⁵ in mixed water- CH_3CN mixtures of varying compositions. The rate of acid catalysed hydrolysis of ethyl formate decreases with increasing percentage of DMF in water-DMF mixtures⁶. These studies on solvent effects go against the theory of Parker⁷ and Roberts⁸ who reported the alkaline hydrolysis of a large

numbers of alkyl benzoate esters in water-DMSO mixtures. Therefore, more investigations are needed to obtain more conclusive information on the effect of dipolar aprotic solvent in binary solvent system.

The effect of mixed solvents (water- CH_3CN and water-DMF) on alkaline hydrolysis of NBPT is reported here. The two organic solvents, CH_3CN and DMF were selected simply because these are the most common water miscible aprotic organic solvents and some kinetic data on closely related reactions are available especially in CH_3CN solvent. DMF, which is exothermically miscible with water, is a particularly useful solvent for our investigations because it could dissolve N-substituted phthalamic acids. Studies on the effects of mixed water-DMF solvent on the rates of such reactions are rare. We, therefore, carry out the kinetic study on the rate of hydrolysis of NBPT in mixed water-DMF. The observed results and probable explanations are described here.

Experimental

Reagent grade phthalic anhydride, NaOH, CH_3CN and DMF were obtained from Merck. All other chemicals used were also of reagent grade commercial products. Distilled water was used throughout. Stock solutions of NBPT (0.01 M) were prepared in CH_3CN and stored at low temperature whenever they were not in use.

Synthesis of N-benzylphthalimide

Benzylamine (2.0 ml, 18.31 mmoles) was added to a solution of phthalic anhydride (1.81 g, 12.22 mmoles) in 10.0 ml glacial acetic acid in a 50 mL round bottom flask. The reaction mixture was refluxed with stirring using silicon oil bath with external temperature maintained at 120-130°C. The reaction was stopped after 5 h when TLC indicated the completion of the reaction. The mixture was allowed to cool to room temperature and then poured into distilled water. The resulting precipitate was filtered through sintered glass and dried to give 2.77 g (95.5%) white solid. Further purification of the crude product was carried out by recrystallization in 95% ethanol afforded a very fine, white crystalline solid (2.07 g, 71.4%), m.pt. 118-119°C (lit.⁹ m.pt. 117-118°C). δ_H (400 MHz, $CDCl_3$, TMS): 4.85 (2H, s,

PhCH₂N), 7.25-7.34 (3H, m, ArH), 7.42-7.44 (2H, d, ArH), 7.70-7.73 (2H, m, ArH), and 7.83-7.87 (2H, m, ArH); δ_C (100 MHz, CDCl₃, TMS): 41.59 (PhCH₂N), 123.34, 127.80, 128.59, 128.66, 133.97 (ArCH), 132.11, 136.33 (ArC), and 168.04 (C=O); IR (nujol suspension, $\nu_{\max}/\text{cm}^{-1}$): 1713.5 (C=O); UV (CH₃CN): $\lambda_{\max} = 293 \text{ nm}$, Abs = 0.363.

Synthesis of N-benzylphthalamic acid

Benzylamine (0.81 g, 7.56 mmoles) was added to a solution of phthalic anhydride (1.01 g, 6.82 mmoles) in 20.0 mL dichloromethane with thorough mixing between additions. The mixture was then stirred vigorously at room temperature for about 30 min. The resulting precipitate was filtered, washed with diethyl ether, and dried under high vacuum. White solid (1.31 g, 75.2%), m.pt. 153-155°C (lit.¹⁰ m.pt. 152-155°C). δ_H (400 MHz, (CD₃)₂CO): 4.58 (2H, s, PhCH₂N), 7.21-7.32 (3H, m, ArH), 7.43-7.44 (2H, d, ArH), 7.51-7.61 (3H, m, ArH), and 7.88-7.89 (1H, d, ArH); δ_C (100 MHz, (CD₃)₂CO): 43.90 (PhCH₂N), 127.64, 128.42, 128.66, 129.09, 130.16, 130.80, 132.29 (ArCH), 131.33, 139.44, 140.25 (ArC), 168.04 (C=O amide), and 169.81 (C=O acid); IR (nujol suspension, $\nu_{\max}/\text{cm}^{-1}$): 3435.7 (OH), 3331.1 (NH), 1703.3 (C=O acid), and 1649.9 (C=O amide).

Kinetic measurements

NBPT, absorb strongly at 300 nm while its alkaline hydrolysis product, N-benzylphthalamate ion (NBPA⁻) has essentially no absorption at this wavelength¹¹. Therefore, the rate of alkaline hydrolysis of NBPT was studied spectrophotometrically at 300 nm by monitoring the disappearance of NBPT as a function of reaction time. The desired ionic strength of the reaction medium was kept constant with sodium chloride. All the kinetic runs were carried out at 35°C. The UV spectra of NBPT in mixed water-CH₃CN and water-DMF solvents revealed suitable wavelengths for kinetic measurements as 300 nm for monitoring the disappearance of NBPT in the organic solvent content range 2-85% and 2-80% (v/v), respectively, as a function of reaction time. Details of kinetic procedure and data analysis were the same as described elsewhere¹².

Pseudo first-order rate constants (k_{obs}) for alkaline hydrolysis of NBPT were calculated from Eq. (1)¹¹:

$$A_{\text{obs}} = \delta_{\text{app}}[X]_0 \exp(-k_{\text{obs}}t) + A_{\infty} \quad \dots(1)$$

where A_{obs} is the observed absorbance at any time t , $\delta_{\text{app}} (= \delta_{\text{NBPT}} - \delta_{\text{NBPA}^-})$, with δ representing molar extinction coefficient) is apparent molar extinction coefficient, $[X]_0$ is the initial concentration of NBPT, $A_{\infty} = [X]_0 \delta_{\text{NBPA}^-}$. The three unknown parameters, δ_{app} , k_{obs} , and A_{∞} were calculated from Eq. (1) using non-linear least squares technique. The reactions were generally carried out for reaction period of more than 6-7 half-lives and sampling method was used if the rate of reaction was too slow.

Product characterization

The alkaline hydrolysis product of NBPT is affirmed as NBPA⁻ ion by comparing the final UV absorption spectra of hydrolytic products with the authentic sample of N-benzylphthalamic acid under the same conditions.

Results and discussion

Alkaline hydrolysis of NBPT

The kinetics of alkaline hydrolysis of NBPT ($2 \times 10^{-4} \text{ M}$) was studied within $[\text{OH}^-]$ range 0.003-0.005 M and at constant temperature of 35°C. The ionic strength was kept constant at 1.0 M by the use of the sodium chloride solution. The value of k_{obs} , calculated from Eq. (1) are reliable because the standard deviations associated with these calculated values are very small. The observed pseudo first-order rate constants, k_{obs} , were found to fit to Eq. (2):

$$k_{\text{obs}} = k_w + k_{\text{OH}}[\text{OH}^-] \quad \dots(2)$$

where k_w and k_{OH} represent rate constants for hydroxide ion-independent and hydroxide ion-dependent hydrolysis of NBPT. The fitting of the observed data to Eq. 2 (Table 1) is evident from the standard deviations of k_{OH} values. The least-squares calculated respective values of k_w and k_{OH} turned out to be $(0.64 \pm 6.9) \times 10^{-3} \text{ s}^{-1}$ and $21.6 \pm 1.7 \text{ M}^{-1}\text{s}^{-1}$. Slightly positive value of k_w with significantly high standard deviations indicates that water-catalyzed hydrolysis of NBPT is insignificant compared to that of hydroxide ion-catalyzed hydrolysis.

The experimentally observed value of k_{OH} of $21.6 \pm 1.7 \text{ M}^{-1}\text{s}^{-1}$ (based on $[\text{OH}^-]$) was converted to $30.9 \pm 2.4 \text{ M}^{-1}\text{s}^{-1}$ (based on activity of hydroxide ion, a_{OH^-}) by dividing $21.6 \pm 1.7 \text{ M}^{-1}\text{s}^{-1}$ with activity coefficient of hydroxide ion, γ_{OH^-} . The value of γ_{OH^-} of 0.70 at 1 M ionic strength was calculated from Davies equation¹³ (which becomes Eq. (3) at 35°C)¹⁴, where μ is the ionic strength:

Table 2 — Values of k_{obs} for alkaline hydrolysis of NBPT in mixed water-acetonitrile and water-DMF^a

MS ₁ ^b (% v/v)	10 ³ k_{obs} ^b (s ⁻¹)	10 ³ k_{calcd} ^c (s ⁻¹)	t_{max} ^d (s)	A_{obs} ^e	MS ₁ ^f (% v/v)	10 ³ k_{obs} ^b (s ⁻¹)	10 ³ k_{calcd} ^c (s ⁻¹)	t_{max} ^d (s)	A_{obs} ^e	10 ⁴ k_{D} ^g (s ⁻¹)
2	52.4 ± 0.4 ^h	53.8	300	0.236	2	39.7 ± 0.6	38.5	200	0.291	0.15 ⁱ
10	41.4 ± 0.4	38.6	300	0.295	5	23.1 ± 0.2	25.3	300	0.35	0.5
20	25.3 ± 0.1	25.4	300	0.334	10	12.8 ± 0.2	12.6	600	0.397	1.1
30	15.0 ± 0.05	16.8	500	0.365	20	5.70 ± 0.1	3.1	1200	0.433	2.5
40	10.6 ± 0.05	11.1	700	0.367	30	2.39 ± 0.07		2400	0.43	4.9
50	7.94 ± 0.04	7.3	900	0.367	40	1.51 ± 0.07		5400	0.419	5.8
60	6.94 ± 0.05		960	0.361	50	0.869 ± 0.06		7000	0.394	3.2
70	6.91 ± 0.09		1300	0.339	60	0.214 ± 0.03		80640	0.401	6.6
80	10.3 ± 0.06		600	0.317						
85	13.8 ± 0.4		500	0.29						

^a[NBPT] = 2×10^{-4} M, [NaOH] = 0.002 M, $T = 35^\circ\text{C}$, $\lambda = 300$ nm;

^bMS₁ = H₂O-CH₃CN;

^cCalculated from Eq.(4) as described in the text;

^dMaximum reaction time attained in the kinetic run;

^e $A_{\text{obs}} = [A_{\text{obs}}^{(\text{max})} - A_{\text{obs}}^{(\text{first})}]$ where $A_{\text{obs}}^{(\text{first})}$ and $A_{\text{obs}}^{(\text{max})}$ represent first and last observed value of A_{obs} , respectively;

^fMS₁ = H₂O-DMF;

^gPseudo first-order rate constants for alkaline (0.002 M NaOH) hydrolysis of DMF at 35°C ¹⁷;

^hError limits are standard deviations;

ⁱObtained from the extrapolation of the plot of k_{D} versus % v/v, DMF¹⁷.

Thus, the validity of rate constants in mixed water-DMF solvent is limited by the uncertainty of the hydroxide ion concentration of the reaction mixtures. The effect of the possible hydrolytic decomposition on hydroxide ion concentration in aqueous-DMF is evident on the basis of previous data¹⁸. We ignored the rate constants in reaction mixtures containing $\geq 30\%$ (v/v) DMF, since the first-order rate constants for the alkaline hydrolysis of DMF, k_{D} , become markedly important under such conditions.

Although theoretical explanations for solvent effects on rates of organic reactions are difficult because of the lack of a perfect theoretical model, some qualitative explanations could be used, at least, in predicting the value of dependent variable (such as k_{obs}) at any value of independent variable (X). The values of k_{obs} , obtained within CH₃CN content range 2-50% (v/v) and DMF content range 2-20% (v/v), showed good fit to empirical Eq. (4)

$$k_{\text{obs}} = k_0 \exp(-\psi X) \quad \dots(4)$$

where k_0 and ψ are empirical constants and X represents % (v/v) content of organic cosolvent in mixed aqueous-organic solvent. The magnitude of ψ is the measurement of the rate-inhibition susceptibility of the mixed aqueous-organic solvent.

The non-linear least squares calculated respective values of k_0 and ψ turned out to be $(58.5 \pm 2.0) \times 10^{-3} \text{ s}^{-1}$ and $(4.16 \pm 0.25) \times 10^{-2} (\% \text{ v/v})^{-1}$ for X = CH₃CN, and $(51.0 \pm 4.7) \times 10^{-3} \text{ s}^{-1}$ and $(1.40 \pm 0.22) \times 10^{-1} (\% \text{ v/v})^{-1}$ for X = DMF. These results show that DMF has much higher inhibitory effect on the reaction rate. The values of k_0 (0.059 s^{-1} and 0.051 s^{-1}) give the average value of second-order rate constant (k'_{OH}) for hydroxide ion-catalyzed hydrolysis of NBPT as $27.5 \text{ M}^{-1}\text{s}^{-1}$, which is not very different from that of k_{OH} ($= 21.6 \text{ M}^{-1}\text{s}^{-1}$) obtained in alkaline hydrolysis of NBPT in nearly pure water solvent.

Acetonitrile (CH₃CN) and N,N-dimethylformamide (DMF) are characterized as dipolar aprotic solvents or recommended by Bordwell *et al.*¹⁹ as dipolar non-HBD (hydrogen-bond donor) solvents. Dipolar aprotic solvents possess large dielectric constants and sizeable dipole moments. These solvents do not act as hydrogen-bond donors since their C-H bonds are not strongly enough polarized. However, they are usually good electron pair donors solvents and hence cation solvators due to the presence of lone electron pairs. The non-linear decrease of k_{obs} values with the increase in the content of organic co-solvent (CH₃CN and DMF) may be explained qualitatively in terms of the stability of solvated ion-pair ($\text{Na}^+\text{:HO}^-$)²⁰. The higher the contents of organic co-solvent, the most

strongly solvated and the less reactive is the nucleophilicity of the reactant hydroxide ion and consequently decreases k_{obs} value.

Acknowledgement

The authors thank the National Scientific Research and Development Council of Malaysia under IRPA Program for financial support (Grant No. 09-02-03-0147).

References

- 1 Reddy P Y, Kondo S, Toru T & Ueno Y, *J Org Chem*, 62 (1997) 2652 and references cited therein.
- 2 Khan M N, *Indian J Chem*, 38B (1999) 953.
- 3 Khan M N, *J Phy Org Chem*, 7 (1994) 412.
- 4 Um I-H, Lee G-J, Yoon H-W & Kwon D-S, *Tetrahedron Lett*, 33 (1992) 2023.
- 5 Um I-H, Yoon H-W, Lee J-S, Moon H-J & Kwon D-S, *J Org Chem*, 62 (1997) 5939.
- 6 Singh L, Singh R T & Jha R J, *J Indian Chem Soc*, 58 (1981) 966.
- 7 Parker A J, *Chem Rev*, 69 (1969) 1.
- 8 Roberts D D, *J Org Chem*, 31 (1966) 4037.
- 9 Aubert T, Fámier M & Guillard R, *Tetrahedron*, 47 (1991) 53.
- 10 Uhle F C, *J Org Chem*, 26 (1961) 2998.
- 11 Khan M N, *Int J Chem Kinet*, 19 (1987) 143.
- 12 Khan M N, *J Chem Soc Perkin Trans 2*, (1990) 435.
- 13 Davies C W, *J Chem Soc*, (1938) 2093.
- 14 Hine J, Via F A & Jensen J H, *J Org Chem*, 36 (1971) 2926.
- 15 Ibrahim I T & Williams A, *J Chem Soc Perkin Trans 2*, (1982) 1459.
- 16 Bunce E & Symons E A, *J Chem Soc Chem Commun*, (1970) 164.
- 17 Bunce E, Kesmarky S & Symons E A, *J Chem Soc Chem Commun*, (1971) 118.
- 18 Kankaanperä A, Scharlin P, Kuusisto I, Kallio R & Bernoulli E, *J Chem Soc Perkin Trans 2*, (1999) 169.
- 19 Reichardt C, *Solvents and Solvent Effects in Organic Chemistry*, 2nd Edn, (VCH, Weinheim) 1990, pp. 69.
- 20 Sim Y-L, Ariffin A & Khan M N, *Int J Chem Kinet*, 36(6) (2004) 316.
- 21 Hine J, *Structural Effects on Equilibria in Organic Chemistry*, (John Wiley & Sons) 1975, pp. 91.
- 22 Brown J, Su S C K & Shafer J A, *J Am Chem Soc*, (1966) 4468.
- 23 Su S C K & Shafer J A, *J Org Chem*, 34 (1969) 926.