

## Effects of Tetraalkylammonium Salts on Alkaline Hydrolysis of *N*-(2-Methoxyphenyl) Phthalimide

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**ABSTRACT** The effects of the concentrations of Me<sub>4</sub>NCl, Pr<sub>4</sub>NCl, Bu<sub>4</sub>NCl, Me<sub>4</sub>NBr, Pr<sub>4</sub>NBr and Bu<sub>4</sub>NBr on the rate of alkaline hydrolysis of *N*-(2-methoxyphenyl)phthalimide (N-2MPHPT) at 35 °C and in H<sub>2</sub>O solvent containing 2 % (v/v) CH<sub>3</sub>CN reveal the formation of ion-pair complexes between solvent-separated loose ion-pair forms (M<sup>n+</sup> ... X<sup>k-</sup>) and N-2MPHPT. The bulky hydrophobic tails of tetraalkylammonium salts and their halide anions inhibit the reaction by blocking the OH<sup>-</sup> nucleophilic attack on the reactive site of N-2MPHPT. Among all the quaternary ammonium salts, Me<sub>4</sub>NCl showed slight inhibition only because of the shielding effect created by the methyl group is very small. However, Bu<sub>4</sub>NBr presents the greatest inhibition on hydrolysis rate because of its strong binding affinity with N-2MPHPT.

**ABSTRAK** Kesan kepekatan garam-garam organik Me<sub>4</sub>NCl, Pr<sub>4</sub>NCl, Bu<sub>4</sub>NCl, Me<sub>4</sub>NBr, Pr<sub>4</sub>NBr dan Bu<sub>4</sub>NBr ke atas kadar hidrolisis beralkali *N*-(2-metoksifenil)phthalimide (N-2MPHPT) pada suhu 35 °C dalam pelarut H<sub>2</sub>O yang mengandungi 2 % (v/v) CH<sub>3</sub>CN menunjukkan pembentukan suatu kompleks pasangan-ion di antara molekul pelarut dan ion dalam bentuk (M<sup>n+</sup> ... X<sup>k-</sup>) dengan N-2MPHPT. Rantai hidrofobik garam tetraalkilammomium yang besar dan anionnya merencat tindak balas ini dengan cara menghalang nukleofil OH<sup>-</sup> dari menyerang kawasan reaktif N-2MPHPT. Di antara kesemua garam ammonium, Me<sub>4</sub>NCl menunjukkan perencatan yang paling sedikit disebabkan kesan perlindungan oleh kumpulan metil yang sangat kecil. Akan tetapi, Bu<sub>4</sub>NBr memberikan kesan perencatan yang paling besar ke atas tindak balas hidrolisis kerana ia terikat kuat dengan N-2MPHPT.

(Tetraalkylammonium Salts, Alkaline Hydrolysis, *N*-(2-Methoxyphenyl)Phthalimide, Hydrophobic Interactions).

### INTRODUCTION

The quaternary ammonium salts find extensive use in a variety of chemical applications as surfactants and phase-transfer catalysts [1]. Tetrabutylammonium chloride, tetraalkylammonium bromide and variety of their derivatives have been investigated for their usefulness in this connection [2-4]. In addition, some tetraalkylammonium salts also constitute an important class of catalyst, due to their wide presence in the synthesis of ketones [5], nitration of phenols [6] and clathrate formation [7] and numerous uses in polymer chemistry [8-10]. Simple electrostatic theory for aqueous electrolyte solutions (extended Debye-Huckel and Bronsted theories) predicts positive salt effects for bimolecular reactions involving charge separation in the transition state [11, 12].

Menninga and Engberts conclude the occurrence of primary kinetic salt effects on the rate of water-catalyzed hydrolysis of some arylsulfonylmethyl perchlorates, which are primarily electrostatic in nature [13]. Some other research work also explains about the rate inhibition by tetraalkylammonium salts as due to ion-pair formation and a specific solvation effect [14]. The aim of this work is to investigate the effects of tetraalkylammonium salts on the rate of hydrolysis of *N*-substituted phthalimide.

### MATERIALS AND METHODS

NaOH, Me<sub>4</sub>NCl, Pr<sub>4</sub>NCl, Bu<sub>4</sub>NCl and bromide salts were of reagent grade and were obtained from Merck and Fluka. All other chemicals used were also commercial products of highest available purity.

Melting point of N-2MPhPT was determined using a Fargo Melting Point Apparatus MP-1D at a heating rate of 10 °C min<sup>-1</sup> and are uncorrected. Infrared (IR) spectra were recorded using a Perkin-Elmer Spectrum RX 1 FTIR spectrometer. All NMR spectra (<sup>1</sup>H and <sup>13</sup>C) were recorded on a JEOL JNM-LA 400 FT NMR spectrometer with tetramethylsilane (TMS, δ = 0) as internal standard and deuterated-chloroform, CDCl<sub>3</sub>, as the solvent. Absorbance of the N-2MPhPT was measured in acetonitrile, CH<sub>3</sub>CN, on a SHIMADZU UV-Visible Spectrophotometer. Distilled water was used as reference unless otherwise stated.

Tetrabutylammonium chloride salt was recrystallized as follows [15]. The crude Bu<sub>4</sub>NCl salt was first dissolved in A.C.R. grade acetone. Diethyl ether was then added drop wise until the solution started forming milky. The solution was left overnight in the chiller. The resulting white crystal of Bu<sub>4</sub>NCl was filtered quickly, washed with diethyl ether and dried under reduce pressure. The stock solution of Bu<sub>4</sub>NCl (2M) was prepared in distilled water.

The stock solution of Me<sub>4</sub>NCl (2M), Me<sub>4</sub>NBr (2M), Pr<sub>4</sub>NCl (2M), Pr<sub>4</sub>NBr (2M) and Bu<sub>4</sub>NBr (2M) were prepared in distilled water and stored at low temperature whenever they were not in use.

#### Synthesis of N-(2-Methoxyphenyl)Phthalimide (N-2MPhPT)

Phthalic anhydride (5.00 g, 33.76 mmol) and *o*-anisidine (2-methoxyaniline) (4.99 g, 40.51mmol) were added into a 50 ml round bottom flask containing 15.0 ml of glacial acetic acid. The reaction mixture was refluxed with stirring for 4 hours, after which TLC indicated the completion of the reaction. The reaction mixture was allowed to cool to room temperature and poured into distilled water. The resulting white precipitates were filtered and dried to give 8.05 g (94.03 %) white solid. Further purification by recrystallization in boiled denaturated ethanol (95 %) gives fine needles of N-(2-methoxyphenyl)phthalimide, 7.49 g, 87.65 %, mp: 165 °C – 168 °C (lit. [16] 158-159 °C); *R*<sub>f</sub> = 0.60 (EtOAc 100%); UV (CH<sub>3</sub>CN): λ<sub>max</sub> = 276nm; IR (CHCl<sub>3</sub>) ν<sub>max</sub>/cm<sup>-1</sup>: 1786.49, 1720.97; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS) δ ppm: 3.79 (s, 3H, PhOCH<sub>3</sub>), 7.04-7.10 (m, 2H, ArH(Ph)), 7.25-7.27 (m, 1H, ArH(Ph)), 7.41-7.46 (m, 1H, ArH(Ph)), 7.75-7.79 (m, 2H, N-ArH-OCH<sub>3</sub>),

7.92-7.96 (m, 2H, N-ArH-OCH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, TMS) δ ppm: 55.85 (s, Ph-OCH<sub>3</sub>), 112.18 (s, N-CAr), 120.32, 120.88, 123.67, 130.01, 130.68, 132.30, 134.11 (m, CAr), 155.46 (s, C=O), 167.38 (s, C=O).

Standard solution (0.01 M) of N-(2-methoxyphenyl)phthalimide (N-2MPhPT) was prepared in CH<sub>3</sub>CN and was always stored at low temperature whenever was not in use.

#### Kinetic Measurements

Kinetics measurements were performed using SHIMADZU UV-Visible Spectrophotometer equipped with UV-1601 PC software, which was standardized with distilled water both as reference and blank sample. The uv spectra of N-2MPhPT and its alkaline hydrolysis product, N-(2-methoxyphenyl)phthalamate ion (N-2MPhP<sup>-</sup>) in aqueous medium containing 2 % v/v CH<sub>3</sub>CN revealed 290 nm as the suitable wavelength for kinetic measurement. The rate of reaction was measured by monitoring the appearance of N-2MPhP<sup>-</sup> as a function of reaction time. The reaction was carried out at a fixed temperature of 35.0°C.

Reaction mixtures having a total volume of 5.0 ml were prepared which contained the required constant amount of N-2MPhPT (0.0002 M) and NaOH (0.001 M), while the concentrations of organic salts and water were varied according to the reaction conditions concerned. These reaction mixtures were kept in a thermostatic water bath maintained at 35.0 °C for about 10 – 15 minutes for temperature calibration. The reaction was initiated by adding 0.10 ml of 0.01 M N-2MPhPT to the reaction mixture. An aliquot of 2 – 3 ml of the reaction mixture was withdrawn periodically and was transferred quickly to a 3 ml quartz cuvette kept in the cell compartment of the spectrophotometer whereby absorbance was recorded at 290 nm. All steps from the start of the reaction until the cuvette was placed into the cell compartment could be completed at less than 20 seconds. This precaution has to be taken to increase the reliability of the observed rate constant. The temperature drop of the reaction mixture after the conical flask was removed from the water bath and until it was placed into the cell compartment was negligible because all these steps were done in less than 20 seconds.

Pseudo first-order rate constant, *k*<sub>obs</sub> for alkaline hydrolysis of N-2MPhPT in the presence of

organic salts were calculated using Equation 1 [17, 18] where the appearance of N-2MPhP<sup>-</sup> was

$$A_{\text{obs}} = E_{\text{app}} [\text{N-2MPhPT}]_0 [1 - \exp(-k_{\text{obs}}t)] + A_0$$

monitored as a function of reaction time, *t*, where  $A_{\text{obs}}$  = observed absorbance of reaction mixture at any time, *t*;  $E_{\text{app}}$  = apparent molar extinction coefficient of the reaction components;  $[\text{N-2MPhPT}]_0$  = initial concentration of N-2MPhPT;  $A_0 = E_{\text{app}}[\text{N-2MPhPT}]_0$ . The reactions were generally carried out for reaction period of more than 6 – 7 halfives. Sampling method was used whenever necessary if the reaction was too slow and needed to keep overnight.

### Product Characterization

The alkaline hydrolysis product of N-2MPhPT was characterized by UV spectrophotometric method and is affirmed as *N*-(2-methoxyphenyl)phthalamate ion (N-2MPhP<sup>-</sup>).

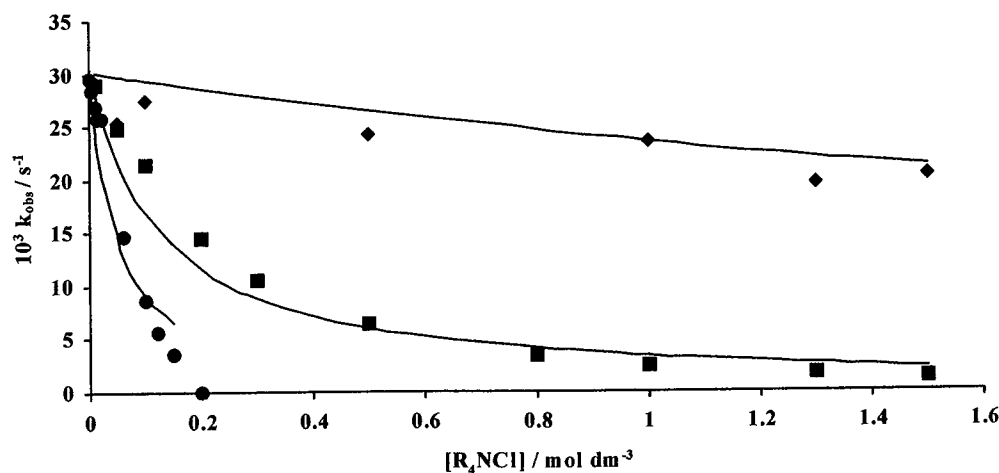
## RESULTS AND DISCUSSIONS

A series of kinetic runs was carried out at different concentrations of salts. The

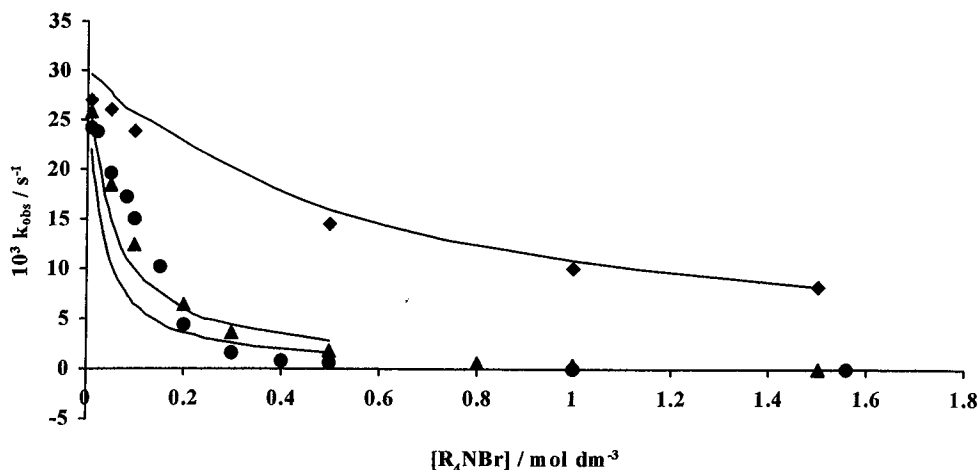
concentrations of N-2MPhPT and NaOH were kept constant at 0.0002 M and 0.001 M, respectively. The temperature for each reaction run was maintained at 35°C.

It is evident that there is different stabilization of the transition state and ground state of the reacting system in the rate determining step. It has been reported elsewhere [19] that the rate determining step in the alkaline hydrolysis of *N*-hydroxyphthalimide involves hydroxide ion attack on the carbonyl carbon of ionized *N*-hydroxyphthalimide. Thus, similar rate-determining step is expected in the present alkaline hydrolysis of N-2MPhPT.

Added salts have marked effects on the reaction rate. The results for all the salt effects in aqueous phase are shown graphically in Figures 1-2. It is evident from these results that the observed rate constant,  $k_{\text{obs}}$ , for all salts decrease with the increase of salt concentrations. The tetrabutylammonium salts show an exponential decrease in  $k_{\text{obs}}$  while the tetramethyl- and tetrapropyl- salts showed mild inhibition only.



**Figure 1.** Observed rate constants,  $k_{\text{obs}}$ , versus different concentrations of tetraalkylammonium chlorides, for alkaline hydrolysis of N-2MPhPT. Reagents and conditions:  $[\text{NaOH}] = 0.001 \text{ M}$  and  $\text{H}_2\text{O}$  solvent. (♦) =  $\text{Me}_4\text{NCl}$ , (◻) =  $\text{Pr}_4\text{NCl}$  and (◉) =  $\text{Bu}_4\text{NCl}$ . The solid lines are drawn through the nonlinear least-squares-calculated points using Equation 3.



**Figure 2.** Observed rate constant,  $k_{obs}$ , versus different concentrations of tetraalkylammonium bromides, for alkaline hydrolysis of N-2MPhPT. Reagents and conditions:  $[NaOH] = 0.001\text{ M}$  and  $H_2O$  solvent. ( $\blacklozenge$ ) =  $Me_4NBr$ , ( $\blacktriangle$ ) =  $Pr_4NB$  and ( $\bullet$ )  $Bu_4NBr$ . The solid lines are drawn through the nonlinear least-squares-calculated points using Equation 3.

**Table 1.** Calculated Values of  $k_s$  and  $K_s$  for Alkaline Hydrolysis of N-2MPhPT for different Tetraalkylammonium Salts at  $[N-2MPhPT]_0 = 0.0002\text{ M}$  and  $[NaOH] = 0.001\text{ M}$ .

Salt	$10^3 k_w / s^{-1}$	$10^3 k_s / s^{-1}$	$K_s^a / M^{-1}$	$K_s^b / M^{-1}$
$Me_4NCl$	30.2	$20.1 \pm 1.8^f$	$5.6 \pm 4.2^f$	$0.3^c \pm 0.1^f$
$Pr_4NCl$	30.2	$-4.1 \pm 0.7$	$4.1 \pm 0.3$	$7.9^c \pm 3.7$
$Bu_4NCl$	30.2	$-25.1 \pm 4.2$	$6.3 \pm 0.8$	$24^d \pm 14$
$Me_4NBr$	30.2	$4.1 \pm 2.1$	$3.4 \pm 0.9$	$1.8^e \pm 0.1$
$Pr_4NBr$	30.2	$-2.3 \pm 0.5$	$13 \pm 1$	$20^e \pm 8$
$Bu_4NBr$	30.2	$-4.3 \pm 1.6$	$10 \pm 2$	$37^e \pm 36$

<sup>a</sup> Calculated from Equation 2 as described in the text.  
<sup>b</sup> Calculated from Equation 3 as described in the text.  
<sup>c</sup> Calculated from a concentration range of 0.01 M – 1.50 M.  
<sup>d</sup> Calculated from a concentration range of 0.001 M – 0.150 M.  
<sup>e</sup> Calculated from a concentration range of 0.01 M – 0.50 M.  
<sup>f</sup> Error limits are standard deviations.

The observed pseudo first-order rate constants,  $k_{obs}$ , were used to evaluate the effects of organic salts on the rate of hydrolysis of N-2MPhPT and can be discussed using Equation 2 [14]. The  $k_{obs}$ ,  $k_s$  and  $K_s$  were calculated using nonlinear least square method base on Equation 2 :

$$k_{obs} = \frac{k_w + k_s K_s [salt]}{1 + K_s [salt]}$$

where  $k_w = k_{obs}$  at  $[salt] = 0$ ;  $k_s$  = pseudo first-order rate constant for hydrolysis of salt-N-2MPhPT complex;  $K_s$  = the salt-substrate complexation equilibrium constant / binding constant;  $[salt]$  = concentration of salt. The nonlinear least squares calculated values of  $k_s$  and  $K_s$  are summarized in Table 1.

Since  $k_s$  values are negative for almost all the tetraalkylammonium salts (Table 1), which mean

that  $k_s$  values are not different from zero because a negative value of a rate constant is meaningless. Thus, it seems that  $k_s K_s [\text{salt}] \ll k_w$  because  $k_s \approx 0$ . So, Equation 2 is reduced to Equation 3. The fitting of the observed data to Equation 3 is evident from the plots of Figures 1-2 where solid lines are drawn through the calculated values of rate constants using Equation 3.

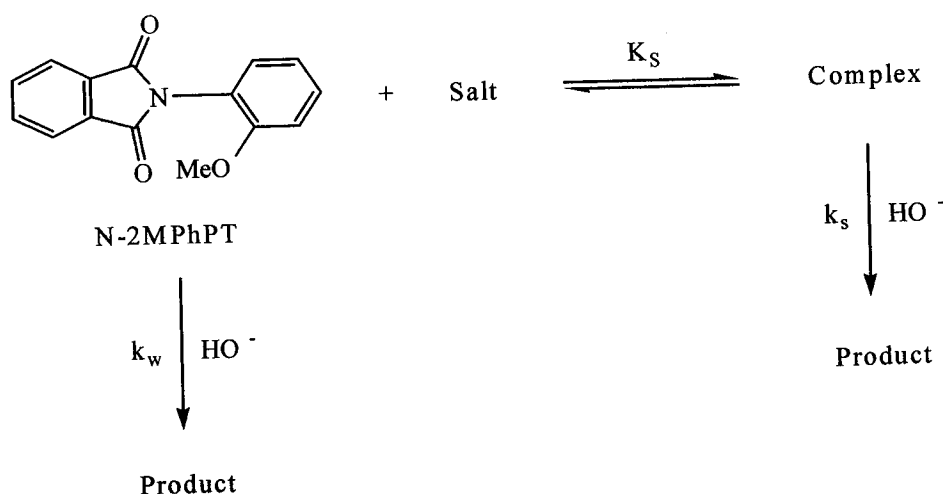
$$k_{obs} = \frac{k_r}{1 + K_s [\text{salt}]}$$

The effects of tetraalkylammonium halide salts on the rate of alkaline hydrolysis of N-2MPhPT may be explained in terms of reaction mechanism shown in Scheme 1. The decrease in  $k_{obs}$  with increase in [salt] is attributed to the interaction of salts with N-2MPhPT. The stacking interaction between N-2MPhPT and tetraalkylammonium salts causes the formation of a substrate-salt complex. The N-2MPhPT-salt complex appeared to be less reactive compared to free N-2MPhPT molecules towards the attack by hydroxide ion.

In discussing the way in which salts inhibited the reactions between N-2MPhPT and hydroxide ion, we believed that the anion of salt tended to exclude the hydroxide ion from the neighborhood of the substrate [20, 21]. The present results fit this postulate, because in all the reactions which we have examined, we found that it is the anion and the bulky hydrophobic tails of the salts are the best inhibitors, as expected in terms of the ability of organic residues to promote hydrophobic bonding [21]. The anion of the

tetraalkylammonium salts,  $\text{Cl}^-$  and  $\text{Br}^-$ , were closer to N-2MPhPT because they have higher hydrophobicity compared to  $\text{OH}^-$ , thus blocking the attack of  $\text{OH}^-$  nucleophiles towards N-2MPhPT. In other words, the inhibition is probably caused by the fact that the reactive sites of the N-2MPhPT were blocked by the salts in the complex. We suspected that ion-pair complex formed between cations of the salts which presumably exist in solvent-separated loose ion-pair forms and anionic N-2MPhPT $^-$ .

Among all the tetraalkylammonium salts,  $\text{Me}_4\text{NCl}$  showed the weakest interaction with N-2MPhPT that resulted in slight inhibition only. However, an unexpected result of this work is the powerful inhibition by  $\text{Bu}_4\text{NBr}$  within a very small concentration range, because in our system, the other tetraalkylammonium salts showed normal inhibitions. Structural study of  $\text{Bu}_4\text{NBr}$  has shown that non-polar aliphatic butyl tails of  $\text{Bu}_4\text{NBr}$  compounds tended to stay around the N-2MPhPT region thus blocked the  $\text{OH}^-$  attack on substrate. Overall, the observed pseudo first-order rate constant,  $k_{obs}$  for salt effects on hydrolysis of N-2MPhPT indicated that the complete inhibition of reaction did not exist. The presence of salts only retarded the rate of reactions.  $K_s$  is the binding constant for the complex formation between N-2MPhPT and the salts. From Table 1, we can see that the  $K_s$  value is highest for  $\text{Bu}_4\text{NBr}$ , which means that strong binding occurred between  $\text{Bu}_4\text{NBr}$  salt and N-2MPhPT compared to other organic salts.



Scheme 1

## CONCLUSION

The rate of alkaline hydrolysis of N-2MPHPT is inhibited by the presence of tetraalkylammonium salts. The rate is decreasing non-linearly with the increasing value of [salts]. The anti-catalysis by tetraalkylammonium salts can be caused due to the formation of molecular complexes between reagent and inhibitor.

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