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# Specific influence of salts on the hydrolysis reaction rate of *p*-nitrophenyl anthranilate in binary acetonitrile–water solvents

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ABSTRACT

The hydrolysis reaction rates of *p*-nitrophenyl anthranilate (*p*-NPA) have been surveyed in aqueous buffer solutions mixed with acetonitrile (MeCN) containing various salts at 50 ± 0.1 °C. Increase in pH of the buffer solution from 8.50 to 10.0 results in an increase of the hydrolysis rate constant [log $(k/\mathrm{s}^{-1})$] in all solutions mixed with 0–75% (v/v) MeCN. The log $(k/\mathrm{s}^{-1})$ values significantly decelerate as MeCN contents increase to about 50% (v/v). With further increment of MeCN contents, however, the reversal increases in log $(k/\mathrm{s}^{-1})$ are observed. All the added salts significantly influence the hydrolysis rate in solutions containing the borate buffer of pH = 9.18. Alkali metal perchlorates ($LiClO_4$ and $NaClO_4$) cause the deceleration with increasing salt concentration. The presence of as low as 0.1 mol $dm^{-3}$ of $NaN_3$ causes a three-fold acceleration, compared to the rate without the salt in no MeCN media. The rate acceleration by $NaN_3$ becomes gradually weaker as the MeCN contents increase. Contrastingly, the rate acceleration by $Et_4NBr$ is enhanced with increasing MeCN contents. In 50% (v/v) MeCN solution, the acceleration in log $(k/\mathrm{s}^{-1})$ caused by added salts is in the order of $NaN_3 > (n\text{-Bu})_4NBr \sim Et_4NBr > Et_4NCl$. The Arrhenius plots in the 50% (v/v) MeCN media without salts and with 0.20 mol $dm^{-3}$ of $LiClO_4$, $NaN_3$ and $Et_4NBr$ salts give the good linearity of high activation energy values in the temperature range of 35 to 60 ± 0.1 °C, suggesting that the hydrolysis reactions are just of temperature dependence. The whole results have been discussed in terms of changes in the water structure and/or activities of $H_2O$ and $OH^-$ in the presence of both the added organic solvent and salts, and also in terms of the nucleophilicity of anions from the added salts in the "modified" media.

## 1. Introduction

The *p*-nitrophenyl ester is known to be an active ester due to the strong electronegativity of the nitro group. This active ester, however, is well-tolerated by the aromatic amine group, which is a nucleophile, in *p*-nitrophenyl anthranilate (*p*-NPA). *p*-Nitrophenyl anthranilate has two different functional groups: an aryl amine that can react with free reducing glycans by reductive amination and an active *p*-nitrophenyl ester that can react with nucleophiles. This bifunctional linker has been used for preparing fluorescent neoglycoproteins from naturally occurring complex glycans [1]. It is worth noting that the linking property of this active ester, *p*-nitrophenyl anthranilate, under different conditions could be affected by its interaction with water.

Hydrolysis of an ester may occur through three pathways: base catalyzed, pH independent, and acid catalyzed reaction pathways [2]. These pathways are independent of each other as demonstrated by Hine [3]. El-Mallah et al. [4] have indicated that the rate of chemical reactions in solution can be influenced by two types of the solvent effects, *i.e.*, nonspecific and specific. Nonspecific solvent effects denote the electrostatic interaction of the solvent molecules with the ionic substances, whereas specific solvent effects denote the chemical interaction due to the presence of electron-donating and/or electron-accepting centers in the solvent molecules.

There is an increased interest in understanding the effects of reaction medium, of both pure solvents and binary mixtures on the rate and equilibrium constants of chemical and biochemical reactions [5–9]. Solvent effects on the kinetic studies of the hydrolysis of various esters have been reported [10–15]. The effects of acetonitrile–water mixtures on the hydrolysis of 4-nitrophenyl chloroformate and heptafluorobutyrate [16], bis(*p*-nitrophenyl) phosphate [17], *p*-nitrophenyl acetate, benzoate [18,19] and anthranilate [20] and oxazolinone [21,22] have been reported.

In addition to solvent effects, the presence of various salts also has been examined regarding their significant impact on reactions of organic compounds. In their report on the hydrolysis of organic compounds, Mabey and Mill [23] have indicated the effects of both solvent composition and added salts. The added salts can lead either to rate acceleration or deceleration, depending on the substrate, the specific salts, and their concentration.

There have been many experimental and computational approaches addressing the issue of water structure in the presence of added salts

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and organic solvent mixtures, since water is a common solvent and many chemical reactions take place in water [24]. Disruption of the tetrahedral water structure in the presence of added salt and organic solvents has been reported [25,26]. We have proposed an innovative idea [27] that the properties of bulk water originate from the intermolecular hydrogen-bonded network among a huge number of $H_2O$ molecules (*e.g.*, $n_w > \sim 10^7$). Water may lose its properties as bulk water to get that of a non-aqueous solvent, such as an alcohol (R–O–H) or even an ether (R–O–R) if the highly "self-assembled structure" of bulk water is disturbed in the following causes: (a) the residual water ($c(H_2O) \sim 10^{-3}$ mol dm$^{-3}$) in organic solvents; (b) aqueous solutions or organic solvent–water mixtures containing salts at high concentrations; (c) nanoscale water droplets in nano-tubes or reversed micellar systems; (d) water on metal electrodes, ion-exchange resins, proteins, organic solvents in the solvent extractions, and glass vessels; (e) water at higher temperatures or under supercritical conditions. Such water can be "reduced" to authentic singular $H_2O$ molecules ["dihydrogen ether," (H)–O–(H)] [28]. Reichardt et al. [29] have concisely interpreted "dihydrogen ether" that, at high salt concentrations [$c(\text{salt}) > 5$ mol dm$^{-3}$], region C, according to the solvation model of Frank and Wen [30], can be abolished and only regions A and B survive, resulting in an aqueous solvent called "dihydrogen ether." Very recently, we [31] have dissolved precious metals, especially, pure gold in the mixed media between dilute nitric acid and seawater successfully, after discovering [32] the fact that dilute nitric acid indeed possesses the strong oxidation ability when dilute nitric acid contains concentrated salts.

In binary solvents between water and many organic solvents, we [28,33–37] have examined the effects of added salts on the solvolysis (hydrolysis) reaction rates of various organic compounds. Then, for the first time, we have been able to explain successfully the concentrated salt effects on solvolysis reactions of haloalkanes and related compounds without resorting to different types of ion pairs. The exponential increases in solvolysis rates of $S_N1$ substrates in the presence of concentrated alkali metal ($M^+$) and alkaline earth metal ($M^{2+}$) perchlorates have been attributed to the favorable carbocation ($R^+$) formation through the association (direct "chemical" interaction) between metal cations ($M^+$ or $M^{2+}$) and the leaving group anion ($X^-$) of a substrate (R–X) in the "modified" solvent. However, the solvolysis (hydrolysis) reaction rate of a typical $S_N2$ substrate is decelerated by the addition of alkali metal or alkaline earth metal perchlorates. The reasons are as follows: (1) the metal cations have no way to give more of the active species for the typical $S_N2$ substrate; (2) the activity of water, which should attack the substrate, decreases in the presence of the metal perchlorates.

In the present study, as part of our interest in studying medium effects on reactions of toxic organic compounds, we report the effects of an organic solvent, *i.e.*, acetonitrile (MeCN), and various salts on the hydrolysis reaction rate of *p*-nitrophenyl anthranilate in binary MeCN–$H_2O$ solvents of 0–70% (v/v) MeCN containing the buffer solution of pH = 9.18 at 50 °C. In the absence of salts, the pH effects from 8.50 to 10.0 were examined in the mixed solvents, 0–75% (v/v) MeCN. The primary mechanism of the hydrolysis reaction of *p*-nitrophenyl anthranilate is depicted in Scheme 1. Both the molecule of $H_2O$ and the hydroxide ion ($OH^-$), which is a prominent nucleophilic anion, can attack the carbonyl carbon of the substrate *p*-NPA, and liberate the *p*-nitrophenoxide ion (which is the leaving group). We would not like to discuss the changes in the reaction rate as just the "medium effects" but would like to try differentiating each factor in the influences on the reaction rate.

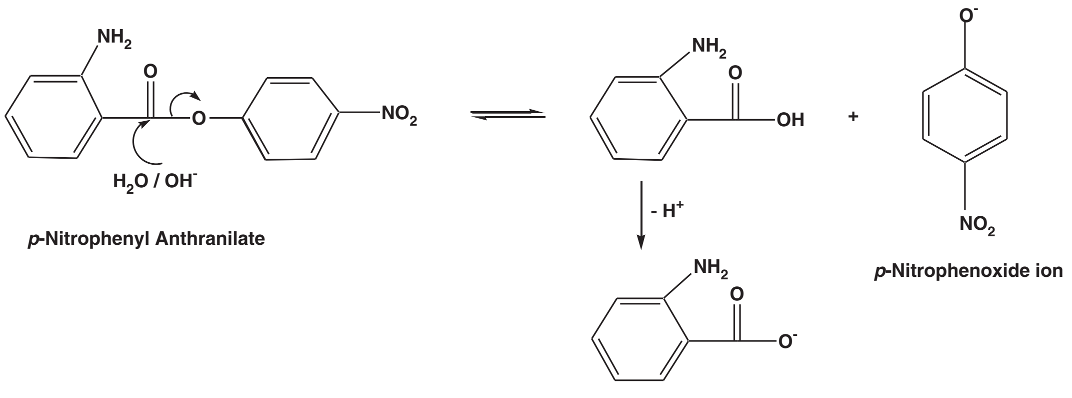
## 2. Experimental

### 2.1. Materials and equipment

All chemicals utilized were commercially available and used as received. *p*-Nitrophenyl anthranilate (4-nitrophenyl 2-aminobenzoate, ≥98.0%) and benzoate (>95%) were from TCI and Wako, respectively. Salts of $LiClO_4$ (≥98.0%), $Et_4NBr$ (≥98.0%), $Et_4NCl$ (≥98.0%), $NaN_3$ (≥98), $(n\text{-Bu})_4NBr$ (≥98.0%), and $Na_2B_4O_7 \cdot 10H_2O$ (≥99.6) and the co-solvent, acetonitrile (of the GR grade), were from Wako. Other salts of $NaClO_4$ (≥98.0%), $Et_4NTsO$ (tosylate or *p*-toluenesulfonate, ≥97%), and $Pr_4NBr$ (≥98.0%) were from Aldrich. Instead of the commercially available (from Wako) buffer solution, we used the carefully prepared (in laboratory) borate buffer solutions of pH ranging from 8.50 to 10.0 in order to avoid the influences of $NaN_3$ contained as the stabilizer in the commercial borate buffer. Pure water purified by MilliQ System was used in all the experiments. A Horiba F-51 digital pH meter was used for measuring pH of the buffered solutions. Raman spectra of $D_2O$ containing MeCN were recorded with a Horiba-Jobin Yvon LabRam Spectrograph HR-800 at room temperature (~23 °C). Excitation for the Raman Spectroscopy was provided by a 514.5 nm argon laser.

### 2.2. Kinetic procedure

Kinetic measurements were performed using a Shimadzu UV–Vis spectrophotometer (Model UV-2550) equipped with a thermostated cell holder whose temperature was controlled within 25 ± 0.1 °C, in a 1.0 cm quartz cuvette. Reaction solutions were prepared by combining the appropriate amounts of water and acetonitrile, the borate buffer of pH = 9.18 (the final concentration of 5.0 mmol dm$^{-3}$) and salts and then were left to stand for about 30 min in a Taitec constant temperature water bath at 50 ± 0.1 °C in order to reach the thermal equilibrium. Prior to the beginning of the reaction, a stock solution of the substrate (*p*-NPA) ($5.0 \times 10^{-3}$ mol dm$^{-3}$) in MeCN was prepared since the substrate is sparingly soluble in pure water. Reactions were initiated by transferring 1.0 mL of the stock solution into a reaction vessel (50 mL) to reach the final substrate concentration of $1.0 \times 10^{-4}$ mol dm$^{-3}$.



**Scheme 1.** Schematic representation of hydrolysis reaction mechanism of *p*-NPA.