SPECIFIC INFLUNCE OF SOLVENTS AND IONS ON THE HYDROLYSIS REACTION RATES OF TOXIC ORGANIC COMPOUNDS

BY

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Acknowledgements

DEDICATION

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To Tesfitti, Kiyitti and Milkitti

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Symbols and Abbreviations

MeCN	Acetonitrile
p-NPA	p-Nitrophenyl anthranilate
p-NPB	p-Nitrophenyl benzoate
CTAB	Cetyltrimethylammonium bromide
CTAC	Cetyltrimethylammonium chloride
cmc	Critical micelle concentration
$E_T(30)$	Solvent polarity parameter
ε_r	Dielectric constant/ relative permittivity
π^*	Polarity / polarizability
α	Hydrogen Bond Donor (HBD)
β	Hydrogen Bond Acceptor (HBA)
AN	Acceptor number
DN	Donor number
B(B*)	Solvent basicity or nucleophilicity
Z	Solvent polarity parameter (Kosower Z)
DMA	Dimethylacetamide

ABSTRACT

The specific influences of solvents and ions on the hydrolysis reactions rates various potentially toxic organic compounds have been investigated under various reactions conditions at constant temperatures of either 50 °C or 35 °C. The rates of the reactions of p-nitrophenyl anthranilate (p-NPA) and tropolone tosylate, which have been investigated in acetonitrile-water (MeCN-H$_2$O) media, have significantly affected by the MeCN contents of the reaction media. Two distinct effects have been witnessed for both compounds based on the contents of the MeCN in the reaction solution. The decrease in rate upon increasing contents of MeCN to about 50-60% (v/v) and a reversal increase in rate upon further increasing the MeCN content to greater than 60% (v/v). This phenomenon has been discussed based on the ideas of change in water structure upon adding MeCN to the aqueous media and/or increase in the OH$^-$ activities especially in medium containing high contents of MeCN. The rates of hydrolysis reactions of both p-NPA and tropolone tosylate have been observed to strongly dependent of the added salt concentration and type, the pH of the media, the concentration of base used and temperature. For the hydrolysis of both compounds, their rates are observed to be strongly dependent on the nucleophilicity of the anions from the added salt. For tropolone tosylate, in addition to nucleophilicty of the anions from the added salts, coordination ability of the cations of the salts with the tropolonate ion also played significant role.

The hydrolysis reaction rates of p-nitrophenyl benzoate (p-NPB) have also been investigated in aqueous buffer of pH = 9.18 media containing surfactants, cetyltrimethylammonium bromide (CTAB) and chloride (CTAC) at 35 °C. Below the cmc value of CTAB or CTAC, the rate constant [log (k /s^{-1})] of p-NPB hydrolysis has once decreased and then begun to increase drastically with increasing surfactants concentration. At the concentrations greater than the cmc value, the log (k /s^{-1}) value has reached the optimal value, i.e., 140- and 200-fold rate acceleration for CTAB and CTAC, respectively, compared to that of without the surfactant. Increase in pH of the buffer also has resulted in an increase of rate of hydrolysis of the substrate p-NPB. The influences of added salts on the hydrolysis rate have been examined. All added salts have affected significantly the p-NPB hydrolysis rate not only in the presence but also in the absence of the surfactants. In solutions with surfactants (> cmc), the

addition of 0.1 mol dm^{-3} of each of the added salts of NaBr, Me$_4$NBr, Et$_4$NBr, Pr$_4$NBr and n-Bu$_4$NBr has significantly decreased the reaction rate. The general rate deceleration caused by the added salts in media containing CTAB surfactant follow the order: NaBr > Me$_4$NBr > Et$_4$NBr > Pr$_4$NBr > n-Bu$_4$NBr. In the absence of surfactant, however, the added bromide salts have accelerated linearly the rate of hydrolysis, except NaBr, with an order of Me$_4$NBr < Et$_4$NBr < Pr$_4$NBr < n-Bu$_4$NBr. Similar effects were observed in the presence of the corresponding chloride salts in solution containing CTAC surfactant. The emerged phenomenon in media containing surfactants have been discussed on the basis of pseudophase model in which the aqueous medium and the micelle are viewed as a separated phases with which the substrate is in thermodynamic equilibrium.

CHAPTER ONE

1. Background of the study

1.1 General Introduction

1.1.1 Basics of Chemical Kinetics

Chemical kinetics as a science began in the middle of the 19th century [1], when Wilhelmy was apparently the first to recognize that the rate at which a chemical reaction proceeds follows definite laws, but although his work paved the way for the law of mass action of Waage and Guldberg, it attracted little attention until it was taken up by Ostwald towards the end of the century, as discussed by Laidler [2]. Wilhelmy also realized that chemical rates depended on the concentrations of the reactants.

The chemical process of transformation of reactants into products is the subject of studying of chemical kinetics [3]. One can say against it that the chemical reaction is also the subject of studying of several other chemical disciplines, such as synthetic and analytical chemistry, chemical thermodynamics and technology. Note that each of these disciplines studies the chemical reaction in its certain aspect. In synthetic chemistry, the reaction is considered as a method for preparation of various chemical compounds. Analytical chemistry uses reactions for the identification of chemical compounds. The chemical thermodynamics studies the chemical equilibrium as a source of work and heat, *etc.* The kinetics also has its specific approach to the chemical reaction. It studies the chemical transformation as a *process that occurs in time according to a certain mechanism* with regularities characteristic of this process. This definition needs to be interpreted.

What precisely does the kinetics study in the chemical process? [1, 2, 4-9]

1st, the reaction as a process that occurs in time, its rate, a change in the rate with the development of the process, the interrelation of the reaction rate and concentration of reactants - all this is characterized by kinetic parameters.

2nd, the influence of the reaction conditions, such as the temperature, phase state of reactants, pressure, medium (solvent), presence of neutral ions, *etc.,* on the rate and other kinetic parameters of the reaction. The final result of these studies is the quantitative empirical correlations between the kinetic characteristics and reaction conditions.

3rd, the kinetics studies the methods for controlling the chemical process using catalysts, initiators, promoters, and inhibitors.

4th, the kinetics tends to open the *mechanism of the chemical process,* to reveal from which elementary steps it consists, what intermediate compounds are formed in it, *via* what routes reactants are transformed into products, and what factors are responsible for the composition of products.

5th, an important task of the kinetics became the study and description of elementary reactions involving chemically active species. *Elementary acts* of the chemical transformation are diverse; they can be theoretically described by the methods of quantum mechanics and mathematical statistics.

6th, the chemical kinetics studies the relation between the structure of particle reactants and their *reactivity.* In most cases, the chemical transformation is preceded by physical processes of the activation of particle-reactants. These processes often accompany chemical processes and manifest themselves, under certain conditions, resulting in the perturbation of the equilibrium particle distribution of the energy. These processes are the subject of the *non-equilibrium kinetics.*

7th, the chemical transformation, under laboratory and technological conditions, is often accompanied by mass and heat transfer. *Macrokinetics* studies these complex processes using mathematical methods for analysis and description. Thus, the subject of the chemical kinetics is the comprehensive study of the chemical reaction: regularities of its occurrence in time, the dependence on the conditions, the mechanism, a relation between the kinetic characteristics with the structure of reactants, energy of the process, and physics of particle activation.

Since the kinetics studies the reaction as a process, it has the specific methodology: the body of theoretical concepts and experimental methods, which allow the study and analysis of the chemical reaction as an evolution process that develops in time. The experimental kinetics possesses various methods to perform the reaction and control it in time. The kinetic methods for studying fast reactions (stop-flow, pulse, *etc.*) have been developed during recent many years along with procedures and methods for the generation and study of active intermediate compounds: free atoms and radicals, labile ions and complexes. The methods for "perturbation" of the chemical reaction during its course were invented. Mathematical simulation and modem computer technique are widely used for the theoretical description of the reaction as a process.

What scientific disciplines are boundaries for the chemical kinetics? First of all, synthetic chemistry, which possesses a large experimental material on chemical reactions, namely, knowing what reactants under which conditions are transformed into these or other products. The structure of matter provides necessary data on the structure of particles, interatomic distances, dipole moments, and others. These data are required for the development of assumed mechanisms of transformations. The chemical thermodynamics makes it possible to calculate the thermodynamic characteristics of the chemical process. The kinetics borrows from mathematics the mathematical apparatus necessary for the description of the process, analysis of the mechanism, and development of correlations. The kinetics uses molecular physics data when the process is analyzed at different phase states of the system where the reaction occurs. Spectroscopy and chromatography provides the kinetics with methods of process monitoring. Laser spectroscopy serves as a basis for the development of unique methods for studying excited states of molecules and radicals.

In turn, results of the chemical kinetics compose the scientific foundation for the synthetic chemistry and chemical technology. The methods for affecting the reaction developed in the kinetics are used for controlling the chemical process and creation of kinetic methods for the selective preparation of chemical compounds. The methods for retardation (inhibition) of chemical processes are used to stabilize substances and materials. Kinetic simulation [10-12] is used for the prognostication of terms of the operation of items. The kinetic parameters of reactions of substances contained in the atmosphere are used for prognosis of process that occur

in it, in particular, ozone formation and decomposition (problem of the ozone layer). The kinetics is an important part of photochemistry [13], electrochemistry [14-17], biochemistry [18-20], radiation chemistry [21-25], and heterogeneous catalysis [26-30] and of many more scientific fields. It is obvious that the rates of chemical reactions depend on a great number of factors, in particular the nature of the reactants, concentrations or pressures, temperature, light, catalysts, solvent used, pH, and etc.

1.1.2 Role of Hydrolysis Reaction as Degradation Mechanism of Toxic Organic Compounds in the Environment

D. Mackay *et.al.* [31] in their book indicated that some 50,000 to 100,000 chemicals believed to being produced commercially by the time of their publication (2006) in a range of quantities with approximately 1000 being added each year. Most of these chemicals are organic chemicals, and many are pesticides and biocides designed to modify the biotic environment. Of these, perhaps 1000 substances are of significant environmental concern because of their presence in detectable quantities in various components of the environment, their toxicity, their tendency to bioaccumulate, their persistence and their potential to be transported long distances. Some of these chemicals, including pesticides, are of such extreme environmental concern that international actions have been taken to ensure that all production and use should cease, i.e., as a global society we should elect not to synthesize or use these chemicals. PCBs, "dioxins" and DDT are examples.

A second group consists of less toxic and persistent chemicals which are of concern because they are used or discharged in large quantities. They are, however, of sufficient value to society that their continued use is justified, but only under conditions in which we fully understand and control their sources, fate and the associated risk of adverse effects. This understanding is essential if society is to be assured that there is negligible risk of adverse ecological or human health effects. Other groups of more benign chemicals can presumably be treated with less care.

It is clear that the fate of chemicals in the environment is controlled by a combination of three groups of factors. First are the prevailing environmental conditions such as temperatures, flows and accumulations of air, water and solid matter and the composition of these media [32, 33]. Second are the properties of the chemicals which influence partitioning and reaction tendencies, i.e., the extent to which the chemical evaporates or associates with sediments, and how fast the chemical is eventually destroyed by conversion to other chemical species [34]. Third are the patterns of use, into which compartments the substance is introduced, whether introduction is episodic or continuous and in the case of pesticides how and with which additives the active ingredient is applied [32].

Most of these toxic organic compounds can potentially be detoxified via various reaction mechanisms such as photooxidation or photocatalysis degradation reactions [35-41], hydrolysis [42-45] and through microbial degradation [46] in which hydrolysis, oxidation, reduction and synthesis plays a major role. Hydrolysis and photolysis are the main abiotic degradation processes in aqueous media [42, 43, 47-50]. Chemical hydrolysis at pH values that are normally found in the environment (pH values 5–9) is a minor process in surface waters [51, 52], but it can be an important degradation way in groundwater, where photodegradation practically does not exist.

Mabey and Mill [43] had explained the reasons why hydrolysis may be a significant chemical process in the environment. First, many hydrolysable chemicals including pesticides and plasticizers, eventually find their way into ground water, streams, and rivers through leaching and runoff. Second, rates of hydrolysis in aquatic systems are independent of commonly used but rapidly changeable indicators of the degradative capacity of the aquatic systems, such as sun light, microbial populations, and oxygen supply. However, rates do depend upon pH, temperature, concentration of chemicals that may change only slowly and seasonally.

For certain chemical structures of hydrolysable chemical groups that are prevalent in environmental chemicals, hydrolysis may be the dominant pathway of their transformation in aquatic system. However, Larson and Weber [53] has clearly stated that hydrolytic process are not limited to the bodies of water such as rivers, streams, lakes and oceans usually associated

with the term aquatic ecosystem. Hydrolysis of organic chemicals also can occur in fog-water [54, 55], biological system [56-58], ground water [59, 60], and the aqueous microenvironment [61, 62].

In general terms, hydrolysis is defined as a chemical transformation in which an organic molecule, RX, reacts with water, resulting in the formation of a new covalent bond with the OH- and cleavage of the covalent bond with X (the leaving group) in the original molecule. The net reaction is the displacement of X by OH$^-$ [63, 64].

$$RX \; + \; H_2O \quad \rightarrow \quad ROH \; + \; X^- \; + \; H^+ \qquad\qquad 1.1$$
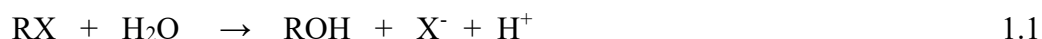
Larson and Weber [53] has explained that hydrolysis is an example of a larger class of reactions referred to as nucleophilic displacement reactions in which the nucleophile (an electron-rich species containing an unshared pair of electrons) attacks an electrophilic atom (an electron-deficient reaction center). This process encompass several types of reaction mechanisms that can be defined by the type of reaction center (*i.e.*, the atom bearing the leaving group, X) where hydrolysis occurs.

1.1.3 Mixed Solvents as a Reaction Media

Reichardt [65] stated that a solvent should not be considered a macroscopic continuum characterized only by physical constants such as density, dielectric constant, index of refraction etc., but as a discontinuum which consists of individual, mutually interacting solvent molecules. According to the extent of these interactions, there are solvents with a pronounced internal structure (*e.g.* water) and others in which the interaction between the solvent molecules is small (*e.g.* hydrocarbons). The interactions between species in solvents (and in solutions) are at once too strong to be treated by the laws of the kinetic theory of gases, yet too weak to be treated by the laws of solid-state physics. Thus, the solvent is neither an indifferent medium in which the dissolved material diffuses in order to distribute itself evenly and randomly, nor does it possess an ordered structure resembling a crystal lattice. Thus, neither of the two possible models – the

gas and crystal models – can be applied to solutions without limitation. Due to the complexity of the interactions, the structure of liquids – in contrast to that of gases and solids – is the least-known of all aggregation states. Therefore, the experimental and theoretical examination of the structure of liquids is among the most difficult tasks of physical chemistry.

Almost all qualitative treatments of solvent effects are based on the simple solvation model, developed by Hughes and Ingold in 1935, for explaining solvent effects on substitution and elimination reactions [66]. The model considers mainly the change of electrical interactions between solvent and reacting species during the activation process. Solvents are thus classified according to their ability to solvate ions and molecules. A serious shortcoming of this approach [65, 67] is the fact that the solvent is considered as a continuum without defined structure and that specific solvent-solute interactions are completely neglected. In addition, changes in the structure of solvents as a result of changes in solvation during the activation process are neglected. Also entropic contributions to solvent effects are not incorporated into this model. Especially in highly structured solvents such as water, entropic contributions to solvent effects can be significant. Notwithstanding the weak points of these qualitative models, these approaches are simple and are readily applied; they are still very popular in practical chemistry.

The nature of the solvent used for an organic reaction has long been known to influence both the kinetics and mechanisms of the processes [68]. In industry, solvents are used in large quantities and, particularly in fine chemical and pharmaceutical production, large amounts are used per mass of final product so that solvent choice is a major part of the environmental performance of a process and its impact on cost, safety and health issues.

The solvent, which makes up approx. 90% of the total mass of a reaction solution, plays an important role for a solution based chemical reaction. Solubility, equilibrium position and reaction rate are all affected by solvent [69]. Many macromolecular compounds dissolve in mixtures better than in pure solvents [65]. Thus, poly(vinyl chloride) is insoluble in acetone as well as in carbon disulfide, but soluble in a mixture of the two. The opposite situation is also known. Malononitrile and N,N-dimethylformamide both dissolve polyacrylonitrile but a mixture of the two does not [65]. Soaps dissolve neither in ethylene glycol nor in hydrocarbons at room

temperature but are quite soluble in a mixture of the two. Here, ethylene glycol solvates the ionic end, and the hydrocarbon the nonpolar end of the fatty acid chain [70]. Binary mixtures of water and organic solvents are extensively employed in organic syntheses [71-75], bio-catalysis [76, 77], hydrolysis and kinetic [78-82], coordination and complex formation phenomenon [83-87], and in studies of reaction mechanisms of, for example, acyl transfer reactions [88-91]. The reasons are partially practical and are often connected with solubility constraints [78].

There is an increased interest in understanding the effects of reaction medium, of both pure solvents and binary mixtures on rate and equilibrium constants of chemical and biochemical reactions. The physico-chemical properties of both substrate and components of the binary mixture affect the solvation of the species of interest, for example, reactants and activated complexes, hence reaction rates and equilibria. Diefallah *et al*. [92] explained that the rate of chemical reactions in solutions can be affected by two solvent effect types: 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. Several factors influence these solvent effects on chemical reaction rates; their relative importance seems to be a function of substrate, detailed mechanism of reaction, and experimental conditions.

Solvent effects in mixed solvents are caused by the interactions of the cosolvent(s) with the reactant(s) in the initial state and with the activated complex in the transition state. These interactions result in changes of the chemical potential of the reactants as well as of the activated complex which affect the Gibbs energy of activation because reactant(s) and activated complex are solvated to a different extent [67]. It is clear that before the reactant anion and the dipolar reactant molecule can come into contact in solution, the solvation shell around the two reactants must be at least partially disrupted. Therefore, the reaction rate in solution is determined primarily by the amount of energy needed to destroy the solvation shells and not by the intrinsic properties of the reactants. The nucleophilicty of nucleophilic species in the reaction solution is also strongly determined by the type of solvent used and their effect on the reaction velocity is much strongly dependent on the solvation shell around them by the solvent in use. For instance,

in addition to the dramatic difference in absolute rates between gas-phase and solution reactions, there are also differences and even reversals in relative rates. For instance, the gas-phase order of increasing nucleophilicity of halogen anions is $I^- < Br^- < Cl^- < F^-$, whereas in protic solvents the reverse order of $I^- > Br^- > Cl^- > F^-$ is found [65].
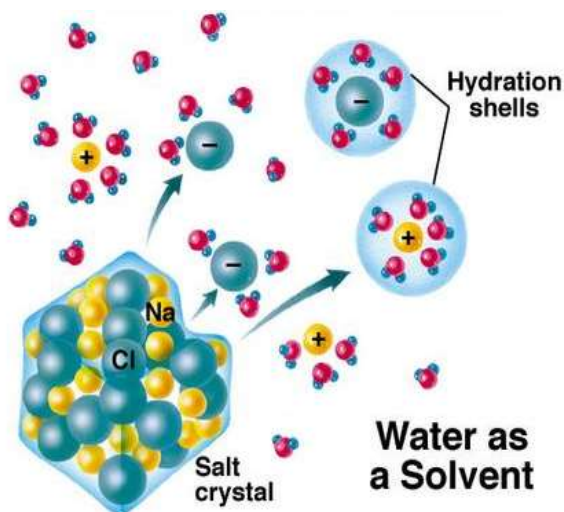
Fig. 1-1 A conceptual representation of the hydration shell of dissolved ions in water [from ref.133]

The knowledge of solvent physical properties such as density, boiling point, viscosity, dielectric constant, surface tension, dipole moment and etc. is fundamental in understanding the behavior of their solutions. Densities and static dielectric constants have a special interest because they are critical for solution chemistry (i.e., change of composition scales (by volume/weight), concentration scales (molal / molar), estimation of ionic activities, determination of equilibrium constants involving ions, reference pH values, reference standard potential of electrochemical cells, etc.) [93, 94]. From the dielectric constants and densities, the activity coefficients of the ions can be calculated at any temperature and composition of the studied range by using the extended Debye-Huckel equation [93]:

$$-\log \gamma = \frac{z^2 A\sqrt{I}}{1+a_0 B\sqrt{I}} \qquad 1.2$$

A and a_0B are the parameters of this equation and can be calculated by using the densities and static dielectric constants and by adopting the Bates-Guggenheim convention, which considers a constant value of 4.56 Å for the Debye radius (a_0). Equations for these parameters are as follows:

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$$A = 1.8246 \times 10^6 \sqrt{\frac{\rho_s}{(\epsilon_s T)^3}} \qquad\qquad 1.3$$

$$a_o B = 1.5 \sqrt{\left(\frac{\epsilon_w}{\epsilon_s}\right)\left(\frac{\rho_s}{\rho_w}\right)} \qquad\qquad 1.4$$

where T is the absolute temperature; ϵ is the static dielectric constant, and ρ is the density, all of them at the working temperature; subscript w indicates pure water; and subscript s indicates the solvent mixture.

Weak electrostatic interactions simply created a loose solvation shell around a solute molecule [95]. It was in this climate of opinion that Hughes and Ingold [66] presented the first satisfactory qualitative account of solvent effects on reactivity by the concept of activated complex solvation. The first solvent property applied to correlate reactivity data was the static dielectric constant ε (also termed ε_r) in the form of dielectric functions as suggested from elementary electrostatic theories. A successful correlation is shown in Fig. 1-2 for the rate of the S_N2 reaction of p-nitrofluorobenzene with piperidine [95].
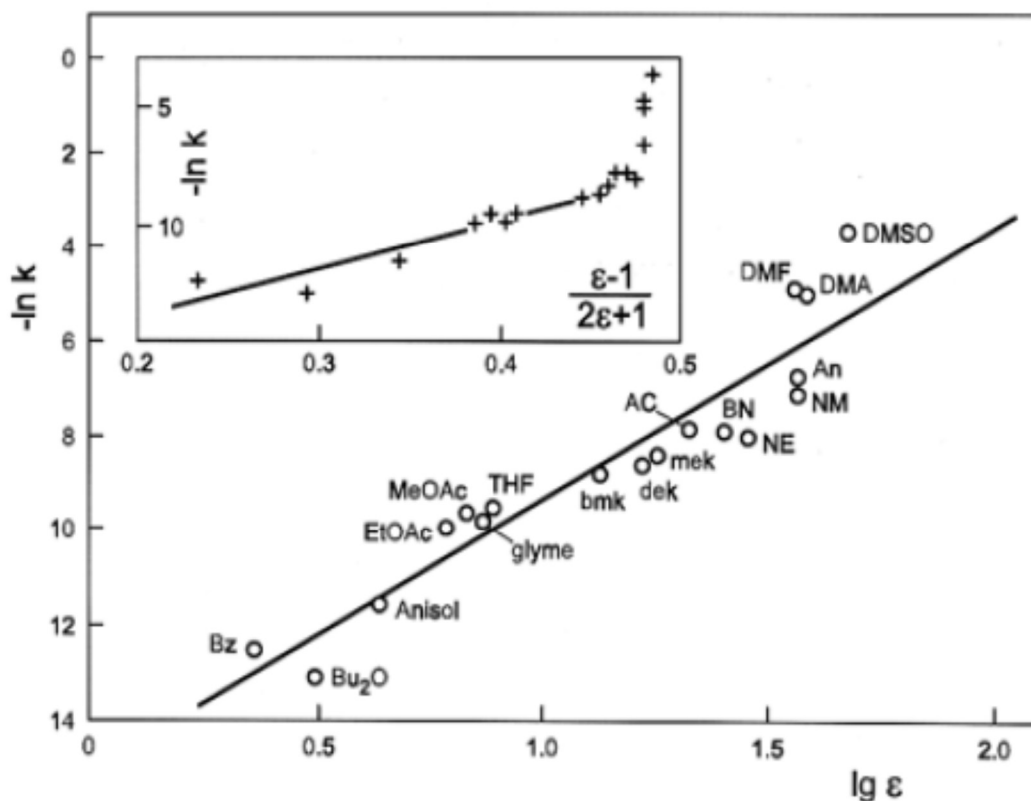
Fig. 1-2 Relationship between second-order rate constants of the reaction of p-nitrofluorobenzene and piperidine and solvent dielectric properties at 50 °C [from ref. 95].

On studying effects of solvents on reactivity of organic compounds, the two outstanding properties of a solvent its donor (nucleophilic, basic, cation-solvating) and acceptor (electrophilic, acidic, anion-solvating) abilities, and solute-solvent interactions has to be carefully considered. Actually, many empirical parameters can be lumped into two broad classes, as judged from the rough interrelationships found between various scales [95].

The one class is more concerned with cation (or positive dipole's end) solvation, with the most popular solvent basicity scales being the Gutmann DN, the Kamlet and Taft β, and the Koppel and Palm B. The other class is said to reflect anion (or negative dipole's end) solvation. This latter class includes the famous scales π^*, α, $E_T(30)$, Z and last but not least, the acceptor number AN.

Cation (or positive dipole's end) solvation

- ✓ Gutmann DN
- ✓ Kamlet and Taft β
- ✓ Koppel and Palm $B\ (B^*)$

Anion (and negative dipole's end) solvation

- ○ Gutmann AN
- ○ Dimroth and Reichardt $E_T(30)$
- ○ Kosower Z
- ○ Kamlet and Taft $\alpha,\ \pi^*$

Some representative relationship between the $E_T(30)$ values and the acceptor number for some solvent is given in Fig. 1-3
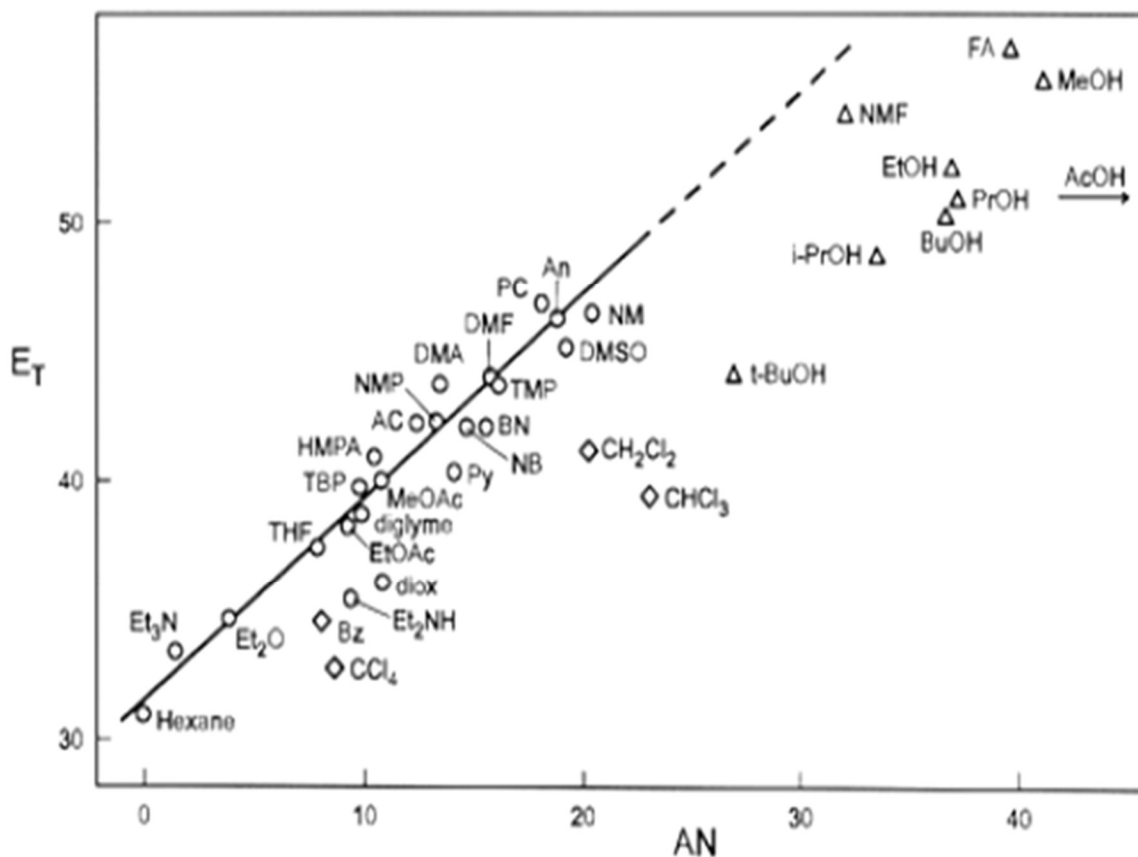
Fig. 1-3 Relationship between the $E_T(30)$ values and the acceptor number. Triangles: protic solvents; Square: aromatic and chlorinated solvents [from ref. 95]

One of the most important parameter which plays a great role in investigating reaction kinetics in solution is solvent polarity. As stated by Richards [96] the simplicity of electrostatic solvation models has resulted in the effect of the dielectric constant (ε) and the permanent dipole moment (μ) being given prominence over other factors and ascribed a special role as parameters of solvent polarity.

In fact, however, the dielectric constant describes only the change in the electric field intensity that occurs between the plates of a condenser when the latter is removed from vacuum and placed in a solvent. One of the methods which have been in use to estimate the solvent polarity is *Z*-values as expressed by Kosower [97] in Fig. 1-4.
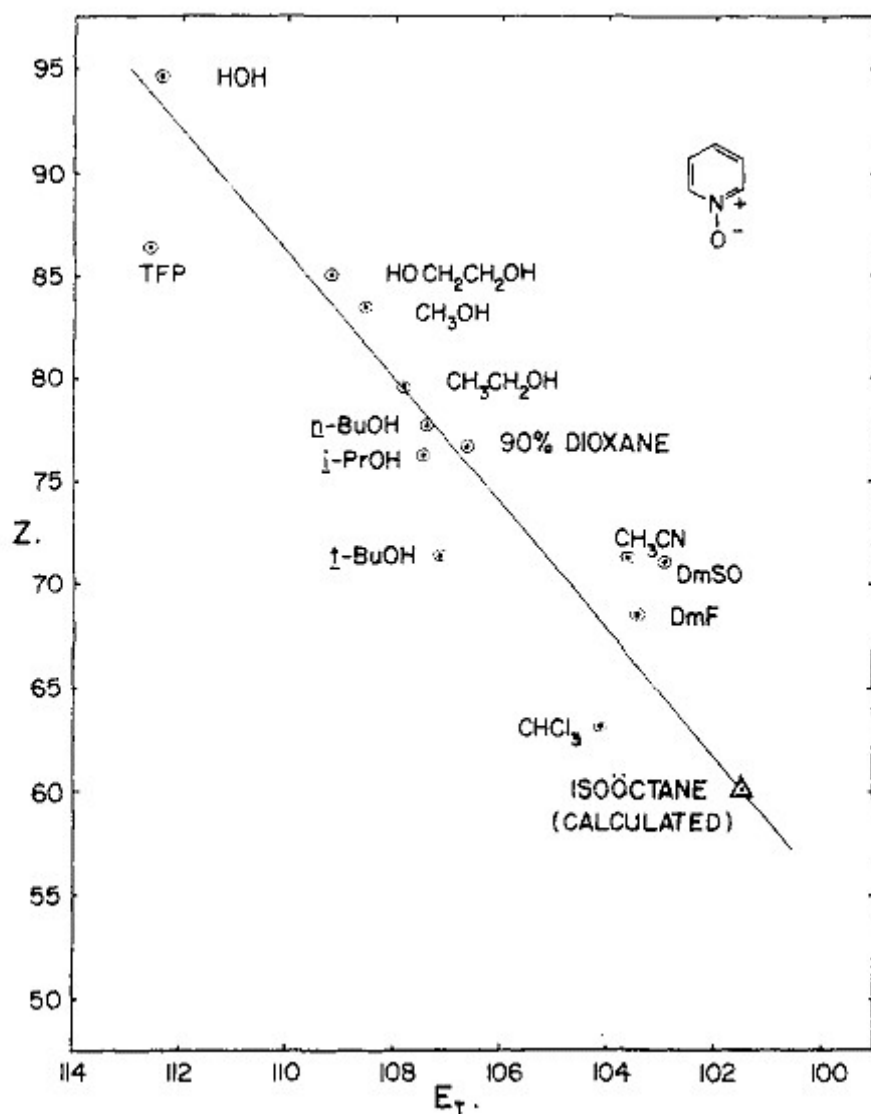
Fig. 1-4 E_T (pyridine-1-oxide vs. Z in fourteen solvents: $E_T = 0.32975Z + 81.693$; TFP = tetrafluoropropanol [from ref. 97].

1.1.4 Bulk-Water Structure and Reaction Kinetics in the Presence of Additives

Under normal condition and in the absence of any additives, it is reasonable to assume that water molecules are highly structured through the hydrogen bonding networks. However, there are ample of evidences [98] indicating the difficulty of exactly mapping the water structure

network even in the absence of any additives and it is still the subject of many scientific researches. Numerous different models, e.g. the "flickering cluster model" of Frank and Wen [99], were developed to describe the structure of water. However, all these models prove themselves untenable for a complete description of the physico-chemical properties of water and an interpretation of its anomalies [100]. According to Horne [98b], Fig. 1-5 should make clear the complexity of the inner structure of water.

Liquid water consists both of bound ordered regions of a regular lattice, and regions in which the water molecules are hydrogen-bonded in a random array; it is permeated by monomeric water and interspersed with random holes, lattice vacancies, and cages. There are chains and small polymers as well as bound, free, and trapped water molecules [98b, 101]. The currently accepted view of the structure of liquid water treats it as a dynamic three-dimensional hydrogen-bonded network, without a significant number of non-bonded water molecules, that retains several of the structural characteristics of ice (i.e. tetrahedral molecular packing with each water molecule hydrogen-bonded to four nearest neighbors), although the strict tetrahedrality is lost [101].

Hojo *et al*. [102], fascinatingly explained that 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 ($c(H_2O)$ ~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)].

Fig. 1-5 Two-dimensional schematic diagram of the three-dimensional structure of liquid water (from ref. 65)

Raman spectroscopy is a technique preferably used for the studies of water structure because the proportions of the intensities the main O−H stretching modes (around 3200 and 3400 cm^{-1}) are thought to reflect well a network of hydrogen bonds as well as its disturbances by the presence of some solutes. Li et al. [103] have reported the Raman spectral changes (shifts) of water with temperature and upon addition of sodium halide salts. Hojo et al. have reported similar shift in Raman spectra of water (D_2O) in the presence of various additives such as organic solvent DMA and Et_4NCl salt [104], Et_4NBr [85], LiCl and NaCl [105], sulfolane and $LiClO_4$ [106] salts, and HCl [107]. We [108] have also reported the effects acetonitrile contents on water structure. This change in "normal water structure" in the presence of additives have been demonstrated to significantly change the reactions kinetics of organic compounds studied under such conditions [104-108].
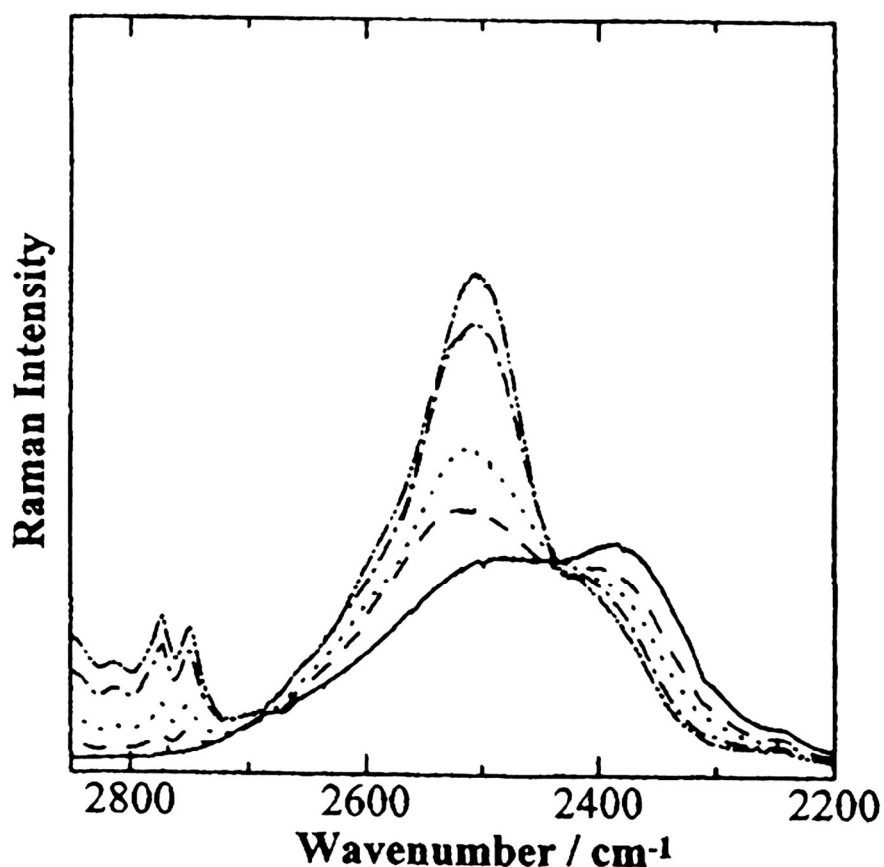
Fig. 1-6 The Raman spectra of D_2O containing various amounts of Et_4NBr at room temperature: (—) no salt; (— —) R = 20; (- - -) R = 10; (— - —) R = 5; (— - - —) R = 3.75 where R = $[D_2O]/[Et_4NBr]$. [from ref. 85]

1.1.5 Interactions and Reactivity in Water and in Mixed Aqueous Solvents

Organic reactivity in water and in mixed aqueous solvents is determined by interactions of water and cosolvents or cosolutes with the reactant(s) and the activated complex [89, 109]. Water-solute interactions reflect the fact that water molecules are small, moderately polarizable and able to form a highly structured hydrogen bonded network. Induced dipole-induced dipole interactions of water with solutes are small, but the dipole moment of water does enable significant dipole-induced dipole and dipole-dipole interactions with solutes. Obviously, an important contribution to the overall solute-solvent interactions in water is hydrogen bonding. Finally, the interaction of water with charged solutes is very strong.

Hydrophobicity and hydrophobic hydration play an important role in the solvation of reactants and activated complex in water and in mixed aqueous solvents [86, 110]. Hydrophobic effects are characterized by intriguing thermodynamic properties and are the result of a combination of water-solute and water-water interactions. Traditionally, hydrophobicity and hydrophobic hydration are considered to be a consequence of the preference of water for interaction with other water molecules over interaction with hydrophobic (*i.e.* apolar) solutes. In a study of solvent effects on reactions in aqueous reaction media, a discussion of hydrophobicity and hydrophobic hydration is essential.

Interactions of reactant(s) and activated complex with cosolvent or cosolute molecules in aqueous solutions involve all forms of dipolar interactions mentioned above, but are strongly mediated by water. The thermodynamics of these interactions strongly depend on the concentration of the solute molecules. In addition, hydrophobic interactions play a significant role in intermolecular interactions between solutes in aqueous media.

1.1.6 Reactions in Micellar Media

A solute molecule is said to dissolve in water solvent when the absolute value of solvation energy (i.e., energy released owing to formation of solvation shell around the solute molecule) becomes equal to or larger than the energy required to form the cavity in the water solvent for embedment of the solute molecule [111]. A surfactant (surface-active) or amphiphile molecule

consists of both hydrophobic (lipophilic or lipid loving) and hydrophilic (lipophobic or lipid-hating) molecular segments. When the hydrophobic segment becomes considerably larger than voids in the three dimensional structural network of water solvent, and the solvation energy for a single molecule is not sufficient to counterbalance the energy needed to form a cavity for embedding the molecule, then the surfactant molecules begin to aggregate, because it is energetically less expensive or easier to form a large cavity than a relatively smaller one.

However, because the surfactant molecules contain both hydrophilic segments (called head groups) and lipophilic segments (generally long methylene chains [C_nH_{2n+1} with n > 8] called tails), packing of head groups and tails during the formation of micelle involves different energetics in terms of molecular interaction. Thus, the shape and size of a micelle depend upon the energetics of the interactions between the adjacent hydrophilic head groups as well as adjacent lipophilic tails [111, 112].
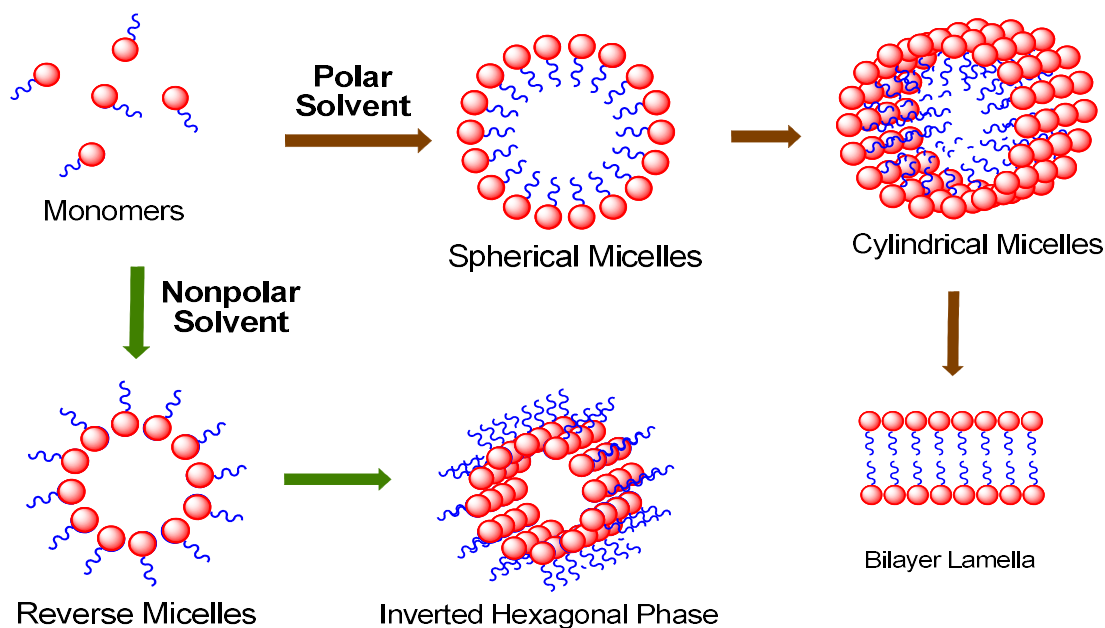
Fig. 1-7 A conceptual representation of micelle formation in polar and nonpolar solvents [from ref. 134].

Based on characteristic physical properties of head groups, surfactants have been categorized as cationic (if the head groups are cationic), anionic (if the head groups are anionic), Zwitterionic (if the head group possess both cationic and anionic sites), and nonionic (if the head

groups are nonionic). The increase in the concentration of a particular surfactant in an aqueous solvent reveals a sudden change in various aqueous surfactant solution properties such as surface tension, equivalent conductivity, solubilization, osmotic pressure, turbidity, self-diffusion, magnetic resonance, Uv-visible/fluorescence spectra of solutes, and reaction rates above a sharp surfactant concentration (Fig. 1.8). The point of intersection of the two linear lines in each plot represents the critical micelle concentration (CMC). Such changes in various physical properties of an aqueous solution of the surfactant are attributed to the formation of an aggregates of the surfactant molecules called micelles above a critical micelle concentration (CMC).
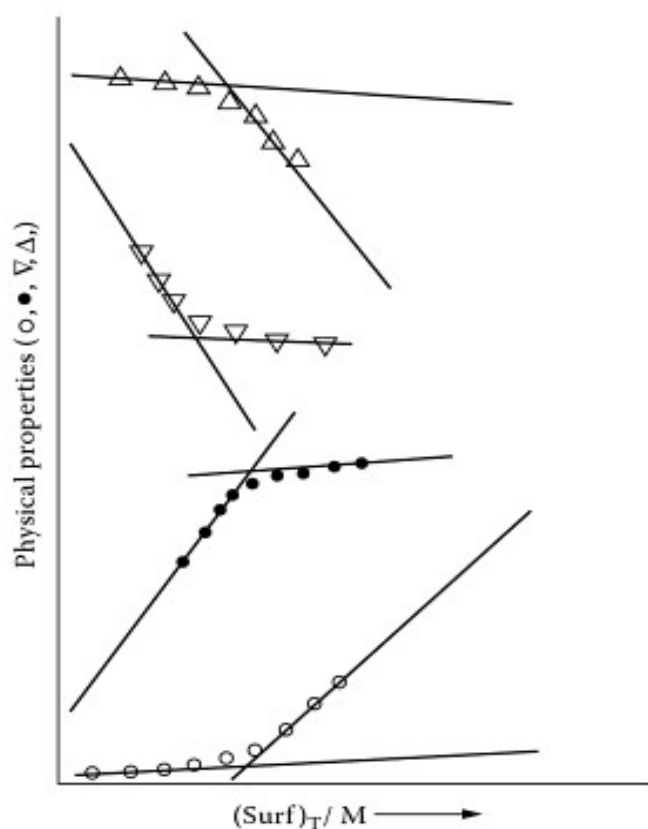
Fig. 1-8 Change in physical properties of micellar aqueous solution as a function of total surfactant concentration, [Surf]$_T$ (from ref. [111]).

Myers [113] explained that in all branches of chemistry, the rate of a chemical reaction can be very sensitive to the nature of the reaction environment. Reactions involving polar or ionic transition states can be especially sensitive to the polarity of the reaction medium. It should not

be too surprising, then, that many chemical reactions, especially those in which one reactant may be soluble in water and the other in oil, can exhibit a significant enhancement in rate when carried out in the presence of surfactant micelles. The presence of the micellar species can provide a beneficial effect through two possible mechanisms:

1. The palisades region of the micelle represents a transition zone between a polar aqueous environment, which may be either the bulk phase or the micellar core, and a nonpolar hydrophobic region. Such a gradient in polarity can serve as a convenient area of intermediate polarity suitable for increased reactant interaction or for optimizing the energy of transition state formation.

2. The potential for the micelle to solubilize a reactant that would not normally have significant solubility in the reaction medium means that it can serve as a ready reservoir of reactant, in effect increasing the available concentrations of reactants. Rate enhancements as high as 10^5 have been reported, which makes such systems very attractive for potential practical applications.

Micelle formation, or micellization, is an important phenomenon not only because a number of important interfacial phenomena, such as detergency and solubilization, depend on the existence of micelles in solution, but also because it affects other interfacial phenomena, such as surface or interfacial tension reduction, that do not directly involve micelles. Micelles have become a subject of great interest to the organic chemist and the biochemist—to the former because of their unusual catalysis of organic reactions [114] and to the latter because of their similarity to biological membranes and globular proteins [112].

Micelles have a wide range of application from altering the rate of organic chemicals reaction rates [115-121] to the pharmaceutical application especially as carriers for drug delivery [122-128]. Torchilin [129] demonstrated that micelles as drug carriers are able to provide a set of unbeatable advantages- they can solubilize poorly soluble drugs and thus increase their bioavailability, they can stay in the body (in the blood) long enough providing gradual accumulation in the required area, their size permits them to accumulate in body regions with

leaky vasculature, they can be targeted by attachment of the specific ligand to the outer surface, and they can be prepared in large quantities easily and reproducibly.

According to Reichardt [65], most chemical studies in this field have concentrated on the effect of micellar surfactants on reaction rates and only a few attempts have been made to investigate the effect that micelles might have in altering the relative extent of competing reactions. For example, in studying the competitive hydrolysis and aminolysis of aryl sulfates in aqueous solution, Fendler et al. have found [130] that cationic micelles such as cetyltrimethylammonium bromide (CTABr) are able to alter the balance between S−O bond fission and C−O bond fission as shown in Eq. (1.5) (from Ref. 65).

$$(1.5)$$
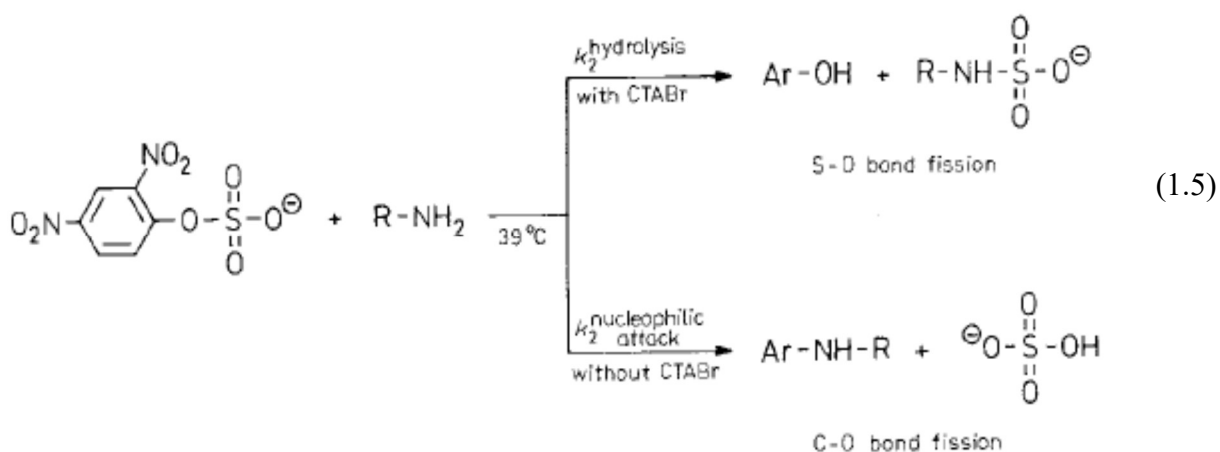
To summarize, solubilization of reactants in micelles can lead to the following effects: local concentration (increase in substrate concentration per unit volume of micelle due to the tendency of hydrophobic organic substrates to be solubilized in micelles), cage (ability of micelles to hold reactive intermediates together long enough), pre-orientational (to solubilize substrates in specific orientation), micro-viscosity (less translational and rotational freedom of incorporated substrates), and polarity effects (change in substrate reactivity due to the variation in micro-polarity) [131].

1.1.7 Summary

About a century ago [95], it was discovered that the solvent can dramatically change the rate of chemical reactions. Since then, the generality and importance of solvent effects on chemical reactivity (rate constants or equilibrium constants) has been widely acknowledged. It can be said without much exaggeration that studying solvent effects is one of the most central topics of chemistry and remains ever-increasingly active. Blokzijl *et.al* [132] pointed out that specific noncovalent interactions in aqueous media are responsible for stabilization of proteins, biological membranes, micelles, and other aggregates in aqueous solutions. Chemical reactivity in aqueous media is also largely governed by these types of interactions, and the presence of inert co-solvents in the reaction medium can seriously affect the rate of the reaction.

As mentioned earlier, there is an increased interest in understanding the effects of reaction media of both pure solvents and binary mixtures on the hydrolysis reaction rates of toxic organic compounds. It is clear that solvents can significantly alter the rate and equilibrium constants of chemical and biochemical reactions. In addition to solvent effects, the presences of added salts also have the ability to significantly alter the reaction rates of organic compounds. The added salts can lead to either rate acceleration or deceleration, depending upon the substrate, the specific salt type and/or their concentrations.

In the frame of the pseudo-phase model, micelles are considered a phase different from aqueous medium, where reaction rates and solubilities of the substrates can vary considerably. In reactions with ionic species, an important fact is the charge of the surfactant head groups and counter-ions. In this way, it is expected that the rate of hydrolysis of hydrophobic esters by OH^- ions will be enhanced by cationic micelles that can include the ester in their core and attract reactive ions of opposite sign, that is, hydroxyl ions. When the counter-ions of the surfactant are non-reactive, for instance, bromide ions, there is a competition between OH^- and Br^- attracted toward the surface of the micelle. In this case the equilibrium ion-exchange constant can be used to quantify the concentration of hydroxyl ions in the micellar surface, together with the

assumption that the degree of association of counter ions to the micelle, can be considered constant; this is essentially the pseudo-phase ion-exchange (PIE) model.

Taking in to consideration the fact that, the study of chemical reaction kinetics under various reaction conditions is of a great interest in various research disciplines, and is still evolving with time, I devoted myself on the study of medium effect on the reaction rates of some selected organic compounds. Accordingly, Chapter Two and Three of this thesis explains the specific influence of the added salts and content of the co-solvent (acetonitrile) on the hydrolysis reaction rates of *p*-nitrophenyl anthranilate (*p*-NPA) and tropolone tosylate, respectively, while Chapter Four is devoted to the study of the specific influence of surfactants (micelle formation) both in the presence and absence of added salts on the hydrolysis reaction rates of *p*-nitrophenyl benzoate (*p*-NPB) in aqueous buffered media.

1.2 Objectives of the study

1.2.1 General Objective

As described earlier there has been an increase of interest in the study of medium effects on the reaction kinetics and thermodynamics of organic compounds. The presence of additives such as organic solvents, salts, surfactants, etc. in general play a great role in altering reaction behavior of organic chemicals. There are literature evidence [94] indicating that at a 15-20 mol% content of MeCN, the water became saturated with it and further addition triggered a marked structural change. Thus, the addition of organic solvent to H_2O as co-solvent obviously results in changes in some physical properties of the solution such as viscosity, dielectric constant, density, etc. These changes in physical properties of the media have been observed to significantly affect the rates of reactions of organic compounds. Hence, the general objective of this study is to investigate and justify the specific influences of solvents, ions and surfactants on the hydrolysis reaction rates of toxic organic compounds.

1.2.2 Specific objectives

The specific objectives of the study include:

i. To determine the specific effects of MeCN contents on the hydrolysis reaction rates of *p*-NPA and tropolone tosylate;

ii. To understand the specific effects of added salts on the hydrolysis reaction rates of *p*-NPA and tropolone tosylate;

iii. To determine the effects of micelle formation on the rates of hydrolysis reactions of *p*-NPB;

iv. To determine the effects of added salts on the hydrolysis reaction rates of *p*-NPB in the presence and absence of surfactants;

v. To apprise the hydrolysis reaction behavior of *p*-NPA, *p*-NPB, and tropolone tosylate in the modified media.

1.3 References

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CHAPTER TWO

2. Specific Influence of Salts on the Hydrolysis Reaction Rate of *p*-Nitrophenyl Anthranilate in Binary Acetonitrile-Water Solvents

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 /s^{-1})] in all solutions mixed with 0 - 75% (v/v) MeCN. The log (k /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 /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$_4$NBr is enhanced with increasing MeCN contents. In 50% (v/v) MeCN solution, the acceleration in log (k /s^{-1}) caused by added salts is in the order of NaN$_3$ > (*n*-Bu)$_4$NBr ~ Et$_4$NBr > Et$_4$NCl. 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$_4$NBr 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$_2$O 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.

Keywords: Hydrolysis reaction rate; buffer solution; acetonitrile; activities of OH$^-$, nucleophilicity, water structure, modified media

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2.1 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). The *p*-Nitrophenyl anthranilate, having 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] as indicated in Scheme 2-1*.

Free reducing glycans + *p*-Nitrophenyl anthranilate (PNPA)

UV active, separable reactive ester

GPNPAs + Protein → Fluorescent neo-glycoprotein
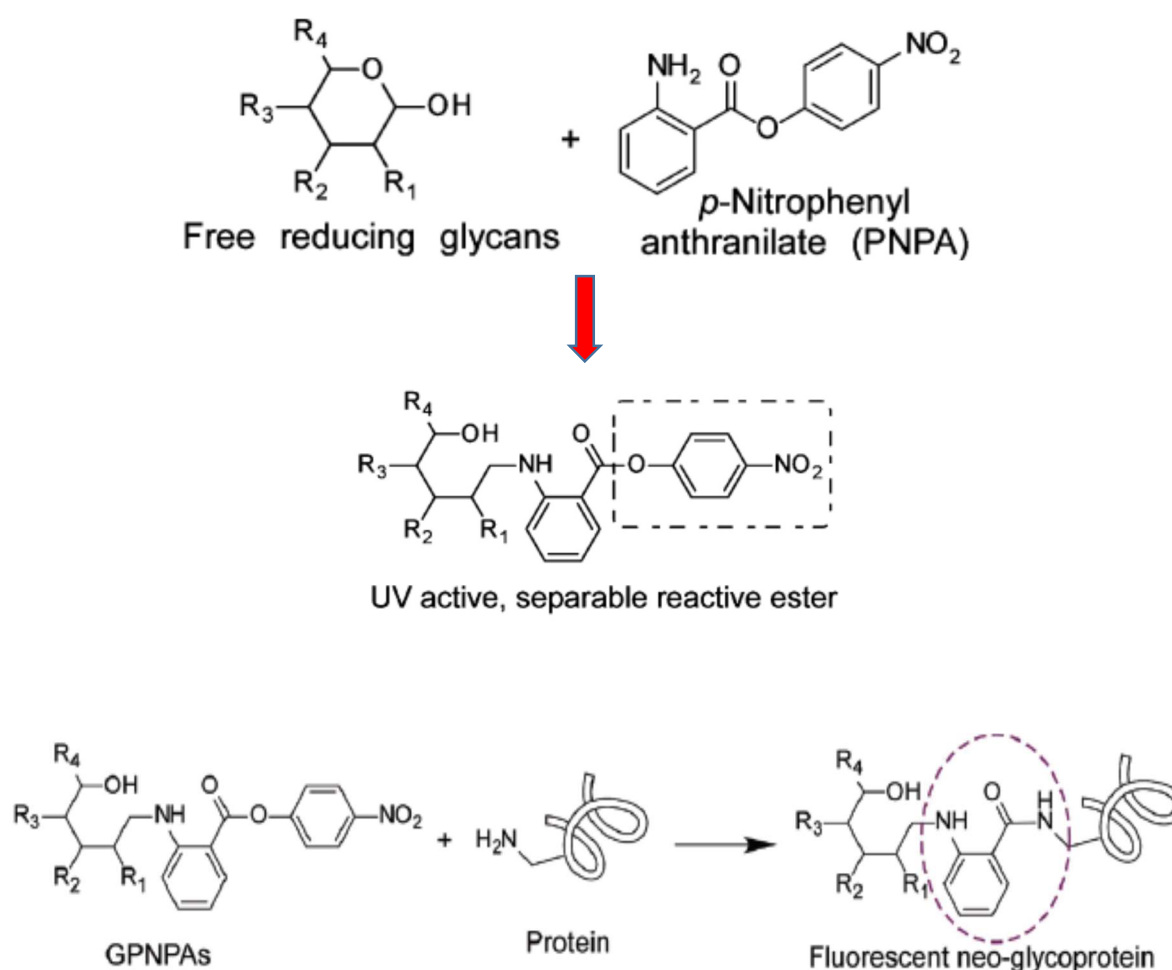
Scheme 2-1 General strategy for using *p*-nitrophenyl anthranilate (*p*-NPA) as a heterobifunctional linker to make neoglycoconjugates and other potential applications. (* from Ref. 1)

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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. Investigation on the hydrolyzability of this special compound is obviously one approach to determine its interaction with water molecules. Hydrolysis of an ester may occur through three path ways: base catalyzed, pH independent, and acid catalyzed reaction path ways [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 have 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 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(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 (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, I will 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 $8.50 – 10.0$ 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 2-2. 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.
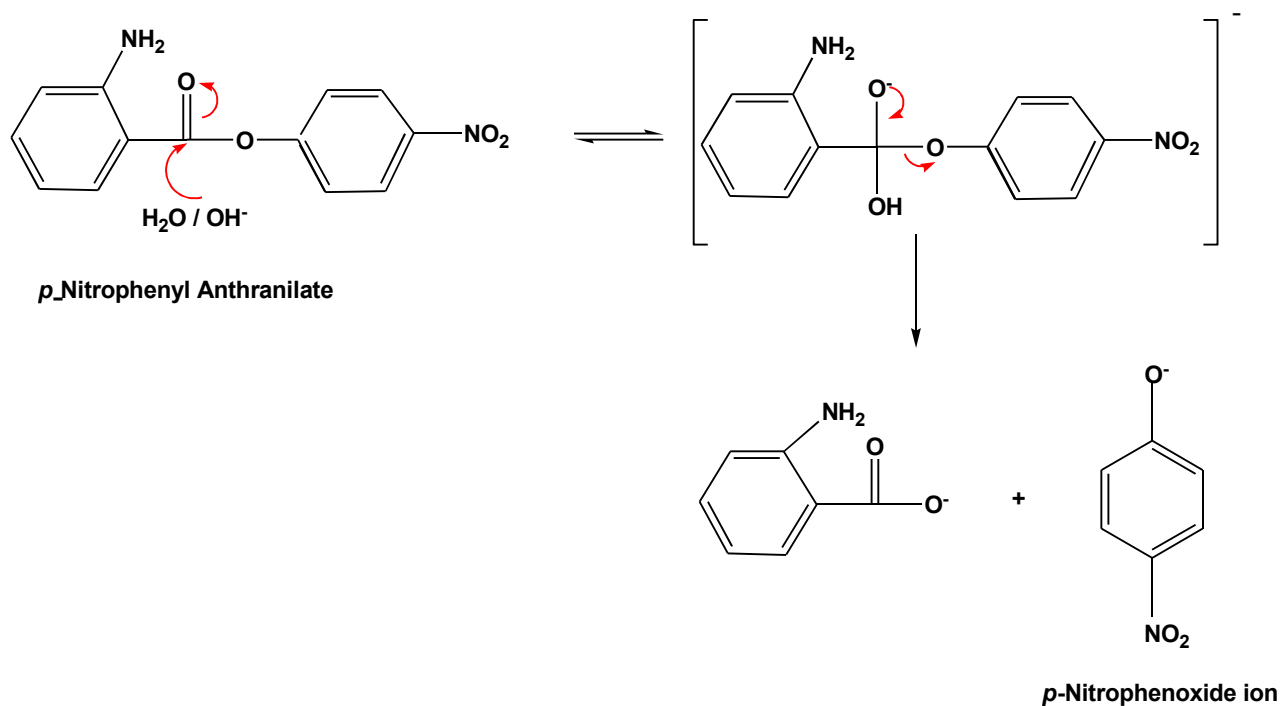
Scheme 2-2 Schematic representation of hydrolysis reaction mechanism of *p*-NPA

2.2 Experimental

2.2.1 *Materials and equipment*

All chemicals utilized were commercially available and used as received. *p*-Nitrophenyl anthranilate (4-nitrophenyl 2-aminobenzoate, $\geq 98.0\%$) and benzoate ($> 95\%$) were from TCI and Wako, respectively. Salts of $LiClO_4$ ($\geq 98.0\%$), Et_4NBr ($\geq 98.0\%$), Et_4NCl ($\geq 98.0\%$), NaN_3 (≥ 98), (n-Bu)$_4$NBr ($\geq 98.0\%$), and $Na_2B_4O_7.10H_2O$ (≥ 99.6) and the co-solvent, acetonitrile (of the GR grade), were from Wako. Other salts of $NaClO_4$ ($\geq 98.0\%$), Et_4NTsO (tosylate or *p*-toluenesulfonate, $\geq 97\%$), and Pr_4NBr ($\geq 98.0\%$) 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 ^{o}C). Excitation for the Raman Spectroscopy was provided by a 514.5 nm argon laser.

2.2.2   *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 ^{o}C, in a 1.0 cm quartz cuvette. Reaction solutions were prepared by combining the appropriate amounts of water, 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 ^{o}C in order to reach the thermal equilibrium. Prior to the beginning of the reaction, a stock solution of the substrate (*p*-NPA) (5.0×10^{-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 1.0×10^{-4} mol dm^{-3}. The samplings of 3 - 4 mL were carried out from reaction solutions at certain time intervals and the sampled solutions were immediately dipped into an ice water bath. The reaction progress was then

followed spectrophotometrically by monitoring the liberation of *p*-nitrophenoxide ion at λ_{max} = *ca*. 400 nm as a function of time. The apparent first order rate constants were obtained from the slopes of plot of ln (A_∞ - A_t) *vs. t*, where A_∞ and A_t are the absorbance values at the reaction final and at time *t*, respectively. All rate constants were obtained from linear plots with correlation coefficients (R^2) of normally 0.999 or more.

2.3 Results and Discussion

At the constant temperature of 50 °C, the rate of hydrolysis reactions of 1.0 x 10^{-4} mol dm^{-3} *p*-nitrophenyl anthranilate (*p*-NPA) were followed in aqueous buffer of pH = 9.18 media containing MeCN-H$_2$O binary solvent of 0 to 75% (v/v) in MeCN. The generation of the *p*-nitrophenolate ion as a result of the hydrolysis can be witnessed by the band appearance at λ_{max} = *ca*. 400 nm with time as shown in Fig. 2-1. The isosbestic point observed at 355 nm indicates the coexistence of the original substrate and the released tropolonate ion.
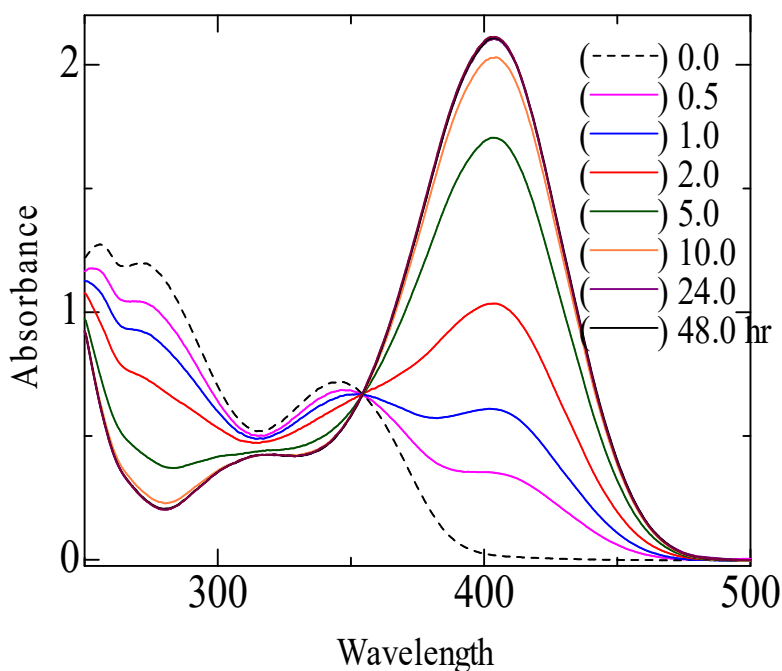
Fig. 2-1 Generation of *p*-nitrophenolate ion with time as the hydrolysis product from *p*-nitrophenyl anthranilate in aqueous borate buffer of pH = 9.18 media containing 20% (v/v) MeCN at 50 °C.

As stated under kinetic measurement sections, pseudo first order rate constants were obtained from the slopes of plot of ln (A_∞ - A_t) *vs.* time (s) curve. Fig. 2-2 shows some of the representative ln (A_∞ - A_t) *vs.* time (s) curves for the hydrolysis of *p*-NPA under previously specified reaction conditions and in the presence of 0 - 50% (v/v) MeCN.
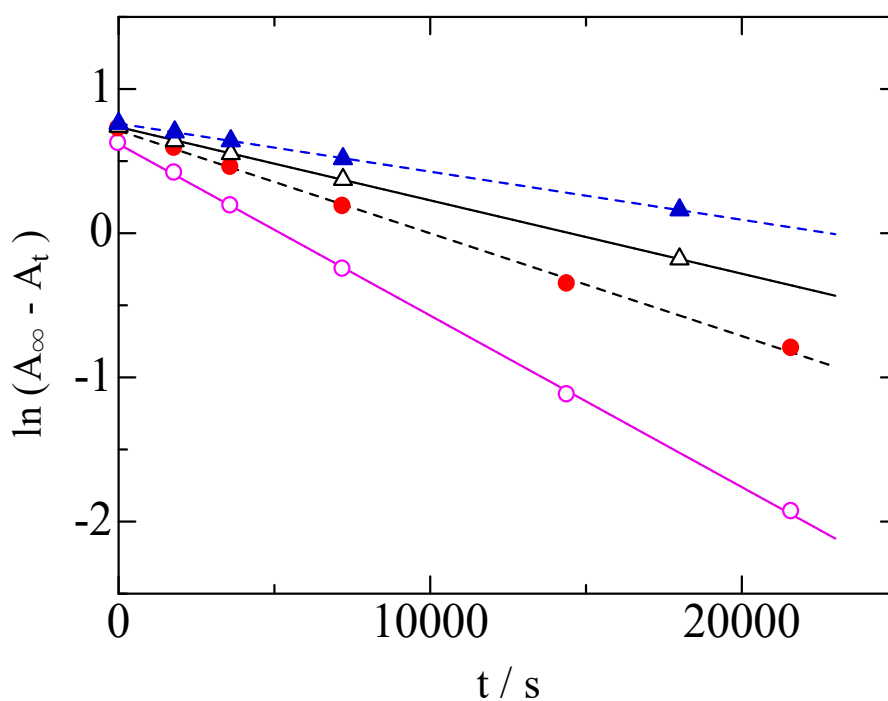
Fig. 2-2 ln (A_∞ – A_t) *vs.* time (s) curves for the hydrolysis of *p*-NPA in aqueous buffer of pH = 9.18 media containing MeCN at 50 ºC: (○) 0; (●) 20, (Δ) 30; (▲) 50% (v/v) MeCN. (R^2 = 0.999).

2.3.1 Effects of pH and MeCN Contents

At the constant temperature of 50±0.1 ºC, the hydrolysis of *p*-nitrophenyl anthranilate (1.0 x 10^{-4} mol dm^{-3}) has been examined in solutions of 0 - 75% (v/v) MeCN as co-solvent with water containing the pH buffer ranging from 8.50 - 10.0. The evaluated first order rate constants [log (k /s^{-1})] increase linearly as -4.55, -3.86, -3.56 and -3.18 with increasing pH of the buffer solutions as 8.50, 9.18, 9.50 and 10.0, respectively, in sole aqueous solutions. The increase in the

rate acceleration is even about 23 times for pH increment from 8.50 to 10.0. In all the solutions containing MeCN up to 75% (v/v), similar increases in the rate constants are evidenced with increasing pH of the buffer, as shown in Fig. 2-3. For instance, the log (k /s^{-1}) value in solution containing 20% (v/v) MeCN increase from -4.76 to -3.44 with the pH increase from 8.50 to 10.0.
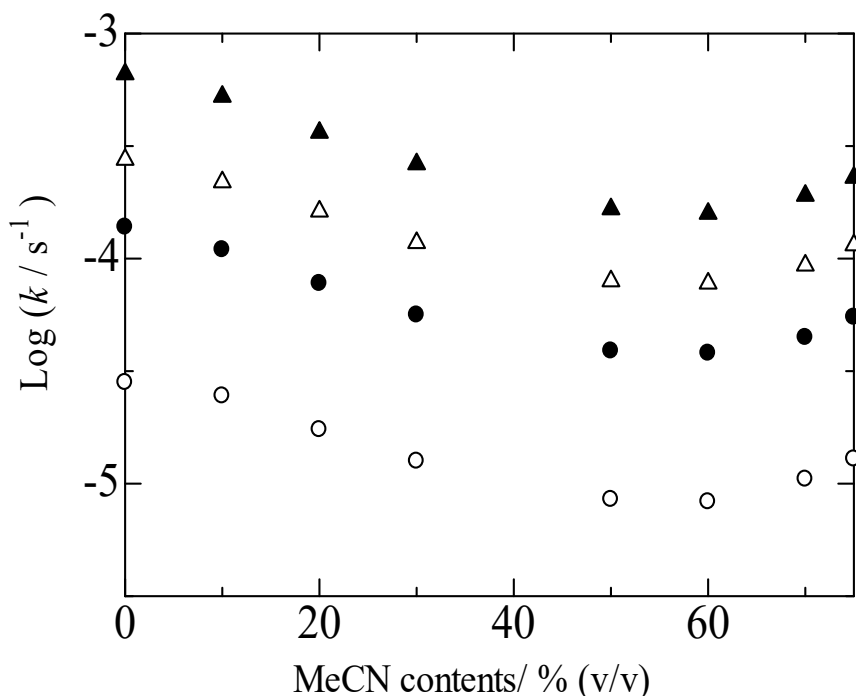
Fig. 2-3 Changes in log (k /s^{-1}) of *p*-NPA hydrolysis with MeCN contents in aqueous borate buffer solutions of various pH values at 50±0.1 °C: (○) 8.50; (●) 9.18; (△) 9.50; (▲) 10.0.

Increasing contents of the organic solvent (MeCN) cause significant changes in the hydrolysis reaction rate of *p*-nitrophenyl anthranilate. With the constant pH buffer of 9.18, the log (k /s^{-1}) value decrease linearly as -3.87, -3.96, -4.11, -4.21, and -4.41 when the MeCN contents increase as 0, 10, 20, 30 and 50% (v/v), respectively (Fig. 2-3). The decrease in hydrolysis reaction rate with increasing MeCN contents is mainly ascribed to an alteration of water properties (as discussed in the final section of the present paper) and hence deterioration of water activities in the presence of the organic solvent, MeCN. El-Mallah *et al.* [4] have noted that MeCN affects the water structure by intercomponent hydrogen bonding due to the basicity difference in the solvent structure. Similarly, Al-Jallal *et al.* [19] have reported a possible disruption of water tetrahedral structure with increasing MeCN contents.

As the MeCN contents increase to larger than about 50% (v/v), however, the completely reversal trends are observed in the reaction rates, *i.e.*, the hydrolysis rate of *p*-NPA increased again as shown in Fig. 3. For the pH = 9.18 buffer, the log (k /s^{-1}) value varies as -4.41, -4.42, -4.34, and -4.26 in solutions mixed with 50, 60, 70, and 75% (v/v) MeCN, respectively. By the way, the hydrolysis rate constants of *p*-nitrophenyl benzoate also give a similar minimum at about 50% (v/v) MeCN with pH = 8.5 and 9.18 at 40 or 50 °C. The appearance of these minima can be attributed mainly to an increase in the OH$^-$ activity due to the increase in dehydration of OH$^-$ by progressive addition of MeCN. Similar increases in hydrolysis rate constants with increasing contents of organic solvents have been reported by Gomez-Tagle *et al.*[17] for bis(*p*-nitrophenyl) phosphate.

Here it might be important to mention that the pK_a value of boric acid increases monotonously as 9.24, 9.57, 10.40, 10.81, 11.25, and 11.84 for 0, 10, 30, 40, 50, and 70% (w/w) MeCN in water at 25 °C [38]. The apparent pH values, by the pH meter measurements after the reaction completion, were found to increase just linearly from 9.23 to 11.23 with increasing MeCN contents up to 75% (v/v).

2.3.2 Influences of Metal Perchlorates on the Hydrolysis Rate

The changes in the hydrolysis reaction rate constant, log(k /s^{-1}), of *p*-nitrophenyl anthranilate were examined in the presence of 0.0 - 1.0 mol dm^{-3} added alkali metal perchlorate salts (LiClO$_4$ and NaClO$_4$) in buffer solutions of pH = 9.18 mixed with 0 – 70% (v/v) MeCN at 50 °C. Fig. 2-4 shows that the log (k /s^{-1}) value decreases linearly with increasing LiClO$_4$ concentration in solutions containing no MeCN. However, the linear curve is altered to concave curves as MeCN contents increase. We have to just note that the log (k /s^{-1}) value without salt in the 70% (v/v) MeCN solvent is larger than that in the 50% (v/v) MeCN solvent (*cf.* Fig. 2-3 and Table 2-1). The hydrolysis rate of *p*-NPA decelerates as the concentration of LiClO$_4$ and/or contents of MeCN increase (with the above exception).
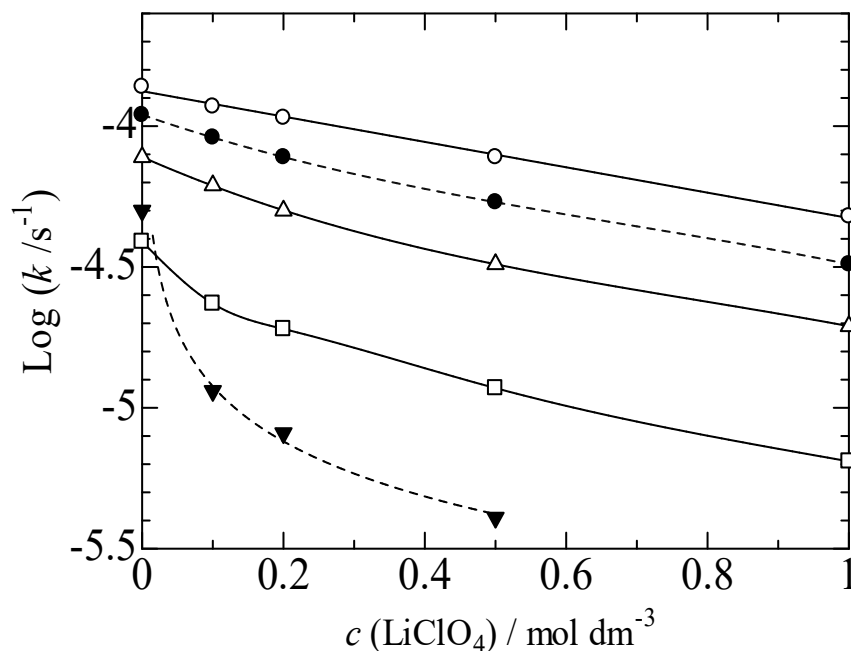
Fig. 2-4 Changes in log (k /s^{-1}) of p-NPA hydrolysis with LiClO$_4$ concentrations in aqueous borate buffer solutions of pH = 9.18 containing MeCN at 50±0.1 ºC: (○) 0; (●) 10; (Δ) 20; (□) 50; (▼) 70% (v/v) MeCN.

The rate deceleration caused by the Na$^+$ salt is slightly smaller than that of the Li$^+$ salt (*cf.* Table 2-1 and Fig. 2-5). This is in agreement with their respective crystal ionic sizes [39] and the ability to be hydrated by water molecules. As the hydrolysis of p-NPA must be an S$_N$2 type reaction, the addition of these neutral metal perchlorate salts may cause the hydrolysis rate to decelerate, which may be due to two interdependent reasons: strong solvation of Li$^+$ and Na$^+$ ions with H$_2$O molecules (the prominent molecules responsible to attack the substrate to initiate the hydrolysis reaction) and/or distortion of water structure (which leads to distraction of the water activity) in the presence of these added salts and MeCN. In the presence of salts in high concentrations, bulk water molecules are consumed for hydrating the ions, therefore, the bulk water region in solution should be reduced [27].
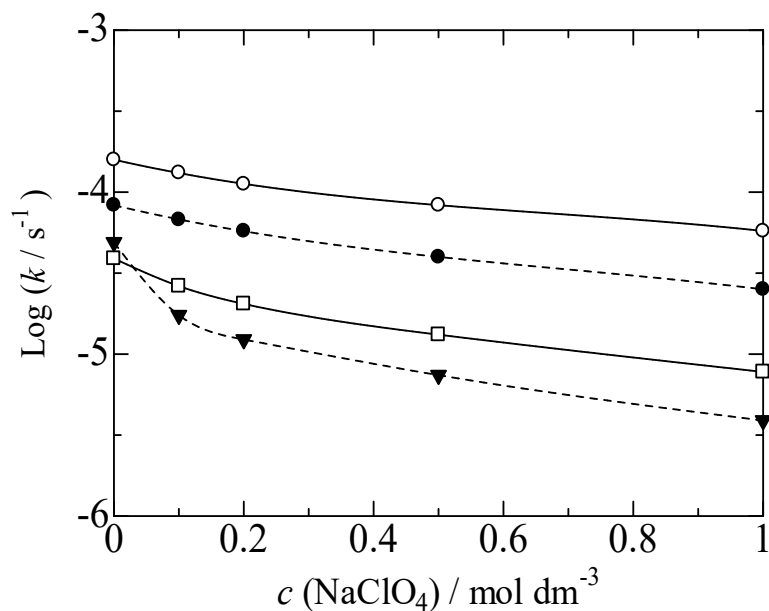
Fig. 2-5 Changes in log (k /s^{-1}) of p-NPA hydrolysis with NaClO$_4$ concentrations in aqueous borate buffer solutions of pH = 9.18 containing MeCN at 50±0.1 °C: (○) 0; (●) 20; (□) 50; (▼) 70% (v/v) MeCN.

Table 2-1 Log (k /s^{-1}) values for the hydrolysis rate of 1.0 x 10^{-4} mol dm^{-3} of p-NPA in the presence of added metal perchlorate salts in solutions containing the pH buffer of 9.18 and MeCN at 50±0.1 °C

Salts	MeCN contents / % (v/v)	c(salt)/ mol dm^{-3}				
		0	0.10	0.20	0.50	1.0
LiClO$_4$	0	-3.87	-3.93	-3.97	-4.11	-4.32
	10	-3.96	-4.04	-4.11	-4.27	-4.49
	20	-4.11	-4.21	-4.30	-4.49	-4.72
	50	-4.41	-4.63	-4.72	-4.93	-5.19
	70	-4.34	-4.94	-5.09	-5.39	-
NaClO$_4$	0	(-3.87)	-3.88	-3.95	-4.08	-4.24
	20	(-4.11)	-4.17	-4.24	-4.40	-4.60
	50	(-4.41)	-4.58	-4.69	-4.88	-5.11
	70	(-4.34)	-4.76	-4.91	-5.13	-5.41

2.3.3 Influences of NaN₃ and Non-metallic Salts on the Hydrolysis Rate

On the hydrolysis rate of *p*-NPA, the influence of various kinds and concentrations of salts from 0.0 - 1.0 mol dm^{-3} were examined in 0.0 - 70% (v/v) MeCN solutions containing the pH = 9.18 buffer. The log (k /s^{-1}) value is greatly affected by the added salts of all kinds used in this study: the salts of NaN₃, Et₄NCl, Et₄NBr, Et₄NTsO, Pr₄NBr, and (n-Bu)₄NBr. Fig. 2-6 shows that NaN₃ causes the remarkable acceleration even at lower concentrations of the salt (≤0.30 mol dm^{-3}), especially in the solution without MeCN. Compared to the system containing no added salt, the addition of 0.10 mol dm^{-3} NaN₃ causes an acceleration by three times. The hydrolysis rate is too fast to be evaluated in the presence of ≥0.50 mol dm^{-3} NaN₃.

The remarkable acceleration in the presence of NaN₃ is in good accordance with strong nucleophilicity of the N₃⁻ ion. In addition to the OH⁻ ion (the prominent nucleophile), the N₃⁻ ion, being a strong nucleophile, can attack the carbonyl carbon of the *p*-NPA substrate and liberate the *p*-nitrophenoxide ion significantly. Edwards and Pearson [40] have reported the following overall nucleophilicity order for S$_N$2 mechanisms in protic media as RS⁻ > ArS⁻ > I⁻ > CN⁻ > OH⁻ > N₃⁻ > Br⁻ > ArO⁻ > Cl⁻ > pyridine > AcO⁻ > H₂O.
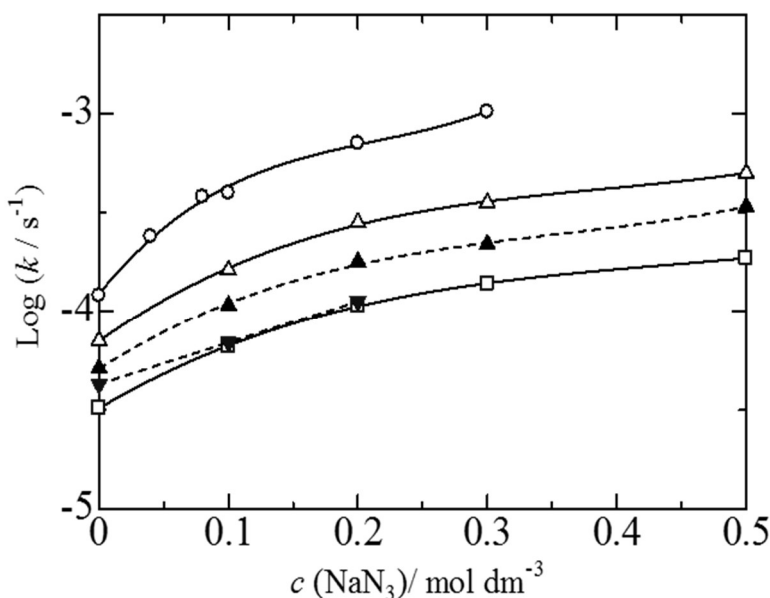
Fig. 2-6 Changes in log (k /s^{-1}) of *p*-NPA hydrolysis with NaN₃ concentrations in aqueous borate buffer solutions of pH = 9.18 containing MeCN at 50±0.1 °C: (○) 0; (△) 20; (▲) 30; (□) 50; (▼) 70% (v/v) MeCN.

However, the rate acceleration observed is not uniform in each solution: the slope of Δlog $(k\,/\text{s}^{-1})$ vs. Δc(NaN$_3$) [0 – 0.1 or 0.2 mol dm^{-3}] decrease as 4.70, 3.20, 2.30 and 1.80 in solutions containing 0, 20, 50, and 70% (v/v) MeCN contents, respectively (cf., Figs. 2-6 and 2-13). The influence of NaN$_3$ become gradually weaker with increasing MeCN contents probably because the activity of N$_3^-$ is reduced by the association of Na$^+$N$_3^-$ in the media of which permittivity [4] and solvation ability [41,42] are certainly decreased. We have to stress that true Gutmann's donor number, DN for bulk water is ca. 40 [42] and not the original value of 18, this value has been evaluated for isolated water molecules dissolved in 1,2-dichloroethane [41].

Fig. 2-7 shows the influences of a non-metallic salt, Et$_4$NBr, on log $(k\,/\text{s}^{-1})$ in buffer solutions containing 0 - 70% (v/v) MeCN, cf. Table 2-2. Generally speaking, the hydrolysis rate of p-NPA increases with increasing Et$_4$NBr concentration. The influence of Et$_4$NBr is rather weak in solutions containing smaller proportions of MeCN. However, its effect prominently becomes stronger as the MeCN contents increase. The slope of Δlog $(k\,/\text{s}^{-1})$ vs. Δc (Et$_4$NBr) is 0.17, 0.30, 0.71, and 1.35 for solutions containing 0, 20, 50, and 70% (v/v) MeCN, respectively. Even though the Br$^-$ ion is a good nucleophile, its ability to attack the carbonyl carbon of the substrate may be hindered with the strong hydration by water in solutions containing lower MeCN contents.
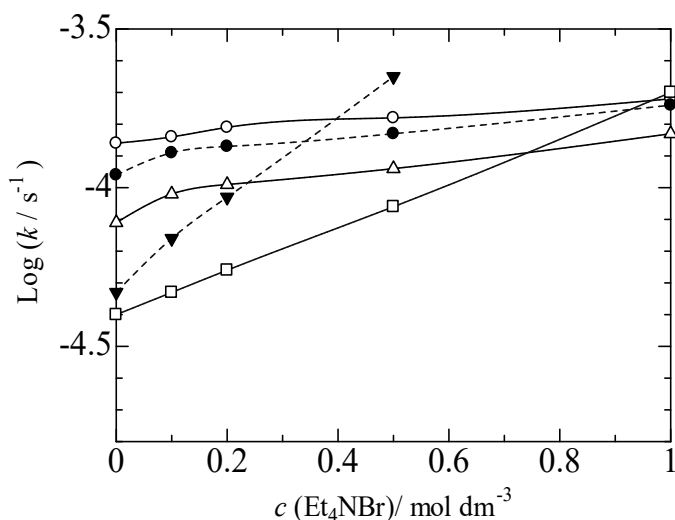
Fig. 2-7 Changes in log $(k\,/\text{s}^{-1})$ of p-NPA hydrolysis with Et$_4$NBr concentrations in pH = 9.18 aqueous buffer solutions containing MeCN at 50±0.1 °C: ($\circ$) 0; ($\bullet$) 10; (Δ) 20; ($\square$) 50; ($\blacktriangledown$) 70% (v/v) MeCN.

Table 2-2 Log (k /s^{-1}) values for the hydrolysis rate of 1.0 x 10^{-4} mol dm^{-3} of p-NPA in the presence of various salts in solutions containing the pH buffer of 9.18 and MeCN at 50±0.1 °C

Salts	MeCN contents / % (v/v)	c(salt)/ mol dm^{-3}					
		0	0.10	0.20	0.30	0.50	1.0
NaN$_3$	0	(-3.87)	-3.40	-3.15	-2.99	-	-
	20	(-4.11)	-3.79	-3.55	-3.45	-3.30	-
	30	(-4.28)	-3.97	-3.75	-3.66	-3.47	-
	50	(-4.41)	-4.18	-3.97	-3.86	-3.73	-
	70	(-4.34)	-4.16	-3.95	-	-	-
Et$_4$NCl	0	(-3.87)	-3.84	-3.83	-	-3.75	-3.63
	20	(-4.11)	-4.09	-4.08	-	-4.01	-3.95
	50	(-4.41)	-4.39	-4.33	-	-	-
	70	(-4.34)	-4.32	-4.28	-	-	-
Et$_4$NBr	0	(-3.87)	-3.84	-3.81	-	-3.78	-3.73
	10	(-3.96)	-3.89	-3.87	-	-3.83	-3.74
	20	(-4.11)	-4.02	-3.99	-	-3.94	-3.83
	50	(-4.41)	-4.33	-4.26	-	-4.06	-3.70
	70	(-4.34)	-4.16	-4.03	-	-3.65	-
Et$_4$NTsO	0	(-3.87)	-3.92	-3.95	-	-4.01	-4.04
	20	(-4.11)	-4.15	-4.14	-	-4.20	-4.15
	30	(-4.28)	-4.29	-4.31	-	-4.29	-4.13
	50	(-4.41)	-4.39	-4.33	-	-4.16	-3.57
	70	(-4.34)	-4.20	-4.04	-3.91	-	-
Pr$_4$NBr	0	(-3.87)	-3.82	-3.80	-	-3.80	-3.81
	20	(-4.11)	-4.00	-4.00	-	-3.99	-3.88
	50	(-4.41)	-4.23	-4.16	-	-3.95	-3.44
	70	(-4.34)	-4.10	-3.93	-3.82	-	-
(n-Bu)$_4$NBr	0	(-3.87)	-3.80	-3.85	-	-3.98	-4.07
	20	(-4.11)	-4.10	-4.13	-	-4.19	-4.11
	30	(-4.28)	-4.20	-4.20	-	-4.19	-3.92
	50	(-4.41)	-4.33	-4.27	-	-4.06	-3.41
	70	(-4.34)	-4.08	-3.91	-3.84	-	-

However, with increasing MeCN contents, particularly ≥50% (v/v) MeCN, the Br⁻ ion may be more free from the solvation (hydration) since the water activities should decrease remarkably in the presence of both large proportions of MeCN and the Et₄NBr salt. Hence, the steep rate acceleration by Et₄NBr can be observed in solutions of higher MeCN contents. The salt Et₄NCl also gives the rate acceleration but much weaker than Et₄NBr. The weaker effect of Cl⁻, compared to that of Br⁻, in solutions of lower MeCN contents is reasonable because of the weaker nuecleoricity of Cl⁻ than that of Br⁻ in protic media [40]. We may mention that the phase separation kept us from evaluating the rate constants in solutions containing both ≥50% (v/v) MeCN and ≥0.50 mol dm⁻³ Et₄NCl (*cf.* Table 2-2). The phase separation phenomena of the binary MeCN-H₂O mixtures by the addition of chloride salts have been reported [43].

Another salt, Et₄NTsO (Fig. 2-8), gives somehow a strange effect on the hydrolysis of *p*-NPA, especially, in solutions of higher MeCN contents. The nuecleophilicity of the tosylate ion should be very weak. In lower MeCN contents, as expected, the log (k /s⁻¹) is not significantly affected (cf. Table 2-2), and even slightly decreases.
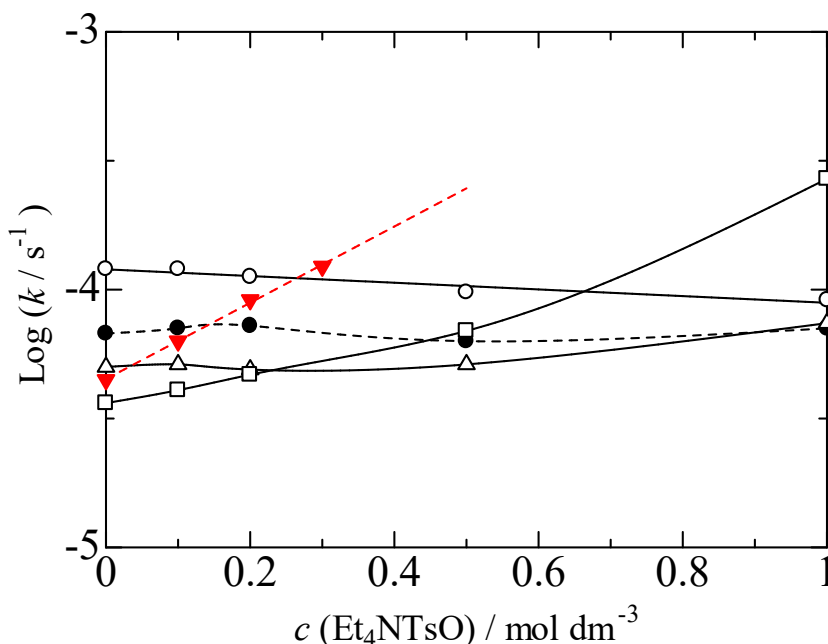
Fig. 2-8 Changes in log (k /s⁻¹) of *p*-NPA hydrolysis with Et₄NTsO concentrations in pH = 9.18 aqueous buffer solutions containing MeCN at 50±0.1 ℃: (○) 0; (●) 20; (Δ) 30; (□) 50; (▼) 70% (v/v) MeCN.

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However, unexpected increases in reaction rates are observed with increasing Et_4NTsO concentration in $\geq 50\%$ (v/v) MeCN media. Now that the nucleophilicity of the tosylate ion is small, we may attribute the unexpected acceleration to an activity increase of OH^- brought by the distortion of water structure with the addition of the very bulky salt, Et_4NTsO.

Both Pr_4NBr and $n\text{-}Bu_4NBr$ salts on the other hand showed a relatively comparable effects on the rates of hydrolysis of p-NPA. In solutions containing less contents of acetonitrile (≤ 20 % (v/v)), the $n\text{-}Bu_4NBr$ salt seems to slightly decelerate the rate (Fig. 2-9) while Pr_4NBr showed no significant difference on the rates of the hydrolysis reaction (Fig. 2-10). This behavior of the two salts is attributed to the destruction of water structure to greater in the presence of the bulkier salt, $n\text{-}Bu_4NBr$, compared with the presence of Pr_4NBr.
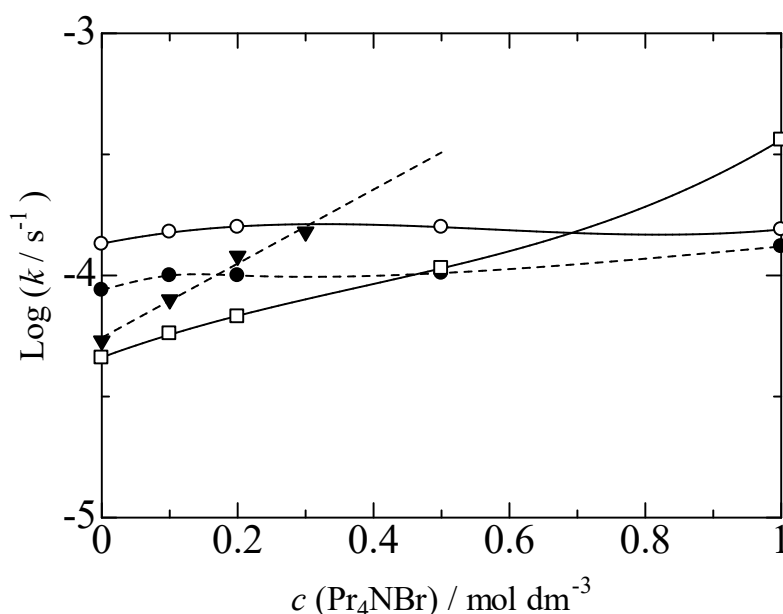
Fig. 2-9 Changes in log (k /s^{-1}) of p-NPA hydrolysis with Pr_4NBr concentrations in pH = 9.18 aqueous buffer solutions containing MeCN at 50±0.1 ºC: (○) 0; (●) 20; (□) 50; (▼) 70% (v/v) MeCN.

At higher contents of MeCN ($\geq$ 50% (v/v)), however, both salts exhibited a comparative rate accelerations. Nevertheless, in the presence of high concentrations of the salts, n-Bu$_4$NBr showed a slight higher rate acceleration compared to Pr$_4$NBr (*cf*. Fig. 2-12).
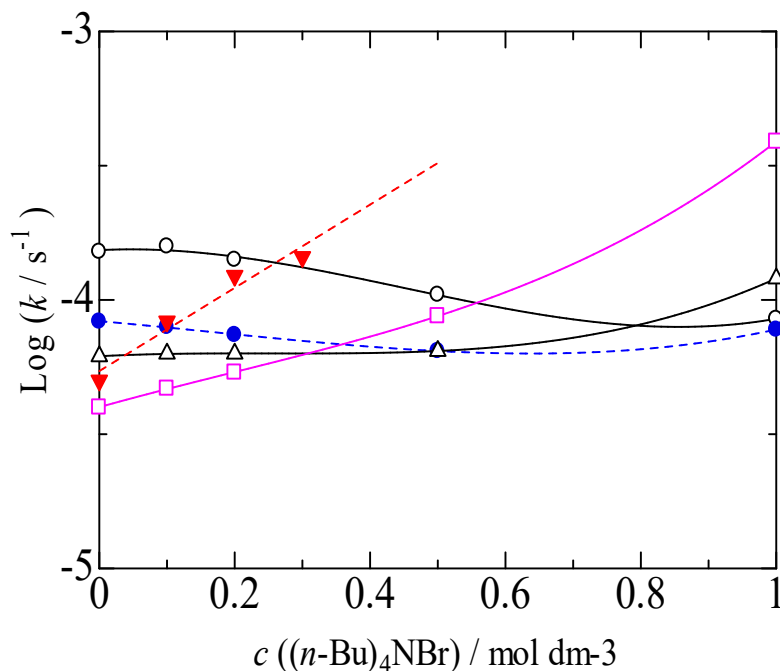
Fig. 2-10 Changes in log (k /s^{-1}) of p-NPA hydrolysis with Et$_4$NTsO concentrations in pH = 9.18 aqueous buffer solutions containing MeCN at 50±0.1 ºC: (○) 0; (●) 20; (△) 30; (□) 50; (▼) 70% (v/v) MeCN.

2.3.4   Cooperative Effects of Salts and MeCN

Fig. 2-11 is a graphical illustration for the changes in the hydrolysis rate of p-NPA hydrolysis with the added tetraethylammonium (Et$_4$NCl and Et$_4$NBr) salts, (n-Bu)$_4$NBr, NaN$_3$, and LiClO$_4$ in no MeCN media at 50 ºC. Here, we can clearly notice that all the NaN$_3$, Et$_4$NCl, and Et$_4$NBr salts accelerate the hydrolysis rate with their respective concentrations. As mentioned above, NaN$_3$ gives the influence significantly stronger than Et$_4$NBr or Et$_4$NCl. In the presence of 0.0 to 1.0 mol dm^{-3} (n-Bu)$_4$NBr (except for 0.10 mol dm^{-3}), the log (k /s^{-1}) value decreases from -3.87 to -4.07. The addition of Pr$_4$NBr causes the log (k /s^{-1}) value to increase

slightly from -3.87 to -3.81 for 0.0 to 1.0 mol dm^{-3} Pr$_4$NBr. This is in agreement with these tetraalkylammonium cation sizes [39] and their distortion effects on water properties/activities. The (*n*-Bu)$_4$N$^+$ cation is larger in size than Pr$_4$N$^+$, and hence is expected to cause more remarkable distraction in water property.

Hojo et al.[32] have discussed that cations such as Et$_4$N$^+$, Pr$_4$N$^+$, and (*n*-Bu)$_4$N$^+$ are, potentially, water "structure breakers" and their effects on the possible water disruption should increase in the order of   Et$_4$N$^+$ < Pr$_4$N$^+$ < (*n*-Bu)$_4$N$^+$. In 20% (v/v) MeCN media, the rate acceleration by NaN$_3$ is found to be weaker than that in no MeCN. The Et$_4$NBr salt shows a stronger effect than Et$_4$NCl. Generally, the rate acceleration decreased in the order of NaN$_3$ > Et$_4$NBr > Et$_4$NCl in solutions of 20% (v/v) MeCN. The salt of (*n*-Bu)$_4$NBr remains still in the salt group of rate deceleration, not so distinct as LiClO$_4$ and NaClO$_4$.
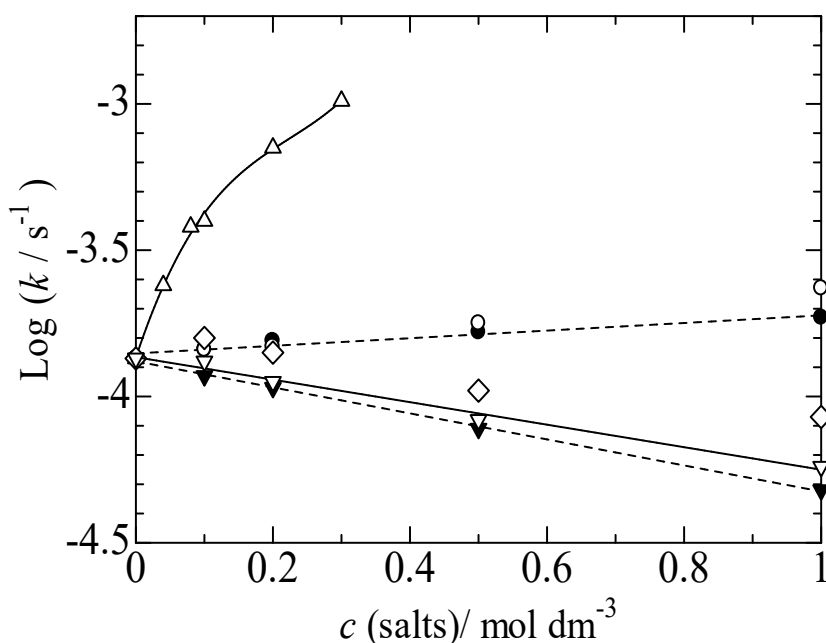
Fig. 2-11 Changes in log (k /s^{-1}) of *p*-NPA hydrolysis with salt concentrations in pH = 9.18 aqueous buffer solutions of containing no MeCN at 50±0.1 ºC: (Δ) NaN$_3$; (○) Et$_4$NCl; (●) Et$_4$NBr; (◊) (*n*-Bu)$_4$NBr; (▼) LiClO$_4$; (▽) NaClO$_4$.

Fig. 2-12 shows the changes of log (k /s^{-1}) in solutions of 50% (v/v) MeCN in the presence of various salts. The most remarkable event in the 50% (v/v) MeCN media is the fact that the hydrolysis rate constant is accelerated by (n-Bu)$_4$NBr. Whereas, this bulky salt causes the deceleration effects in zero and 20% (v/v) MeCN media. The rate acceleration caused by the increasing concentration of Pr$_4$NBr or (n-Bu)$_4$NBr is significantly enhanced with increasing MeCN contents. For instance, the log (k /s^{-1}) value in the presence of 1.0 mol dm^{-3} of (n-Bu)$_4$NBr in 50% (v/v) MeCN media is as high as -3.41, which is much larger than -3.70 for 1.0 mol dm^{-3} Et$_4$NBr. The presence of bulky salts, such as Pr$_4$NBr and (n-Bu)$_4$NBr, in the solution containing the larger volume of an organic solvent can destroy the bulk water structure largely, *cf.* ref. [34].
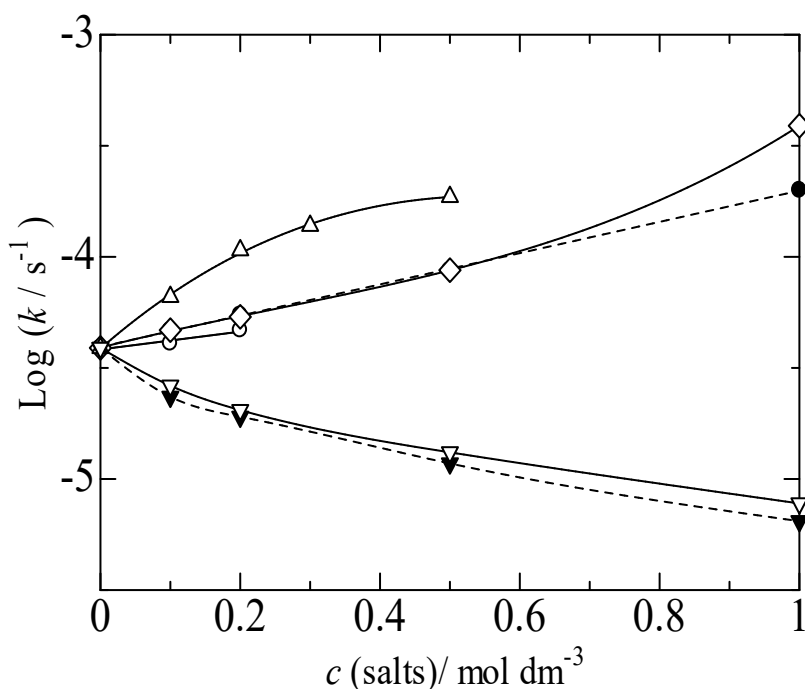
Fig. 2-12 Changes in log (k /s^{-1}) of *p*-NPA hydrolysis with salt concentrations in pH = 9.18 aqueous buffer solutions containing 50% (v/v) MeCN at 50±0.1 °C: ($\triangle$) NaN$_3$; ($\circ$) Et$_4$NCl; ($\bullet$) Et$_4$NBr; ($\lozenge$) (n-Bu)$_4$NBr; ($\blacktriangledown$) LiClO$_4$; ($\triangledown$) NaClO$_4$.

Hence, the hydrolysis reactions in such solutions should be quite different from the corresponding reactions in dilute aqueous media. For the solutions containing salts up to 0.50 mol dm^{-3}, the rate accelerations reduce in the order of NaN$_3$ > (n-Bu)$_4$NBr ~ Et$_4$NBr > Et$_4$NCl in

50% (v/v) MeCN media. At 1.0 mol dm^{-3}, however, the influence of (n-Bu)$_4$NBr is superior to that of Et$_4$NBr, which is ascribed to mainly the destruction of water properties to a greater extent and/or the increase in nucleophilicty of the Br$^-$ ion (and also the OH$^-$ ion).

Fig. 2-13 shows the changes in the slopes of Δlog (k /s^{-1}) /Δc (salt) *vs.* MeCN contents [% (v/v)] in the presence of various salts. Here we can clearly notice that the acceleration by NaN$_3$ (of lower concentrations, ≤0.20 mol dm^{-3}) is extremely larger than any other salts used, even though, its effect become weaker as the MeCN contents increase. On the other hand, the effects caused by Et$_4$NBr and (n-Bu)$_4$NBr salts are enhanced with increasing MeCN contents.
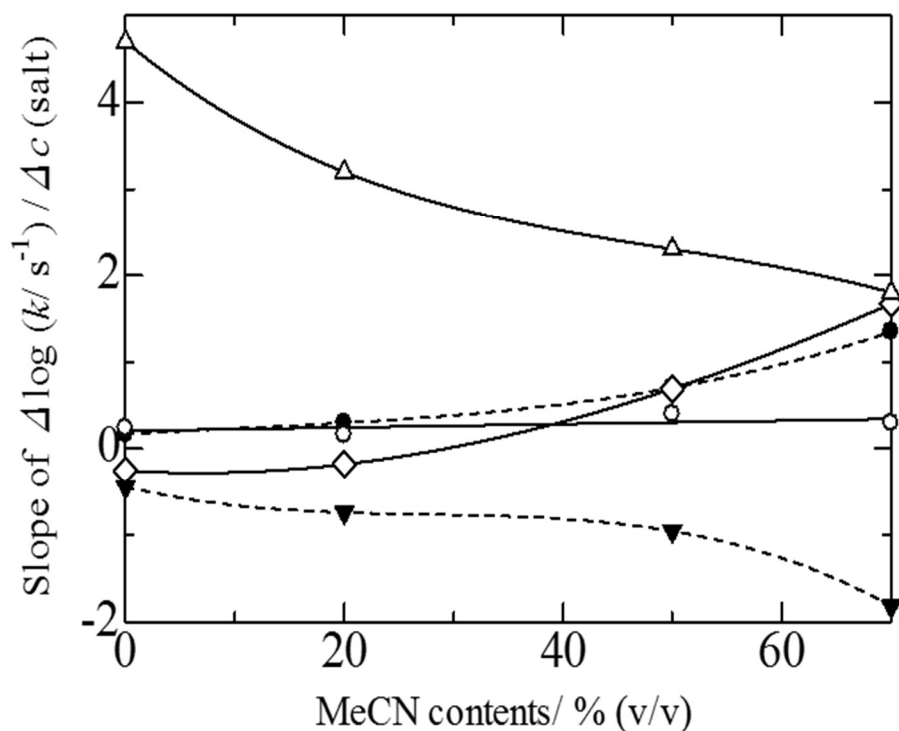
Fig. 2-13 Changes in slopes of Δlog (k /s^{-1}) / Δc (salt) *vs.* MeCN contents for hydrolysis of *p*-NPA in aqueous buffer solutions of pH = 9.18 at 50±0.1 ℃ containing salts: (Δ) NaN$_3$; (○) Et$_4$NCl; (●) Et$_4$NBr; (◊) (n-Bu)$_4$NBr; (▼) LiClO$_4$.

It is clear that the small acceleration effect initiated by Et$_4$NCl is not significantly altered, *i.e.*, a rather uniform effect, although its effect at higher concentrations ($\geq$0.50 mol dm^{-3}) in $\geq$50% (v/v) MeCN media cannot be evaluated because of the phase separation (*vide supra*). In 70% (v/v) MeCN media, as the general rule, the rate acceleration caused by added salts is in the order of NaN$_3 \sim$ (*n*-Bu)$_4$NBr > Et$_4$NBr > Et$_4$NCl and the deceleration by LiClO$_4$ (or NaClO$_4$). The ClO$_4^-$ ion has no nucleophilicity, therefore, LiClO$_4$ (or NaClO$_4$) cannot assist the hydrolysis of this S$_N$2 substrate. The rate deceleration becomes remarkably as both its salt concentration and the MeCN contents increase because more water molecules are involved in solvating Li$^+$ (or Na$^+$) ions and the bulk water properties should be reduced.

2.3.5 Temperature Dependence

Fig. 2-14 shows the Arrhenius plots of log (k /s^{-1}) in binary MeCN-H$_2$O mixed solvents (buffered with pH = 9.18) of 0 - 30 % (v/v) MeCN. The relationship between log (k /s^{-1}) and T^{-1} is linear over the temperature range of 35 – 60 °C (or 65 °C) for 10, 20, and 30 % (v/v) MeCN, whereas the relation gives convex curves at lower temperatures, *i.e.*, < 50 and < 40 °C for 0.0 and 5.0 % (v/v) MeCN, respectively.
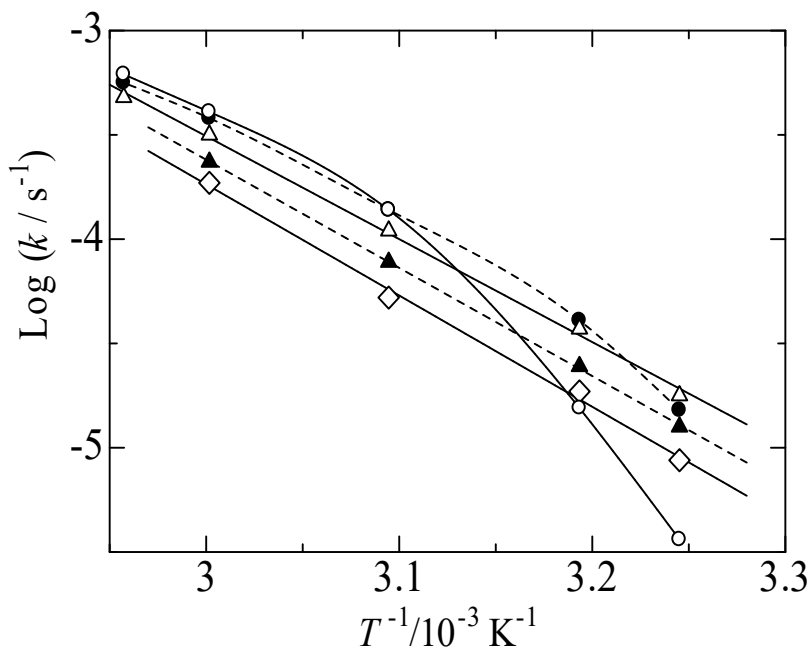
Fig. 2-14 Arrhenius plots of log (k /s^{-1}) in binary MeCN-H$_2$O mixed solvents (buffered with pH = 9.18) : ($\circ$) 0.0; ($\bullet$) 5.0; ($\blacktriangledown$) 10; ($\triangle$) 20; ($\lozenge$) 30 % (v/v) MeCN.

The activation energy (E_a) values are evaluated from the straight part to be 91.5, 93.8, 94.6, 99.6, and 102.1 kJ mol^{-1} for the 0.0, 5.0, 10, 20, and 30% (v/v) MeCN media. It is possible to notice that the log (k /s^{-1}) values of p-NPA give a maximum at 5.0 or 10% (v/v) MeCN for 40 or 30 °C, respectively, while the rate constant decreases just monotonously with increasing MeCN contents (in 0.0, 5.0, 10, 20, and 30% media) at the higher temperatures, $e.g.$ 60 °C. In an additional study, we have examined the hydrolysis rate of p-nitrophenyl benzoate in the binary MeCN-H$_2$O media. The log (k /s^{-1}) values of p-nitrophenyl benzoate give a maximum at about 10% (v/v) MeCN (buffered with pH = 8.50 and 9.18) at 40 or 50 °C.

Fig. 2-15 shows the Arrhenius plots of log (k /s^{-1}) in 50% (v/v) MeCN-H$_2$O buffered solution (with pH = 9.18) in the presence of various salts. All the 50% (v/v) MeCN-H$_2$O solution systems give the good linearity from 35 to 60 °C, resulting in the activation energy (E_a) of 107.0, 98.8, 84.2, and 104.2 kJ mol^{-1} for no salt, LiClO$_4$, NaN$_3$, and Et$_4$NBr of 0.2 mol dm^{-3}, respectively. These large values of the activation energy in the systems with added salts suggest that the hydrolysis reaction of the substrate is just of temperature dependence.
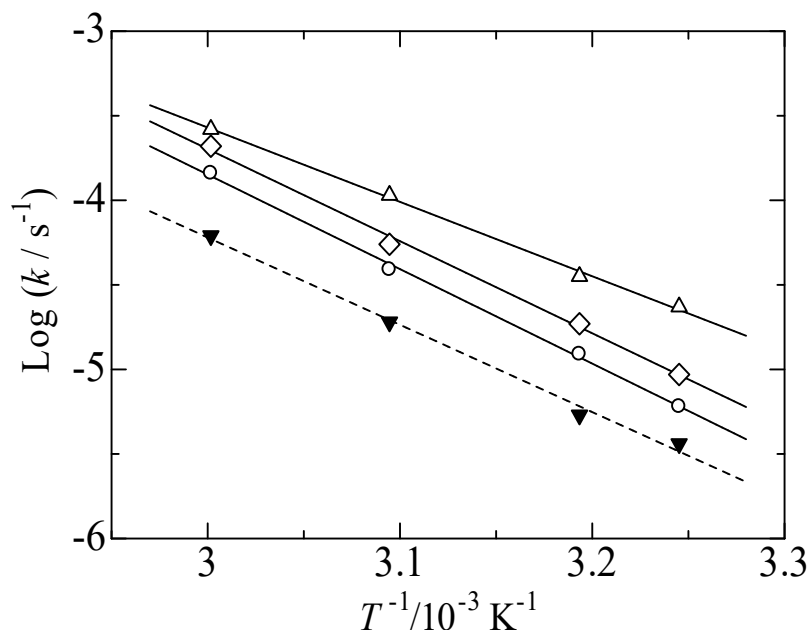
Fig. 2-15 Arrhenius plots of log (k /s^{-1}) in 50% (v/v) MeCN-H$_2$O buffered solution (with pH = 9.18) in the presence of various salts: (○) no salt; (▼) 0.20 mol dm^{-3} LiClO$_4$; (Δ) 0.20 mol dm^{-3} NaN$_3$; (◊) 0.20 mol dm^{-3} Et$_4$NBr.

2.3.6 Changes in Raman spectra of water (D₂O) with the addition of MeCN

Raman spectroscopy has been often employed to investigate the dynamical structure of water for a long time [44-46]. It is a technique preferably used for studies of water structure because the proportions of intensities of main OH stretching modes (around 3200 and 3400 cm^{-1}) are thought to reflect well the network of hydrogen bonds as well as its disturbance by the presence of other substances like solutes and organic solvents [34]. Distortion of water structure in the presence of added solvents and salts, or with increasing temperature, have been extensively investigated and reported [33, 34, 37, 47].

Fig. 2-16 shows the change in Raman spectra of D₂O with increasing MeCN contents [0 - 90% (v/v)] at room temperature. Pure D₂O gives an OD stretching band with two peaks at around 2380 and 2500 cm^{-1}, which are assigned to strongly hydrogen bonded D₂O and weakly hydrogen-bonded D₂O, respectively [48].
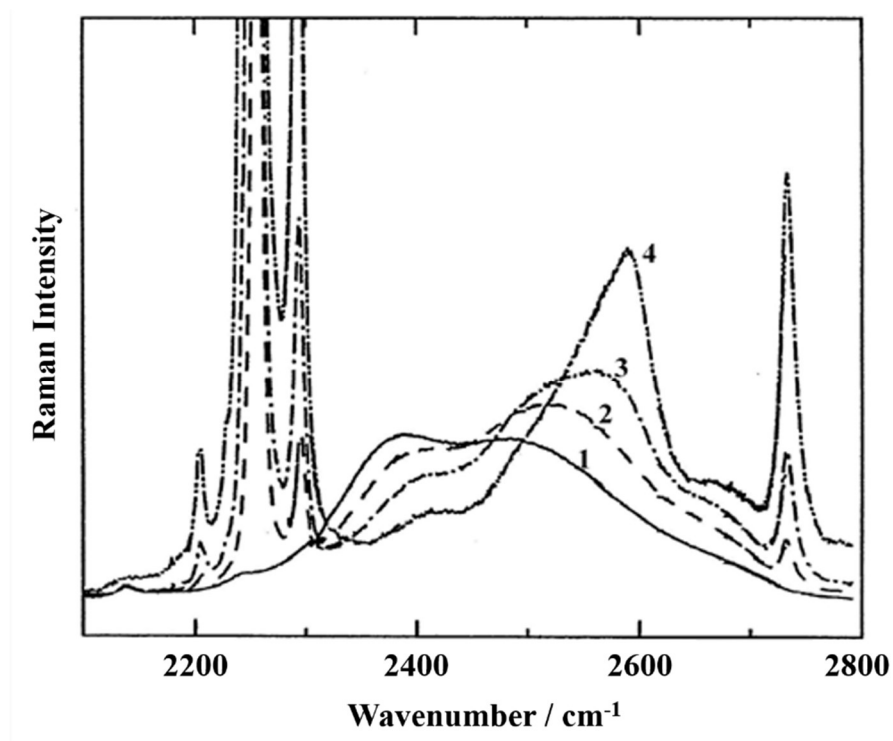
Fig. 2-16 Changes in Raman spectra of D₂O with increasing contents of acetonitrile: (1) 0; (2) 50; (3) 75; (4) 90% (v/v) MeCN.

Upon addition of MeCN to D_2O, the peak intensity at around 2500 - 2600 cm^{-1} increases while the intensity at around 2380 cm^{-1} decreases. The increase in MeCN contents causes further decrease and increase in the peak intensity (I_1 and I_2) at around 2400 and 2500 -2600 cm^{-1}, respectively. The ratios of Raman OD band intensities (I_1/I_2) around 2400 and 2500 - 2600 cm^{-1} are significantly changed with MeCN contents.

The Raman intensity ratios (I_1/I_2) decrease as 1.03, 0.72, 0.53, and 0.23 with increasing contents of MeCN as 0, 50, 75, and 90% (v/v), respectively, witnessing the distortion of the D_2O bulk structure in the presence of the organic solvent. At the same time, peaks at 2380 and 2500 cm^{-1} shift to higher wavenumbers as the MeCN contents increase. At 90% (v/v) MeCN, the wavenumber of weakly hydrogen bonded D_2O seemed to approach even that of D_2O monomer ($v_1 = 2671$ cm^{-1}) in the gas phase [49].

2.4 Conclusion

The hydrolysis reaction rate of *p*-nitrophenyl anthranilate (*p*-NPA) is greatly influenced by pH, added salts of various kinds and MeCN contents in binary MeCN-H_2O mixed solvents. Increase in MeCN contents up to 50% (v/v) retards the hydrolysis reaction of *p*-NPA, whereas, further increments of MeCN cause the reversal increases in log (k /s^{-1}). Metal perchlorate salts, such as LiClO$_4$ and NaClO$_4$, decelerate the hydrolysis rate in all the media. It is concluded that the significant changes in the hydrolysis rate constant are dependent upon not only the activities of H_2O and OH$^-$ but also the nucleophilicities (toward the carbonyl carbon atom in *p*-NPA) of the anions (N$_3^-$, Cl$^-$, Br$^-$, and TsO$^-$) from added salts in the "modified" aqueous solution, where the hydrogen bonding structure of the bulk water is distorted by the addition of foreign substances, *i.e.*, the organic solvent and the salts.

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CHAPTER THREE

3. Specific Salt Effects on the Hydrolysis Reaction Rate of Tropolone Tosylate in Binary MeCN-H₂O Media Containing *n*-Bu₄NOH

ABSTRACT

The hydrolysis reaction rates of tropolone tosylate have been investigated in 20 - 90% (v/v) MeCN-H$_2$O binary media containing *n*-Bu$_4$NOH at 50 $^\circ$C. Increasing concentration of *n*-Bu$_4$NOH causes an increase in the hydrolysis rate. Two diverse effects have been observed with increasing content of MeCN, *i.e.*, a decrease in the rate and the successive increase for up to the 60% (v/v) MeCN and further increasing MeCN proportions. At a constant *n*-Bu$_4$NOH concentration, the added salts (0.0 - 1.0 mol dm^{-3}) have caused various influences on the "pseudo" first order rate constant [log (k/s^{-1})] of the substrate. Among alkali metal and alkaline earth metal perchlorates, NaClO$_4$ and Ba(ClO$_4$)$_2$ cause the obvious rate acceleration especially in the media of higher MeCN proportions. However, LiClO$_4$ and Ca(ClO$_4$)$_2$ cause the rate deceleration, whereas Mg(ClO$_4$)$_2$ has resulted in a total suppression of the hydrolysis reaction. All the salts of NaN$_3$, Et$_4$NCl, and Et$_4$NBr appear to increase the log (k/s^{-1}) value in the order of Et$_4$NCl ~ Et$_4$NBr < NaN$_3$. The Arrhenius plots of the hydrolysis in the 50% (v/v) MeCN-H$_2$O binary media containing 2.0 mmol dm^{-3} *n*-Bu$_4$NOH in the presence of various kinds of salts have been evaluated. All the salt systems have given a good linearity from 35 to 60 $^\circ$C with the activation energy (E_a) of 83.7, 79.3, 81.9, 79.1, 87.1, and 79.1 kJ mol^{-1} for no salt, 0.50 mol dm^{-3} LiClO$_4$, NaClO$_4$, Ba(ClO$_4$)$_2$, Et$_4$NBr, and NaN$_3$, respectively. These large values suggest that the hydrolysis reactions in the presence of various salts are controlled by the normal temperature dependent and non-catalytic mechanism with the ions from the added salt. The emerged scenarios have been discussed in terms of changes in the structure of bulk water and/or activities of H$_2$O and OH$^-$ in the presence of both the added organic solvent and salts, and also in terms of the nucleophilicities of anions or the coordination abilities of the metal ions in the "modified" media.

Keywords: Hydrolysis rate constant; bulk water structure; nucleophilicity; coordination ability; apparent pH values; kinetics

3.1 Introduction

Hydrolysis is one of the most important and frequently used chemical degradative process implied for the chemical decomposition of toxic organic compounds in the environment [1]. The degradative process of these toxic organic compounds is basically affected by key factors such as pH, temperature, solvent composition, metal ion catalysis, ionic strength, buffer effects, *etc*. This important chemical transformation process encompasses the transfer of a range of ester groups to nucleophiles, including water [2]. These group transfer reactions includes phosphoryl [3, 4], sulfuryl (sulfate and/or sulfonate) [5, 6] and other related group-transfer reactions [7]. Sulfate hydrolysis has directly important biological roles in, for instance, cellular signaling [8] and detoxification [9] and sulfonate esters can be used by bacteria as sulfur sources in environments with low sulfate concentrations [10, 11] as sulfonates and sulfate esters are widespread in nature, and make up over 95% of the sulfur content of most aerobic soils [12].

The rate of chemical reactions in solutions can be affected by two types of solvent effects [13]: 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. Several factors influence these solvent effects on chemical reaction rates; their relative importance seems to be a function of substrate, detailed mechanism of reaction, and experimental conditions [14]. A solvent would not only provide a background for the reaction to occur but also stabilize the reactants and activated complex by solvating them [15]. According to Gholami and Habibi [16], solvent–solute interactions are much more complex in reactions involving a neutral molecule and strongly solvated species, in particular, the alkoxide and hydroxide ions, may be partially or completely dominated by the mixed solvents than by pure solvents because of preferential solvation by any of the components present in the solvent mixture. The preferential solvation in a binary solvents mixture has an important role in solution chemistry for explaining spectroscopic, equilibrium, and kinetic data [17–19].

The obvious interest of water as a solvent, its efficiency in solvating ionic and dipolar solutes, and its poor ability to solvate non-polar molecules, have fueled vast efforts to understand

the properties of aqueous solutions [20]. The reasons for the preference for the use of solvent mixtures are manifold, including the amelioration of certain physical properties, such as the density, viscosity, volatility, *etc.*, or of their chemical properties, such as stability, inflammability, and not least, their ability to dissolve certain substances [21, 22]. It is very important and crucial to think of the changes in water properties/activities up on the addition of salts of various kinds and/or organic solvents as co-solvent with water. It is obvious that added salts of various kind have significant impact on reaction rates of organic compounds and their effects might be rate acceleration or deceleration, depending upon the substrate, the specific salts type and concentrations. Mabey and Mill [23] have pointed out the effects of both added salts and solvent composition on the hydrolysis of organic compounds.

Recently, there have been many experimental and computational approaches addressing the issue of water structure in the presence of added salts and organic solvent mixtures. Disruption of the tetrahedral water structure in the presence of added salt and organic solvents have been reported [24, 25]. Hojo *et al.* [26] have proposed an innovative idea that the properties of bulk water may originate from the intermolecular hydrogen-bonded network among a huge number of H_2O molecules (*e.g.*, $n_w > \sim 10^7$). Water can lose its properties as bulk water to get that of a nonaqueous 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 [also called "dihydrogen ether," (H)-O-(H)] [27].

Reichardt *et al.* [28] have concisely interpreted "dihydrogen ether" that, at high salt concentrations [c(salt) > 5 mol dm^{-3}], region C, according to the solvation model of Frank and Wen [29], can be abolished and only regions A and B survive, resulting in an aqueous solvent called "dihydrogen ether." The idea of "dihydrogen ether" has made it possible for us to discover

not only the incredible exhibition of the high oxidation potential from dilute nitric acid containing salts [30] but also the phenomena of pure gold dissolution in dilute nitric or nitrous acid solution containing various halide salts [31]. In our arguments [30], LiCl of higher concentrations indeed can destroy the bulk water structure because the hydrogen bonding structure highly developed around the Li^+ ion may be similar to but not exactly the naturally "self-assembled structure" of bulk water.

Interestingly, reaction mechanisms of alkaline hydrolysis of sulfonate esters have seen revival interest recently [32, 33]. In particular, a recent study on the alkaline hydrolysis of a series of benzene aryl sulfonates by Babtie *et al*. [2], has demonstrated that direct nucleophilic attack on sulfonate sulfur is the predominant reaction pathway of the hydrolysis reaction of sulfonate esters. Likewise, there has been an increase of interest in studies on effects of reaction medium, both sole solvents and/or binary mixtures, on the reaction rate and equilibrium constants of various organic compounds [34-38]. For instance, the effects of acetonitrile-water mixtures on the hydrolysis of 4-nitrophenyl chloroformate and heptafluorobutyrate [39], bis(*p*-nitrophenyl) phosphate [40], *p*-nitrophenyl acetate, benzoate [41, 42] and anthranilate [43, 44]and oxazolinone [45] have been reported.

In the present work, I report the influences of various salts on the hydrolysis reaction rate of tropolone tosylate in 20 - 90% (v/v) $MeCN-H_2O$ binary media containing *n*-Bu$_4$NOH. The concentration of *n*-Bu$_4$NOH (2.0 mmol dm^{-3}) is kept to be 20 times higher than that of the substrate (tropolone tosylate). The dissociation constant of tropolone in aqueous solution has been reported pK_a = *ca.* 6.7 [46], therefore, it should be an easy task for tropolone to deprotonate completely even in the binary media, which contain *n*-Bu$_4$NOH.

The simplified form of primary mechanism for the hydrolysis reaction of the substrate is indicated in Scheme 3-1. The attack by the OH$^-$ ion (the prominent nucleophile) and/or the H_2O molecule is expected to be on the sulfonyl sulfur center in such a way that the UV-active group, the tropolonate ion, is liberated. We would like to explain experimental results based on various

factors such as nucleophilicities of anions, coordination abilities of metal ions and/or changes in properties/activities of water or the hydroxide ion upon the addition of salts as well as an organic solvent, acetonitrile.
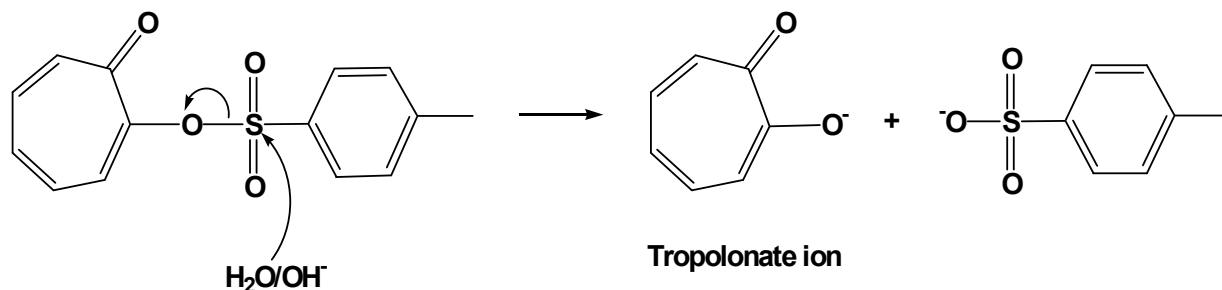
Scheme 3-1 The proposed mechanism for the hydrolysis of tropolone tosylate

3.2 Experimental

3.2.1 Materials and equipment

All chemicals and salts utilized were commercially available and used as received. Tropolone tosylate [7-oxocyclohepta-1,3,5-trien-1-yl 4-methylbenzenesulfonate ($\geq$99.0%)] was from TCI, all of $LiClO_4$ ($\geq$98.0%), Et_4NBr ($\geq$98.0%), Et_4NCl ($\geq$98.0%), NaN_3 ($\geq$98%), 0.5 mol dm^{-3} n-Bu_4NOH and acetonitrile (99.5%) were from Wako. Other salts of $NaClO_4$ ($\geq$98.0%), $Mg(ClO_4)_2$ (99%), $Ca(ClO_4)_2$ $4H_2O$ (99%), $Ba(ClO_4)_2$ ($\geq$97%), and tropolone ($\geq$98.0%) were from Aldrich. Water purified by MilliQ System was used in all the experiments. A Horiba F-51 digital pH meter was used for measuring the apparent pH of the reaction solutions.

3.2.2 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$\pm$0.1 $^{\circ}$C, in a 1.0 cm quartz cuvette. Reaction solutions were prepared by combining the appropriate amounts of water, acetonitrile, the n-Bu_4NOH (the final concentration of 2.0 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, the 5.0 x 10^{-3} mol dm^{-3} stock solution of the substrate (tropolone tosylate) was prepared in a suitable volume of acetonitrile (as the substrate is sparingly soluble in pure water). Then, reactions were initiated by transferring a 1.0 mL of the stock solution into a reaction vessel (50 mL) to reach the final substrate concentration of 1.0 x 10^{-4} mol dm^{-3}. The samplings of 3 - 4 mL were carried out from reaction solutions at certain time intervals and the sampled solutions were immediately dipped into an ice water bath.

The reaction progress was then followed spectrophotometrically by monitoring the liberation of tropolonate ion at around $\lambda_{max} = ca.$ 396 nm as a function of time. The "pseudo" first order rate constants were obtained from the slopes of ln (A_∞ - A_t) vs. time (s), where A_∞ and A_t are the values of absorbance at the final of the reaction and at time t, respectively. In fact, each A_∞ was evaluated from 1.0 x 10^{-4} mol dm^{-3} tropolone in MeCN-H$_2$O media containing 2.0 mmol dm^{-3} n-Bu$_4$NOH in the presence of the corresponding salts. All rate constants were evaluated from the linear parts with correlation coefficients (R^2) of normally 0.998 or better and the uncertainties for log (k /s^{-1}) should be ±0.01.

3.3 Results and Discussion

3.3.1 Influences of Acetonitrile Contents and n-Bu$_4$NOH Concentrations

At the constant temperature of 50 °C, we have evaluated the hydrolysis reaction rate of tropolone tosylate (1.0 x 10^{-4} mol dm^{-3}) containing 2.0 mmol dm^{-3} n-Bu$_4$NOH in 20 to 90 % (v/v) MeCN-H$_2$O binary media. The generation of the tropolonate ion as a result of the hydrolysis can be witnessed by the band appearance at $\lambda_{max} = ca.$ 396 nm (and also around 330 nm) with time as shown in Fig. 3-1. Two isosbestic points have been observed at 266 and 323 nm, which indicate the coexistence of the original substrate and the released tropolonate ion.
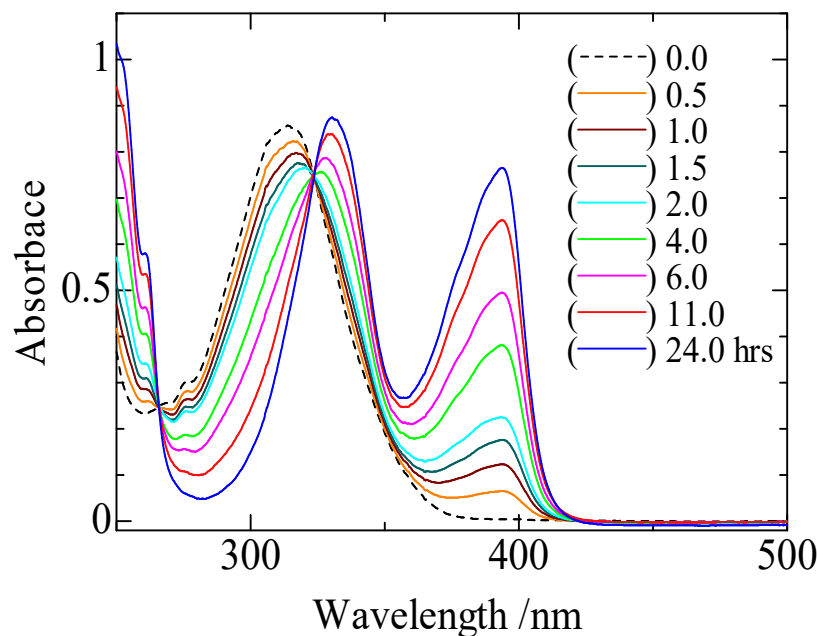
Fig. 3-1 Generation of the tropolonate ion with time from tropolone tosylate in the 20% (v/v) MeCN-H_2O solvent at 50 °C.

Fig. 3-2 shows the changes in the "pseudo" first order rate constant [log (k /s^{-1})] of the tropolone tosylate hydrolysis with the MeCN contents in binary MeCN-H_2O media containing a constant concentration (2.0 mmol dm^{-3}) of n-Bu$_4$NOH. The log (k /s^{-1}) value gradually decreases as -4.66, -4.79, -4.91, and -4.93 with increasing MeCN contents of 20, 30, 50, and 60% (v/v), respectively. With further increase in MeCN contents, 70, 80, and 90% (v/v), however, the log (k /s^{-1}) value reversely increases as -4.85, -4.72, and -4.32, respectively.

With increasing MeCN contents, we [43] have observed a similar decrease and the successive increase in the hydrolysis rate of p-nitrophenyl anthranilate. Destruction of water structure, which would result in deterioration of the property or activity of water, is responsible for the rate deceleration with increasing contents of MeCN. El-Mallah *et al*. [13] have noted that MeCN affects the water structure by intercomponent hydrogen bonding due to basicity difference in the solvent structure. Al-Jallal *et al*. [45], on the other hand, have reported the possible disruption of water tetrahedral structure with increasing MeCN contents.

The minimum appearance can be attributed to two contrary factors, that is, the decrease in water activity and an increase in the OH$^-$ activity during the progressive addition of MeCN. Gomez-Tagle *et al.* [40] also have reported a decrease and the successive increase in the hydrolysis rate of bis(*p*-nitrophenyl) phosphate with increasing contents of DMSO or MeCN.
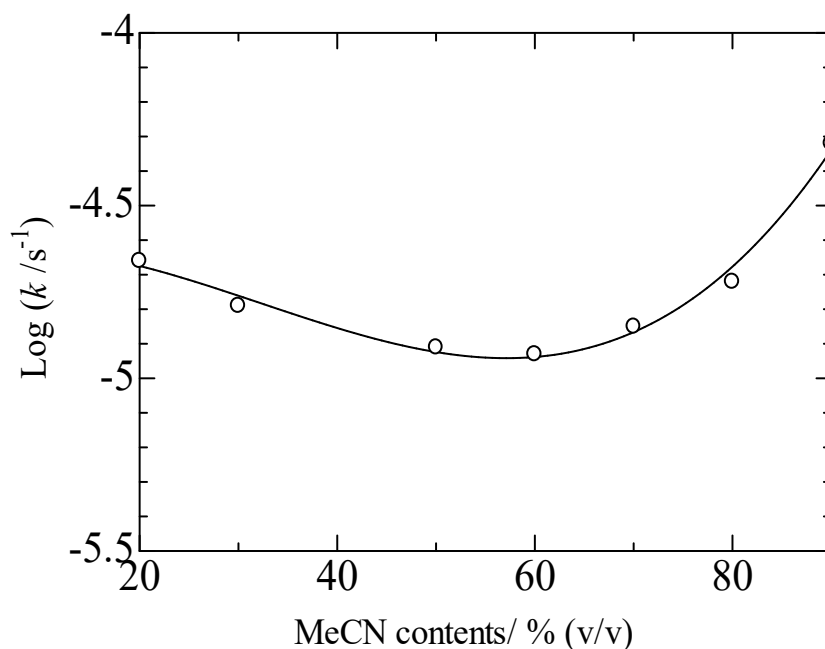
Fig. 3-2 Changes in log (k/s^{-1}) for tropolone tosylate hydrolysis with MeCN contents in media containing 2.0 mmol dm^{-3} of *n*-Bu$_4$NOH at 50 °C.

We have examined the influence of *n*-Bu$_4$NOH concentrations on the hydrolysis of tropolone tosylate. In 20% (v/v) MeCN-H$_2$O media, the log (k /s^{-1}) increases as -4.90, -4.66, -4.20, and -3.87 with increasing *n*-Bu$_4$NOH concentration of 1.0, 2.0, 5.0, and 10.0 mmol dm^{-3}, respectively. The acceleration is reasonable and a normal phenomenon, since the OH$^-$ ion attacks the sulphonyl sulfur center of the substrate to liberate the tropolonate ion.

3.3.2 Influences of Metal Perchlorates on the Hydrolysis Reaction Rate

The influences of alkali metal and alkaline earth metal perchlorates, such as LiClO$_4$, NaClO$_4$, Mg(ClO$_4$)$_2$, Ca(ClO$_4$)$_2$, and Ba(ClO$_4$)$_2$, on the hydrolysis rate have been surveyed in the binary media of 20 - 90% (v/v) MeCN-H$_2$O containing 2.0 mmol dm^{-3} *n*-Bu$_4$NOH at 50 °C. The

rate constants [log (k /s^{-1})] obtained are listed in Table 3-1. Fig. 3-3 shows the influences of LiClO$_4$ on the hydrolysis rate.
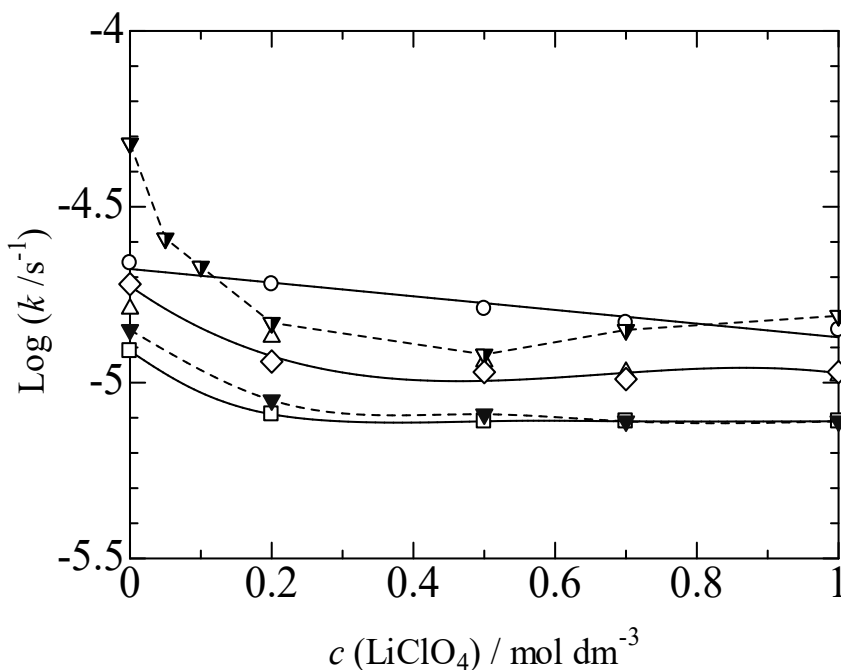
Fig. 3-3 Influences of LiClO$_4$ on log (k/s^{-1}) of the tropolone tosylate hydrolysis in binary MeCN-H$_2$O media containing 2.0 mmol dm^{-3} n-Bu$_4$NOH at 50 °C: (○) 20; (△) 30; (□) 50; (▼) 70; (◇) 80; (▽) 90% (v/v) MeCN.

In general, the log (k /s^{-1}) value decreases gradually with increasing concentration of LiClO$_4$ in all the media of 20 - 90% (v/v) MeCN-H$_2$O. Nevertheless, for media of 50 - 80% (v/v) MeCN, the rate decrement has become not so significant with increasing LiClO$_4$ concentration of higher than 0.50 mol dm^{-3}, and finally for media of 90% (v/v) MeCN, further increase in LiClO$_4$ concentration higher than 0.50 mol dm^{-3} has given a slight but obvious rate increment.

Table 3-1 Log (k /s^{-1}) values for the hydrolysis rate of 1.0 x 10^{-4} mol dm^{-3} of tropolone tosylate (containing 2.0 mmol dm^{-3} n-Bu$_4$NOH) in the presence of added metal perchlorate salts in binary MeCN-H$_2$O solvents at 50 °C

Salts	MeCN contents / % (v/v)	c(salt)/ mol dm^{-3} 0.0	0.1	0.2	0.3	0.5	0.7	1.0
LiClO$_4$	20	-4.66	-	-4.72	-	-4.79	-4.83	-4.85
	30	-4.79	-	-4.87	-	-4.94	-4.97	4.98
	50	-4.91	-	-5.09	-	-5.11	-5.11	-5.11
	70	-4.85	-	-5.05	-	-5.09	-5.11	-5.11
	80	-4.72	-	-4.94	-	-4.97	-4.99	-4.97
	90	-4.32	-4.67	-4.83	-	-4.92	-4.85	-4.81
NaClO$_4$	20	-4.66	-	-4.66	-	-4.68	-4.66	-4.66
	30	-4.79	-	-4.85	-	-4.84	-4.83	-4.80
	50	-4.91	-	-4.99	-	-4.94	-4.88	-4.86
	70	-4.85	-	-4.85	-	-4.80	-4.75	-4.68
	80	-4.72	-	-4.70	-	-4.63	-4.60	-4.48
	90	-4.32	-4.35	-4.30	-	-4.19	-4.05	-3.94
Ca(ClO$_4$)$_2$	20	-4.66	-4.68	-4.68	-4.70	-4.72	-	-
	50	-4.91	-5.11	-5.02	-5.03	-5.05	-	-
	80	-4.72	-	-	-	-	-	-
Ba(ClO$_4$)$_2$	20	-4.66	-4.48	-4.46	-	-4.44	-	-
	30	-4.79	-4.65	-4.62	-	-4.49	-	-
	50	-4.91	-4.76	-4.67	-	-4.46	-	-

Contrasting with $LiClO_4$, sodium perchlorate causes a significant rate acceleration in all the media of up to 90% (v/v) MeCN, except the solution of 20% (v/v) MeCN, in which the log (k /s^{-1}) value remains constant for 0.0 – 1.0 mol dm^{-3} $NaClO_4$ (Fig. 3-4). It is worth mentioning that $NaClO_4$ fairly accelerates the rate while $LiClO_4$ causes the deceleration, despite our expectation that both salts would possibly accelerate the rate to a certain extent due to the interaction between the alkali metal and tropolonate ions through the coordination forces. It is well known that tropolone is a member of naturally occurring compounds possessing metal-chelating property [47]. Hojo *et al.*[48, 49] have demonstrated the distinct features of interactions between the tropolonate ion and alkali metal ions (particularly Li^+ and Na^+) not only in MeCN [48] but also in ethanol [49]. Nakasuka and Tojima [50] have reported the complex formation constants of the tropolonate ion with Li^+ and Na^+ even in aqueous solution.
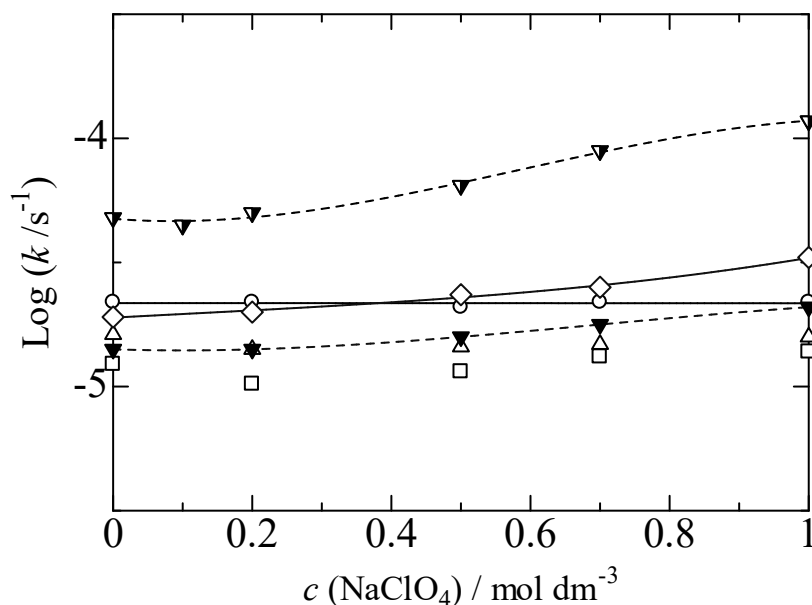
Fig. 3-4 Influences of $NaClO_4$ on the tropolone tosylate hydrolysis in binary MeCN-H_2O media containing 2.0 mmol dm^{-3} *n*-Bu$_4$NOH at 50 ℃: (○) 20; (△) 30; (□) 50; (▼) 70; (◇) 80; (▽) 90% (v/v) MeCN.

In the presence of the alkali metal perchlorates, the UV bands of the tropolonate ion released from the substrate have given blue shifts. In the medium of 50% (v/v) MeCN, for instance, the addition of 0.50 mol dm^{-3} salts cause blue shifts from 396 nm to *ca.* 386 nm with

LiClO$_4$ and to 389 nm with NaClO$_4$. These blue shift values suggest that the interaction of Li$^+$ with the tropolonate ion should be stronger than that of Na$^+$ in the solution.

Therefore, the rate deceleration caused by LiClO$_4$ may be accounted for with other reasons such as the loss of the OH$^-$ ion through some interaction between Li$^+$ and OH$^-$ ions. To evaluate the possible interaction between Li$^+$ and OH$^-$, we have assessed the apparent pH values of the reaction media of 50% (v/v) MeCN-H$_2$O in the presence of 0.0 to 1.0 mol dm^{-3} LiClO$_4$. A fair decrease in pH from 12.34 to 10.78 has been observed with the addition of 1.0 mol dm^{-3} LiClO$_4$. This decrease in the apparent pH is a good evidence for some interaction between Li$^+$ and OH$^-$ ions or the hydrolysis of the Li$^+$ ion itself.

The curious changes (*cf.* Fig. 3-3) in the rate constant with LiClO$_4$ should be accounted for through the following cumulative effects: (a) the interaction between the dominant nucleophile OH$^-$ and Li$^+$, (b) the disruption of water structure/properties upon addition of salts and (c) the larger coordinating interaction between Li$^+$ and tropolonate ions in the lesser solvating media, such as 90% (v/v) MeCN-H$_2$O. Therefore, the slight but obvious rate increment with 0.5 – 1.0 mol dm^{-3} LiClO$_4$ in 90% (v/v) MeCN can be explained by the increased complex formation force (Li$^+$-L$^-$) as well as lesser hydrolysis of Li$^+$ itself. The rate acceleration caused by NaClO$_4$, however, is most probably due to the coordination of Na$^+$ ions with the tropolonate ion and the consistency in the apparent pH (or the free OH$^-$ activity) even with the addition of NaClO$_4$ (*vide infra*).

It may be of importance to mention that the solvent physical properties are completely different in sole solvents and mixed solvents. Gagliardi *et al*. [51] have reported the changes in static dielectric contents for MeCN-H$_2$O mixtures at different temperatures. For instance, an increase in contents of MeCN as 0, 20, 50, 80, 90, and 100% (w/w) results in the decreases of ε_r to be 69.90, 62.99, 49.99, 38.84, 35.39, and 32.36, respectively, at 50 $^\circ$C. We have proposed the changes of bulk water properties in harmony with the distortion of hydrogen bonding structure of bulk water upon the addition of MeCN, which can be observed by means of ^{1}H NMR [26] and Raman spectroscopy [43].

As for the alkaline earth metal perchlorates, quite different influences among the salts have been observed. $Ba(ClO_4)_2$ perceptibly accelerates the rate while $Ca(ClO_4)_2$ causes no significant effect, whereas $Mg(ClO_4)_2$ causes the total suppression of the reaction. The acceleration by $Ba(ClO_4)_2$ has become distinctly stronger in the media of higher MeCN contents [*e.g.* 50% (v/v)], as shown in Fig. 3-5. However, the precipitation in the media of larger than 50% (v/v) MeCN-H_2O prevented us from examining the influences of $Ba(ClO_4)_2$ on the hydrolysis reaction. The remarkable rate acceleration by $Ba(ClO_4)_2$ in media of higher MeCN proportions should be based on the strong coordination between Ba^{2+} and tropolonate ions.

Hirai and Oka [46] have reported the stability constants (1:1 chelate) of Mg^{2+}, Ca^{2+}, and Sr^{2+} with the tolopolonate ion (L^-) to be $\log K_1 = 3.8$, 3.1, and 2.5, respectively, in aqueous solution. The extrapolation with the ionic radii or the ionization potentials may provide us with $\log K_1 \gtrsim ca.$ 2.0 for the BaL^+ chelate complex (*cf.* Scheme 2-2). It is certain that the interaction of L^- with alkaline earth metal ions increases in the order of $Ba^{2+} < Sr^{2+} < Ca^{2+} < Mg^{2+}$ in an aqueous solution. Andreu and Timasheff [52] have also reported the strong 1:1 chelate (complex) formation ability of Mg^{2+} with tropolone.
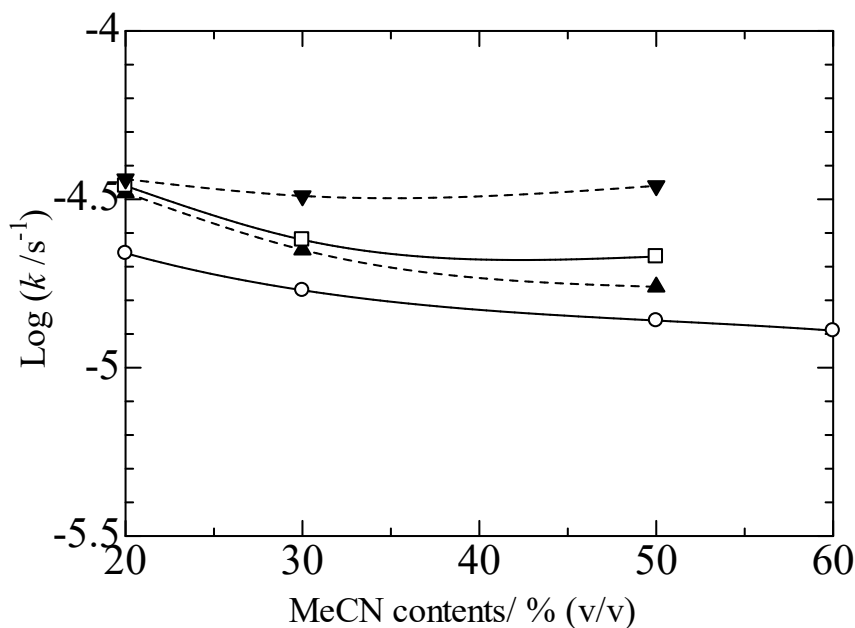
Fig. 3-5 Changes in $\log (k/s^{-1})$ for tropolone tosylate hydrolysis with MeCN contents in MeCN-H_2O media containing 2.0 mmol dm^{-3} *n*-Bu_4NOH in the presence of $Ba(ClO_4)_2$ at 50 °C: (○) 0.0; (▲) 0.10; (□) 0.20; (▼) 0.50 mol dm^{-3} $Ba(ClO_4)_2$.

The Ca(ClO$_4$)$_2$ salt has exhibited no substantial effect on the hydrolysis rate (Fig. 3-6). In 50% (v/v) MeCN, the addition of 0.0, 0.10, 0.20, 0.30, and 0.50 mol dm^{-3} Ca(ClO$_4$)$_2$ gives the log (k /s^{-1}) values of -4.91, -5.11, -5.02, -5.03, and -5.05, respectively.

Fig. 3-6 Changes in log (k/s^{-1}) for tropolone tosylate hydrolysis with Ca(ClO$_4$)$_2$ concentrations in MeCN-H$_2$O mixed solvent containing 2.0 mmol dm^{-3} n-Bu$_4$NOH at 50 °C: (●) 20; (□) 50 % (v/v) MeCN.

The weak influence by Ca(ClO$_4$)$_2$ on log (k /s^{-1}) should be due to some interactions between Ca^{2+} and the OH$^-$ ion. With the largest coordination ability among the alkaline earth metal ions, however, Mg(ClO$_4$)$_2$ unpredictably has come out as a strong reaction suppressor. In the presence of up to 0.50 mol dm^{-3} of Mg(ClO$_4$)$_2$, no sign of progress in hydrolysis reaction has been given in 20 or 50 (v/v) MeCN-H$_2$O. The band at around 396 nm (*cf.* Fig. 3-1), which corresponds to the tropolonate ion delivered from the hydrolysis, has not appeared even after 24 h (Fig. 3-7). This phenomenon can be attributed to the strong interaction of Mg^{2+} ion with the OH$^-$ ion.

Even apparent pH values in the solutions may be helpful for the discussion. By means of the glass electrode, we have measured the apparent pH values of the reaction solutions of 50% (v/v) MeCN-H$_2$O in the presence of 0.0 to 0.50 mol dm^{-3} Mg(ClO$_4$)$_2$ (Fig. 3-8). Added Mg(ClO$_4$)$_2$ has caused a significant decrease in apparent pH of the hydrolysis reaction media.

With the addition of 0.50 mol dm^{-3} Mg(ClO$_4$)$_2$, the pH value has sharply dropped to 8.32 from 12.30 in solution containing no salt.
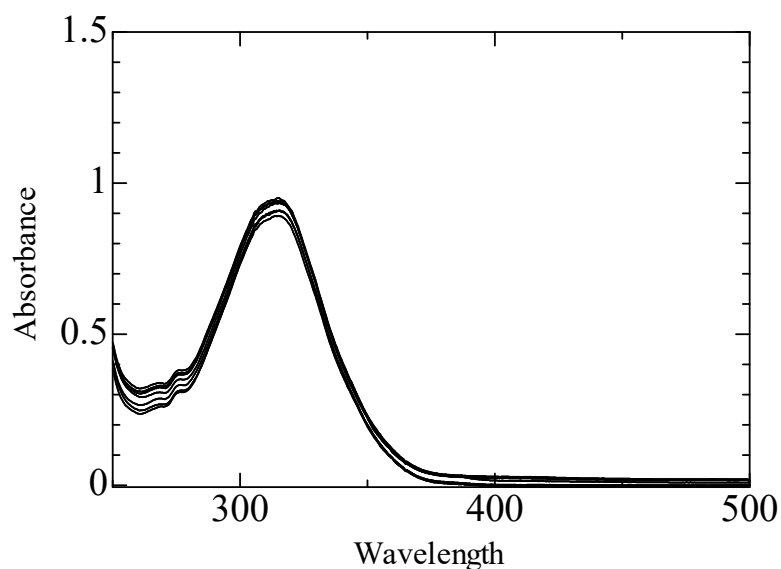
Fig. 3-7 UV spectrum for the hydrolysis of tropolone tosylate in binary aqueous solvent of 20% (v/v) MeCN containing 0.2 mol dm^{-3} Mg(ClO$_4$)$_2$ and 2.0 mmol dm^{-3} n-Bu$_4$NOH at 50 °C after followed for 24hr.
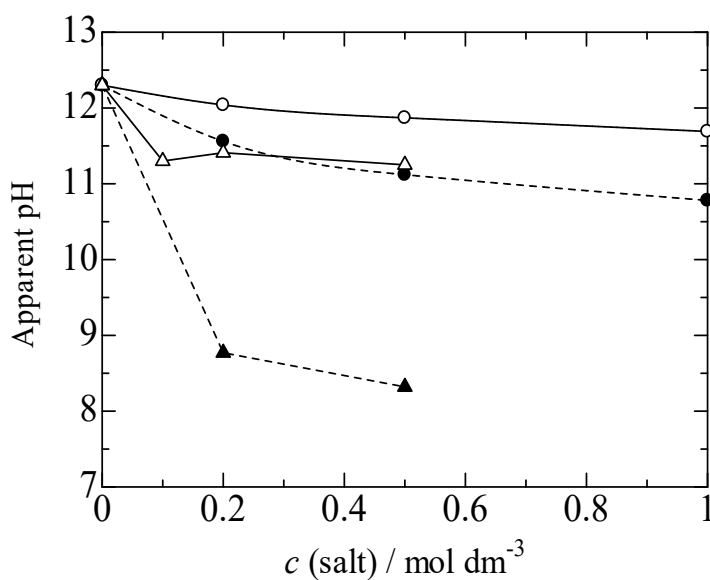
Fig. 3-8 Changes in apparent pH values of reaction media of 50% (v/v) MeCN containing 2.0 mmol dm^{-3} n-Bu$_4$NOH in the presence of salts: (●) LiClO$_4$; (○) NaClO$_4$; (▲) Mg(ClO$_4$)$_2$; (△) Ba(ClO$_4$)$_2$.

The remarkable pH decrease is a clear evidence that the Mg^{2+} ion indeed consumes the OH^- ion. Consequently, it is fair enough to conclude that the reaction suppression with $Mg(ClO_4)_2$ is certainly caused by the consumption of the OH^- ion through the strong interaction between Mg^{2+} and OH^-. The fact that $Ba(ClO_4)_2$ causes the rate acceleration (as described above) suggests that, in a simple expression, Ba^{2+} interacts more strongly with the tropolonate ion (L^-) rather than the OH^- ion. It is true that the M^{2+}-L^- formation constant for Ba^{2+} is the least among all the M^{2+} (*vide supra*), but the apparent pH value in the presence of $Ba(ClO_4)_2$ may have evidenced a weak interaction between Ba^{2+} and OH^- ions.

We can notice that the apparent pH changes of the reaction solutions caused by $LiClO_4$ and $Ba(ClO_4)_2$ is very comparable (*cf.* Fig. 3-8). Even though, both salts have caused the opposite effects on the reaction rate. The opposite effects between Li^+ and Ba^{2+} should be caused by great difference in coordination abilities toward the tropolonate ion. The Ba^{2+} ion has stronger coordination ability than the Li^+ ion with the tropolonate ion, and finally the rate acceleration and not deceleration has been brought by $Ba(ClO_4)_2$. The complexes of the metal ions with the tropolonate ion are depicted in Scheme 3-2.
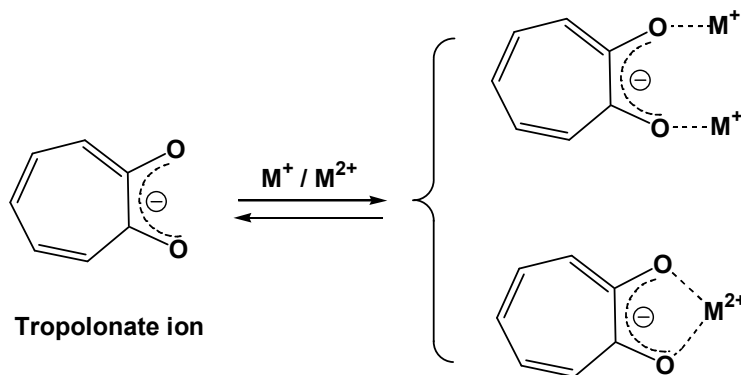
Tropolonate ion

Scheme 3-2 The coordinated species between the tropolonate ion and alkali metal (M^+) or alkaline earth metal (M^{2+}) ions; the cationic $(M^+)_2L^-$ species has been termed to be a "reverse" coordinated species (*cf.* ref. 26).

As a brief summary of this section, Mg^{2+} and Ca^{2+} ions have quite strong interaction with the OH^- ion (needless to say, which is the dominant nucleophile in the hydrolysis reaction). As the final result, $Mg(ClO_4)_2$ plays as a reaction suppressor while $Ca(ClO_4)_2$ causes an insignificant rate deceleration or no major effect, and finally $Ba(ClO_4)_2$ is a distinguished rate accelerator.

Yatasimirskii and Vasilev [53] have compiled the equilibrium constants of complex compounds including MOH^+ for Mg^{2+}, Ca^{2+}, and Ba^{2+} with OH^- to be log K = 2.6, 1.3, and 0.64, respectively, in aqueous solution. Obviously, the interaction between Ba^{2+} and OH^- is much weaker than that of Mg^{2+} or Ca^{2+}. The interaction between Na^+ and OH^- (the formation constant of NaOH: log K = -0.48) is also much weaker than that Li^+ and OH^- (log K = 0.18). The consumption of free OH^- ions in the solution can be brought about by the chemical interaction between the metal ions and OH^-.

It is of importance to mention that, the interaction between the metal ions and the *p*-toluenesulfonate ion (*cf.* Scheme 3-1) could also partly contribute to the rate enhancement, in addition to the interactions (coordination) between M^+ or M^{2+} and the tropolonate ion. The strong coordination interactions of the metal ions with the *p*-toluenesulfonate ion have been demonstrated by ourselves in not only MeCN [54] but also alcohols [55].

We should discuss the degree of dissociation of metal perchlorates at higher concentrations. The association constant of $LiClO_4$ in MeCN has been reported so small (*e.g.*, K_a = 13.6 observed by conductometry) [56] that $LiClO_4$ can be regarded eventually as a strong electrolyte under the conditions. It is true that any "strong" electrolyte is apt to turn to be a "weak" electrolyte at higher concentrations, such as > 0.1 mol dm^{-3}. However, only Coulombic interaction can operate between Li^+ and ClO_4^- because the ClO_4^- ion has no coordination ability even though the alkali metal ion indeed accepts the lone pairs of a (ligand) anion. Therefore, the bond interaction between Li^+ and ClO_4^- of the ion-pair of $LiClO_4$, abundantly present at higher concentrations, should be weak enough to dissociate when Li^+ is attracted by any other stronger chemical interaction, such as coordination of an X^- anion. Ion association of alkaline and alkaline-earth metal perchlorates in MeCN has been discussed from the view point of solvent-shared (SIP) and contact ion pairs (CIP) [57]. A conductometric study has been reported for the ion association between M^{2+} and the perchlorate ion by Kalugin *et al.* [58].

3.3.3 Influences of Non-metal Salts (Et₄NCl, Et₄NBr) and NaN₃

The influences of Et$_4$NCl, Et$_4$NBr, and NaN$_3$ salts of various concentrations ranging from 0.0 to 1.0 mol dm^{-3} on the hydrolysis rate have been examined in media of various MeCN contents containing 2.0 mmol dm^{-3} n-Bu$_4$NOH at 50 °C. The rate constants obtained with all the salts are listed in Table 3-2. Figs. 3-9 and 3-10 show the influences of Et$_4$NCl and Et$_4$NBr, respectively, on the hydrolysis rate.
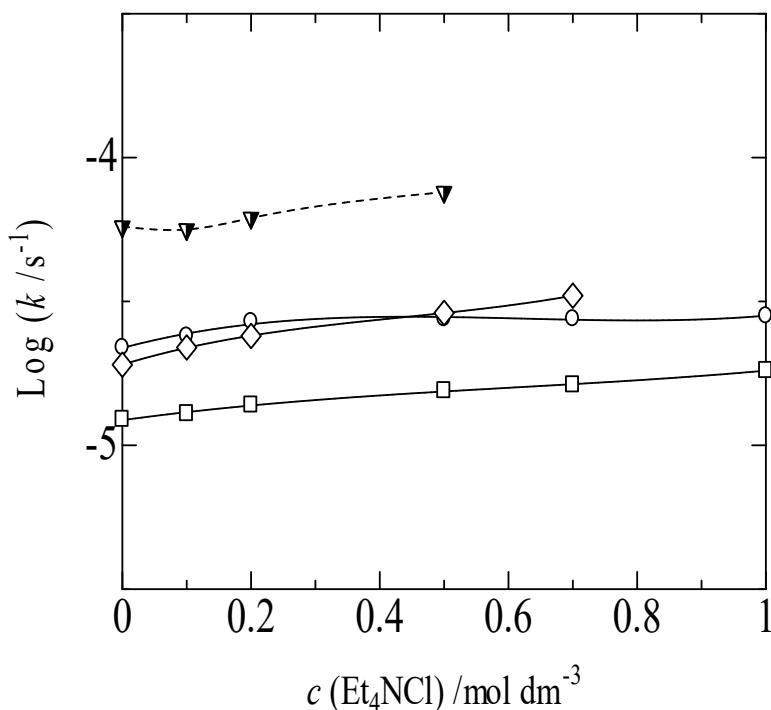
Fig. 3-9 Influences of Et$_4$NCl on the tropolone tosylate hydrolysis in binary MeCN-H$_2$O media containing 2.0 mmol dm^{-3} n-Bu$_4$NOH at 50 °C: (○) 20; (□) 50; (◇) 80; (▼) 90% (v/v) MeCN.

In the reaction media of 20% (v/v) MeCN, both Et$_4$NCl and Et$_4$NBr have given no significant effect on log (k/s^{-1}). However, in all the media of 50 – 90% (v/v) MeCN, the log (k/s^{-1}) value fairly increases with increasing concentrations of both Et$_4$NCl and Et$_4$NBr. The influence of Et$_4$NBr is rather weak in media containing smaller proportions of MeCN. However, its effect has gradually become stronger as the MeCN contents increase. The rate accelerating effects caused by both Et$_4$NCl and Et$_4$NBr salts are mainly due to the nucleophilic properties of

Cl⁻ and Br⁻ ions. Edwards and Pearson [59] have reported the following overall nucleophilicity order or S_N2 mechanisms in protic media as $RS^- > ArS^- > I^- > CN^- > OH^- > N_3^- > Br^- > ArO^- > Cl^- >$ pyridine $> AcO^- > H_2O$.

Table 3-2 Log (k /s^{-1}) values for the hydrolysis rate of 1.0×10^{-4} mol dm^{-3} of tropolone tosylate (containing 2.0 mmol dm^{-3} n-Bu$_4$NOH) in the presence of azide and halide salts in binary MeCN-H$_2$O solvents at 50 °C.

Salts	MeCN contents / % (v/v)	c(salt)/ mol dm^{-3}						
		0.0	0.1	0.2	0.3	0.5	0.7	1.0
NaN$_3$	20	-4.66	-4.57	-4.53	-4.44	-4.24	-	-
	30	-4.79	-	-4.54	-	-4.34	-	-
	50	-4.91	-4.74	-4.63	-4.54	-4.43	-	-
	60	-4.93	-4.74	-4.60	-4.47	-	-	-
	70	-4.85	-4.63	-4.45	-4.32	-	-	-
Et$_4$NCl	20	-4.66	-4.62	-4.57	-	-4.56	-4.56	-4.55
	50	-4.91	-4.89	-4.86	-	-4.81	-4.79	-4.74
	80	-4.72	-4.66	-4.62	-	-4.54	-4.48	-
	90	-4.32	-4.25	-4.21	-	-4.12	-	-
Et$_4$NBr	20	-4.66	-4.70	-4.76	-	-4.72	-4.68	-4.69
	50	-4.91	-4.90	-4.87	-	-4.80	-4.75	-4.63
	70	-4.85	-4.84	-4.84	-4.75	-4.66	-4.59	-4.53
	80	-4.72	-4.66	-4.53	-4.51	-4.48	-4.41	-
	90	-4.32	-4.17	-4.13	-4.07	-4.04	-	-
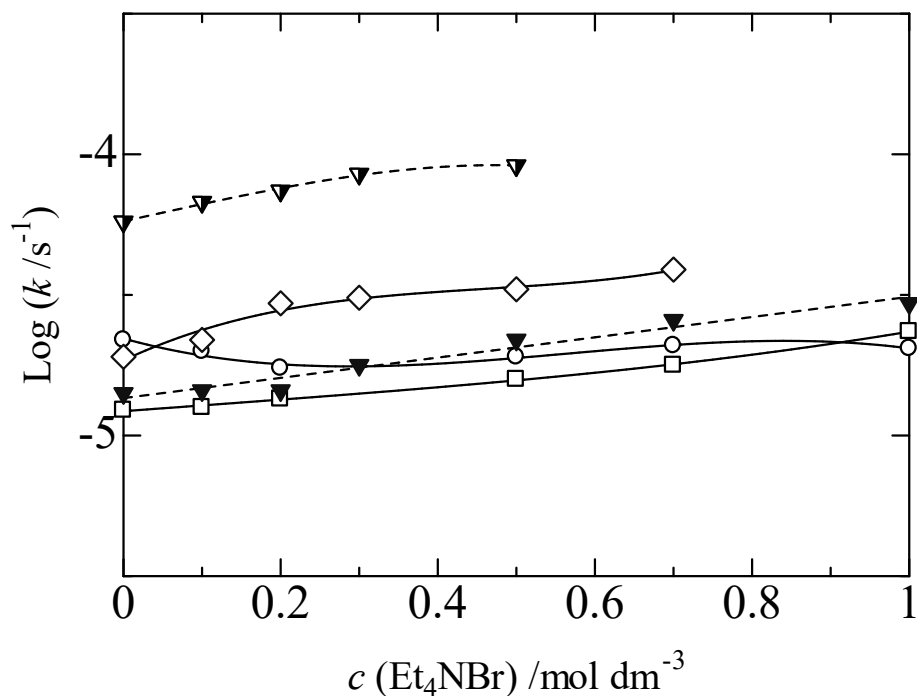
Fig. 3-10 Influences of Et$_4$NBr on log (k/s^{-1}) for the tropolone tosylate hydrolysis in binary MeCN-H$_2$O media containing 2.0 mmol dm^{-3} n-Bu$_4$NOH at 50 °C: (○) 20; (□) 50; (▼) 70; (◇) 80; (▽) 90% (v/v) MeCN.

Even though the Br$^-$ ion is a good nucleophile, its ability to attack the sulfonyl sulfur in the substrate may be hindered with the strong hydration by water in the lower MeCN content of 20% (v/v). However, with increasing MeCN contents, particularly ≥50% (v/v) MeCN, the Br$^-$ ion may be more free from the solvation (hydration) since the water activities should decrease remarkably in the presence of both large proportions of MeCN and the Et$_4$NBr salt. Hence, a fairly rate acceleration by Et$_4$NBr can be observed in solutions of higher MeCN contents. The Et$_4$NCl salt also gives the rate acceleration but slightly weaker than Et$_4$NBr. By means of Raman spectroscopy, we [27c, 35, 36] have found that the bulk water structure is much destroyed indeed by the addition of organic solvents and Et$_4$NCl or Et$_4$NBr.

Fig. 3-11 shows a notable change in log (k/s^{-1}) with the added NaN$_3$ salt. The azide ion has caused a remarkable acceleration in the hydrolysis rate in all the media of 20 - 70% (v/v). In

20% (v/v) MeCN, for instance, log (k /s^{-1}) has increased as -4.66, -4.57, -4.53, -4.44, and -4.24 upon the addition of 0.0, 0.1, 0.2, 0.3, and 0.5 mol dm^{-3} NaN$_3$, respectively (*cf.* Table 3-2).
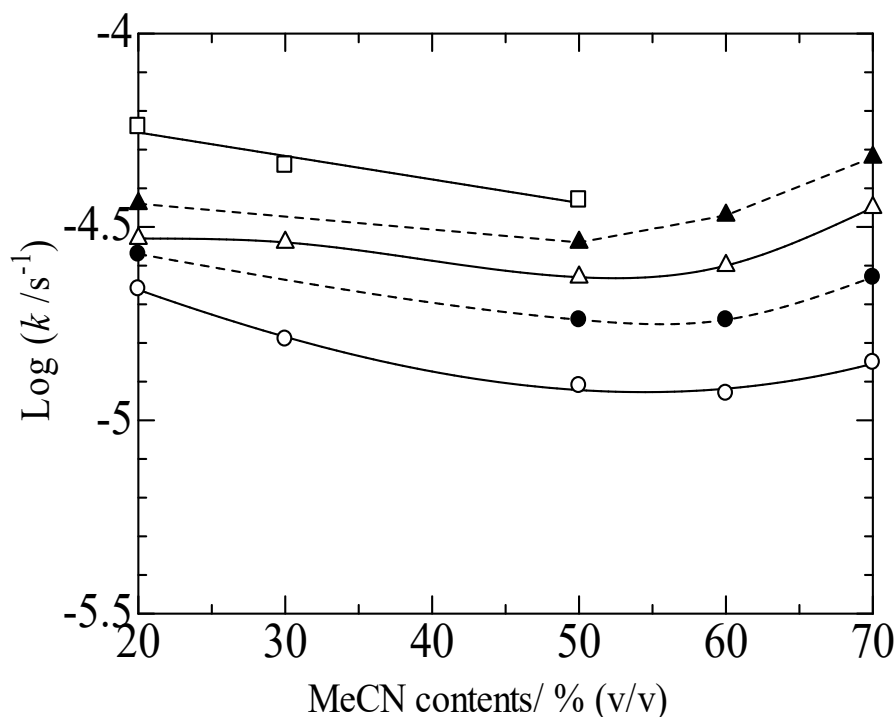
Fig. 3-11 Changes in log (k/s^{-1}) for the tropolone tosylate hydrolysis with MeCN contents in binary MeCN-H$_2$O media containing 2.0 mmol dm^{-3} n-Bu$_4$NOH in the presence of NaN$_3$ at 50 °C: (○) 0.0; (●) 0.1; (△) 0.2; (▲) 0.3; (□) 0.5 mol dm^{-3} NaN$_3$.

The remarkable acceleration in the presence of NaN$_3$ is in good agreement with the strong nucleophilicity of the N$_3^-$ ion. In addition to the OH$^-$ ion (the dominant nucleophile), the N$_3^-$ ion can attack the sulfonyl sulfur of the substrate to liberate the tropolonate ion. However, we would like to note that the addition of NaN$_3$ has changed the UV spectrum of the tropolonate ion at around 396 nm. The clear band peak has been lost to be just a shoulder and the intensity of the appeared band has gradually decreased in the presence of NaN$_3$. Therefore, we have made use of the earlier stage of the reaction for evaluating the rate constant. The peak deformation and the decrease in intensity can be attributed to the decomposition or some different chemical transformation of tropolone tosylate with time. However, the original absorption bands (λ_{max} = *ca.* 330 and 396 nm) of the tropolonate ion from tropolone with n-Bu$_4$NOH in 20 or 50% (v/v) MeCN-H$_2$O has not deformed at all even after 24 h at 50 °C.

3.3.4 Cooperative Effects of MeCN and Salts

Different behavior in the hydrolysis has been shown by the various salts, as mentioned above. The effects of every salt employed in the present system are certainly dependent on the contents of MeCN as the co-solvent with water. Fig. 3-12 shows the graphical illustration of effects of alkali and alkaline earth metal perchlorates [$LiClO_4$, $NaClO_4$, $Ca(ClO_4)_2$, and $Ba(ClO_4)_2$], NaN_3, and tetraethylammonium halides (Et_4NCl and Et_4NBr) on log (k/s^{-1}) in 20% (v/v) MeCN-H_2O media at 50 °C.
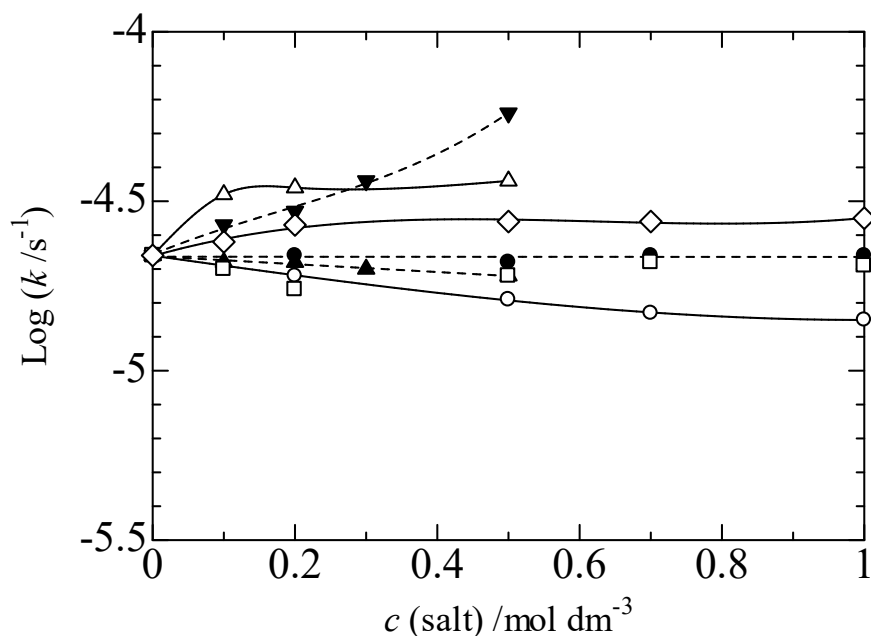
Fig. 3-12 Changes in log (k/s^{-1}) for the tropolone tosylate hydrolysis with salt concentrations in 20% (v/v) MeCN-H_2O binary media containing 2.0 mmol dm^{-3} n-Bu$_4$NOH at 50 °C: (○) $LiClO_4$; (●) $NaClO_4$; (Δ) $Ba(ClO_4)_2$; (▲) $Ca(ClO_4)_2$; (▼) NaN_3; (□) Et_4NBr; (◇) Et_4NCl.

It can be clearly seen that NaN_3 and $Ba(ClO_4)_2$ accelerate the reaction with their respective concentrations while $LiClO_4$ and $Ca(ClO_4)_2$ decelerate a certain extent. The rate acceleration caused by NaN_3 is rather smooth and linear. However, the rate increment by $Ba(ClO_4)_2$ seems to be significant until its concentration reaches $ca.$ 0.1 mol dm^{-3} but further

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increase in its concentration gives no significant acceleration. All $NaClO_4$, Et_4NCl, and Et_4NBr cause no significant effects. The overall effects of the salts mentioned in 20% (v/v) $MeCN-H_2O$ have followed the order of $NaN_3 > Ba(ClO_4)_2 > Et_4NCl > Et_4NBr \sim NaClO_4 \ (> Ca(ClO_4)_2 > LiClO_4)$, especially at around 0.50 mol dm^{-3}.

With the higher MeCN proportions, the stronger effects have been exerted by some of the salts. Fig. 3-13 shows the changes of log (k /s^{-1}) in 50% (v/v) $MeCN-H_2O$ media in the presence of various salts. Both NaN_3 and $Ba(ClO_4)_2$ have exhibited remarkable and seemingly linear rate acceleration.
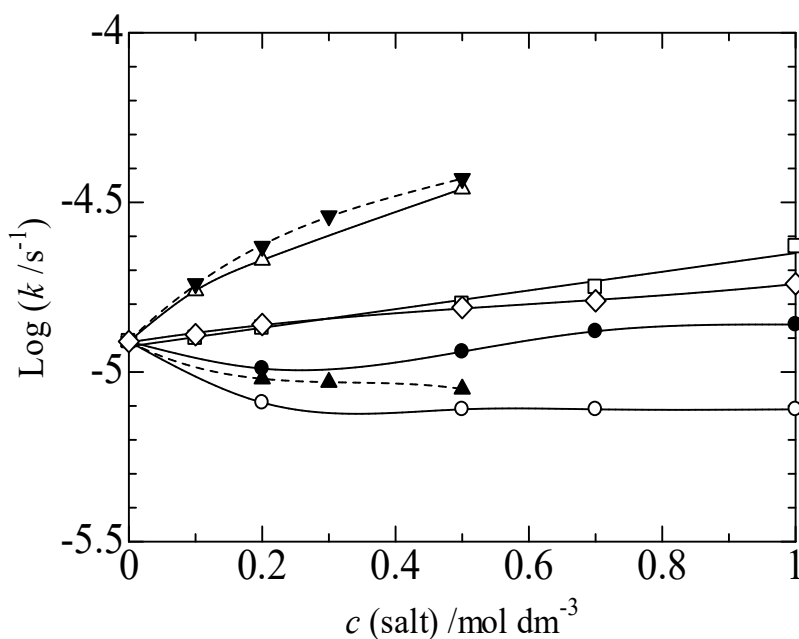
Fig. 3-13 Changes in log (k/s^{-1}) for the tropolone tosylate hydrolysis with salt concentrations in 50% (v/v) $MeCN-H_2O$ binary media containing 2.0 mmol dm^{-3} n-Bu$_4$NOH at 50 °C: (○) $LiClO_4$; (●) $NaClO_4$; (△) $Ba(ClO_4)_2$; (▲) $Ca(ClO_4)_2$; (▼) NaN_3; (□) Et_4NBr; (◇) Et_4NCl.

Et_4NCl and Et_4NBr salts also have given a linear acceleration with their concentrations. The effects of Et_4NBr have become even greater than those of Et_4NCl, particularly at their

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respective higher concentrations. The addition of up to 0.20 mol dm^{-3} of LiClO$_4$ and NaClO$_4$ causes the deceleration. With the further increase in their concentrations (0.50 – 1.0 mol dm^{-3}), however, we can notice the successive acceleration for NaClO$_4$ and no significant change for LiClO$_4$. In 50% MeCN-H$_2$O media, generally speaking, the rate acceleration caused by the added salts has followed the order of NaN$_3$ ~ Ba(ClO$_4$)$_2$ > Et$_4$NBr > Et$_4$NCl > NaClO$_4$ and the deceleration by LiClO$_4$ and Ca(ClO$_4$)$_2$.
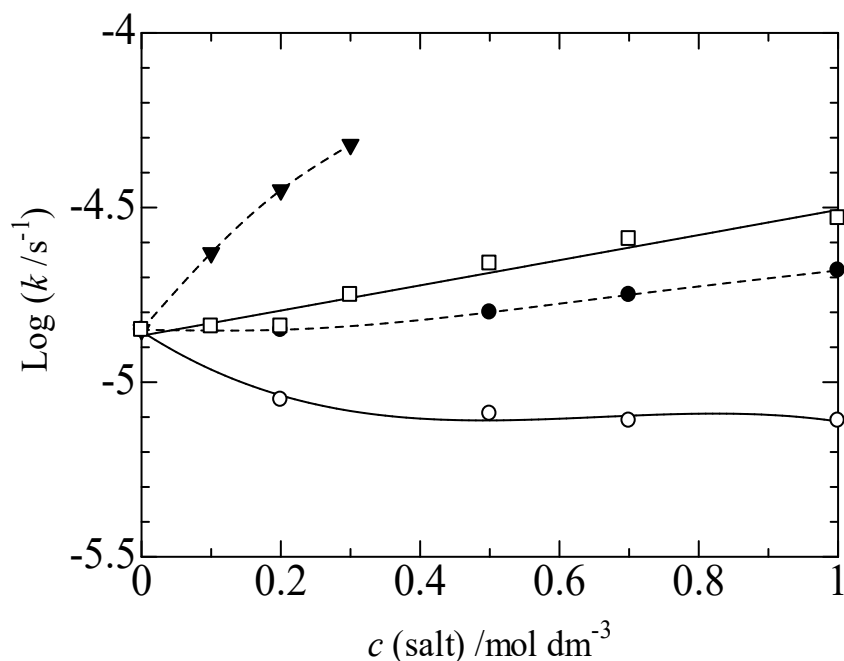
Fig. 3-14 Changes in log (k/s^{-1}) for the tropolone tosylate hydrolysis with salt concentrations in 70% (v/v) MeCN-H$_2$O binary media containing 2.0 mmol dm^{-3} n-Bu$_4$NOH at 50 °C: (○) LiClO$_4$; (●) NaClO$_4$; (▼) NaN$_3$; (□) Et$_4$NBr.

In 70% (v/v) MeCN-H$_2$O media, the rate deceleration are still caused by LiClO$_4$, while a linear acceleration are caused by NaClO$_4$ with the increasing salt concentration (*cf.* Fig 3-14). Among added salts in 70% (v/v) MeCN-H$_2$O media, the rate acceleration has followed the order of NaN$_3$ > Et$_4$NBr > NaClO$_4$.

3.3.5 Temperature Dependency

Fig. 3-15 shows the Arrhenius plots for hydrolysis of the substrate in the 50% (v/v) MeCN-H_2O binary media (containing 2.0 mmol dm^{-3} of n-Bu$_4$NOH) in the presence of various salts. All the salt systems have given a good linearity in the range from 35 to 60 ℃. The observed activation energy (E_a) values are 83.7, 79.3, 81.9, 79.1, 87.1, and 79.1 kJ mol^{-1} for no salt, 0.50 mol dm^{-3} LiClO$_4$, NaClO$_4$, Ba(ClO$_4$)$_2$, Et$_4$NBr, and NaN$_3$, respectively. The good linearity in the plots and those large E_a values suggest that the hydrolysis reactions in the presence of various salts are controlled by the normal temperature dependent and non-catalytic mechanism with the ions from the added salt.
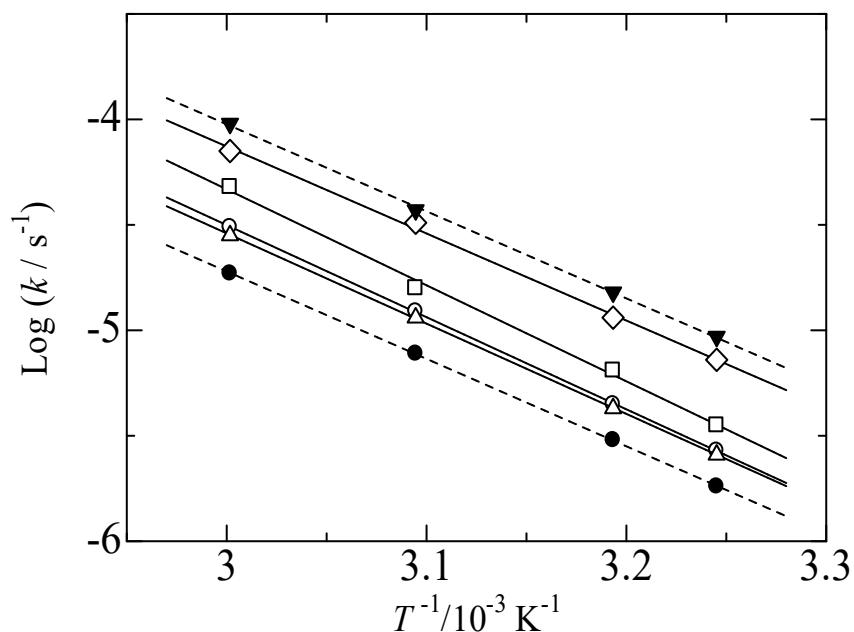
Fig. 3-15 Arrhenius plots of log (k/s^{-1}) for the tropolone tosylate hydrolysis in 50% (v/v) MeCN-H_2O binary media containing 2.0 mmol dm^{-3} n-Bu$_4$NOH in the presence of 0.50 mol dm^{-3} salts at 50 ℃: (○) no salt; (●) LiClO$_4$; (△) NaClO$_4$; (◇) Ba(ClO$_4$)$_2$; (▼) NaN$_3$; (□) Et$_4$NBr.

3.4 Conclusions

The hydrolysis reaction rate [log (k/s^{-1})] of tropolone tosylate is basically influenced by the kind of salts, contents of MeCN, and concentrations of n-Bu$_4$NOH. Increasing concentration

of n-Bu$_4$NOH causes an increase in the rate, while two diverse effects have been observed with increasing contents of MeCN depending on the changes of the activities of H$_2$O and OH$^-$. Among alkali metal and alkaline earth metal perchlorates, both NaClO$_4$ and Ba(ClO$_4$)$_2$ can cause the obvious rate acceleration especially in media of higher MeCN proportions. However, LiClO$_4$ and Ca(ClO$_4$)$_2$ salts cause the rate deceleration, whereas Mg(ClO$_4$)$_2$ is a total suppressor of the hydrolysis reaction. All the salts of NaN$_3$, Et$_4$NCl, and Et$_4$NBr appear to increase the log (k/s^{-1}) value, with the nucleophilicities of the anions, following the order of Et$_4$NCl ~ Et$_4$NBr < NaN$_3$. It is concluded that the significant changes in the hydrolysis rate constants are dependent on not only activities of H$_2$O and the OH$^-$ ion but also the coordination between cations (Li$^+$, Na$^+$, Ca^{2+}, Mg^{2+}, and Ba^{2+}) and the tropolonate ion released from the substrate.

At the same time, we have to take into account the loss of the free OH$^-$ ions through the interaction between OH$^-$ and the metal ions of Li$^+$, Mg^{2+}, or Ca^{2+}. Nucleophilicities of the anions (N$_3^-$, Cl$^-$, and Br$^-$) from the added salts may be altered in the "modified" aqueous solution, where the hydrogen bonding structure of the bulk water is potentially distorted by the addition of foreign substances, $i.e.$, the organic solvent and the salts. We have to declare that it might be almost impossible to analyze such kinetic data by examining precisely the activity coefficients of ions (or solutes) in the solution containing organic solvents and foreign salts at higher contents or concentrations.

3.5 References

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CHAPTER FOUR

4. Influences of micelle formation on the hydrolysis reactions rate of *p*-nitrophenyl benzoate (*p*-NPB) in aqueous buffered media

ABSTRACT

The hydrolysis reaction rates of *p*-nitrophenyl benzoate (*p*-NPB) have been investigated in aqueous buffer of pH = 9.18 media containing surfactants, cetyltrimethylammonium bromide (CTAB) and chloride (CTAC) at 35 °C. Below the cmc value of CTAB or CTAC, the rate constant [log (k /s^{-1})] of *p*-NPB hydrolysis has once decreased and then begun to increase drastically with increasing surfactants concentration. At the concentrations greater than the cmc value, the log (k /s^{-1}) value has reached the optimal value, i.e., a 140- or 200-fold rate acceleration for CTAB or CTAC, respectively, compared to that without the surfactant. Increase in pH of the buffer also has resulted in an increase of rate of hydrolysis of the substrate *p*-NPB. The influences of added salts on the hydrolysis rate have been examined. All added salts have affected significantly the *p*-NPB hydrolysis rate not only in the presence but also in the absence of the surfactants. In solutions with surfactants (> cmc), only 0.1 mol dm^{-3} of each of the added salts of NaBr, Me$_4$NBr, Et$_4$NBr, Pr$_4$NBr and *n*-Bu$_4$NBr has significantly decreased the reaction rate. The general rate deceleration caused by the added salts in media containing CTAB surfactant follow the order: NaBr > Me$_4$NBr > Et$_4$NBr > Pr$_4$NBr > *n*-Bu$_4$NBr. In the absence of surfactant, however, the added bromide salts have accelerated linearly the rate of hydrolysis, except NaBr, with an order of Me$_4$NBr < Et$_4$NBr < Pr$_4$NBr < *n*-Bu$_4$NBr. The emerged phenomenon in media containing surfactants have been discussed on the basis of pseudophase model in which the aqueous medium and the micelle are viewed as a separated phases with which the substrate is in thermodynamic equilibrium. The effects of added salts in aqueous medium have been discussed by taking into considerations the change in water structure, activities of the OH$^-$ ion and/or the nucleophilicity of the anions from the added salts.

Keywords: Micelle, surfactants, pseudophase model, aqueous phase, nucleophilicty, water structure

4.1 Introduction

Micelles are especially simple spherical supramolecules, which are formed by amphiphiles (surfactants) in water or media similar to water above the concentration of the surfactants (called critical micelle concentration-cmc) at which micelles starts to form [1]. A micellar system appears to be homogeneous since these aggregates are of colloidal size; however, in reality the absorbed reactants are in a micro-heterogeneous two-phase system [2]. These systems have been recognized as potentially useful model matrices to study the processes that occur in the complex plasma or cell membrane of living cells and also play a vital role in pharmaceutical industry and other industrial systems [3]. The feature that makes a micelle special with respect to its functioning as a micro- or nanoreactor is the proximity of extremely polar and nonpolar regions [1]. They provide micro-environments different from bulk water, and besides they may exert a concentration effect because they can shift equilibrium position.

The effect of micelles on reactions can, according to Brown *et al*. [4], be ascribed to a combination of the following factors: one, the dielectric constant in the micelle is lower than in water, which causes a solvent effect. Second, the transition state of the reaction can be stabilized by interaction with the polar head groups, and the third is the reactants are concentrated relative to the surrounding water phase through interactions with the micelle surface or through insertion into the micelle itself, thus leading to an increased rate of bimolecular reactions. The acidity or basicity of ionic amphiphiles can be significantly higher on the surface of micelles than in the surrounding aqueous phase. The concentration effect can be considered as dominant in many cases.

In the frame of the pseudo-phase model, micelles are considered as a phase different from aqueous medium, where reaction rates and solubilities of the substrates can vary considerably. In reactions with ionic species, an important fact is the charge of the surfactant head groups and counter-ions. In this way, it is expected that the rate of hydrolysis of hydrophobic esters by OH^- ions will be enhanced by cationic micelles, which can include the ester in their core and attract reactive ions of opposite sign, that is, hydroxide ions. Basically, these rate effects can be

attributed to electrostatic and hydrophobic interactions between the substrate and the surfactant aggregate and in some cases to alterations in the structure of the surrounding water [5].

The solvolysis/hydrolysis of esters and related nucleophilic reactions in micellar system have been extensively investigated. Enzymatic and enzyme-analogous systems including micelles have a practical significance for the hydrolytic detoxifications of organic compounds [6-9] and even for treatment of waste water [10-12]. Micelles can cause an acceleration or inhibition of a given chemical reaction rates relative to the equivalent reaction in an aqueous medium depending upon the types of surfactant used for micelle formation [13-20].

Certain basic phenomena are observed time after time, although there action in the ionic bilayer of the aggregate, the Stern layer, competes with the reaction of the free substrate in the aqueous phase during the hydrolysis reactions in a micellar medium. Reactivity maxima are frequently found for substrates of a certain chain length in reactions in micellar aggregates, which leads to the conclusion that there must be an optimal reaction site for the reactions where the rate is increased the most. The proximity of the reaction partners (hydroxide ions and the carbonyl group of the ester in the case of alkaline ester hydrolysis) in the Stern layer determines the higher rate of reaction relative to that in aqueous media [1, 13-16, 18-20].

The effects of added salts on the hydrolysis reaction rates of esters in both aqueous and binary solvent media have been extensively studied. Mabey and Mill [21] have reported the effects of both solvent composition and added salt effects on the hydrolysis of organic compounds. The added salt can potentially lead to either rate acceleration or retardation depending upon the substrate, types of the salt and their concentrations as well as the reaction mechanisms. We [22-27] have critically investigated and reported the significant changes in the hydrolysis (solvolysis) of various organic compounds in binary solvent media containing added salts. Several factors potentially contribute for the changes in rates of hydrolysis reaction rates of organic compounds in both aqueous and binary solvent media containing added salts. These includes, the change in "normal" water structure [22, 28, 29], the increase in the hydroxide ion (OH^-) activity, coordination formation ability of the metal ions with both the substrate and the prominent nucleophile, OH- ion, and nucleophilicty of the cations from the added salt in the modified reaction media [22-27].

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Hojo *et al*. [30], fascinatingly explained that 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)]. Reichardt *et al.* [31] have concisely interpreted "dihydrogen ether" that, at high salt concentrations [$c(salt) > 5$ mol dm^{-3}], region C, according to the solvation model of Frank and Wen [32], can be abolished and only regions A and B survive, resulting in an aqueous solvent called "dihydrogen ether."

As we noted earlier, there are a huge line of information on the effects of reaction rates of organic compounds in micellar media just like the reactions in aqueous media. However, as far as our knowledge is concerned, the detail information on the effect of added salts (specially alkaline and alkali earth metal salts and nonmetal salts) on the (hydrolysis) reaction rates of organic compounds in micellar media compared with that of in aqueous or binary solvent media is in lack or limited. There are some evidences on the effects of transition metal ions on the rate of hydrolysis of esters [33-36] in micellar media.

So, in the present study, as part of our interest in studying medium effects on the reaction rates of organic compounds, we extended our investigation on the effects of added salts of various kinds on the hydrolysis reaction rates of *p*-nitrophenyl benzoate (*p*-NPB) in micellar media. We have also investigated the change in rates of the target molecule (*p*-NPB) with change in pH of the buffer from 8.50 to 10.0. The reaction rates were examined in solutions containing of cetyltrimethylammonium bromide (CTAB) and chloride (CTAC) surfactants both in the presence and absence of added salts at 35 °C. The simplified form of primary mechanism for the hydrolysis reaction of the substrate is indicated in Scheme 4-1. The attack by the OH$^-$ ion (the prominent nucleophile) and/or the H_2O molecule is expected to be on the carbonyl carbon center

in such a way that the UV-active group, the *p*-nitphenolate ion, is liberated. We would like to explain experimental results based on various factors such as micellar catalysis, nucleophilicities of anions, coordination abilities of metal ions and/or changes in properties/activities of water or the hydroxide ion upon the addition of salts.
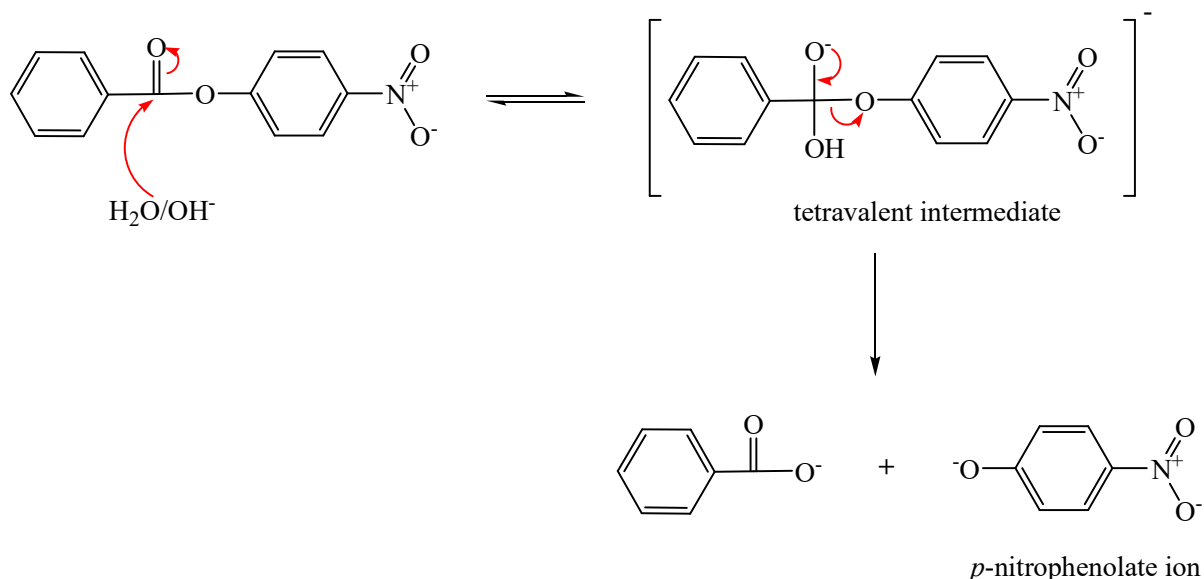
Scheme 4-1 proposed mechanism for alkaline hydrolysis of *p*-nitrophenyl benzoate

4.2 Experimental

4.2.1 Materials and equipment

All chemicals and salts utilized were commercially available and used as received. The target compound, *p*-nitrophenyl benzoate (>97.0%) was obtained from Alfa Aesar, England, and *p*-nitrophenol (>99.0%) was from TCI. Surfactants Cetyltrimethylammonium bromide (CTAB) (>98.0) and Cetyltrimethylammonium chloride (CTAC) (>95.0%) were both purchased from Wako. Salts of NaCl (99.5%), NaBr (99.5%), $LiClO_4$ ($\geq$98.0%), Et_4NBr ($\geq$98.0%), Et_4NCl ($\geq$98.0%), $(n\text{-}Bu)_4NBr$ ($\geq$98.0%), 0.5 mol dm^{-3} $n\text{-}Bu_4NOH$, $Na_2B_4O_7.10H_2O$ ($\geq$99.6) and the co-solvent, acetonitrile (of the GR grade), were all from Wako. Other salts of $NaClO_4$ ($\geq$98.0%), Me_4NBr ($\geq$98.0%), Pr_4NBr ($\geq$98.0%) and n-Bu_4NCl (>97%) were all from Aldrich. Instead of the commercially available 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. Distilled water purified by the MilliQ System was used in all the experiments. A Horiba F-51 digital pH meter was used for measuring the apparent pH of the reaction solutions.

4.2.2 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, surfactants cetyltrimethylammonium bromide (CTAB) and cetyltrimethylammonium chloride (CTAC), the borate buffer of pH = 9.18 (with 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 35 ± 0.1 °C in order to reach the thermal equilibrium.

Prior to the beginning of the reaction, the 5.0×10^{-3} mol dm^{-3} stock solution of the substrate (*p*-nitrophenyl benzoate) was prepared in a suitable volume of acetonitrile (as the substrate is sparingly soluble in pure water). Then, reactions were initiated by transferring a 1.0 mL of the stock solution into a reaction vessel (50 mL) to reach the final substrate concentration of 1.0×10^{-4} mol dm^{-3}. The samplings of 3 - 4 mL were carried out from reaction solutions at certain time intervals and the sampled solutions were immediately dipped into an ice water bath.

The reaction progress was then followed spectrophotometrically by monitoring the liberation of *p*-nitrophenolate ion at λ_{max} = *ca*. 400 nm as a function of time. The "pseudo" first order rate constants were then obtained from the slopes of ln $(A_\infty - A_t)$ *vs*. time (s), where A_∞ and A_t are the values of absorbance at the final of the reaction and at time t, respectively. All rate constants were evaluated from the linear curves with correlation coefficients (R^2) of normally 0.999 or better and the uncertainties for log (k/s^{-1}) is less than or equal to ±0.01.

4.3 Results and discussion

The rates of hydrolysis reactions of *p*-nitrophenyl benzoate (*p*-NPB) has been investigated under various reaction conditions in the presence and absence of surfactants cetyltrimethylammonium bromide (CTAB) and chloride (CTAC) at a constant temperature of 35 ℃. The generation of UV spectrums as a result of the hydrolysis reaction were followed at a wavelength of λ_{max} = *ca*. 400 nm with time as indicated in Fig. 4-1. The isosbestic point observed at 320 nm indicates the coexistence of the original substrate and the released tropolonate ion. Some of the representative ln (A$_\infty$ – A$_t$) *vs* time curves for the hydrolysis reaction of the target compound from which the rates were calculated as explained under section 4.2.2 is given in Fig. 4-2.
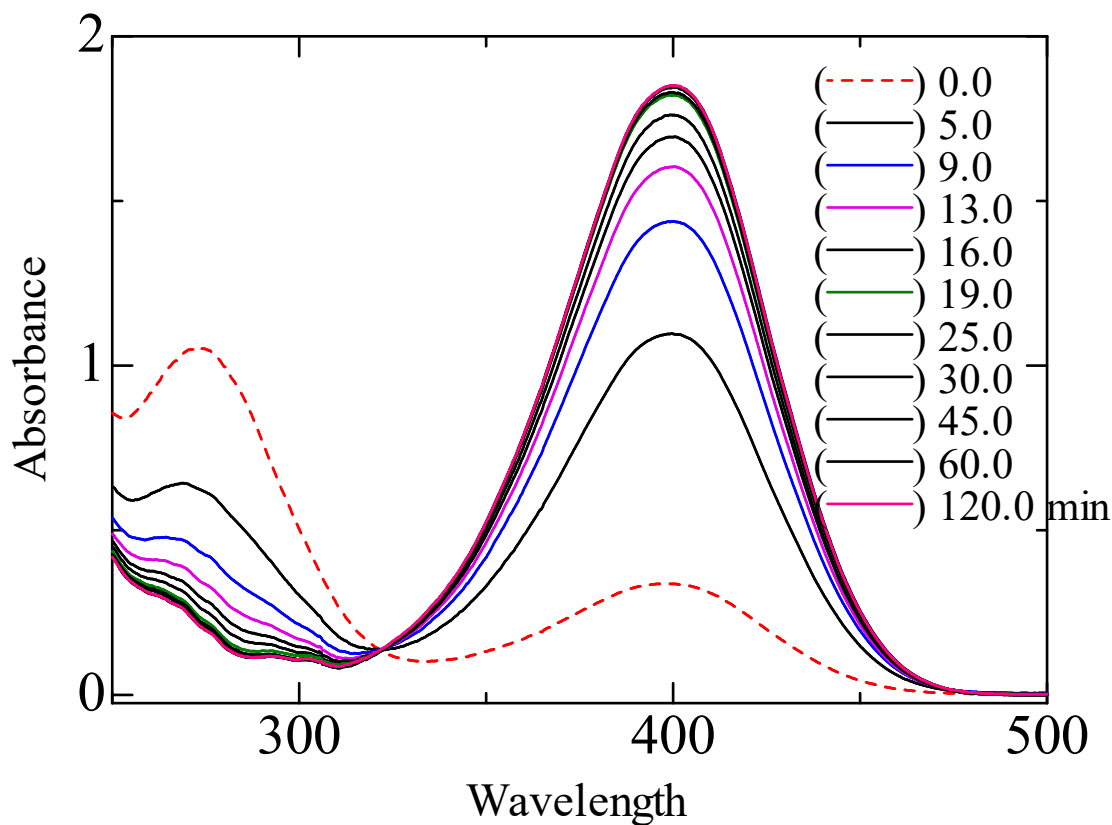
Fig. 4-1 Generation of *p*-nitrophenolate ion with time as the hydrolysis product from *p*-nitrophenyl benzoate in aqueous borate buffer of pH = 9.18 media containing 2.0 x 10^{-3} mol dm^{-3} CTAB at 35 ℃.
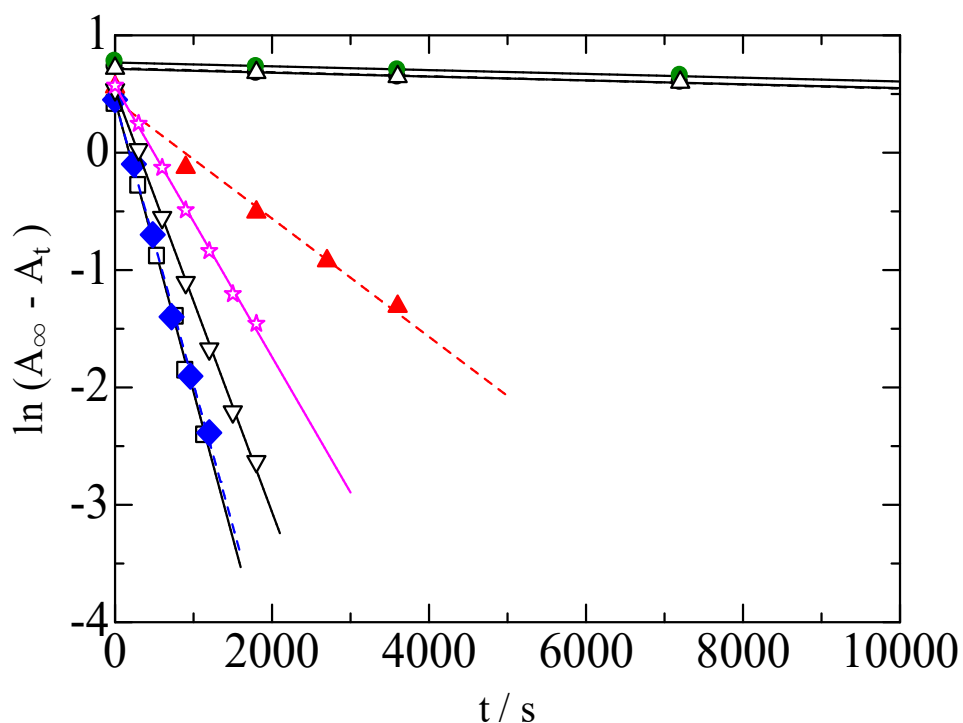
Fig. 4-2 ln(A∞ – At) vs. time curve for the hydrolysis of *p*-NPB in aqueous borate buffer solutions of pH = 9.18 containing various concentration of surfactant CTAB at 35°C: (○) 0.0; (●) 1.0×10^{-4}; (△) 5.0×10^{-4}; (▲) 9.8×10^{-4}; (□) 2.0×10^{-3}; (◆) 5.0×10^{-3}; (▽) 1.0×10^{-2}; (☆) 2.0×10^{-2} mol dm^{-3} CTAB.

4.3.1 Effects of pH

The effects of change in pH of the buffer solution on the hydrolysis reactions rate of *p*-NPB is investigated in aqueous media at 35 ºC. The rate constant [log ($k/$ s^{-1})] is linearly increased as -5.44, -4.74, -4.40, and -4.03 with the increase in pH of the buffer as 8.50, 9.18, 9.50, and 10.0, respectively, as shown in Fig. 4-3. The increase in rate is a normal and expected phenomenon which happens due to an increase in the prominent nucleophile, OH⁻, concentration or activity with increasing the pH of the buffer.
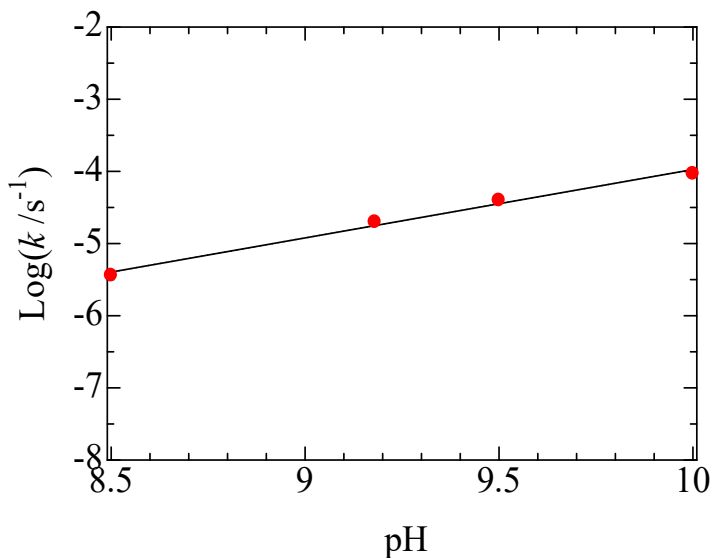
Fig. 4-3 Changes in log (k/s^{-1}) with pH of the buffer for the hydrolysis of *p*-NPB in aqueous solution at 35 °C.

4.3.2 Determination of Critical Micelle Concentration (cmc)

Micelle formation is accompanied by a sudden change in many solution properties such as surface tension, conductivity, viscosity, light scattering, and the like. These properties may be used to determine the critical micelle concentration (cmc) for a particular surfactant under specified set of conditions. In this investigation, spectroscopic method developed by Small and Carey [37] was employed to determine cmc values of both CTAB and CTAC surfactants. When the absorbance of the solution with the increasing concentration of the surfactant is measured, the absorbance (A) at λ_{max} or λ_{max} vs surfactant concentration plots show two straight lines with different slope.

The intersection of these two lines is taken as the cmc value of the surfactant. Fig. 4-4 and 4-5 show changes of slope in the plots of the maximum wavelength (λ_{max}) *vs* concentration the surfactant CTAB and CTAC, respectively, in aqueous borate buffer of pH 9.18 media using *p*-nitrophenol as a probe at 35 °C. The cmc values determined using this method is 9.12 x 10^{-4} mol dm^{-3} for CTAB and 1.26 x 10^{-3} mol dm^{-3} for CTAC. The corresponding value in aqueous media is reported as 9.8 x 10^{-4} mol dm^{-3} for CTAB at 35 °C [38] and 1.3 x 10^{-3} mol dm^{-3} for CTAC at 30 °C [3]. It is worth mentioning here that the cmc value of surfactants varies with the types of

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probes used in the determination methods. This is due to the interactions between the surfactant monomers and probes, which alters the micellization process as stated by Fuguet *et al*. [39] and others [40, 41].
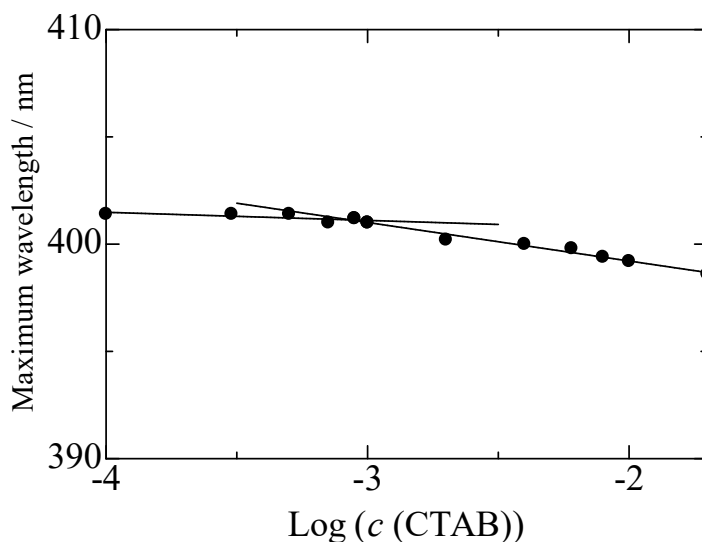
Fig. 4-4 Variation of λ_{max} of absorption *vs*. the logarithm of surfactant concentration for the spectrophotometrical determination of CMC for CTAB in solution containing 5.0 mM borate buffer (pH = 9.18) at 35 °C. *p*-Nitrophenol is used as a probe.
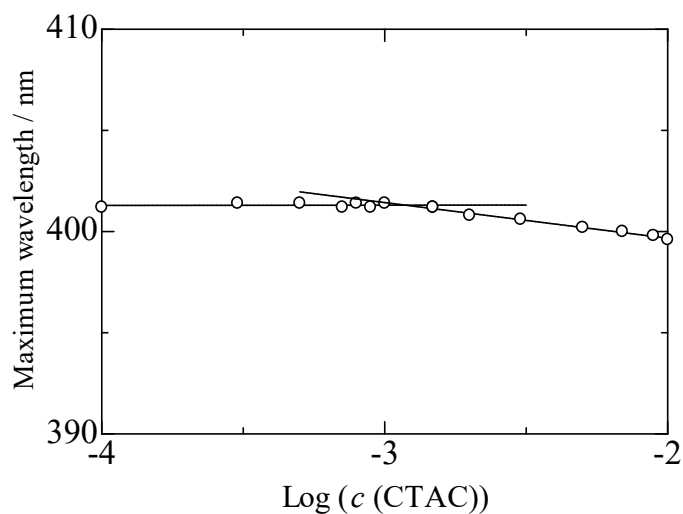
Fig. 4-5 Variation of λ_{max} of absorption *vs*. the logarithm of surfactant concentration for the spectrophotometrical determination of CMC for CTAC in solution containing 5.0 mM borate buffer (pH = 9.18) at 35 °C. *p*-Nitrophenol is used as a probe.

4.3.3 Hydrolysis of *p*-NPB in the presence of cationic surfactants CTAB and CTAC

Fig. 4-6 depicts the effect of CTAB and CTAC surfactants on the alkaline hydrolysis of *p*-NPB in aqueous buffer of pH = 9.18 media at 35 °C. It is found out that the rates of reactions showed no significant change upon addition of up to 5.0×10^{-4} mol dm^{-3} of both CTAB and CTAC surfactants. As indicated earlier (*cf.* section 4.3.2), the critical micellar concentration (cmc) values determined under the set of reaction conditions is 9.12×10^{-4} and 1.26×10^{-3} mol dm^{-3} for CTAB and CTAC, respectively. From the concentration-rate profile data (cf. Table 4-1 and Fig. 4-6), we can see that below the cmc value the rate constants for the hydrolysis of *p*-NPB are either independent on surfactant concentration or slightly decelerated. In the presence small concentrations (up to 5.0×10^{-4} mol dm^{-3}) of both CTAB and CTAC surfactants, a slight rate deceleration is observed. This rate deceleration is mainly attributed to the decrease in water activity due to the added surfactants, which are not fully formed micelles yet. However, the rate is sharply increased on further increasing both surfactants concentration and reach to maximum at CTAB concentration of 2.0×10^{-3} mol dm^{-3} and CTAC concentration of 4.0×10^{-3} mol dm^{-3}.
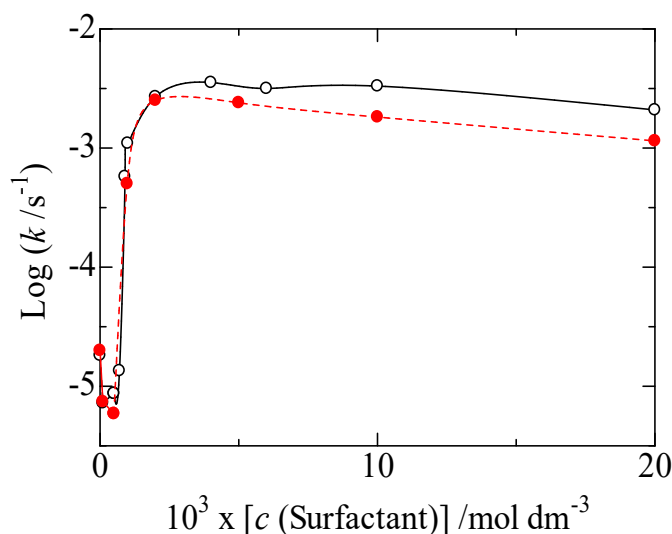
Fig. 4-6 Changes in log (k /s^{-1}) values with surfactant concentration for the hydrolysis of p-NPB in aqueous buffer solution of pH = 9.18 media at 35 °C: (○) CTAC; (●) CTAB.

At the optimal point a 140-fold rate acceleration is observed for CTAB compared with the rate in solution containing no CTAB. Similarly a 200-fold rate acceleration obtained for CTAC at its optimal point compared with solution containing no CTAC. A further increase in

both CTAB and CTAC surfactants concentration, however, leads to no significant change or a gradual decrease in the rate of the hydrolysis reactions of the substrate. It worth mentioning here that at concentrations $> 2.0 \times 10^{-3}$ mol dm^{-3}, the rate deceleration effect caused by surfactant CTAB is slightly higher than CTAC. This is directly related to the nonreactive counter ions, Br^{-} and Cl^{-}, abilities of interaction with the charged surface of the micelle upon increasing their concentrations. It is obvious that the Cl^{-} ion is more hydrated with water molecules than Br^{-} under similar conditions, and hence has less ability to compete with the reactive counter ion, OH^{-}, for the micellar charged surface. As a result the rate deceleration caused by Cl^{-} ion is slightly smaller than the effects of its counterpart Br^{-} ion.

Table 4-1 Effects of surfactants (CTAB and CTAC) concentrations upon the hydrolysis of 1.0 x 10^{-4} mol dm^{-3} of *p*-nitrophenyl benzoate (*p*-NPB) in aqueous buffer solution of pH = 9.18 at 35 °C.

10^3 [substrate] / mol dm^{-3}	(CTAB)		(CTAC)	
	k_{obs}/s^{-1}	Log (k_{obs}/s^{-1})	k_{obs}/s^{-1}	Log (k_{obs}/s^{-1})
0.0	1.82×10^{-5}	-4.74	1.82×10^{-5}	-4.74
0.1	7.42×10^{-6}	-5.13	7.10×10^{-6}	-5.14
0.5	5.90×10^{-6}	-5.23	8.64×10^{-6}	-5.06
0.7	-	-	1.34×10^{-4}	-4.87
0.9	-	-	5.75×10^{-4}	-3.24
0.98	5.04×10^{-4}	-3.30	-	-
1	-	-	1.10×10^{-3}	-2.96
2	2.49×10^{-3}	-2.60	2.68×10^{-3}	-2.57
4	-	-	3.56×10^{-3}	-2.45
5	2.41×10^{-3}	-2.62	3.39×10^{-3}	-2.47
6	-	-	3.13×10^{-3}	-2.50
10	1.80×10^{-3}	-2.74	3.28×10^{-3}	-2.48
20	1.15×10^{-3}	-2.94	2.11×10^{-3}	-2.68

This type of rate profile, *i.e.* the appearance of a rate maximum, for the hydrolysis reactions of various organic compounds in the presence of cationic surfactants is well documented in literatures [8, 13-18, 20, 42-45]. These literature evidences strongly suggested that in micellar media, most reactions occur on the surface of micelle, at or near the highly charged double layer commonly called Stren layer (Scheme 4-2). The more evident feature of Fig. 4-6 is the enhancement in the reaction rates originated by the presence of the cationic surfactants CTAB and CTAC. This is a reasonable behavior taking into account that *p*-NPB is hydrophobic in nature and tend to associate to the micelles by hydrophobic effect, mainly. Besides, the reaction is with an anion, OH⁻, the counter ion of the micelle, this supramolecular assembly acts as a micro-reactor increasing the concentration of the two reactants in a medium, in any case, different from bulk water. The kinetic treatment of such phenomenon is considered based upon the so-called pseudophase model as discussed under section 4.3.4 below.
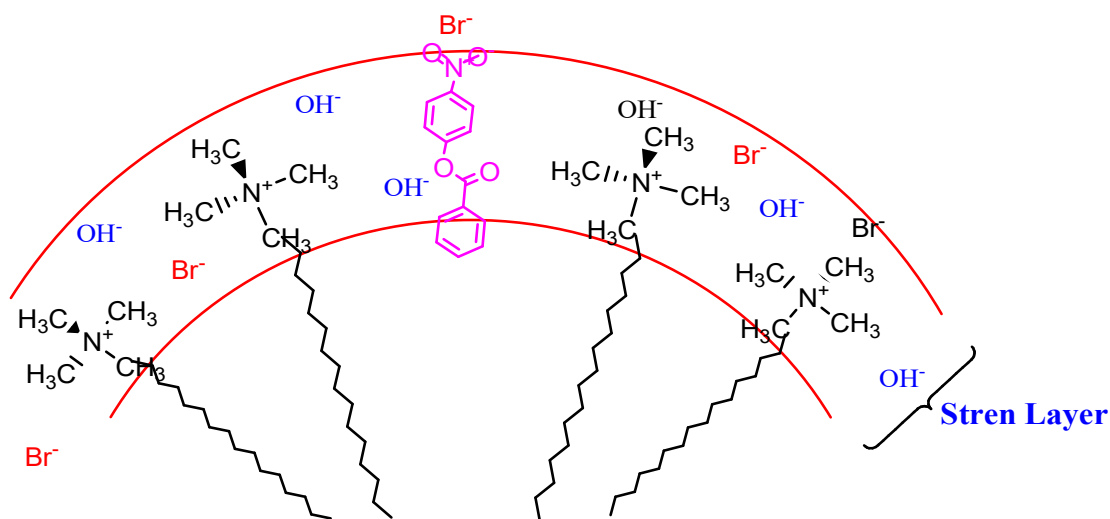
Scheme 4-2 A hypothetical orientation of *p*-nitrophenyl benzoate bound to micelles of CTAB

The decrease in rate of reactions at higher surfactant concentrations in most of the micelle catalyzed bimolecular reactions is a well-known phenomenon. At higher surfactants concentration, the total number of micelles is increased and the local molalities of the organic substrate and OH⁻ ions in and around Stern layer of micellar surface are decreased. As a result, the net concentrations of reactant are diluted with the increase in the concentrations of surfactants and, thereby, causing a decrease in the reaction rate.

As a general remark, the catalytic or inhibitive effect of micelles on the values of rate constants can be explained in terms of the partitioning of the reactants in the aqueous and micellar pseudophases. The variation in the values of rate constant with the variation in surfactant concentration is, therefore, attributed to:

i. variation in the local concentration of the reactants in the aqueous and micellar pseudophases;

ii. variation in the polarity of the media (aqueous and micellar pseudophases); and/or

iii. different rates of reaction in the aqueous and micellar pseudophases.

4.3.4 Kinetic Treatment of Micellar Effects

A kinetic treatment of micellar effects on the hydrolysis reaction rates of organic compounds requires some approximations. From a purely formal approach, the Michaelis-Menten methods known from enzyme chemistry can be recognized [1]. The reactive organic molecule, for instance *p*-NPB in this particular case, is considered to be distributed in both the aqueous and micellar phases in accordance with their hydrophilic or hydrophobic characteristics. The molecules are oriented with the micelles in a manner that suits their polarity. The reactive anion, the OH⁻ ion, is also distributed in the aqueous and Stern layer of the micellar region (as hypothetically indicated in Scheme 4-2). Its concentration in the micellar pseudophase can be optimized on the basis of ion exchange model. The mechanism of hydrolysis occurring in the presence of micelles can be presented as follows (Scheme 4-3).
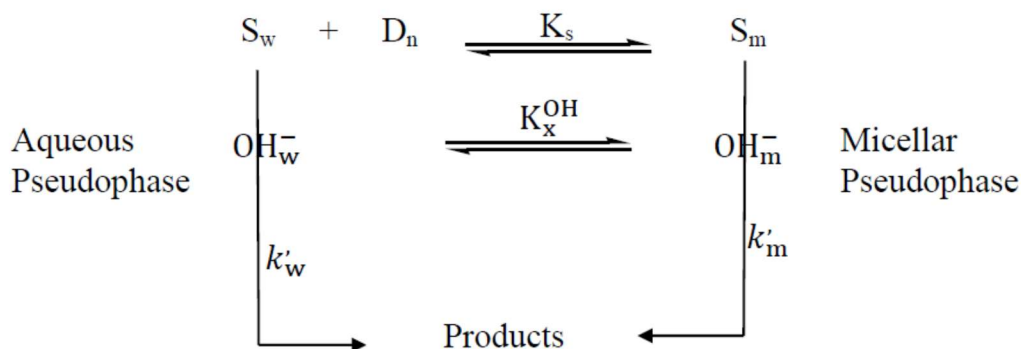
Scheme 4-3 Pseudophase ion exchange model for the hydrolysis reaction in aqueous and micellar media

In scheme 4-3, S_w and S_m represents substrates in aqueous and micellar media, respectively. k'_w and k'_m are pseudo-first order rate constants in aqueous and micellar pseudophases, respectively. K_s is the binding constant of the substrate to the micelle and mathematically given by Eq. (4-1):

$$K_S = \frac{[S_m]}{[S_w][D_n]} \tag{4-1}$$

D_n is the micellized surfactant (D_n = [D] − cmc, where D is the total surfactant concentrations) and cmc is the critical micelle concentration. The observed rate constant can be described mathematically as Eq. (4-2), a derivation of the Michaelis-Menten equation.

$$k_{obs} = \frac{k'_w + k'_m K_S[D_n]}{1 + K_S[D_n]} \tag{4-2}$$

The rate constants in the respective pseudophases (k'_w and k'_m) are given by Eq. (4-3) and (4-4), respectively.

$$k'_w = k_w[OH^-_w] \tag{4-3}$$

$$k'_m = \frac{k_m[OH^-_m]}{D_n} \tag{4-4}$$

Competition of the nucleophile with the counter ion of the surfactant must be taken into account in the case of bimolecular reactions with an uncharged hydrophobic substrate and an ionic nucleophile in a cationic micelle. This is possible by the introduction of an ion-exchange equilibrium [Eq. (4-5)], with which the ionic concentrations in the aqueous and the micellar pseudophase can be calculated.

$$OH^-_m + X^-_w \overset{K^{OH}_X}{\rightleftharpoons} OH^-_w + X^-_m \tag{4-5}$$
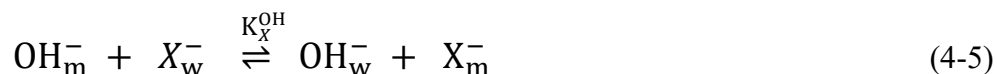
and K^{OH}_X is given as Eq. (4-6)

$$K_x^{OH} = \frac{[OH_w^-][X_m^-]}{[OH_m^-][X_w^-]} \tag{4-6}$$

where K_x^{OH} is equilibrium constant for the binding of the counter ion, X^- and hydroxide ions (OH^-) to the micellar surface. In this expression, X_m^- and X_w^- are surfactant counterions existing in the micellar and aqueous phases, respectively.

For OH^- as a reactive ion and Br^- as a non-reactive micelle counterions, the ion-exchange equilibrium can be expressed as Eq. (4-7).

$$OH_m^- + Br_w^- \overset{K_{Br}^{OH}}{\rightleftharpoons} OH_w^- + Br_m^- \tag{4-7}$$
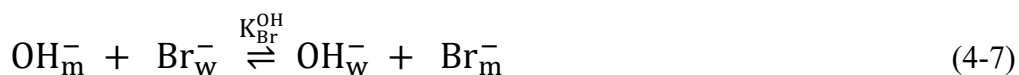
And equilibrium constant for the binding of the counter ion, Br^- and hydroxide ions (OH^-) to the micellar surface is given as Eq. (4-8).

$$K_{Br}^{OH} = \frac{[OH_w^-][Br_m^-]}{[OH_m^-][Br_w^-]} \tag{4-8}$$

4.3.5 Effects of Bromide Salts on the Hydrolysis of *p*-NPB in the Presence and Absence of Surfactant CTAB

In Fig. 4-7, first-order rate constants [Log $(k \ /s^{-1})$] (given in Table 4-1) for the hydrolysis of *p*-nitrophenyl benzoate in aqueous media containing 5.0 mmol dm^{-3} of borate buffer of pH = 9.18 in the presence of 5.0 x 10^{-3} mol dm^{-3} cetyltrimethylammonium bromide (CTAB) are plotted as a function of the concentration of several added bromide salts. All the salts studied are inhibitors and 0.1 mol dm^{-3} of each of them is sufficient to convert the surfactant catalyzed reactions into the inhibited one.

For instance, 0.1 mol dm^{-3} of NaBr caused the rate constant [log $(k \ /s^{-1})$] to drop from -2.62 to -4.04 and further increase in concentration of NaBr resulted in gradual deceleration of the rate of hydrolysis reaction of *p*-NPB. The Me4NBr, Et4NBr, Pr4NBr and *n*-Bu4NBr salts also caused significant rate deceleration upon addition of 0.1 mol dm^{-3} of each of them. However, upon increasing their concentrations (especially to greater than 0.2 mol dm^{-3}) the rate

deceleration effects observed seems to be gradually diverted (though not so significant) and an attention-grabbing phenomenon of a slight rate acceleration effect was observed (*cf.* Fig 4-7 and Table 4-2). The behavior of rate deceleration caused by added salts can be rationalized by assuming a competition between the reactant and the electrolyte for the "binding site" on or in the micelle.

The effects of electrolytes on micellar catalyzed reactions are, therefore, preferably discussed in terms of their competition with the reagents for the available binding sites as well as their ability to alter the micellar structure. Therefore, the Br^-, a counter ion of the micelle, competes for the micellar surface with the prominent nucleophile, the OH^- ion. Accordingly, with increasing concentrations of bromide salts, the Br^- ion displaces the OH^- from the micellar surface and hence resulted in abrupt rate deceleration. Interestingly, the rate deceleration observed seems to depend on the hydrophobicity of the cations of the salts. The general rate deceleration caused by the added salts follow the order: $NaBr > Me_4NBr > Et_4NBr > Pr_4NBr > n\text{-}Bu_4NBr$.

Fig. 4-7 Changes in log (k /s^{-1}) values with bromide salt concentration for the hydrolysis of *p*-NPB in aqueous buffered solution of pH = 9.18 containing 5.0 x 10^{-3} mol dm^{-3} CTAB at 35 °C: (◊) NaBr; (●) Me$_4$NBr; (○) Et$_4$NBr, (▲) Pr$_4$NBr, (△) *n*-Bu$_4$NBr.

It is worth noticing that, further increase in the concentration of Me_4NBr, Et_4NBr, Pr_4NBr and n-Bu_4NBr salts, especially in the higher concentration ranges of 0.5 – 1.0 M, resulted in a reversal effect of slight rate acceleration. This phenomenon might be attributed to the changes in micellar structure and to some part to destruction of water structure to the greater extent by the added high concentration of bulky salts, and as a result an increase in activities of the OH⁻ ion. At this point it is also important to think about the neutralization of the micellar surface by the added high concentration of Br- ions and change it to something similar to a neutral foreign material added to reaction solution which has only the ability of breaking water structure. Hence, in such media, the increase in activity of the prominent nucleophile, the OH⁻ ion, play a great role in increasing the rates of reaction to some extent. In addition, the nucleophilicity of the Br⁻ ion, which is basically available in large quantities in the media, could possibly contribute to the small rate reversal effect noticed.

Table 4-2 Effects of added bromide salts on the hydrolysis of p-NPB (1.0×10^{-4} mol dm^{-3}) in aqueous buffer solution of pH = 9.18 containing 5.0×10^{-3} mol dm^{-3} CTAB at 35°C.

Salt concentrations / mol dm^{-3}	Log (k_{obs} / s^{-1})				
	NaBr	Me$_4$NBr	Et$_4$NBr	Pr$_4$NBr	n-Bu$_4$NBr
0.0	-2.62	-2.62	-2.62	-2.62	-2.62
0.1	-4.04	-3.97	-3.84	-3.85	-3.81
0.2	-4.28	-4.21	-4.00	-3.94	-3.90
0.3	-4.55	-4.24	-4.05	-3.94	-3.89
0.5	-4.64	-4.26	-4.06	-3.87	-3.77
0.7	-4.75	-4.23	-3.95	-3.77	-3.65
1.0	-4.89	-4.18	-3.86	-3.60	-3.55

The rate deceleration effect caused by the added NaBr can also be justified by the apparent pH of the reaction solution. The apparent pH of the reaction solution measured after the completion of the hydrolysis reaction showed decrement with the increase in concentration of

NaBr. This phenomenon is attributed to the possible interaction of Na^+ ion with the OH^- ion. The other salts, however, caused no significant change in apparent pH especially in the presence of about 0.3M of each of them, after which a slight increase in apparent pH is observed as indicated in Fig. 4-8. This evidence is also one supporting phenomenon to justify the slight reversal rate acceleration upon addition of high concentration of the bromide salts, except NaBr salt.
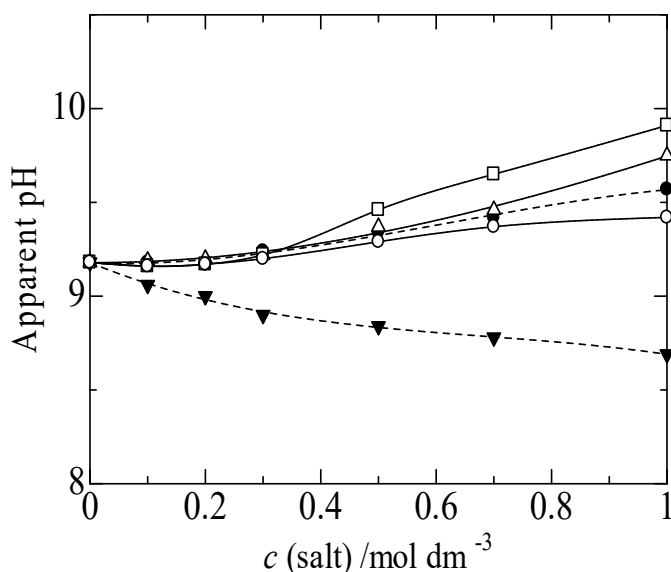
Fig. 4-8 Changes in apparent pH of reaction solution with salt concentration for the hydrolysis of *p*-NPB in aqueous buffer of pH = 9.18 media containing 5.0 x 10^{-3} mol dm^{-3} CTAB at 35 °C: (▼) NaBr; (○) Me_4NBr; (●) Et_4NBr, (Δ) Pr_4NBr, (□) *n*-Bu_4NBr.

Similarly the effects these bromide salts on the hydrolysis reaction rates of *p*-NPB in aqueous buffer of pH 9.18 media in the absence of CTAB is also investigated (Fig. 4-9). In the absence of CTAB surfactant, the NaBr salt once again linearly decelerates the hydrolysis reaction rate of *p*-NPB. The log (k /s^{-1}) values decreased as -4.85, -4.90, -4.94, -4.94, -5.10, -5.20 and -5.37 with the increase in NaBr concentration as 0.1, 0.2, 0.3, 0.5, 0.7 and 1.0 mol dm^{-3}, respectively (Table 4-3). The other bromide salts such as Me_4NBr, Et_4NBr, Pr_4NBr and *n*-Bu_4NBr, however, are noticeably and linearly accelerated the rate of the hydrolysis reactions of *p*-NPB in solution containing no CTAB. For instance, in the presence of added Et_4NBr the log (k /s^{-1}) values increased as -4.69, -4.59, -4.50, -4.27, -4.13 and -3.94 upon increasing its concentration as 0.1, 0.2, 0.3, 0.5, 0.7 and 1.0 mol dm^{-3}, respectively. Generally, the rate

acceleration effect imposed by the added bromide salts increases with the increase in the hydrophobicity (size) of cations of the salt from the added salts. As can be seen from Fig. 4-9, the higher rate acceleration is caused by the bulkiest salt of n-Bu$_4$NBr. The larger the cations of the salt or the bulkier the salt, the more it distracts water structure/or activity. This will lead to an increase in the activity of the prominent nucleophile, the OH$^-$ ion, and hence an increase rate of the hydrolysis reaction of the substrate. The general rate acceleration effect follow the order of Me$_4$NBr < Et$_4$NBr < Pr$_4$NBr < n-Bu$_4$NBr.

In aqueous media and in the absence of surfactant, in addition to changes in water structure, which is basically results in an increase in the OH$^-$ ion activity, upon the addition of anionic salts, the nucleophilicty of the anions from the added salt should also be taken into consideration to justify the observed phenomenon. Therefore, the rate acceleration caused by the added bromide salts, except NaBr, should be attributed to the increase in the activities of the OH$^-$ in the media where water structure is distracted to the greater extent by the added salts. In such media, the attack by Br$^-$ ion (a nucleophile) on the target compound, the p-NPB, to liberate the p-nitrophenolate in addition to the OH$^-$ ion should also contribute to the rate acceleration resulted.

Fig 4-9 Changes in log (k /s^{-1}) values with bromide salt concentration for the hydrolysis of p-NPB in aqueous buffered solution of pH = 9.18 in the absence of surfactant at 35 °C: (◊) NaBr; (●) Me$_4$NBr; (○) Et$_4$NBr, (▲) Pr$_4$NBr, (Δ) n-Bu$_4$NBr.

Table 4-3 Effects of added bromide salts on the hydrolysis of p-NPB (1.0×10^{-4} mol dm^{-3}) in aqueous buffer solution of pH = 9.18 in the absence of CTAB at 35°C.

Salt concentrations / mol dm^{-3}	Log (k_{obs} / s^{-1})				
	NaBr	Me$_4$NBr	Et$_4$NBr	Pr$_4$NBr	n-Bu$_4$NBr
0.0	-4.74	-4.74	-4.74	-4.74	-4.74
0.1	-4.85	-4.68	-4.69	-4.61	-4.56
0.2	-4.90	-4.61	-4.59	-4.41	-4.33
0.3	-4.94	-4.55	-4.50	-4.32	-4.06
0.5	-5.10	-4.47	-4.27	-3.96	-3.64
0.7	-5.20	-4.35	-4.13	-3.54	-3.60
1.0	-5.37	-4.21	-3.84	-3.44	-3.54

4.3.6 Effects of Chloride Salts on the Hydrolysis of p-NPB in the Presence and Absence of Surfactant CTAC

The effects of chloride salts such as NaCl, Et$_4$NCl and n-Bu$_4$NCl on the hydrolysis reaction rates of p-NPB were investigated in aqueous buffer of pH = 9.18 medium containing 5.0 x 10^{-3} mol dm^{-3} CTAC surfactant at 35 °C. All the salts decelerated the rate of hydrolysis reaction rates of p-NPB and 0.1 mol dm^{-3} of each of them is found to be enough to cause significant rate deceleration as similarly mentioned earlier for CTAB surfactant. The NaCl salt instigated a continuous rate deceleration as its concentration is increased as can be witnessed from Fig. 4-10 and Table 4-4. The effects of Et$_4$NCl and n-Bu$_4$NCl salts however, resulted in insignificant rate change upon further increasing their concentration. Nevertheless, they showed a similar slight rate acceleration behavior with bromide salts in media containing CTAB surfactant (*cf.* Fig. 4-7) especially at their respective concentration of ≥ 0.5 mol dm^{-3}. The rate deceleration caused by the chloride salts follow the order of NaCl > Et$_4$NCl > n-Bu$_4$NCl.
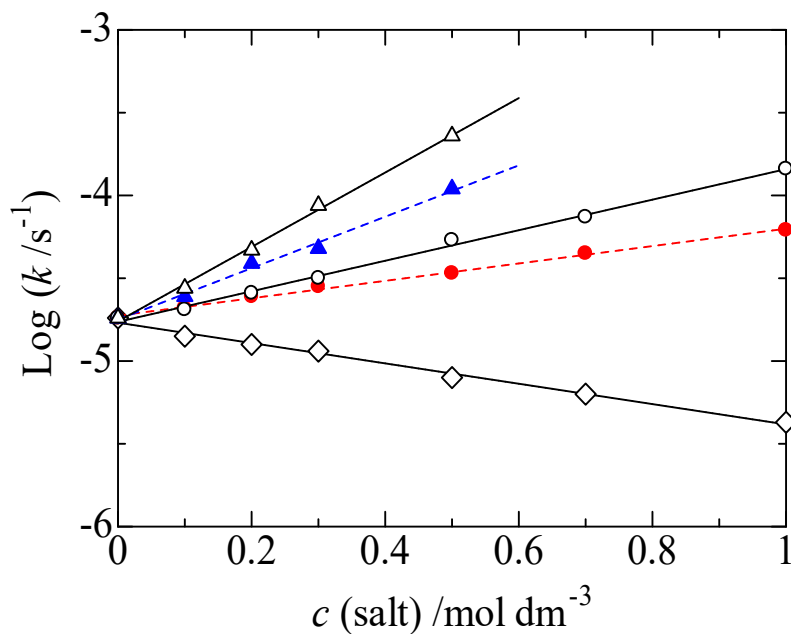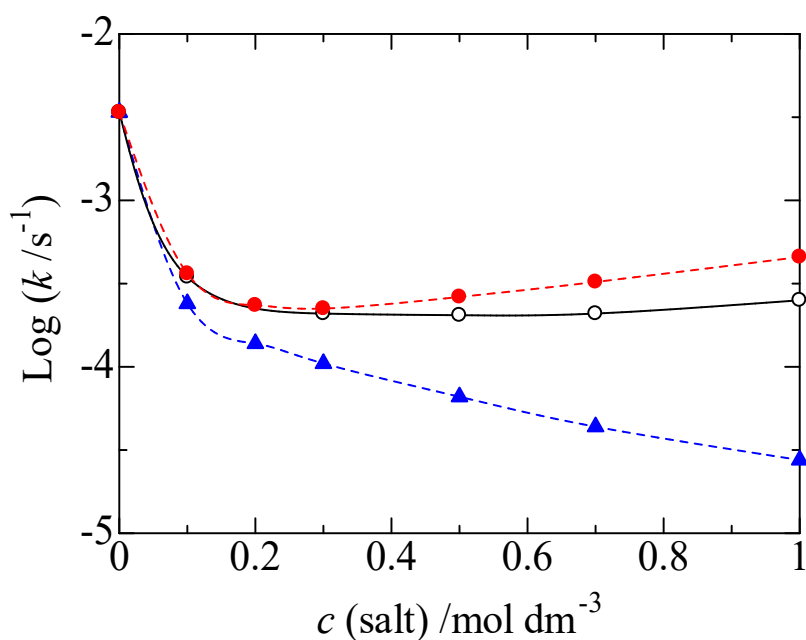
Fig. 4-10 Changes in log (k /s^{-1}) values with chloride salt concentration for the hydrolysis of *p*-NPB in aqueous buffered solution of pH = 9.18 containing 5.0 x 10^{-3} mol dm^{-3} CTAC at 35 °C: (▲) NaCl; (○) Et$_4$NCl, (●) *n*-Bu$_4$NCl.

Table 4-4 Effects of added chloride salts on the hydrolysis of *p*-NPB (1.0 x 10^{-4} mol dm^{-3}) in aqueous buffer solution of pH = 9.18 containing 5.0 x 10^{-3} mol dm^{-3} CTAC at 35°C.

Salt concentrations / mol dm^{-3}	**Log (k_{obs} / s^{-1})**		
	NaCl	Et$_4$NCl	*n*-Bu$_4$NCl
0.0	-2.47	-2.47	-2.47
0.1	-3.62	-3.46	-3.44
0.2	-3.86	-	-3.63
0.3	-3.98	-3.68	-3.65
0.5	-4.18	-3.69	-3.58
0.7	-4.36	-3.68	-3.49
1.0	-4.56	-3.60	-3.34

Cordes and Dunlap [19] have reported similar rate deceleration upon addition of various kinds of salt for the hydrolysis of *p*-nitrophenyl hexanoate in the presence of CTAC in aqueous buffer of pH = 10.15 media. They indicated that all added salts are inhibitors and specially 0.1 M concentration of bromide and nitrate ions are sufficient to convert the surfactant-catalyzed reaction to uncatalyzed (inhibited) one. However to broader sense, information on the effects of salts on reactions rate of organic compounds in micellar media is in lack compared with the wide range of data available for similar type of reactions either in aqueous media or in mixed solvent media.

We have investigated the detailed effects of various kinds of salts (especially in the presence of large concentrations of the salts) on the hydrolysis reaction rates of p-NPB in the presence and absence of surfactants CTAB and CTAC. We have found out that, at certain concentrations of the salts the rates of the hydrolysis of p-NPB is recovered and showed increment with increasing the concentration of the added salts (except NaBr and NaCl salts).

In the absence of CTAC surfactant, the NaCl salt once again significantly decelerated the hydrolysis reaction rate of *p*-NPB (Fig. 4-11). The $\log (k /s^{-1})$ values decreased as -4.74, -5.01, -5.12, -5.18, -5.34, -5.48 and -5.65 with the increase in NaCl concentration as 0.0, 0.1, 0.2, 0.3, 0.5, 0.7 and 1.0 mol dm^{-3}, respectively (Table 4-5). The rate deceleration caused by NaCl salt is stronger than that caused by NaBr salt. This is associated with their ability to distract water structure and/or activity. The Cl$^-$ ion is smaller in size compared to the Br$^-$ ion and hence hydrated strongly by water. This will lead to the greater distraction of water activity in the presence of Cl$^-$ than Br$^-$ ion and as a result a stronger rate deceleration effect on the target molecule *p*-NPB.

The Et$_4$NCl and *n*-Bu$_4$NCl salts, however, caused the rate to fairly accelerate with their respective concentrations. This is attribute to the nucleophilicity of the Cl$^-$ ion. The rate acceleration caused by Et$_4$NCl and *n*-Bu$_4$NCl salts is slightly weaker than their counter bromide salt, which is associated to the nucleophilicty difference between the Cl$^-$ and Br$^-$ ions.

Table 4-5 Effects of added chloride salts on the hydrolysis of p-NPB (1.0×10^{-4} mol dm^{-3}) in aqueous buffer solution of pH = 9.18 in the absence of CTAC at 35°C.

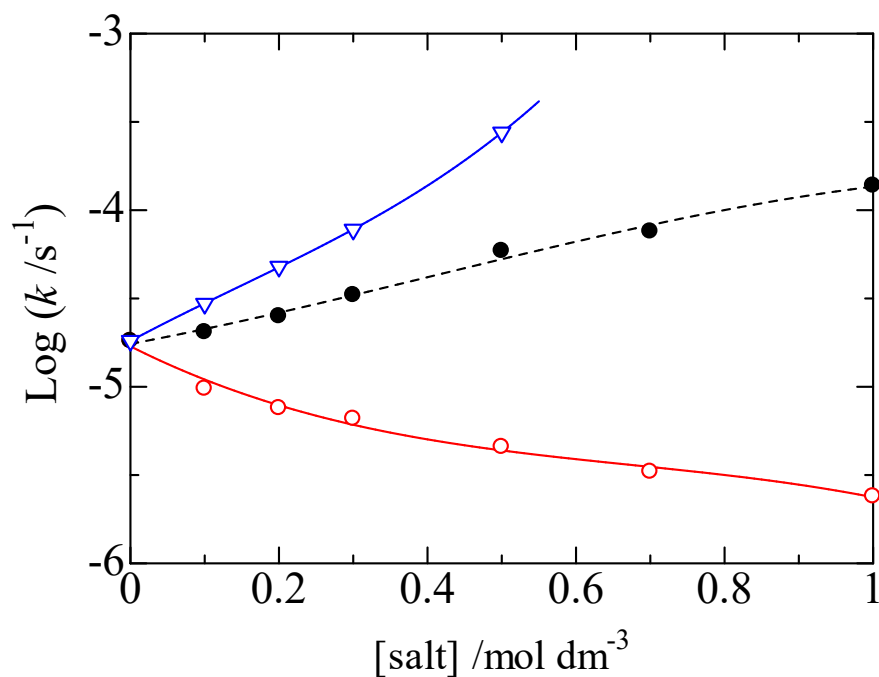| Salt concentrations / mol dm^{-3}	Log (k_{obs} / s^{-1})		
	NaCl	Et$_4$NCl	n-Bu$_4$NCl
0.0	-4.74	-4.74	-4.74
0.1	-5.01	-4.69	-4.53
0.2	-5.12	-4.60	-4.32
0.3	-5.18	-4.48	-4.11
0.5	-5.34	-4.23	-3.56
0.7	-5.48	-4.12	-
1.0	-5.65	-3.86	-

Fig 4-11 Changes in log (k /s^{-1}) values with chloride salt concentration for the hydrolysis of p-NPB in aqueous buffered solution of pH = 9.18 in the absence of surfactant at 35 °C: (○) NaCl; (●) Et$_4$NCl; (△) n-Bu$_4$NCl

4.4 Conclusions

The concentration-rate profile obtained in this study is multiphase: below the cmc of the surfactants, the rate constants for the hydrolysis reactions of p-NPB are independent of surfactant concentration. Above the cmc values, the rate constants rise rapidly with increasing concentration of the surfactants. At the optimal surfactants concentration of 2.0 and 4.0 mM for CTAB and CTAC, respectively, a rate augmentation of greater than 100-fold is observed compared with the solutions containing no surfactants under the studied reaction conditions. Further increasing surfactants concentration however, caused a gradual rate deceleration. Profiles of these type can be rationalized on the basis of (i) the necessity of micelles for "catalysis"; (ii) a progressively adsorption of a great fractions of the substrate into the micellar phase until that fraction approaches unity with increasing surfactants concentration; and (iii) inhibition of the micellar reaction by the counter ions of the surfactants themselves.

It can be clearly seen that the rate of p-NPB hydrolysis is significantly affected by the added salts which depends on the media used. All added salts inhibited the rates in solutions containing both CTAB and CTAC surfactants and 0.1 mol dm^{-3} of each is observed to be sufficient to significantly decelerate the rate. The general rate deceleration caused by the added salts follow the order of: NaBr > Me$_4$NBr > Et$_4$NBr > Pr$_4$NBr > n-Bu$_4$NBr for bromide salts in the presence of 5.0 x 10^{-3} mol dm^{-3} of CTAB and NaCl > Et$_4$NCl > n-Bu$_4$NCl for chloride salts in the media containing CTAC surfactant. However, in the absence of surfactants, except NaBr, all added bromide salts linearly accelerated the rates of hydrolysis reactions of p-NPB in the general order of: Me$_4$NBr < Et$_4$NBr < Pr$_4$NBr < n-Bu$_4$NBr. Similar order of rate acceleration (Et$_4$NCl < n-Bu$_4$NCl) is witnessed in the presence of chloride salts as well.

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General Summary

The hydrolysis reaction rates [log (k/s^{-1})] of all substrates studied are basically influenced by all kinds of salts investigated, contents of MeCN, pH, temperature, concentrations of n-Bu$_4$NOH and to a greater extent by presence of surfactants (micelle formation). Increasing the pH of the buffer and concentration of n-Bu$_4$NOH generally causes an increase in the rate of ester hydrolysis reactions. This is a normal phenomenon that could be accounted for the increase in concentrations of the prominent nucleophile, the OH$^-$ ion, in the reaction media and/or to the increase in activity of the OH$^-$ ions.

The acetonitrile added to water were assumed to occupy cavities in the water network structure, which remain intact while the cavities were field. There are literature evidence indicating that at a 15-20 mol% content of MeCN, the water became saturated with it and further addition triggered a marked structural change. Thus, the addition of organic solvent to H$_2$O as co-solvent obviously results in changes in some physical properties of the solution such as viscosity, dielectric constant, density, etc. These changes in physical properties of the media have been observed to significantly affect the rates of reactions of organic compounds. So, from the results of our investigation on the effects of MeCN-H$_2$O mixture on the hydrolysis of some organic compounds, which are potentially toxic, we obtained that the rates of hydrolysis such compounds are significantly affected by the successive addition of acetonitrile to water as co-solvent.

Generally speaking, the results obtained showed two diverse effects of acetonitrile contents on the hydrolysis reaction rates of the investigated organic compounds (p-NPA and p-NPB). These effects are a decrease in rate upon addition of up to 50 - 60% (v/v) MeCN and a reversal increase in rate with further increasing in MeCN content. The phenomenon of this type could be attributed to two interrelated factors. The decrease in hydrolysis reaction rate with increasing MeCN contents is mainly attributed to an alteration of water properties and hence deterioration of water activities in the presence of the organic solvent, MeCN. The appearance of these minima as the MeCN contents increase to larger than about 60% (v/v), however, can be attributed mainly to an increase in the OH$^-$ activity due to the increase in dehydration of OH$^-$ by progressive addition of MeCN.

In addition to solvent effects, the presence of various salts also expected to have a significant effect on the rates of hydrolysis reactions of toxic organic compounds. The added salts can lead either to rate acceleration or deceleration, depending on the substrate, the specific salts, and their concentration. In this study, all added salts have exhibited significant effects on the rates of hydrolysis reactions of the studied organic compounds in both aqueous and binary solvent media. Their respective effect obviously showed dependency on many factors such as: (a) coordination ability of the metal ions with the substrate or living group; (b) hydration ability of the ions, (c) dissociation ability of the salt, (d) nucleophilicty of the anions from the added salts, (e) bulkiness of the salts or their ability to destruct water structure, (f) degree of the interaction between the cations from the salt and the prominent nucleophile, OH^- ions, etc. These factors must be taken into consideration to justify the hydrolysis reaction rate changes of any organic compounds studied in the presence of added salts.

Micelles provide an unusual medium which may affect the rates of the reaction in many ways. They are proficient in bringing together the reactants within their small volumes. They can also stabilize and orient substrates in order to change their reactivity. Therefore, they can modify the reaction rates, mechanisms, etc. The effects of micelles might be either rate acceleration or deceleration depending upon the type of surfactants used for micelle formation. We have witnessed the rate acceleration effect of cationic surfactants CTAB and CTAC on the hydrolysis reaction rates of *p*-NPB. A multiphase concentration-rate profile obtained in this study shows, below the cmc of the surfactants, the rate constants for the hydrolysis reactions of *p*-NPB are independent of surfactant concentration. Above the cmc values, the rate constants rise rapidly with increasing concentration of the surfactants.

At the optimal surfactants concentration of 2.0 and 4.0 mM for CTAB and CTAC, respectively, a rate increase of greater than 100-fold is observed compared with the solutions containing no surfactants under the studied reaction conditions. Further increasing surfactants concentration however, caused a gradual rate deceleration. Profiles of these type can be rationalized on the basis of (i) the necessity of micelles for "catalysis"; (ii) a progressively adsorption of a great fractions of the substrate into the micellar phase until that fraction

approaches unity with increasing surfactants concentration; and (iii) inhibition of the micellar reaction by the counter ions of the surfactants themselves. All the added salts changed the surfactant catalyzed reaction to uncatalyzed one upon addition of 0.1M of each of them.

In conclusion, the changes in the structure of bulk water and/or activities of H_2O and OH^- in the presence of both the added organic solvent and salts, and also the nucleophilicities of anions or the coordination abilities of the metal ions in the "modified" media could predominantly plays a great role in modifying the rates of reactions of toxic organic compounds in general. In addition, the micelles showed a strong "catalytic effect" on the hydrolysis reaction rate of p-NPB studied in this investigation in particular and similar rate enhancement is expected for similar hydrolysis reactions rates of toxic organic compounds in general. Generally, we believe that this work will offer a framework on the effects of reaction media and additives on the rates of hydrolysis reactions of toxic organic compounds.

Lists of Publications

1. Leta Danno Bayissa, Yoshihito Ohmae, Masashi Hojo; **Specific influence of salts on the hydrolysis reaction rate of *p*-nitrophenyl anthranilate in binary acetonitrile–water solvents**. *Journal of Molecular Liquids* 199 (2014) 294-300.

2. Leta Danno Bayissa and Masashi Hojo; **Specific salt effects on the hydrolysis reaction rate of tropolone tosylate in binary MeCN-H$_2$O media containing *n*-Bu$_4$NOH**. *Journal of Molecular Liquids 215 (2016) 293-301.*

3. Leta Danno Bayissa and Masashi Hojo, **Influences of micelle formation on the hydrolysis reactions rate of *p*-nitrophenyl benzoate (*p*-NPB) in aqueous buffered media**. (Under preparation**)**

Lists of presentations on international symposiums and meetings

1. Specific Influence of Solvents and Ions on the Hydrolysis Reaction Rates of Toxic Organic Compounds, *International seminar*, Changzhou University, Changzhou, China, December 2015.

2. Specific salt effects on the hydrolysis reaction rate of tropolone tosylate in binary MeCN-H_2O media containing n-Bu$_4$NOH, *38th Symposium on Solution Chemistry of Japan*, Kochi, October 2015.

3. Specific salt effects on the hydrolysis reaction rate of tropolone tosylate in binary MeCN-H_2O media containing n-Bu$_4$NOH, *Japan Society for Analytical Chemistry (JSAS) 64th Annual Meeting*, Kyushu University, Kyushu, September 2015.

4. Effects of Solvents and Ions on the Solvolysis of Toxic Organic Compound, 第 3 回若手研究者シーズ発表会-計測と分析, 広島大学グローバルキャリアデザインセンター, July 2015.

5. Effects of Added Organic Solvent and Salts on the Hydrolysis Reaction Rate of *p*-Nitrophenyl Anthranilate in Aqueous Buffer Solution, *Japan Society for Analytical Chemistry (JSAS) 63rd Annual Meeting*, Hiroshima University, Higashi-Hiroshima, September 2014.

6. Specific influence of salts on the hydrolysis reaction rate of *p*-nitrophenyl anthranilate in binary acetonitrile-water solvent, 第 20 回中国四国支部分析化学若手セミナー, 高知, 平成 26 年 7 月 27 日.

7. Effects of Solvents and Solutes on the Rates of Solvolysis Reactions of p-Nitrophenyl Anthranilate in Aqueous Buffer Solutions, *2014 Conference on Physical Chemistry*, Shenzhen, China, January 2014.

8. Effects of Solvents and Solutes on the Rates of Solvolysis Reactions of p-Nitrophenyl Anthranilate in Aqueous Buffer Solutions, *Japan Society for Analytical Chemistry (JSAS) 62nd Annual Meeting*, Kinki University, Osaka, September 2013.

9. Effects of Solvents and Solutes on the Rates of Solvolysis Reactions of p-Nitrophenyl Anthranilate in Aqueous Buffer Solutions, *Green Science Joint Seminar 2013,* Kochi University, Kochi, August 2013. (Excellent oral presentation awarded).