Organic Reaction in Mixed Aqueous Solvents and their Kinetics

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ABSTRACT

Organic reactions carried out in mixed aqueous solvents have attracted considerable attention because these solvent systems provide an environmentally friendly, economical, and versatile alternative to pure organic solvents. Mixed aqueous solvents, consisting of water combined with organic co-solvents such as methanol, ethanol, acetone, dimethyl sulfoxide (DMSO), or acetonitrile, significantly influence the rate, mechanism, and selectivity of organic reactions. The physicochemical properties of these solvent mixtures, including dielectric constant, viscosity, polarity, hydrogen-bonding ability, and solvation characteristics, alter the stability of reactants, intermediates, transition states, and products, thereby affecting reaction kinetics.

Keywords: Organic reactions ,Mixed aqueous solvents ,Reaction kinetics ,Solvent effects, Solvent composition , Reaction mechanism ,Rate constant , Activation energy ,Transition state , Solvent polarity

INTRODUCTION:

Organic reactions are significantly influenced by the nature of the solvent in which they occur. Among various solvent systems, mixed aqueous solvents—combinations of water with organic solvents such as methanol, ethanol, acetone, dimethyl sulfoxide (DMSO), acetonitrile, or dioxane—have attracted considerable attention because they provide a versatile medium for investigating reaction mechanisms and solvent effects. These mixed solvent systems combine the unique properties of water, including its high polarity, hydrogen-bonding ability, and environmentally friendly nature, with the tunable physicochemical characteristics of organic solvents. As a result, they offer an effective means of controlling reaction rates, selectivity, and product distribution.[1,2]

The kinetics of organic reactions in mixed aqueous solvents is an important area of physical organic chemistry. Reaction kinetics involves the study of the rates at which chemical reactions occur and the factors that influence these rates. Changes in solvent composition can alter the dielectric constant, viscosity, polarity, hydrogen-bonding interactions, and solvation of reactants, intermediates, and transition states. These changes directly affect activation energy, rate constants, and reaction pathways. Consequently, kinetic investigations in mixed aqueous media provide valuable insights into the molecular mechanisms governing organic transformations.

Mixed aqueous solvents are widely employed in studies of nucleophilic substitution, elimination, hydrolysis, oxidation, reduction, esterification, and acid-base catalyzed reactions. The variation in water content often leads to measurable changes in reaction rates, enabling researchers to evaluate solvent–solute interactions and determine activation parameters such as activation energy (Ea), enthalpy of activation ($\Delta H^{\ddagger}$), entropy of activation ($\Delta S^{\ddagger}$), and Gibbs free energy of activation ($\Delta G^{\ddagger}$). These parameters contribute to a deeper understanding of reaction mechanisms and the influence of solvent structure on chemical reactivity.

The increasing emphasis on green chemistry has further enhanced the importance of mixed aqueous solvents. Water is a sustainable, non-toxic, inexpensive, and environmentally benign solvent. By partially replacing hazardous organic solvents with water, mixed solvent systems reduce environmental impact while maintaining or even improving reaction efficiency. This approach supports the development of cleaner, safer, and more sustainable chemical processes for laboratory research and industrial applications.

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The study of organic reactions in mixed aqueous solvents has practical significance in pharmaceuticals, fine chemicals, polymer synthesis, agrochemicals, and biochemical processes, where solvent optimization is essential for improving reaction efficiency and product yield. Understanding solvent effects on reaction kinetics enables chemists to design more efficient synthetic routes, optimize industrial processes, and predict reaction behavior under different conditions. Therefore, the investigation of organic reactions in mixed aqueous solvents and their kinetics remains an important and continuously evolving field that bridges physical chemistry, organic chemistry, and green chemistry.[3-5]

Mixed solvent effect on reaction rate and mechanism of reaction: A **mixed solvent** is a combination of two or more solvents, usually water with an organic solvent such as methanol, ethanol, acetone, dioxane, acetonitrile, or dimethyl sulfoxide (DMSO). The use of mixed solvents is common in chemical kinetics because they allow systematic variation of solvent properties such as dielectric constant, polarity, viscosity, hydrogen-bonding ability, and solvation characteristics. These changes significantly influence both the **rate** and **mechanism** of chemical reactions.[6-7]

Effect of Mixed Solvents on Reaction Rate

The rate of a reaction in a mixed solvent depends on how the solvent affects the reactants, transition state, intermediates, and products.

Dielectric Constant

- The dielectric constant (ε) measures the ability of a solvent to reduce electrostatic forces between charged species.
- Increasing the proportion of an organic solvent generally lowers the dielectric constant.
- Reactions involving ions are highly sensitive to this change.
- Ionic reactions are often slower in solvents with lower dielectric constants because ion separation becomes less favorable.

Solvation of Reactants and Transition State

- Solvent molecules surround dissolved species through solvation.
- If the transition state is more strongly solvated than the reactants, the activation energy decreases and the reaction rate increases.
- Conversely, preferential solvation of the reactants stabilizes them, increasing activation energy and reducing the reaction rate.

Hydrogen Bonding

- Mixed solvents alter hydrogen-bonding interactions.
- Hydrogen bonding can stabilize charged intermediates or transition states.
- Strong hydrogen-bond donors often accelerate nucleophilic substitution and proton-transfer reactions.

Viscosity

- Increasing solvent viscosity decreases molecular diffusion.
- Diffusion-controlled reactions become slower in highly viscous solvent mixtures.

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Preferential Solvation

- In mixed solvents, one solvent component may preferentially surround the reactants while another surrounds the transition state.
- This selective solvation often produces non-linear changes in reaction rates as solvent composition changes.

Effect of Mixed Solvents on Reaction Mechanism

Mixed solvents can alter not only the reaction rate but also the reaction pathway.

Change in Reaction Pathway

Changing solvent composition may favor one mechanism over another.

Example

- SN1 reactions are favored in highly polar solvents because carbocations are stabilized.
- SN2 reactions are favored in less polar aprotic solvents where nucleophiles remain highly reactive.

Stability of Reaction Intermediates

Carbocations, carbanions, radicals, and ion pairs have different stabilities in different solvent mixtures. Greater stabilization often changes the preferred mechanism.

Ion Pair Formation

Lower dielectric constant solvents promote ion-pair formation.

Ion pairs are less reactive than free ions, causing both reaction rate and mechanism to change.

Proton Transfer Reactions

The extent of proton transfer depends on solvent acidity and basicity.

Mixed solvents modify proton availability and therefore influence acid–base catalysis.

Solvent Parameters Affecting Kinetics[8-9]

The principal solvent properties influencing reaction kinetics include:

- Dielectric constant
- Dipole moment
- Solvent polarity
- Hydrogen-bond donor ability
- Hydrogen-bond acceptor ability
- Viscosity
- Solvophobic interactions
- Preferential solvation

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Examples

Hydrolysis of tert-butyl chloride

- Faster in water-rich mixtures due to better stabilization of the carbocation intermediate.
- Rate decreases as the proportion of organic solvent increases.

SN2 Reactions

- Faster in water–DMSO or water–acetone mixtures because nucleophiles are less strongly solvated.

Ester Hydrolysis

- Acid- and base-catalyzed ester hydrolysis rates vary significantly with methanol–water and ethanol–water compositions due to changes in proton activity and solvation.

Electron Transfer Reactions

- Mixed solvents influence reorganization energy and electron-transfer rates through changes in polarity.

Theoretical Interpretation

Several theories explain mixed solvent effects:

- Transition State Theory**:** Solvent affects the free energy of activation (ΔG‡).
- Electrostatic Theory**:** Reaction rates depend on solvent dielectric constant.
- Preferential Solvation Theory**:** Reactants and transition states experience different local solvent environments.
- Linear Solvation Energy Relationships (LSER**):** Correlate reaction rates with solvent polarity and hydrogen-bonding parameters. [10]

Applications

Mixed solvent studies are important in:

- Organic synthesis
- Pharmaceutical formulation
- Drug stability studies
- Catalysis
- Biochemical reactions
- Environmental chemistry
- Industrial process optimization
- Mechanistic investigations

Thermodynamic approach of reaction rate in solution: The thermodynamic approach to reaction rates in solution explains how the rate of a chemical reaction is governed by the thermodynamic properties of the reactants, products, and especially the activated complex (transition state). This approach is based on the

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Transition State Theory (TST)**,** developed by Henry Eyring, which relates the reaction rate constant to thermodynamic activation parameters.

Introduction

Chemical reactions in solution involve the conversion of reactants into products through the formation of an unstable activated complex or transition state. The rate at which this occurs depends not only on the concentration of reactants but also on the free energy required to reach the transition state. Thermodynamic parameters such as Gibbs free energy (ΔG‡), enthalpy (ΔH‡), and entropy (ΔS‡) of activation play a crucial role in determining reaction rates.[11,12]

Transition State Theory

According to Transition State Theory, the reaction proceeds as:

$$\text{Reactants} \rightleftharpoons \text{Activated Complex} \rightarrow \text{Products}$$

The activated complex exists in equilibrium with the reactants and then decomposes into products.

The rate constant is given by the **Eyring equation**:

$$k = k_B T/h \exp^{(-\Delta G‡/RT)}$$

where:

- **k** = rate constant
- $\mathbf{k_B}$ = Boltzmann constant
- **h** = Planck's constant
- **T** = absolute temperature
- **R** = gas constant
- **ΔG‡** = Gibbs free energy of activation

Activation Parameters

The Gibbs free energy of activation is related to enthalpy and entropy by

$$\Delta G‡ = \Delta H‡ - T\Delta S‡$$

Substituting into the Eyring equation gives

$$k = k_B T/h \exp^{(\Delta S‡/R)} \exp^{(-\Delta H‡/RT)}$$

This equation shows that the reaction rate depends on both enthalpy and entropy of activation.

(a) Enthalpy of Activation (ΔH‡)

- Represents the energy barrier for the formation of the activated complex.
- Higher ΔH‡ means a slower reaction.
- Lower ΔH‡ leads to a faster reaction.

(b) Entropy of Activation (ΔS‡)

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- Indicates the degree of order in the transition state.
- Positive ΔS‡ implies a less ordered transition state and generally increases the reaction rate.
- Negative ΔS‡ indicates a more ordered transition state and usually decreases the reaction rate.

(c) Gibbs Free Energy of Activation (ΔG‡)

- Determines the overall ease of reaching the transition state.
- Lower ΔG‡ corresponds to a higher reaction rate. [13,14]

Effect of Solvent

In solution, solvents significantly influence the activation parameters.

- Polar solvents stabilize charged reactants or transition states through solvation.
- Hydrogen-bonding solvents may stabilize or destabilize intermediates depending on the reaction mechanism.
- Mixed aqueous solvents modify dielectric constant, viscosity, and solvent structure, thereby affecting ΔH‡ and ΔS‡.
- Preferential solvation changes the stability of reactants and the activated complex, resulting in changes in reaction rate.

Thermodynamic Interpretation

The reaction rate increases when:

- The activation free energy (ΔG‡) decreases.
- The activation enthalpy (ΔH‡) decreases.
- The activation entropy (ΔS‡) becomes more positive.
- The solvent stabilizes the transition state more than the reactants.

Conversely, reactions become slower when the activation barrier is increased by unfavorable solvent effects.

Applications

The thermodynamic approach is widely applied in:

- Studying organic reaction mechanisms in aqueous and mixed solvents.
- Investigating solvent effects on SN1, SN2, and elimination reactions.
- Drug stability and pharmaceutical kinetics.
- Catalysis and enzyme-catalyzed reactions.
- Industrial process optimization through solvent selection. [15,16,17]

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CONCLUSION

Organic reactions carried out in mixed aqueous solvents demonstrate that solvent composition plays a decisive role in controlling both reaction kinetics and reaction mechanisms. Variations in the proportion of water and organic co-solvents alter key physicochemical properties such as dielectric constant, polarity, viscosity, hydrogen-bonding ability, and preferential solvation, which directly influence the stability of reactants, intermediates, and transition states. These changes are reflected in the observed rate constants, activation energy, and thermodynamic activation parameters ($\Delta H‡$, $\Delta S‡$, and $\Delta G‡$), providing valuable insight into the molecular processes governing chemical reactivity.

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