Efficiency of Lithium Cations in Hydrolysis Reactions of Esters in Aqueous Tetrahydrofuran

Kazuhiko Hayashi,* Yoshimi Ichimaru, Kirara Sugiura, Azusa Maeda, Yumi Harada, Yuki Kojima, Kanae Nakayama, and Masanori Imai

College of Pharmacy, Kinjo Gakuin University; 2–1723 Omori, Moriyama-ku, Nagoya 463–8521, Japan.

Received January 6, 2021; accepted March 26, 2021; advance publication released online March 31, 2021

Lithium cations were observed to accelerate the hydrolysis of esters with hydroxides (KOH, NaOH, LiOH) in a water/tetrahydrofuran (THF) two-phase system. Yields in the hydrolysis of substituted benzoates and aliphatic esters using the various hydroxides were compared, and the effects of the addition of lithium salt were examined. Moreover, it was presumed that a certain amount of LiOH was dissolved in THF by the coordination of THF with lithium cation and hydrolyzed esters even in the THF layer, as in the reaction by a phase-transfer catalyst.

Key words  lithium; ester; hydrolysis; phase transfer catalyst

Introduction

Saponification typically involves the use of an aqueous solution of water and other organic solvents and is performed with an excess of hydroxides (KOH, NaOH, LiOH) in a single- or two-phase system. It is known that the rate of a saponification reaction is altered by steric and electronic effects as well as by the solvent due to specific interactions of solvent molecules with the reactions. In this context of saponification, there have been a number of reports about the effect of aqueous LiOH on the reaction rate. These reports noted that LiOH was an effective base for the hydrolysis of esters but did not explain the mechanism. In addition, many of these cases used tetrahydrofuran (THF) as the organic solvent with aqueous LiOH. We have already established an efficient method for cyclization to highly strained bicyclic molecules with a lithium cation. Those results prompted us to clarify the action of LiOH in a water/THF solution. We discuss herein the role of LiOH in hydrolysis by comparing the differences in yields between various hydroxides (KOH, NaOH, LiOH) used for the hydrolysis of benzoates and aliphatic esters.

Results and Discussion

Ethyl benzoates were hydrolyzed using hydroxides (KOH, NaOH, LiOH) at 25 °C in a water/THF solution, and the reaction solutions were observed to be two-layered before and after the reaction. Evidently, THF did not completely dissolve in the aqueous solutions of hydroxides due to a salting-out effect under our reaction conditions, despite THF generally showing miscibility with water. The results of the reaction in the water/THF two-phase system are summarized in Table 1. Interestingly, the hydrolysis by LiOH proceeded at a higher yield than that by NaOH or KOH in the case of every substrate except ethyl hydroxybenzoates (entry 7).

Next, ethyl para-chlorobenzoate with salts (LiCl, NaCl, KCl) was hydrolyzed to verify the efficacy of the lithium cation, as shown in Table 2. In the presence of NaCl, a higher yield was obtained with LiOH than with NaOH (entries 1, 3); this result showed the same tendency as the reaction without NaCl (Table 1 entry 4). However, the reaction using NaOH with LiCl proceeded with about the same yield as that using LiOH with NaCl (entries 1, 2). This result indicates that the lithium cation accelerated hydrolysis in the water/THF two-phase system. The same results as described above were obtained in the hydrolysis by KOH with salts (entries 4–6).

Subsequently, the effects of solvents and substrates were confirmed in order to identify the cause of the acceleration by lithium cations in this reaction. Table 3 lists the reactions of ethyl para-chlorobenzoate carried out in a water/C2H5OH single-phase system, a water/N,N-dimethylformamide (DMF) single-phase system, a water/1,4-dioxane single-phase system, and in the following two-phase systems: water/toluene, water/CH2Cl2, water/diethyl ether, and water/cyclopentyl methyl ether. The lithium cation did not clearly accelerate hydrolysis in any of those solvent systems, unlike in the water/THF two-phase system.

In addition, the reactions of ethyl benzoate (PhCO2C2H5), ethyl 3-phenylpropanoate (PhCH2CH2CO2C2H5), and ethyl cinnamate (PhCH = CHCO2C2H5) were performed in the water/THF two-phase system, as shown in Table 4. The lithium cation dramatically accelerated the reactions of ethyl 3-phenylpropanoate (PhCH2CH2CO2C2H5) and ethyl cinnamate (PhCH = CHCO2C2H5), which have higher lipophilicity than ethyl benzoate (PhCO2C2H5).

To explain these results, here we speculate on the possible mechanisms underlying hydrolysis by LiOH in the water/THF two-phase system. Generally, two-phase water/organic solvent hydrolysis proceeds mainly in the water layer or at the interface between the organic and aqueous layers and can proceed in the organic layer only by the use of a phase-transfer catalyst. This is because hydroxides are poorly soluble in the organic layer of a water/organic solvent two-phase system and would hydrolyze esters even in the THF layer, which is why they showed significantly higher yields.
with LiOH than with NaOH or KOH. The absence of the clear lithium cation effect in the water/toluene, water/CH₂Cl₂, water/diethyl ether, or cyclopentyl methyl ether two-phase system can be attributed to the insolubility of lithium cations in toluene, CH₂Cl₂, diethyl ether, and cyclopentyl methyl ether by poor coordination with the lithium cation 30); the hydroxides were completely soluble in the single-phase solvent, and the hydrolysis with LiOH proceeded in the same way as that with NaOH and KOH in a water/C₂H₅OH, water/DMF, or water/1,4-dioxane single-phase system. Additionally, the reason why lithium cations had no effect on the hydrolysis of ethyl hydroxybenzoates could be that ethyl hydroxybenzoates were dissolved in the aqueous hydroxides and were hydrolyzed entirely in the water layer (Table 1 entry 7).

### Conclusion

Ethyl benzoate derivatives with hydroxides (KOH, NaOH, LiOH) were hydrolyzed in a water/THF two-phase system. The addition of lithium salts accelerated the reaction (Tables 1, 2). Our examination of the effects of substrates and solvents led us to speculate that a certain amount of LiOH was dissolved in the THF by the coordination of the THF with lithium cations 26–29) and hydrolyzed esters, as in the reaction

---

**Table 1. Hydrolysis of Ethyl Benzoates with Hydroxides in Water/THF Two-Phase System**

| entry | R-     | time (h) | yield of acid (%) | ortho | meta | para |
|-------|--------|----------|-------------------|-------|------|------|
| 1     | -OCH₃  | 12       | LiOH 78           | LiOH 79 | LiOH 10 |
|       |        |          | NaOH 42           | NaOH 29 | NaOH 4  |
|       |        |          | KOH 36            | KOH 42  | KOH 5  |
| 2     | -CH₃   | 60       | LiOH 14           | LiOH 98 | LiOH 97 |
|       |        |          | NaOH 5            | NaOH 83 | NaOH 37 |
|       |        |          | KOH 9             | KOH 91  | KOH 51  |
| 3     | -NO₂   | 0.5      | LiOH 7            | LiOH 100 | LiOH 99 |
|       |        |          | NaOH 3            | NaOH 35 | NaOH 69 |
|       |        |          | KOH 3             | KOH 29  | KOH 39  |
| 4     | -Cl    | 6        | LiOH 28           | LiOH 100 | LiOH 92 |
|       |        |          | NaOH 10           | NaOH 52 | NaOH 14 |
|       |        |          | KOH 11            | KOH 43  | KOH 13  |
| 5     | -Br    | 6        | LiOH 16           | LiOH 99  | LiOH 99 |
|       |        |          | NaOH 7            | NaOH 48 | NaOH 16 |
|       |        |          | KOH 7             | KOH 37  | KOH 14  |
| 6     | -I     | 6        | LiOH 6            | LiOH 96  | LiOH 85 |
|       |        |          | NaOH 2            | NaOH 17 | NaOH 10 |
|       |        |          | KOH 2             | KOH 13  | KOH 8  |
| 7     | -OH    | 15       | LiOH 45           | LiOH 100 | LiOH 38 |
|       |        |          | NaOH 48           | NaOH 100 | NaOH 53 |
|       |        |          | KOH 66            | KOH 100  | KOH 72 |

---

**Table 2. Hydrolysis of Ethyl p-Chlorobenzoate with Additives**

| entry | hydroxide | additive | yield of acid (%) |
|-------|-----------|----------|-------------------|
| 1     | LiOH      | NaCl     | 100               |
| 2     | NaOH      | LiCl     | 100               |
| 3     | NaOH      | NaCl     | 31                |
| 4     | LiOH      | KC1      | 99                |
| 5     | KOH       | LiCl     | 87                |
| 6     | KOH       | KC1      | 19                |

---

* a) Determined by HPLC analysis (Experimental “General Procedure for Hydrolysis of Esters”).
Table 3. Solvent Effects in Hydrolysis of Ethyl \( p \)-Chlorobenzoate

\[
\begin{align*}
\text{Cl} & \quad \text{OC}_2\text{H}_5 \\
\xrightarrow{1) \text{hydroxide (3 mol eq.), solvent, 25 °C, reaction time}} & \quad \text{Cl} \\
\xrightarrow{2) 1 \text{ mol/L HCl}} & \quad \text{OH}
\end{align*}
\]

| entry | solvent       | reaction system | reaction time (h) | hydroxide | yield of acid (%)\(^a\) |
|-------|---------------|-----------------|-------------------|-----------|--------------------------|
| 1     | EtOH / H₂O (1 : 1) | single-layered  | 0.25              | LiOH      | 85                       |
|       |               |                 |                   | NaOH      | 72                       |
|       |               |                 |                   | KOH       | 83                       |
| 2     | DMF / H₂O (1 : 1) | single-layered  | 0.25              | LiOH      | 60                       |
|       |               |                 |                   | NaOH      | 74                       |
|       |               |                 |                   | KOH       | 68                       |
| 3     | 1,4-dioxane / H₂O (1 : 1) | single-layered  | 0.25              | LiOH      | 22                       |
|       |               |                 |                   | NaOH      | 17                       |
|       |               |                 |                   | KOH       | 8                        |
| 4     | toluene / H₂O (1 : 1) | two-layered    | 72                | LiOH      | 51                       |
|       |               |                 |                   | NaOH      | 21                       |
|       |               |                 |                   | KOH       | 38                       |
| 5     | CH₂C₂H₅ / H₂O (1 : 1) | two-layered   | 48                | LiOH      | 66                       |
|       |               |                 |                   | NaOH      | 64                       |
|       |               |                 |                   | KOH       | 47                       |
| 6     | diethyl ether / H₂O (1 : 1) | two-layered | 18                | LiOH      | 58                       |
|       |               |                 |                   | NaOH      | 63                       |
|       |               |                 |                   | KOH       | 69                       |
| 7     | cyclopentyl methyl ether / H₂O (1 : 1) | two-layered | 18                | LiOH      | 34                       |
|       |               |                 |                   | NaOH      | 22                       |
|       |               |                 |                   | KOH       | 16                       |

\(^a\) Determined by HPLC analysis (Experimental “General Procedure for Hydrolysis of Esters”).

Table 4. Hydrolysis of Aliphatic Esters in Water/THF Two-Phase System

\[
\text{RCO}_2\text{C}_2\text{H}_5 \xrightarrow{1) \text{hydroxide (3 mol eq.), THF - H}_2\text{O (1 : 1), 25 °C, reaction time}} \text{RCO}_2\text{H}
\]

| entry | \( R \) | reaction time (h) | hydroxide | yield of acid (%)\(^a\) |
|-------|---------|-------------------|-----------|--------------------------|
| 1     | \( \text{OC}_2\text{H}_5 \) | 6      | LiOH      | 28                       |
|       |         |                   | NaOH      | 14                       |
|       |         |                   | KOH       | 14                       |
| 2     | \( \text{OC}_2\text{H}_5 \) | 3      | LiOH      | 96                       |
|       |         |                   | NaOH      | 14                       |
|       |         |                   | KOH       | 12                       |
| 3     | \( \text{OC}_2\text{H}_5 \) | 15     | LiOH      | 94                       |
|       |         |                   | NaOH      | 18                       |
|       |         |                   | KOH       | 17                       |

\(^a\) Determined by HPLC analysis (Experimental “General Procedure for Hydrolysis of Esters”).
by a phase-transfer catalyst. This solubility of lithium cations in THF accelerates hydrolysis.

Experimental

General HPLC analyses to determine yield were carried out on a Shimadzu LC-20A LC system and a Shimadzu SPD-20A UV detector with a wavelength of 254 nm. All commercially available reagents and solvents were used directly as received from the vendors unless otherwise stated. A 3.0 mol/L solution of LiOH was prepared by exact adjustment to a 50-mL volume with distilled water after 0.150 mol of LiOH·H₂O was dissolved in approximately 10 mL of distilled water. Using the same method, 3.0 mol/L solutions of NaOH and KOH were also prepared. The same 10-mL round-bottomed, covered flasks and the same stirring bars were used for all reactions, and the three reactions (hydrolyses by LiOH, NaOH, and KOH) were carried out simultaneously. The reactions were carried out on a Shimadzu Thermal Robo TR-S Water Bath) using a supermagnetic stirrer (ISHII MS-1). The stirrer rotation speed was the same for all reactions. The reaction mixture was analyzed by means of HPLC.

General Procedure for Hydrolysis of Esters To a THF (1.0 mL) solution of ester (1.0 mmol) was added a 3.0 mol/L solution of hydroxide (LiOH, NaOH, or KOH) (1.0 mL, 3.0 mmol), and the reaction mixture was stirred at 25 ± 0.02°C in a constant-temperature water bath (As-One Thermal Robo TR-S Water Bath) using a supermagnetic stirrer (ISHII MS-1). The stirrer rotation speed was the same for all reactions. The reaction mixture was analyzed by means of HPLC.

Conflicts of Interest The authors declare no conflict of interest.