Reaction Mechanisms of Hydrothermal Hydrolysis of Organic Halides and Tosylates

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To understand the chemical mechanisms and effect of the hydroxide ion on hydrolysis under hydrothermal conditions, optically active secondary alkyl halides and sulfonates were studied in a variety of aqueous solvents at 200-250 °C in sealed vessel. The hydrolysis mostly proceeded with inversion stereochemistry via S_N2 reaction except for the reaction affected by neighboring group which stabilizes carbocation.

1. Introduction

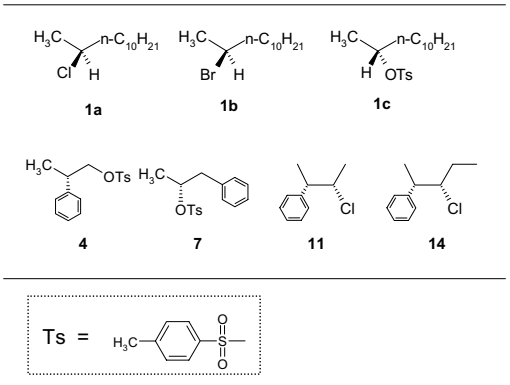
In recent years, considerable attention has been paid to processes involving subcritical or supercritical water as a method for decomposing organic pollutants, such as organic chlorides. Since the toxicities of chlorinated compounds generally depend on the carbon–chlorine bonds, the dechlorination treatment is required for the protection of our environment. On the other hand, the hydroxide ion is one of the most common bases in chemistry and also considered to be one of the most gentle nucleophiles in organic synthesis [1]. S_N2 reactions are highly useful in organic synthesis, because they enable us to convert one functional group to another. If we want to favor the S_N2 mechanism for the reaction of an alkyl halide, we should use a relatively unhindered alkyl halide or sulfonate, a strong nucleophile, a polar aprotic solvent, and a high concentration of nuleophile [2]. It is reported that the hydroxide ion plays an important role as a nucleophile in subcritical and supercritical water reactions [3, 4]. Super-heated water possesses higher ability of dissolving non-polar organic compounds because of its lower dielectric constant than that the ambient water [5]. We have reported hydrolysis of dichloromethane in alkaline water under hydrothermal conditions [1a]. The nucleophilic attack of the hydroxide ion to the carbon of dichloromethane in S_N2 manner was concluded to be the main reaction route.

In this study, we investigate the hydrothermal reactions of the optically active secondary halide and sulfonate to elucidate the stereochemistry of hydrolysis reaction. The effect of the hydroxide ion in hot water and reaction mechanisms of hydrothermal hydrolysis has been discussed.

2. Experimental Methods

Starting materials used in this study are listed in Table 1. Enantiomerically pure compounds mentioned in the upper row were prepared to examine the stereochemistry changes caused by inversion or racemization via S_N1 or S_N2 reaction. *S*-2-chlorododecane (**1a**) (>98%ee) was prepared from *R*-2-dodecanol which was formed from *R*-propylene oxide and *n*-nonylmaganesium bromide in the presence of copper iodide. 2-*S*-bromododecane (**1b**) and 2-*R*-dodecanyl tosylate

Table 1. Starting materials used in this study



(**1c**) were prepared in a similar way to *S*-2-chlorododecane to examine the effect of leaving group. Tosylates (**4**, **7**) and chlorides (**11**, **14**) including phenyl group on β-position which may stabilize carbocation were also used as starting materials. The chlorides (**11**, **14**) were prepared from 2-phenyl-propionaldehyde and methyl or ethylmaganesium bromide in the presence of copper iodide. The starting material was treated with various solvent conditions (acidic, neutral, and basic water) as shown in Table 2. A mixture of the starting material (2.0 mmol) and solvent (10 ml) was put in a 30 ml PTFE container which was held in a stainless vessel (Fig. 1) [1a,6,7]. The autoclave was heated at 250 °C for 2 h. After the whole was cooled down to room temperature, the reation mixture was extracted with hexane. The combined organic phases were washed by saturated aqueous solution of NH_4Cl and dried over Na_2SO_4. After concentration in a vacuum, $CHBr_3$ (0.1 mmol) was added to the concentrated reaction mixture as an internal standard for ^1H NMR analysis of the product distribution. The enantiomeric purity of the produced alcohol (**2**) from the hydrothermal hydrolysis was determined by ^{19}F NMR analysis after the conversion into Mosher's ester [8].

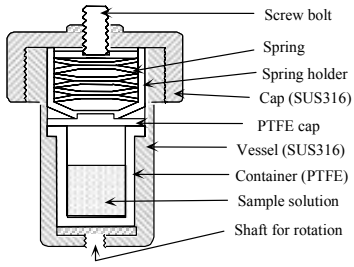


Fig. 1. A batch type autoclave including PTFE container employed for the hydrothermal reactions.

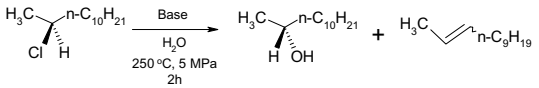
Table 2. A variety of solvents used.

Solvent	Concenteration (mol·dm^{-3})	pH at 250ºC
H_2O	—	~5.5
LiOH	2, 0.2	
NaOH	2, 0.2, 0.25	
KOH	2, 0.2	
CsOH	2, 0.2	
H_2SO_4	0.0005	~3
0.0005 M H_2SO_4 + 0.05 Na_2SO_4		~6.5

3. Results and Discussion

3.1. Enantioselectivity of hydrolysis products of secondary halide and tosilates

Table 3. Hydrolysis of *S*-2-chlorododecane.



1a > 98 ee **2** **3**

Scheme 1. Hydrolysis of 1a

Base	Yield of 2 / %	%ee	Yield of 3 / %
2.0 M LiOH	25	83	75
2.0 M NaOH	66	86	34
0.25 M NaOH	60	81	34
2.0 M KOH	40	86	42
2.0 M CsOH	40	83	30

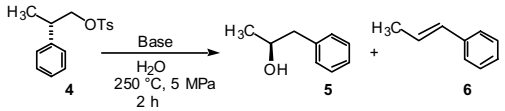
In all cases, hydrolysis reaction took place in competition with the elimination reaction which afforded alkene (**3**). High enantiomeric purity (81–86 %ee) in alcohol formation was obtained in the presence of base which had contributed an inversion stereochemistry via nucleophilic hydrolysis under hydrothermal conditions. In contrast, reaction with acidic or neutral water extremely reduced both the alcohol yield (~10%) and the enantiomeric purity. The dependency of the yield on the concentration of base indicates that the hydroxide ion plays an important role in the dechlorination and also nucleophilic substitution in the hydrothermal reactions.

3.2. The effect of leaving group on hydrothermal hydrolysis

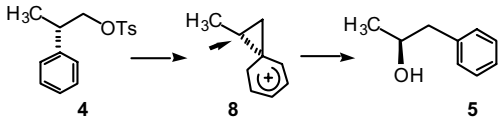
To examine the effect of leaving group, 2-*S*-bromododecane (**1b**) and 2-*R*-dodecanyl tosylate (**1c**) were examined for the hydrolysis under hydrothermal conditions. As shown in Scheme 1, the good leaving groups improved the stereospecificity slightly, but increased the ratio of elimination product (**3**). The loss of stereo-specificity in the hydrolysis reaction (Table 3 and Scheme 1) implies contribution of S_N1 like reaction.

The possibility of racemization that comes from a S_N2 type reaction by the conjugated base (i.e. Cl^-, Br^-, and TsO^-) may be excluded, because of their low concetration and low nucleophilicity. In these S_N1 like reactions, carbocation intermediate even in a basic condition should contribute to the reaction pathway in some extent.

Table 4. Hydrolysis of S-2-phenylpropyl tosylate.



Base	Yield of **5** /%	%ee	Yield of **6** /%
0.2 M NaOH	63	56	30
0.2 M CsOH	61	53	35



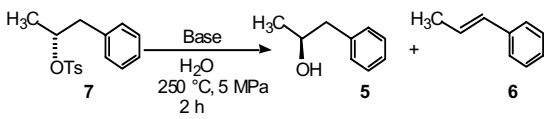
Scheme 2. Hydrolysis of **4** via benzonium ion **8**.

3.3. The effect of neighbouring group

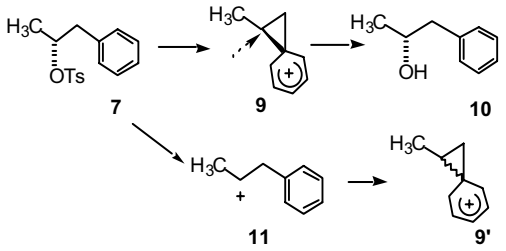
We tried to examine the effect of neighbouring group which may stabilize the carbocation [9]. As shown in Table 4, *S*-2-phenylpropyl tosylate (**4**) was treated with basic water under hydrothermal conditions. Phenyl group will stabilize carbocation on the β-position through the benzonium ion [10]. The product of the hydrolysis reaction was secondary alcohol (**5**) in 53–56%ee. The formation of the product was explained as shown in Scheme 2.

In Table 5, results of hydrolysis of *R*-3-phenyl-2-propyl tosylate (**7**) under hydrothermal condition are shown. The hydrolysis product was secondary alcohol **5** with slight stereospecificity. The results can be explained as shown in Scheme 3. A direct nucleophilic attack gave **5** with inversion stereochemistry, while the neighbouring phenyl group made a route to the enantiomer **10** possible through stereospecifically formed benzonium ion **9** (Scheme 3). At the stage of the formation of the benzonium ion, secondary cation **11** which may

Table 5. Hydrolysis of tosyl *S*-1-phenyl-2-propyl tosylate.



Base	Yield of **5** /%	%ee	Yield of **6** /%
0.2 M NaOH	25	4	45
0.2 M CsOH	40	12	40

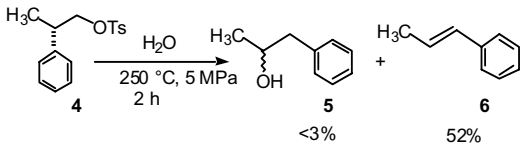


Scheme 3. Hydrolysis of **7** via benzonium ion **9** and formation of recamic benzonium ion **9'**.

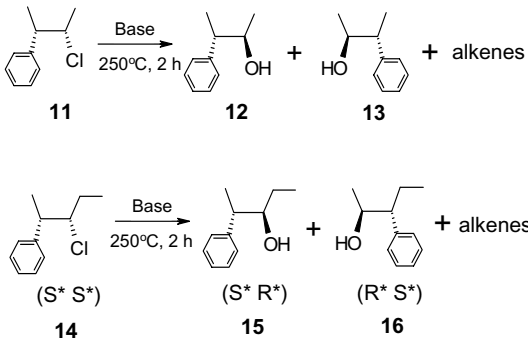
route to the elimination product **6** also causes a racemization of benzonium cation **9'**.

Even though the nucleophilicity of the hydroxide ion is increased under hydrothermal conditions, the presence of base is crucial for these reactions. As shown in Scheme 4, without an addition of base, **4** gave only the alkene **6**.

To confirm more the stabilization of the carbocation by the neighbour phenyl group, we have checked products distribution from hydrolysis of other chlorides (**11**, **14**) as shown in Scheme 5. In either case, products yielded via benzonium ion and those via S_N2 reaction were obtained and there is almost no evidence via S_N1 reaction.



Scheme 4. Hydrolysis of **4** without base.



Scheme 5. Hydrolysis of **11** and **14** and formation of alcohols via benzonium cation (**12** and **15**) and via S_N2 reaction (**13** and **16**).

4. Conclusions

In the present work, main pathway of hydrolysis of secondary halides and tosylates in basic water under hydrothermal condition is shown to be S_N2 like, as the inversion of stereochemistry is observed. We have shown the existence of benzonium ion even in the basic water under hydrothermal condition. Although the hydrothermal condition seems to be drastic, such a delicate intermediate as benzonium ion can survive during the reaction.

Acknowledgements

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References and Notes

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