# Effects of Counter Cations in Selective Monohydrolyses of Symmetric Diesters

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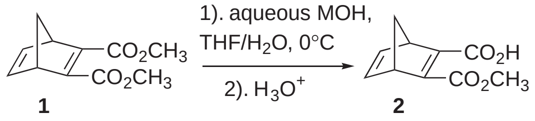
Monohydrolyses of symmetric diesters were carried out using several aqueous inorganic bases, LiOH, NaOH, KOH, and CsOH. The more reactive bases showed higher selectivities in the monohydrolyses of acyclic symmetric diesters.

Alkaline hydrolysis or saponification of esters is one of the most fundamental reactions in organic synthesis. The most common way to achieve this saponification is by using alkali metal inorganic bases such as LiOH and NaOH in an alcohol solvent. Half-esters are very versatile building blocks that can be obtained by selective monohydrolysis of symmetric diesters.[1] However, practically, such a task is more typically accomplished by enzymes,[2] a process which provides no foundation for prediction of reactivity. Practical non-enzymatic monohydrolyses of symmetric diesesters are quite rare.[3] Recently, we have reported a highly efficient selective monohydrolysis reaction using aqueous NaOH in THF/$H_2O$ media (Scheme 1).[4] This reaction enables monohydrolysis of a series of symmetric diesters in modest to quantitative yields affording corresponding pure half-esters under mild conditions in a very straightforward manner. The mechanism for this selectivity is not understood yet, and therefore we are expanding the mechanistic scope of this reaction.

Although there are some studies comparing the differences in counter cations among these alkali metals in saponifications for simple monoesters,[5] no systematic studies of these effects on selectivities of monohydrolysis of polyester systems have been reported. Here we report these effects on our selective monohydrolyses of symmetric diesters.

In our monohydrolysis reaction, one characteristic factor is the geometrical trend. The selectivity is particularly high when the diesters are fixed as 1,1- or 1,2-diesters, and the yields are even quantitative or close to quantitative, probably due to potential conformational bias caused by electrostatic attractive interactions between two closely-located alkoxycarbonyl groups.[4] For acyclic diesters, we observed reduced selectivity, probably due to reduced conformational lock, although the reaction mixture is still clean under the same conditions and therefore separation and purification of the product half-ester is straightforward.

Table 1.



| M | Reaction time/min | Yield/% of **2** |
|---|---|---|
| Li | 60–70 | >99 |
| Na | 60–70 | >99 |
| K | 30–40 | >99 |
| Cs | 30–40 | >99 |

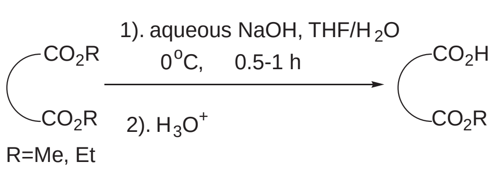
In fact, when the cyclic 1,2-diester, **1**, was monohydrolyzed by applying several bases, LiOH, NaOH, KOH, and CsOH, all of these reactions proceeded very efficiently, yielding only the corresponding half-esters in quantitative yields (Table 1), although we noticed some differences in the reactivities judging from the reaction time. Namely, the reactivities are generally proportional to the size of the counter cations.

Therefore, for further studies, in order to examine the effect of the counter cations, we used acyclic symmetric diesters, which are expected to show more differences in the selectivities.

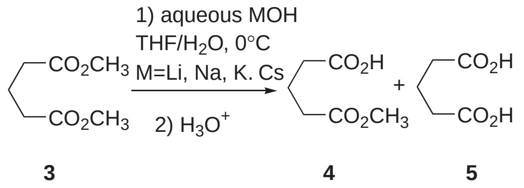
The following acyclic 1,3-dimethylester, dimethyl glutarate **3**, was hydrolyzed by applying the same conditions as we reported earlier but varying the types of counter cations (Scheme 2). As we reported for acyclic 1,2-dimethylester, dimethyl succinate, these monohydrolyses produced the corresponding half-ester,[6] **4**, in rather modest yields accompanying formation of the diacid, **5**.[7] However, the reaction was quite clean, as expected, producing only the anticipated half-ester, **4**, and the diacid, **5**.

The monohydrolyses were conducted by applying the same conditions as those reported by Niwayama earlier,[4] with variation only in the counter cations: $Li^+$, $K^+$, and $Cs^+$. The molar amount of these reagents was maintained identical to that reported earlier (1.7 molar amount). Table 2 below summarizes the results of the product distributions immediately after the starting diester, **3**, has been consumed. The percentage yields and product ratios were determined from the relative intensities of the integral curves of the methyl and methylene signals in the $^1$H NMR spectra of the crude reaction mixture after it was worked up.[8]

As can be seen from Table 2, in the monohydrolysis of **3**



Scheme 1.



Scheme 2.

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Table 2.

| | LiOH | | | NaOH | | |
|---|---|---|---|---|---|---|
| Reaction time/min | **4**/% | **5**/% | Ratio **4**:**5** | **4**/% | **5**/% | Ratio **4**:**5** |
| 20 | 66.2 | 33.8 | 1.96 | 67.8 | 32.2 | 2.11 |
| 25 | 61.1 | 38.9 | 1.57 | 67.4 | 32.6 | 2.07 |
| 30 | 59.2 | 40.8 | 1.45 | 61.4 | 38.6 | 1.59 |
| 35 | 55.9 | 44.1 | 1.27 | 60.9 | 39.1 | 1.56 |
| | KOH | | | CsOH | | |
| Reaction time/min | **4**/% | **5**/% | Ratio **4**:**5** | **4**/% | **5**/% | Ratio **4**:**5** |
| 10 | 86.8 | 13.2 | 6.58 | 82.2 | 17.8 | 4.62 |
| 15 | 74.5 | 25.5 | 2.92 | 67.8 | 32.2 | 2.11 |
| 20 | 69.0 | 31.0 | 2.23 | 64.6 | 35.4 | 1.82 |
| 25 | 67.9 | 32.1 | 2.12 | 51.9 | 48.1 | 1.08 |

The boxes indicate the point at which the starting diester **3** has been consumed.

with LiOH or NaOH, the starting diester was consumed after 20 min, at which stage the selectivities showed comparable results. However, when the same monohydrolosis was performed with KOH and CsOH, the starting diester was consumed within a shorter period of time (ca. 10 min), indicating enhanced reactivity, as in the case of the monohydrolysis of **1**.

Interestingly, the selectivity for forming the half-ester was also enhanced when KOH or CsOH was applied, as opposed to what would be expected from the general tendency. The selectivity was particularly high when KOH was applied. This order is about the same as the reactivity observed above; namely, the selectivity to form predominantly the half-ester is K > Cs > Na ≥ Li, which is roughly consonant with the reactivity. The differences in the selectivity are particularly prominent at the stage when the starting diester, **3**, has just been consumed (the top row for each base, within the box). As expected, the yield of the half-ester, **4**, decreased, with more diacid, **5**, being formed as the time passed in all the cases, although after the first 5–10 min of the starting diester's being consumed, dramatic change in the ratio **4**:**5** was not observed in any of the cases.

These selectivities are also roughly correlated to the electropositive character of the counter cations (Cs ≥ K > Na ≥ Li).[9] Therefore it is possible to assume that counter cations are participating in the initial stage of the reaction where the discrimination is about to occur in order to bring the two identical ester groups into close proximity by electrostatic effects. These electrostatic effects should play a more important role in such "free" acyclic systems than in rigid cyclic systems. The enhanced size and "softness" of the counter cations are also expected to provide advantages for the affinity in general. The somewhat reversed selectiviy between potassium and cesium cations may be attributed to the increased size and softness of the Cs cation, which is likely to make the coordination with the hard oxygen rather looser than the harder cation, $K^+$.

In summary, we found that several counter cations can control the selectivities in monohydrolyses of acyclic symmetric diesters. As opposed to the generally expected tendencies, more reactive bases showed higher selectivities, with KOH yielding the highest selectivity. Primary factors are likely to be attributed to the electropositive character and size of the counter cations.

## Experimental

The typical procedure for monohydrolysis of diester **3** is as follows: Diester **3** (213 mg, 1.33 mmol) was dissolved in 2.2 mL of THF, and 22.2 mL of water was added. The reaction mixture was cooled to 0 °C by being immersed in an ice-water bath. To this reaction mixture was added 8.9 mL of a 0.25 M aqueous solution of the inorganic base dropwise with stirring. The reaction mixture was stirred for the indicated period of time, and acidified with 1 M HCl at 0 °C, saturated with NaCl, extracted with ethyl acetate four to five times, and dried with magnesium sulfate. When the starting diester, **3**, was consumed, the $^1$H NMR spectra of the concentrated residues of these extracts were used to determine the ratios of the products from the relative intensities of the integral curves of the methyl and methylene signals.

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6 The spectrum data are as follows: Half-ester (**4**); colorless oil, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.88–2.09 (2H, m), 2.39 (2H, t, $J = 7.2$ Hz), 2.41 (2H, t, $J = 7.2$ Hz), 3.66 (3H, s); $^{13}$C NMR (75 MHz, acetone-$d_6$) $\delta$ 174.8, 173.7, 51.5, 33.3, 33.1, 20.8; IR (neat, cm$^{-1}$): 3500–2500, 1736, 1712, 1442, 1154; Anal. Calcd for $C_{10}H_{10}O_4$: C, 49.31; H, 6.90%. Found: C, 49.62; H, 6.99%.

7 The spectrum data are as follows: Diacid (**5**, glutaric acid); white solid (mp 97.0–97.5 °C (lit. 97.5 °C)[10]) $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 1.87 (2H, quint, $J = 7.5$ Hz), 2.39 (4H, t, $J = 7.5$ Hz); $^{13}$C NMR (75 MHz, acetone-$d_6$) $\delta$ 174.5, 30.3, 20.9; IR (neat, cm$^{-1}$): 3500–2500, 1695, 1407, 1206; Anal. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10%. Found: C, 45.08; H, 5.88%.

8 We confirmed, by occasional comparison, that the product ratios of **4** and **5** determined from the $^1$H NMR of the reaction mixture and those from isolated yields were quite close, differing only by negligible degrees ($<\pm6\%$). Separation of **4** and **5** was accomplished by silica gel column chromatography using hexane/ethyl acetate (3/1), ethyl acetate, then chloroform/methanol (9/1) as elution solvents.

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