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Zeolite-Catalyzed Macrolactonization of ω-Hydroxyalkanoic Acids in a Highly Concentrated Solution

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Abstract: Lactonization of 15-hydroxypentadecanoic acid to 15-pentadecanolide on dealuminated HY zeolite was successfully performed in a concentrated toluene solution (0.2 M). Addition of a bulky organic base to the reaction system suppressed the lactonization. It was concluded that the lactonization was promoted at specific acid sites on the external surface of the zeolite.

The formation of large-ring lactones from the corresponding ω-hydroxyalkanoic acids is generally difficult because intermolecular condensations competitively proceed. Several synthetic methods for the macrolactonization have been developed.[1-8] Especially, the 'in-pore' reactions using a solid acid, dealuminated HY zeolite (DAHY), is unique in making use of porous material as a catalyst, thereby providing the specific microenvironment where the lactonization takes place.[8] Our interest in the DAHY-catalyzed macrolactonization led us to reinvestigate the 'in-pore' method using DAHY, and we discovered a more efficient and practical procedure for the reaction.

In the 'in-pore' method,[8] DAHY(Si/Al=5.5) was impregnated with the melted 15-hydroxypentadecanoic acid (mp 83°C) to incipient wetness at 90°C, and then a hydrocarbon solvent such as n-decane or n-heptane was added in order to extract lactone products out of the zeolite cavities because the hydroxy acid is sparingly soluble in hydrocarbon but the lactone is soluble. We considered that, even in the 'in-pore' method, all the melted hydroxy acid was not completely accommodated in the zeolite cavities during the reaction, and that a condensation reaction simultaneously proceeded on the external surface of the zeolite in a very concentrated state (i.e., a neat liquid state), thus the undesired intermolecular condensation (oligomerization) predominated. Therefore, if a suitable solvent which can dissolve the polar hydroxy acid and deliver it into the hydrophilic cavities of DAHY is used, the concentration of the hydroxy acid would be reduced on the external surface of the zeolite, suppressing the intermolecular condensation. In addition, compared with the 'in-pore' procedure, it is more straightforward to mix the catalyst, reactant, and solvent at a time to conduct the lactonization, which is called a 'mix-together' method. Furthermore, the 'mix-together' method would be applicable to a variety of ω-hydroxyalkanoic acids having high melting points.

For the 'mix-together' reaction, in a flask were mixed DAHY(Tosoh Corp., HSZ-360HUA; Si/Al=7.0, 0.15 g) catalyst predried at 400°C/0.6 mmHg for 2 h, ω-hydroxyalkanoic acid (1 mmol), and

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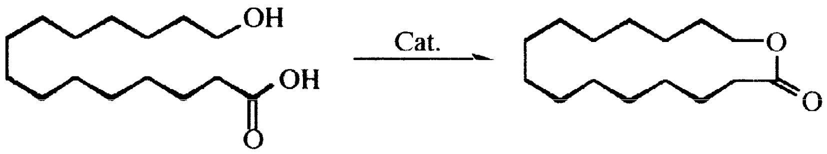
Table 1. Lactonization of 15-Hydroxypentadecanoic Acid on Dealuminated HY Zeolite [a]



Entry	Method	Catalyst / g	Solvent	Conditions	15-Pentadecanolide yield / %
1	'in-pore'	0.3	n-heptane (bp 98 °C)	reflux (24 h)	16
2	'in-pore'	0.3	toluene (bp 110 °C)	reflux (24 h)	20
3	'mix-together'	0.3	n-heptane	reflux (15 h)	21
4	'mix-together'	0.3	toluene	reflux (15 h)	32
5[b]	'mix-together'	0.3	toluene	reflux (15 h)	37
6	'mix-together'	0.3	n-decane	110 °C (15 h)	19
7	'mix-together'	0.3	1,2-diethoxyethane	110 °C (15 h)	6
8[b]	'mix-together'	0.15	toluene	reflux (72 h)	50
9[b]	'mix-together'	0.075	m-xylene(bp 139 °C)	reflux (24 h)	51

[a] Reactant: 1.0 mmol, solvent: 5.0 ml. [b] Under azeotropic dehydrating conditions.

solvent (5 ml) at room temperature, and then the mixture was heated with stirring. As work-up, the catalyst was separated by filtration, and washed with tetrahydrofuran to collect the products and the reactant. The lactone product was isolated by Kugelrohr distillation.[9]

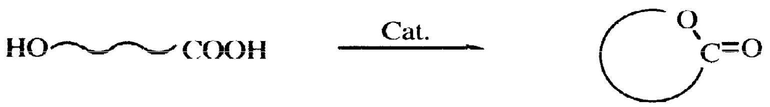
Table 1 summarizes the comparison between the 'in-pore' and 'mix-together' reactions of 15-hydroxypentadecanoic acid to 15-pentadecanolide. In all entries, no diolide (32-membered lactone) was detected. In general, the 'mix-together' reactions gave higher yields of the lactone than the 'in-pore' reactions (entries 1-4). Aromatic solvents such as toluene and m-xylene were found to be suitable because of their high dissolving ability toward 15-hydroxypentadecanoic acid (entries 4, 5, 8, 9); for instance, more than 40 g of the acid is soluble in 100 ml of toluene at 80°C. A relatively basic solvent, 1,2-diethoxyethane, greatly retarded the acidic zeolite-catalyzed lactonization (entry 7).

The lactonization was promoted more smoothly by an azeotropic removal of water (entries 4, 5).[10] Decreasing the amount of catalyst had positive effects on the lactone yield because putting the produced lactone into contact with the catalyst promoted the further transformation into oligomers.

The ratio of Si/Al in DAHY zeolite also affected the lactone yield critically: Si/Al=7.0, 50%; Si/Al=14.5, 9% (entries 10, 11 in Table 2). This fact implies that the distribution of aluminum sites in the zeolite crystal structures is responsible for the successful macrolactonization.

According to the 'mix-together' method, large-membered lactones with little ring-strain such as 15-

Table 2. Effects of Si/Al Ratios in Dealuminated HY, Size of Lactone, and Addition of a Bulky Base on Macrolactonization [a]



Entry	Si/Al ratio	Reactant	Additive	Monolide yield/%
10	7.0	$HO(CH_2)_{14}COOH$	none	50
11	14.5	$HO(CH_2)_{14}COOH$	none	9
12	7.0	$HO(CH_2)_{11}COOH$	none	10
13	7.0	$HO(CH_2)_{15}COOH$	none	55
14	7.0	$HO(CH_2)_6O(CH_2)_9COOH$	none	55
15	7.0	$HO(CH_2)_{18}COOH$	none	45
16	7.0	$HO(CH_2)_{14}COOH$	4,7-diphenyl-1,10-phenanthroline (0.01mmol)	7

[a] Cat.: DAHY 0.15 g, reactant: 1.0 mmol, toluene: 5.0 ml. Under azeotropic dehydrating conditions for 72h.

pentadecanolide, 16-hexadecanolide, 10-oxa-16-hexadecanolide, and 19-nonadecanolide were produced in a highly concentrated solution (0.2 M) from their linear precursors in 45-55% yields (entries 10, 13-15). It can be expected that more strained lactones like 12-dodecanolide would be formed successfully if the lactone formation proceeds in the narrow space of DAHY. Actually, however, 12-hydroxydodecanoic acid was transformed into 12-dodecanolide only in 10% yield (entry 12). Interestingly, the ring-size dependence of the lactone yields by use of DAHY resembles that in the case of using p-toluenesulfonic acid as a homogeneous acid catalyst under high dilution conditions (in 0.005 M benzene solution, 12-dodecanolide=16 %; 15-pentadecanolide=67 %).[1]

The molecular dimensions of 19-nonadecanolide were estimated to be 0.92 nm x 1.1 nm by MM2 calculation, which is much larger than the size of pore openings of DAHY (0.73 nm).[11] Accordingly, the 19-nonadecanolide may not be formed inside the pores of DAHY.

To poison the acid sites on the external surface of DAHY, a rigid, bulky base, 4,7-diphenyl-1,10-phenanthroline (molecular dimensions: 0.83 nm x 1.3 nm) was added, which is too large to enter the pore openings of DAHY. The lactonization of 15-hydroxypentadecanoic acid in the presence of the bulky base was suppressed to 7 % yield, compared to that without the base in 50% yield (entries 10, 16).

Based on the above two findings, it can be concluded that the lactonization of ω-hydroxyalkanoic acids on DAHY was mainly conducted on the external surface of the zeolite rather than in the internal cavities of the zeolite.

It is worth mentioning that the 'mix-together' reactions are performed in a much more concentrated solution (0.2 M solution), compared with the conventional methods under 'high dilution' conditions (0.002 M~0.04 M).[1, 2, 4-7] For example, the use of p-toluenesulfonic acid (5 mol%) in place of DAHY resulted in only 10% yield of 15-pentadecanolide in a 0.2 M toluene solution under azeotropic reflux conditions for 72 h.

Why the zeolite surface is a suitable reaction medium for macrolactonization has yet to be elucidated. We suppose that acid sites are distributed on the surface of DAHY(Si/Al=7.0) such that a hydroxyl group and a carboxyl group of ω-hydroxyalkanoic acid can be adsorbed on the acid sites in proximity, thus facilitating lactonization.

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