

Selective Macrolactonization using Zeolite Molecular Sieves

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'In-pore' reactions of 15-hydroxypentadecanoic acid on dealuminated HY zeolite effected intramolecular esterification exclusively to give the monomeric lactone, pentadecanolide.

Even if large ring compounds are generally stable, they are often difficult to synthesize from chain compounds; intermolecular reactions are more likely to occur than intramolecular ring closure. Preparation of large ring lactones from the corresponding ω -hydroxy acids suffers from this synthetically difficult problem. Several techniques with this specific problem in mind have recently been developed, and these are generally based on high dilution, some form of functional activation through prior derivatisation, and/or template effect of catalytic esterification agents.¹

Zeolites are structurally unique in having cavities or pores with molecular dimensions. Acidic catalytic sites within such a structure provide the basis of molecular shape-selective catalysis.^{2,3} A particular type of shape selectivity, product selectivity, arises when, among the multiplicity of products that could be formed, only those with the appropriate shape and size can pass through the channels as products. Increasing attention is being paid to zeolites as catalysts or reagent supports in fine chemical synthesis.^{4,5} It occurred to us that acid catalysed reaction of ω -hydroxy carboxylic acids might be constrained in such a shape-selective environment to effect internal macrocyclic esterification selectively, repressing intermolecular esterification leading to dimeric and polymeric condensation. We now report on a synthetically useful new approach towards the preparation of pentadecanolide (exaltolide), an important perfume constituent included in angelica root oil, directly from 15-hydroxypentadecanoic acid by using zeolites as catalysts, without resorting to high dilution techniques.

Dealuminated HY (DAHY: $\text{SiO}_2/\text{Al}_2\text{O}_3 = 11.0$), HY ($\text{SiO}_2/\text{Al}_2\text{O}_3 = 4.6$), rare earth exchanged Y (REY: $\text{SiO}_2/\text{Al}_2\text{O}_3 = 4.6$), and amorphous $\text{SiO}_2\text{-Al}_2\text{O}_3$ ($\text{SiO}_2/\text{Al}_2\text{O}_3 = 11.9$) catalysts were activated by calcination in air at 400 °C for 2 h before reactions. Reactions were carried out under an inert gas in two ways, unless otherwise noted. For 'neat' reactions, catalysts were made to contact the melted reactant (m.p.

Table 1 Esterification of 15-hydroxypentadecanoic acid on solid acids

Catalyst ^a	Method	T/°C	t/h	Yield (%)	
				Monolide	Diolide
DAHY	Neat ^b	90	6	2.1	4.3
DAHY	Neat ^{b,c}	90	6	1.3	0
DAHY	In pore ^d	90	6	9.8	0
DAHY	In pore ^d	90	24	14.3	0
DAHY	In pore ^d	120	3	14.0	0
HY	In pore ^d	90	6	0.10	0
REY	In pore ^d	90	6	0.29	0
$\text{SiO}_2\text{-Al}_2\text{O}_3$	Neat ^b	90	6	0.45	14.3
$\text{SiO}_2\text{-Al}_2\text{O}_3$	In pore ^e	90	6	0.63	15.0

^a DAHY = Dealuminated HY: $\text{SiO}_2/\text{Al}_2\text{O}_3 = 11.0$, HY: $\text{SiO}_2/\text{Al}_2\text{O}_3 = 4.6$, REY = rare earth exchanged Y: $\text{SiO}_2/\text{Al}_2\text{O}_3 = 4.6$, $\text{SiO}_2\text{-Al}_2\text{O}_3$ (amorphous): $\text{SiO}_2/\text{Al}_2\text{O}_3 = 11.9$. ^b Reactant: 10 mmol, catalyst: 0.5 g. ^c 0.049 mmol of perfluorotributylamine was added. ^d Reactant: 2.0 mmol, catalyst: 0.6 g. ^e Reactant: 2.3 mmol, catalyst: 1.0 g.

83 °C) in the absence of solvent; the reactant also behaving as a reaction medium. For 'in-pore' reactions, catalysts were impregnated with the melted reactant to incipient wetness at 90 °C and then *n*-decane was added as a reaction medium. In all cases the catalysts were washed with tetrahydrofuran (THF) at the end of the reaction to extract the products and the reactant from the pores.

The pertinent results are shown in Table 1. The 'neat' reaction on DAHY gave more dimeric lactone, the diolide, than monomeric lactone, the monolide pentadecanolide. Diolide formation was inhibited and monolide formation was slightly decreased by addition of perfluorotributylamine, which was too large (critical diameter 1.04 nm) to enter into the pores and should cover only the zeolite external surface. Taken together, these observations suggest that the monolide was mainly formed in the pores of Y zeolite and the diolide only on its external surface. Consistent with this hypothesis, the 'in-pore' reactions on DAHY were able to afford the monolide selectively. Although it is not clear whether intermolecular esterification occurred in the cavity of Y zeolite, dimeric and polymeric forms of lactones are evidently too large to pass through the pore openings. In contrast, the critical diameter of the monolide is estimated to be 0.83 nm, about the same as that of mesitylene (0.84 nm), which was found to be slightly smaller than the pore openings of Y-zeolites.⁶

In the 'in pore' reaction, *n*-decane is assumed to play a role not only as a medium but also as an extracting solvent which can dissolve only the products and not the reactant. The use of THF as the solvent resulted in a very low conversion, probably because the weakly basic THF covered acidic sites.

Irrespective of the reaction pathways, no selective formation of the monolide occurred on amorphous SiO₂-Al₂O₃, whose average diameter was estimated to be 13 nm. Hence in the non-shape-selective environment diolide formation prevailed. Other products consisting of polymeric residues were not characterized. Zeolites HY and REY having low SiO₂/Al₂O₃ ratios exhibited poor activity. This result may be ascribed to the low hydrophobicity of zeolites with low SiO₂/Al₂O₃ ratios.⁷

Table 1 shows that the monolide yield did not exceed 15% in the 'in-pore' reactions on DAHY. The IR spectrum of the

recovered catalyst showed strong bands ascribed to lactone and no bands assignable to CO₂H or OH groups. The relatively low yield of monolide is possibly due mainly to the strong adsorption of the product pentadecanolide on the zeolite internal surface; DAHY impregnated with pentadecanolide to incipient wetness desorbed only ca. 15% of the occluded pentadecanolide on extraction with hot THF or *n*-decane. To overcome this problem, esterification at higher temperatures was attempted. The DAHY sample, impregnated with 15-hydroxypentadecanoic acid in the same way as for the 'in pore' reactions, was placed in a pyrolysis tube directly connected to a flame ionization detector. Heating of the probe at 250 °C under a He flow for 20 s resulted in a 32% yield of monolide with 80% selectivity. Partial degradation of 15-hydroxypentadecanoic acid occurred, but no diolide formation was observed. Heating at higher temperatures led to lower selectivity for monolide formation, because of extensive degradation.

We are currently investigating the applicability of these methods to the preparation of other types of macrocyclic compounds from the corresponding α,ω -bifunctional compounds.

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