Chapter 2 - Studies on (poly)Esterification Reactions with Commercially Available Bi(III)-Compounds

Esterification is a common reaction used in organic synthesis, and is applied in various industries such as the pharmaceutical, fragrance, material, and coating industries. Conventionally, Fischer esterification is performed in the presence of a Brønsted acid to catalyze the condensation of carboxylic acids and alcohols. This approach results often in efficient esterification. However, undesired side-reactions such as ether formation, incompatibility with acid-sensitive substrates, and the negative impact of acidic waste, are the major drawbacks of the Fischer esterification. To this end, various alternative esterification methods have been established such as the use of solid acid catalysts, Lewis acids, and other (organic) reagents. Lewis acids are particularly interesting due to their good catalytic activity in low amount and therefore low waste production. In this chapter, we study a series of Bi(III)-compounds as Lewis acid catalysts for esterification reactions. In general, the studied Bi(III)-compounds led to moderate esterification yields at best. Among them, Bi$_2$O$_3$ and Bi(OTf)$_3$ respectively lead to 62% yield and full conversion. Together with AkzoNobel, we select Bi$_2$O$_3$ and Bi(OTf)$_3$ to carry out polyesterification studies, and whereas Bi$_2$O$_3$ is not a sufficiently active catalyst, Bi(OTf)$_3$ results in efficient polyesterification but significant ether formation is also observed. Hence, we conclude that Bi$_2$O$_3$ and Bi(OTf)$_3$ are not a good alternative to replace the current polyesterification methods used in industry. Furthermore, due to the poor esterification results and the ether formation in Bi(III)-catalyzed reactions, we propose that Bi(III)-compounds are not worthwhile for further esterification studies.
2.1 Introduction

In the 21st century, polymers, in society known as “plastics”, are essential materials used in daily life in various applications including automotive, building, aerospace, and pharmacy.\[^{[1]}\] With the view of sustainability, the polymers synthesized from petroleum are difficult to degrade on reasonable time scales.\[^{[9]}\] To this end, polyesters are more ecofriendly alternatives because their ester linkages can undergo hydrolysis (albeit slowly) which assists in biodegradation.\[^{[9,10]}\] In terms of the application of polyesters, thermosetting polyesters such as unsaturated polyester resins are widely used due to their mechanical, electrical, and chemical characteristics.\[^{[11,12]}\] For instance, poly(ethylene terephthalate), known as PET and Dacron, is one of the world’s leading synthetic fibers and used to produce commodities such as drinking bottles.\[^{[11,13]}\] In addition, polyesters are also introduced to conduct research on drug delivery, which can contribute to pharmaceutical development.\[^{[14–16]}\] The fundamental step of producing polyesters is esterification,\[^{[11]}\] and this reaction also has been widely used in industries and academia. There are several types of esterification methods developed including carboxylic acid activation with organic reagents, Fischer esterification, and Lewis acid-catalyzed esterification. Although catalyst-free esterification reactions are desired, these are generally inefficient, require very high temperature, and lead to poor results.\[^{[17]}\] In this chapter, several esterification methods by direct condensation between carboxylic acids and alcohols will be discussed. We are particularly interested in Lewis acid-catalyzed reactions since these result in less chemical waste and side reactions compared to the use of organic reagents or Brønsted acids. Furthermore, we will illustrate our studies on Bi(III)-catalyzed esterification reactions. Although Bi(III)-compounds are frequently applied as Lewis acids to catalyze organic reactions,\[^{[18]}\] Bi(III)-catalyzed esterification reactions have not been well-studied. The current industrially used catalysts for (poly)esterification reactions might be banned in the future due to their toxicity. Therefore, as Bi(III)-compounds are non-toxic compounds, we are interested in studying their reactivity in esterification. Furthermore, together with AkzoNobel, we selected the best performing Bi(III)-compounds to analyze their catalytic activity in polyesterification reactions.
2.2 Currently Used Methods for Esterification Reactions

2.2.1 Esterification by Activation of the Carboxylic Acid with Organic Reagents

Mukaiyama et al. developed the preparation of esters by treating carboxylic acids with tertiary amines and 1-alkyl-2-halopyridinium salts (Scheme 1).[19,20] Tertiary amines function as the base to deprotonate the carboxylic acid, which is followed by nucleophilic substitution of 1-methyl-2-halopyridinium salt 1 leading to the intermediate acyloxypyridinium salt 2. The resulting intermediate 2 undergoes attack by an alcohol yielding the carboxylic ester 3, 1-methyl-2-pyridone, and an ammonium salt. By this method, equimolar amounts of carboxylic acids and alcohols are utilized to synthesize various carboxylic esters including sterically hindered ones in good yields.

![Scheme 1: Synthesis of carboxylic esters using 1-methyl-2-halopyridinium iodide salts][19]

Organic base, or more appropriate; nucleophile, mediated esterification reactions can also be promoted by catalytic 4-dimethylaminopyridine (DMAP).[21–23] Sakakura et al. have reported DMAP-catalyzed esterification of l-menthol 4 and isobutyric anhydride (Scheme 2).[22] Using this method, the desired product 5 was obtained in quantitative yield even without the use of solvent and auxiliary base.

![Scheme 2: DMAP-catalyzed esterification between l-menthol 4 and isobutyric anhydride by Sakakura et al.](image)
As for the mechanism (Scheme 3), DMAP attacks the anhydride forming pyridinium species 6, which is followed by the attack of the alcohol leading to the regeneration of DMAP and formation of the ester.\cite{22}

Another commonly used esterification reaction in organic synthesis is the Steglich esterification, which uses \(N, N'\)-dicyclohexylcarbodiimide (DCC) as promoter to facilitate the condensation of carboxylic acids with alcohols in the presence of catalytic DMAP.\cite{24} The addition of DMAP accelerates the DCC-activated esterification reaction.\cite{25} In terms of the plausible mechanism (Scheme 4), DCC is first attacked by a carboxylic acid forming the DCC-activated acyloxy moiety 7, which is followed by the addition of DMAP to form acylpyridinium 8 and dicyclohexylurea 9. The resulting 8 is sensitive to nucleophilic attack by the alcohol leading to the formation of the ester and regeneration of DMAP.\cite{7,17,25}

The byproduct dicyclohexylurea 9 may cause problems in the purification.\cite{26} To this end, alternative carbodiimides such as \(N, N'\)-diisopropylcarbodiimide (DIC) and \(N\)-ethyl-\(N'\)-(3-dimethylaminopropyl)carbodiimide (EDC) have been introduced. Especially for EDC-mediated reactions, the byproduct can be removed by aqueous workup.\cite{24}
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Steglich esterification reactions are widely used in natural product synthesis and medicinal chemistry. \(^{[27–29]}\) Furthermore, current advances in catalyzing the Steglich esterification use kinetic resolution of racemic trans-cycloalkane-1,2-diols by oligopeptide multicatalysts to enantioselectively obtain esters.\(^{[30,31]}\) Schreiner et al. have developed an oligopeptide multicatalyst which contains 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and imidazole moieties to carry out enantioselective esterification (Scheme 5).\(^{[32]}\) The alcohol is oxidized to the carboxylic acid by the TEMPO moiety. DIC subsequently activates the carboxylic acid, which is followed by acylation of the imidazole moiety of the multicatalyst. The steric control of the catalyst leads to enantioselective addition of a diol to the acylium imidazolium ion yielding the \((S,S)\)-diol 10 and \((R,R)\)-ester 11.

Scheme 5: Kinetic resolution of rac-cyclohexane diol by esterification catalyzed by an oligopeptide multicatalyst according to Schreiner et al.

The Mitsunobu reaction is another common technique to achieve esterification in organic synthesis. It usually includes the use of more than stoichiometric amounts of a phosphine and azodicarboxylate reagents in the reaction and is accompanied by inversion of configuration.\(^{[17]}\) The mechanism of the Mitsunobu esterification proceeds via three steps, including adduct formation, activation, and nucleophilic attack (Scheme 6).\(^{[33]}\) In the stage of adduct formation, the phosphine attacks azodicarboxylate 12 forming a phosphine-azodicarboxylate adduct 13 with a positive charge on the phosphine. Alcohols can add to the positive-charged phosphine to result in the activated alcohol 14 and hydrazinedicarboxylate 15. The phosphine-activated alcohol 14 are subject to be attacked by the carboxylate resulting in ester 16 and the phosphine oxide. The inversion of configuration to afford 16 resulting from \(S_N\)2 type nucleophilic attack of the carboxylate.
The Mitsunobu reaction is often implemented in the total synthesis of natural products. Georg et al. applied Mitsunobu esterification to stereoselectively and efficiently couple the alcohol 17 and carboxylic acid 18 for the synthesis of lactimidomycin analogue 20 (Scheme 7). The obtained major product 19 possesses the R configuration at C11. Under Mitsunobu conditions, (4S)-alcohol 17 is activated, followed by S_n2 type nucleophilic attack of acid 18 leading to inversion of the configuration. Low temperature is required in order to obtain the desired product in high diastereomeric ratio. Further steps to cross-couple the alkyne and iodide lead to lactimidomycin analogue 20.
Although Steglich and Mitsunobu esterification reactions can effectively couple alcohols and carboxylic acids, there are some disadvantages in both reactions. The use of a carbodiimide for Steglich reactions gives rise to the formation of ureas as byproducts, which sometime are difficult to separate.[38] As for Mitsunobu esterification, this reaction suffers from the inevitable use of an excess amount of phosphine leading to problematic purification.[17]

In recent years, XtalFluro-E has been introduced for esterification reactions to facilitate the formation of amides and esters.[38–40] For instance, Paquin et al. carried out an XtalFluro-E-mediated esterification to couple 4-nitrobenzoic acid and trifluoroethanol yielding the corresponding carboxylic ester in excellent yield (Scheme 8).[38] Furthermore, the byproducts resulting from this methodology are water-soluble, which facilitate the purification.

Scheme 8: XtalFluor-E mediated esterification between 4-nitrobenzoic acid and trifluoroethanol by Paquin et al.

Although the discussed methods are used for esterification reactions of complex or labile molecules, catalytic methods without using multiple organic reagents are preferred for industrial applications.

2.2.2 Fischer Esterification

Acid catalyzed esterification is another effective approach to synthesize carboxylic esters. For example, the Fischer esterification, a Brønsted acid-catalyzed reaction, has been implemented in the synthesis of bioactive molecules.[41,42]
polymerization,\textsuperscript{[15]} and surface modification of nano-materials.\textsuperscript{[43-45]} Strong mineral acids (often sulfuring acid) are usually required and water is the by-product.\textsuperscript{[46-48]} Although Fischer esterification is an effective and atom-efficient method, the starting materials and product have to be resistant to acid and primary alcohols are preferred. The Fischer esterification reaction is not efficient with tertiary alcohols since, under the acidic conditions, tertiary alcohols may dehydrate to form an alkene.\textsuperscript{[49]} S\textsubscript{N}1 type nucleophilic attack of acids to the intermediate cations is not a prominent route to produce carboxylic esters, and mediocre yields are the result (Scheme 9).\textsuperscript{[50]}

![Scheme 9: The Fischer esterification reactions carried out by Hamzah et al.](image)

In addition to soluble mineral acids, solid acids also can contribute to novel and environmentally-benign Fischer esterification procedures for industry and academia due to their reusability through simple recovery.\textsuperscript{[51,52]} The mechanism of solid acid-catalyzed esterification reactions is similar to homogeneous Brønsted acid-catalyzed esterification, but the catalytic performance of solid catalysts is affected by their surface hydrophobicity, which is especially true for the coupling of lipophilic acids and alcohols.\textsuperscript{[53]} There are three possible cases of surface interaction between carboxylic acids and Brønsted acid sites on the catalysts (Figure 1).\textsuperscript{[53]} First, if there is an isolated Brønsted acid site surrounded by a hydrophobic environment, it is likely for the hydrophobic chain of the lipophilic acid to adsorb parallel to the surface of the solid catalyst (Figure 1, a). Second, if there are a few catalytic sites in the vicinity, the fatty acid molecules can adsorb perpendicularly to the surface of the catalyst, with the lipophilic chains forming a hydrophobic environment (Figure 1, b). Finally, if the surface of the catalyst is very acidic and/or hydrophilic, the by-product water is adsorbed on the surface inactivating the solid acid catalyst (Figure 1, c).\textsuperscript{[53]}
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Figure 1: Surface interaction of the solid acid catalyst and fatty acids according to the available acidic sites. (a) interaction of fatty acids with isolated acid sites is parallel to the surface, (b) interaction with close acid sites is perpendicular to the surface, (c) interaction with strong acid is hampered by water adsorbed on the surface

A recent application of solid acid catalysts for esterification has been published by Minakawa et al. using macroporous p-hydroxy phenylsulfonic acid-formaldehyde resin 21 to catalyze esterification reactions (Scheme 10).[5] The catalyst 21 was able to effectively convert acetic acid and benzyl alcohol into the corresponding ester without continuous removal of water during the reactions. The observed conversion of the catalyzed reaction by resin 21 was 96%, while the homogeneous counterpart, p-hydroxy phenylsulfonic acid-catalyzed reactions performed under the same conditions only afforded 79% conversion.[5]

Scheme 10: Macroporous p-hydroxy phenylsulfonic acid-formaldehyde resin-catalyzed esterification of benzyl alcohol and acetic acid by Minakawa et al.
Fischer esterification is an efficient and direct method to condense carboxylic acids and alcohols. The resulting reaction mixtures in principle can be easily purified without column chromatography. Therefore, this esterification method is more applicable to industry than organic reagent-mediated method. However, Fischer esterification requires neutralization after reaction leading to salt formation, which is disadvantageous for the sustainability. Furthermore, the corrosive nature of Brønsted acids can degrade the reaction setups, and lead to additional maintenance cost for industry. Additionally, some undesired side reactions such as ether formation and elimination can happen under acidic conditions. On the other hand, Lewis acid-catalyzed esterification results in low waste production and less side-reactions. Thus, it is a more attractive method for the industrial applications.

2.2.3 Lewis Acid-catalyzed Esterification

High-valent Lewis acidic metal salts and organometallics have displayed distinctive activity on direct esterification. Yamamoto et al. found that HfCl₄(THF)₂, less than 0.2 mol% catalyst loading, was efficient in the esterification of various carboxylic acids with primary and secondary alcohols (>90% yield) at reflux in toluene.[54] The esterification with tertiary alcohols did not proceed due to steric hindrance and the reaction was less fast with benzoic acid.

Zirconium is another group 4 metal efficient in esterification reactions.[55–57] Lundberg et al. discovered that zirconocene triflate (Zr(Cp)₂(CF₃SO₃)₂)THF displayed some catalytic activity in esterification reactions.[57] At 80 °C in trifluoromethyl benzene, 2 mol% of Zr catalyst converted equimolar amounts of benzoic acid and benzyl alcohol into the ester in 78% yield. Under the same conditions, the studied fatty acids and unsaturated fatty acids were esterified with benzyl alcohol in >90% yields. However, substituted benzoic acids usually gave moderate yields (<50%). Aliphatic alcohols and hetero 2-thiophene ethanol were proven to be efficient esterification coupling partners for this developed method (73-93%). On the other hand, due to the steric hindrance and reduced nucleophilicity of alcohols, trifluoroethanol, adamantyl alcohol, and cholesterol only led to the corresponding esters in poor to moderate yields (29-49%).
Titanium(IV) compounds are another good candidate for esterification reactions due to their Lewis acidity and low toxicity.\textsuperscript{[58–61]} Wolzak et al. studied the esterification activity of Ti(IV) aminotriphenolate 22-26 and compared that with the activity of Ti(OiPr)\textsubscript{4}.\textsuperscript{[61]} The esterification reactions were performed with 1 eq. benzoic acid in 10 eq. heptanol and 5 mol\% of catalysts at 150 °C for 6 h. The activity of the synthesized Ti(IV) complexes 22-26 did not match that of Ti(OiPr)\textsubscript{4} (19-62\% vs 79\%, table 1). The less sterically hindered complexes 25 and 26 had a higher reactivity toward ester formation than the more hindered complexes, resulting in 48\% and 62\% yield respectively. The trend in activity of 22-24 (23>22>24) corresponds indicating that a more Lewis acidic Ti(IV) complex results in higher reactivity.

<table>
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<td>6%</td>
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<tr>
<td>Ti(OiPr)\textsubscript{4}</td>
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Table 1. Ti(IV) aminotriphenolates-catalyzed esterification of benzoic acid and heptanol by Wolzak et al.

Furthermore, they observed the amphoteric nature of the catalysts (Lewis acidity of Ti(IV) complexes with Brønsted basicity of a Ti-bound and in situ formed carboxylate group) is essential for catalytic ability. The reaction mechanism of this Ti-catalyzed esterification was proposed and examined by DFT-D3 calculations at the BP86/TZ2P level of theory (Scheme 11). The reaction begins with the acetic
acid/acetate complex A, followed by the rotation of apical acetic acid to give B. The facile nucleophilic attack of alcohol to the apical acetic acid results in complex C, within which the combined action of a Brønsted basic acetate and a Lewis acidic Ti center gives rise to the amphoteric nature of the catalyst. Afterward, apical rotation of the acetal leads to complex E, facilitating formation of ester and water to give F. The consecutive loss of water and ester results in an overall slightly exergonic process ($\Delta G = -2.0 \text{ kcal/mol}$). The transition states, TS$_{DE}$ and TS$_{DF}$, have comparable free energy and thus both can be the rate determining transition state. This finding is in strong contrast with the common assumption that Lewis acidity is the sole crucial factor of the catalytic activity.\[61\]

Scheme 11. Proposed mechanism of Ti(IV) aminotriphenolate-catalyzed esterification by Wolzak et al.
In addition to transition metals, some post-transition metals (metals from group 13-16) are utilized to catalyze esterification reaction. Aluminum is one of the most abundant elements in the Earth crust, and multivalent organoaluminum complexes result in tremendous development of aluminum-catalyzed chemistry including esterification and polymerization reactions. Huang et al. have demonstrated a Lewis acid-catalyzed esterification of levulinic acid using aluminum catalysts (Scheme 12). In Huang’s research, the final product methyl levulinate (ML) was obtained in a yield of 96.6% when the levulinic acid was treated with methanol and an Al₂(SO₄)₃ catalysts after heating at 110 °C for 90 minutes (Scheme 12, condition a). As the esterification reactions were aided by microwave, the reaction yield of ML could reach 99.4% in only 10 min (Scheme 12, condition b). On the other hand, when the anions of the aluminum catalyst were replaced by chlorides and nitrates, the yields of the microwave esterification reactions reduced to 83.9% and 70.9% respectively (Scheme 12, condition d and e). The results suggest that the coordinating anions affect the Lewis acidity of the catalytic center, which further influences the esterification performance of the catalyst.

Scheme 12: Aluminum-catalyzed esterification of levulinic acid and methanol by Huang et al.

Mono- and dialkyltin(IV) complexes show good catalytic activity and stability in transesterification, esterification, and polyesterification reactions. The alkyl substituents of the tin complexes, generally n-butyl or n-octyl, appear to be pivotal for their catalytic performance since the strong Lewis acid SnCl₄ is not a good esterification catalyst. According to Wolzak et al., at 150 °C, 1 mol% of n-BuSnO₂H catalyzed the esterification of 1 eq. benzoic acid and 10 eq. heptanol to afford 82% yield of heptyl benzoate in 6 h. The proposed mechanism of the monoakyltin(IV) complex was examined by DFT calculations at the BP86-D3/def2-TZVP//M06-2X-D3/def2-TZVP/def2-QZVPP level of theory (Scheme 13). In the
presence of acid and alcohol, BuSnO$_2$H starts forming a resting state composed of monomer 27 and dimer 28. Both complexes are at the same energy level and can form intermediate I. The coordinating alkoxy group on I can accommodate another alcohol via a hydrogen bonding. Subsequently, nucleophilic attack of the alcohol results in intermediate II, in which the Lewis basic ethoxy group accommodates the hydrogen atom from another ethanol. A rotation pre-organizes intermediate III to form IV facilitating the breakage of the C-O bond resulting in ester and water (V). The following consecutive loss of water and ester closes the catalytic cycle of the BuSnO$_2$H-catalyzed esterification reaction. The rate determining step is the C-O bond breakage with a $\Delta G = 20$ kcal/mol.$^{[66]}$ Although the organotin-catalyzed esterification leads to good results, the toxic nature of organotin compounds leads to their restricted utilization in Europe.$^{[67,68]}$

Scheme 13. Proposed mechanism of organotin-catalyzed esterification by Wolzak et al.
Mild and solid Lewis acids are usually easier to handle than corrosive Brønsted acids. If the Lewis acid is not toxic, post-treatments and purification of the ester product, e.g. coatings, are essentially not required after the esterification. Therefore, this method is of particular interest in industrial applications. On the other hand, without purification of the product ester, the catalyst still remains in the mixture. Therefore, the Lewis acid catalysts have to be nontoxic in order to be applied in product as daily commodities. Currently, the conditions used for polyesterification in industry still require high energy (>200 °C), and some of the active catalysts are phased out due to their toxicity. The ideal catalysts should have low toxicity and low environmental impact. Furthermore, the active catalyst should catalyze the reactions at lower temperature (aiming for <200 °C). Therefore, together with AkzoNobel, we are looking for a sustainable method to perform (poly)esterification. We decided to study the esterification ability of Bi(III)-compounds since they are good Lewis acids and non-toxic. The following section will discuss our studies on Bi(III)-catalyzed (poly)esterification.

2.3 Studies on Bismuth-catalyzed Esterification

Bismuth is a noncorrosive metal with low toxicity, and the complexes show moderate to strong Lewis acidity. Some Bi(III)-compounds are used as a Lewis acid to catalyze various organic reactions including Diels-Alder reactions, aldol reactions, and Friedel-Crafts alkylation and acylation reactions. However, esterification with bismuth catalysts is not well studied. Ramos et al. studied the esterification of fatty acids with methanol using Bi$_2$O$_3$ as the Lewis acid catalyst. When the reaction was performed at 140 °C for 2 h using 2 eq. MeOH and 1 eq. lauric acid, 5 wt% Bi$_2$O$_3$, in relation to the mass of fatty acid, this led to conversions up to 87%. Inspired by the study, we were interested in investigating a series of Bi(III) Lewis acids on esterification. We aimed to find an efficient bismuth-based esterification catalyst for large-scale synthesis of esters and polyesters, ultimately to provide an alternative efficient catalytic system for coating industry.
To study the catalytic activity of Bi(III)-compounds (1 mol%), we performed the reaction of benzoic acid and heptanol (1:10 molar ratio) at 150 °C for 6 h (Table 2). An excess of heptanol was used to drive the reaction to completion without the use of dehydrating reagents or azeotropic distillation. Since the esterification reaction is autocatalytic because of the benzoic acid in the system, the reaction without a catalyst led to 20% conversion. With BuSnO₂H, an industrially used catalyst by AkzoNobel, 80% conversion to the ester was observed. We used the result of the BuSnO₂H-catalyzed esterification as the reference to study the reactivity of Bi(III)-compounds. Afterward, we started to study the reactivity of the commercially available Bi(III)-compounds. Bi₂O₃ resulted in 62% conversion so less than the reference catalyst. According to Ramos’s studies, Bi₂O₃ is converted into Bi(III) carboxylate, which is the active catalytic species in the esterification. We expected that Bi(OH)₃, Bi(OAc)₃, and Bi(III) citrate would form the same catalytic species as Bi₂O₃ and thus would provide similar esterification results. Bi(OH)₃ and Bi(OAc)₃ however, only led to about 40% conversion. In theory, one unit of Bi₂O₃ leads to two active Bi(III) species, which could explain higher conversion of Bi₂O₃-catalyzed reaction at the same catalyst loading. We halved the catalyst loading of Bi₂O₃ and found out the conversion was reduced by 25%, which suggests Bi₂O₃, Bi(OH)₃, and Bi(OAc) have similar catalytic ability. Bi(III) citrate did not dissolve in the reaction mixture. Therefore, the expected active Bi(III) carboxylate was not formed leading to only 19% conversion. Bi(NO₃)₅·5H₂O also showed similar reactivity as Bi(OH)₃ and Bi(OAc)₃, while BiPO₄ only led to 14% conversion due to its low solubility in the mixture. BiCl₃, although it was entirely dissolved in the mixture, only showed the same result as the uncatalyzed reaction. On the other hand, Bi(OTf)₃ led to full conversion to the ester. We initially assumed the substantial improvement of the conversion resulted from strong Lewis acidity of Bi(OTf)₃. However, we also observed a significant amount of ether formed during the reaction, which is a typical phenomenon of Brønsted acid-catalyzed esterification. Furthermore, metal triflates have been suggested as an easy-to-handle species to generate triflic acid. According to Lherbet et al., Bi(OTf)₃ is an easily handled precursor for triflic acid in esterification reactions. As the role of Bi(III) was not clear from these experiments, we started to investigate the activity of Bi(OTf)₃ in the presence of base.
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![Chemical structure diagram](image)

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<td>10</td>
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Table 2. Bi(III)-catalyzed (1 mol%) esterification of benzoic acid and heptanol. 5 mmol benzoic acid and 50 mmol heptanol reacted at 150 °C for 6 h. 5 mmol of pentadecane was used as the internal standard to determine the yields by GC. BuSnO₂H, an industrially used catalyst, is the reference catalyst for the esterification.

Figure 2 shows the results of Bi(OTf)₃ and HOTf-catalyzed esterification reactions in the presence of base. In order to completely neutralize (in situ) HOTf in the reaction mixture, 5 mol% of the base was added to the 1 mol% catalyzed reaction. Without the addition of base, Bi(OTf)₃ and HOTf gave full conversion to the ester. On the other hand, the ether formation ratio of Bi(OTf)₃ and HOTf-catalyzed esterification was 0.79 and 1 respectively (peak area of ether divided by that of the internal standard). In the presence of 2,6-di-tert-butyl 4-methylpyridine (DTBMP), full conversion of the Bi(OTf)₃ and HOTf-catalyzed esterification reactions was also observed. As pyridinium triflate has been used as an acid catalyst for glycosylation,[76] we propose that it is also an efficient acid catalyst to perform Fischer esterification. On the other hand, the ether formation was diminished by adding DTBMP, reducing the ratio to about 0.1. In the presence of Na₂CO₃, the Bi(OTf)₃-catalyzed reaction led to 34% conversion, while the HOTf-catalyzed reaction only gave 14% conversion. We assume that the HOTf was completely neutralized by the Na₂CO₃, and therefore the reaction without Bi(III) was comparable to the non-catalyzed reaction. On the other hand, the neutralized...
Bi(OTf)$_3$ still has Bi(III) present to form Bi(III) carboxylate as the active catalytic species. Hence, the neutralized Bi(OTf)$_3$ still marginally catalyzed the reaction to give moderate conversion.

After our studies on the commercially available Bi(III) Lewis acids, we decided to further study the polyesterification catalyzed by Bi$_2$O$_3$ and Bi(OTf)$_3$ due to their good to excellent catalytic ability among the tested catalysts. Together with AkzoNobel, we used adipic acid, cyclohexanedicarboxylic anhydride, and phthalic anhydride as the polyesterification “acceptors”, and neopentyl glycol as the “linker”. The polyesterification reaction is usually performed at >200 °C with a catalyst, but we decided to perform the reaction at 150 °C to be able to compare to our model esterification conditions. Toluene was used as the solvent to assist the azeotropic removal of water. We determined the conversion of the reaction by monitoring the acid value (AV). AV is a number used to quantify the amount of...
free acids in a given amount of substrate (Formula 1a). The lower the AV, the higher the conversion of the reaction. We performed the reaction under the conditions described in scheme 14.

Scheme 14. The model conditions for the Bi$_2$O$_3$ and Bi(OTf)$_3$-catalyzed polyesterification. The reaction was performed with 0.8 mol acid, 0.8 mol anhydride, 2.7 mol alcohol, and 2 mol% catalyst in 70 mL toluene at 150 °C. A small amount of reaction mixture was collected every 1-2 h for the determination of the AV.

According to figure 3, the use of BuSnO$_2$H, the industrially used catalyst, the Bi$_2$O$_3$ and the reaction without catalyst led to similar conversions. The AV of those reactions was around 160-180 mg KOH/g, and reduced to around 90 mg KOH/g after 7 h. On the other hand, Bi(OTf)$_3$ led to an AV = 18 mg KOH/g in 2 h suggesting the carboxylic acid in the Bi(OTf)$_3$-catalyzed reaction was efficiently consumed. However, the AV only represents the amount of free acid in the mixture and fails to indicate if side reactions such as ether formation occur. Hence, we measured the hydroxyl value (HV) at the end of the polyesterification reaction. HV is defined as the number of milligrams of KOH needed to neutralize the acetic acid taken up on acetylation of 1 g of a chemical substance that contains free hydroxyl groups (Formula 1b). The AV is the correcting factor of the determined HV since that is also titrated with KOH. In theory, 0.4 eq. neopentyl glycol, equivalent to 0.8 eq. free hydroxyl groups, remains in the mixture if the polyesterification is complete, and therefore the minimal theoretical HV is 44.88 mg KOH/g (AV = 0 mg KOH/g). The HV of the Bi(OTf)$_3$-catalyzed reaction was found 30 mg KOH/g, which is significantly lower than 44.88 mg KOH/g. Therefore, we conclude that the use of Bi(OTf)$_3$ also results in ether formation in the polyesterification system although ester formation seemed to be efficient.
Chapter 2

\[ a) AV = \frac{(M_{W_{KOH}}) \times (Conc_{KOH}) \times (V_{sample})}{W_{sample}} \]

\[ b) HV = \frac{(M_{W_{KOH}}) \times (Conc_{KOH}) \times (V_{blank} - V_{sample})}{W_{sample}} + AV \]

**Formula 1.** Determination of the hydroxyl value HV. \( M_{W_{KOH}} \) = molecular weight of KOH = 56.1 g/mol, \( Conc_{KOH} \) = concentration of KOH for titration (M), \( V_{blank} \) = amount of KOH needed to titrate blank (mL), \( V_{sample} \) = amount of KOH needed to titrate (acetylated) sample (mL), \( W_{sample} \) = weight of the sample used for acetylation before titration (g).

![Figure 3. The conversion over time determined by the AV. Conditions: either 1 eq. adipic acid, or 1 eq. cyclohexanedicarboxylic anhydride, or 1 eq. phthalic anhydride, and 3.4 eq. neopentyl diol were esterified at 150 °C with 0.5 mol% of catalyst. Water was removed by azeotropic distillation to drive the reaction to completion.](image)

Based on the results, we conclude that Bi\(_2\)O\(_3\) and BuSnO\(_2\)H are not effective Lewis acid catalyst to catalyze the polyesterification in our experiments. Since the BuSnO\(_2\)H-catalyzed reaction also led to poor polyesterification results at low temperatures (<200 °C), it is difficult to judge the performance of Bi\(_2\)O\(_3\). On the
other hand, according to the previous esterification studies, Bi$_2$O$_3$ is not as efficient as BuSnO$_2$H in catalyzing the esterification of benzoic acid and heptanol. Hence, we decided to not further study esterification reactions with Bi$_2$O$_3$. As for Bi(OTf)$_3$, it efficiently converts the starting materials into the polyesters, but it also caused significant ether formation. Ether formation is an unfavorable side reaction in industry since it affects the quality of the polyester product. Therefore, Bi(OTf)$_3$ is also not an ideal alternative to replace the current catalytic system used in industry.

2.4 Conclusion

To conclude the studies of the commercially available Bi(III) catalysts, we found that Bi(III) Lewis acids are not particularly active in esterification reactions. Bi$_2$O$_3$, Bi(OH)$_3$, and Bi(OAc)$_3$ show moderate catalytic activity but the efficiency does not outcompete the industrially used tin catalyst. Although Bi(OTf)$_3$ leads to full conversion in ester formation, the reaction predominantly undergoes a Fischer esterification mechanism, that is, H$^+$ is the active catalyst. In addition, Bi(OTf)$_3$ leads to significant ether formation. Bi$_2$O$_3$ and Bi(OTf)$_3$ were also used to study a polyesterification reaction. Bi$_2$O$_3$ did not accelerate the reaction, while Bi(OTf)$_3$ efficiently converted the starting materials into polyesters. However, again ether formation was observed. Since the studied Bi(III) catalysts either led to low conversion or significant ether formation, they are not a good alternative for the esterification system in industry. Hence, we propose further studies on Bi(III)-catalyzed esterification is not worthwhile.

2.5 Acknowledgement

The sustainable esterification project was a collaborative project with Dr. Lukas Wolzak of the University of Amsterdam. Dr. K. J. van den Berg and Dr. J. Flapper, AkzoNobel are acknowledged for the supervision and suggestions. AkzoNobel is also acknowledged for the expertise and facilities for the polyesterification studies.
2.6 Experimental

Solvents and Reagents

All Bi(III)-compounds, heptanol, benzoic acid, and pentadecane for the esterification studies were commercially available and used without further purification. Adipic acid, cyclohexanedicarboxylic anhydride, phthalic anhydride, and neopentyl glycol were provided by AkzoNobel.

Analysis

GC analysis

An Agilent GC-FID instrument equipped with a Hewlett Packard GC carousel 18596C autosampler, a 6890 series gas chromatograph with a split/splitless injector, and a 6890 FID detector, was used for the analysis of conversion and selectivity of the esterification reaction. The gas chromatograph was equipped with a J&W DB-5ht 5975T column (30.0 m × 250 µm × 0.10 µm). The injector temperature was kept at 350 °C. The helium carrier gas flow rate was kept at 1.7 mL/min. The temperature of the oven started from 40 °C and increased to 200 °C at a rate of 5 °C/min. The temperature was further increased to 350 °C at a rate of 50 °C/min. The temperature of FID was kept at 300 °C with a combination of H₂ (40 mL/min) and air flow (300 mL/min); in which N₂ was used as a makeup flow (25 mL/min). The AV and HV were determined by an automatic titrator (Metrohm) with a 1 M aqueous KOH solution.

AV determination

To a 150 mL beaker, the indicated amount of reaction mixture was added according to the estimated AV (Table 3). To the beaker, 90 mL of EtOH/xylene (1:1) was added to dissolve the mixture. The mixture was stirred, heated if necessary, until the mixture was entirely dissolved. The resulting solution was titrated with an automatic titrator with 1 M KOH aqueous solution.

<table>
<thead>
<tr>
<th>Estimated AV (mg KOH/g)</th>
<th>Sample size (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3. Required sample size for titration according to estimated AV

Acetylation for HV determination

To a 150 mL beaker, the indicated amount of reaction mixture was added according to the estimated HV (Table 4). The mixture was dissolved in acetone and stirred until homogeneous. 20 mL DMAP in acetone (25 g/ 2.5 L) was added to the solution and mixed for 1 min. To the solution, 5 mL acetic anhydride was added followed by stirring at rt for 10 min. The resulting mixture was titrated with an automatic titrator with 1 M KOH aqueous solution.
Studies on Esterification and (poly)Esterification with Commercially Available Bi(III)-Compounds

<table>
<thead>
<tr>
<th>Estimated HV (mg KOH/g)</th>
<th>Sample size (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-50</td>
<td>8</td>
</tr>
<tr>
<td>50-100</td>
<td>4</td>
</tr>
<tr>
<td>100-200</td>
<td>2</td>
</tr>
<tr>
<td>200-400</td>
<td>1</td>
</tr>
<tr>
<td>400-800</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 4. Required sample size for acetylation according to estimated HV

Conditions for the Bi(III)-catalyzed esterification reactions

The esterification studies were performed in a carousel reaction station (Radley) without dehydrating reagents or azeotropic removal of water. 5 mmol benzoic acid, 50 mmol heptanol, and 5 mmol pentadecane were added to a thread glass reaction tube (24*150 mm) equipped with a stirring bar. A Bi(III)-catalyst was added to the mixture, sealed and placed on the reaction station. The mixture was heated at 150 °C for 6 h. After 6 h, the mixture was cooled down and the conversion was analyzed by GC-FID.

Conditions for Bi(III)-catalyzed polyesterification studies

The esterification studies were performed with a Dean-Stark setup for azeotropic removal of water. To a 1 L flask, either adipic acid (119 g, 0.8 mol), or cyclohexanedicarboxylic anhydride (127 g, 0.8 mol), or phthalic anhydride (123 g, 0.8 mol), and neopentyl (281 g, 2.7 mol), and toluene (70 g) were added. After placing the flask on the setup, the mixture was heated to 120 °C and stirred with overhead stirring. 5 mol% of the catalyst was added to the mixture, and the mixture was heated to 150 °C. The formed water was collected and the amount of collected water was weighted every h to estimate the conversion. A small amount of reaction mixture was collected every h for determination of AV by titration. The reaction was stopped and cooled down after 7 h.

2.7 References


Studies on Esterification and (poly)Esterification with Commercially Available Bi(III)-Compounds


