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Hemiacetal esters: synthesis, properties and applications of a versatile functional group

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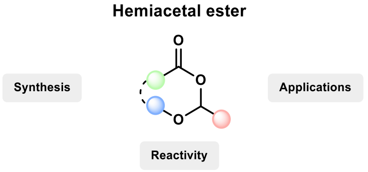
TOC Graphic



Abstract

The present perspective article provides an overview of the hemiacetal ester (HAE) chemical functionality and its use in organic synthesis and polymer science. The objective of this account is to expose the high potential of the HAE functionality in both molecular and macromolecular chemistry, through the highlight of its rich and peculiar reactivity and the description of the achievements in polymer chemistry involving this group. This perspective article presents a summary of the different synthetic routes described so far to produce HAEs, whether this led to linear or cyclic compounds. It also outlines the very rich and complex reactivity of the HAE functional group through a thorough description of its dissociation under a thermal or ionic stimulus, its hydrolysis/alcoholysis susceptibility, and its ability to undergo exchange reactions. Finally, the successful use of HAEs for various applications in organic and polymer chemistry is also described, including, but not limited to, their use as protecting groups, initiators of polymerization, building-blocks in polymer synthesis, or as exchangeable linkages in covalent adaptable networks.

1. Introduction

Acylated (hemi)acetals, also known as hemiacetal esters (HAEs) or esteracetals, can be seen as a subclass of acetals in which one of the constitutive RO– group is replaced by an ester (RCOO–). This function was first reported by Claisen in 1898 from a condensation between a carboxylic acid and an acetal,[1] but was extensively investigated only in the past 40 years, mostly in the polymer field. The belated development of this functionality probably stems from its lability and high reactivity: HAEs are indeed more prone to hydrolysis and decomposition by acids than standard acetals and also show a certain thermal instability. Because of this marked reactivity and sensitivity, they were often seen as transient species or as reactive intermediates and rarely isolated. As far as synthetic organic chemistry is concerned, if carbohydrate synthesis has made extensive use of 1-*O*-acetylglycosides as one of the most common precursors of glycoside donors (and among the most stable ones),[2,3] the generic HAE functionality has been mostly exploited as temporary protecting groups for carboxylic acids.[4] This last application has been widened in polymer chemistry since such blocking of carboxylic acids improved the solubility of polyacids in solvents, facilitated polymerization reactions, and enhanced the stability of epoxy-acid coating solutions while allowing the release of the reactive acid group upon heating or acidic hydrolysis.[5,6] Polymer chemistry has granted HAEs with even more attention since they were also used as initiators of living cationic polymerization of vinyl ethers,[7,8] or homopolymerized to poly(esteracetals) under Lewis or Brønsted acid activation.[9,10]

This review aims to gather and summarize the literature devoted to this functional group, focusing on the synthetic routes, the reactivity/stability, and the applications in which they were involved (Figure 1). A second goal is to highlight the versatility of this functional group that offers wide possibilities in synthetic and materials chemistry, despite its moderate thermal and hydrolytic stability.

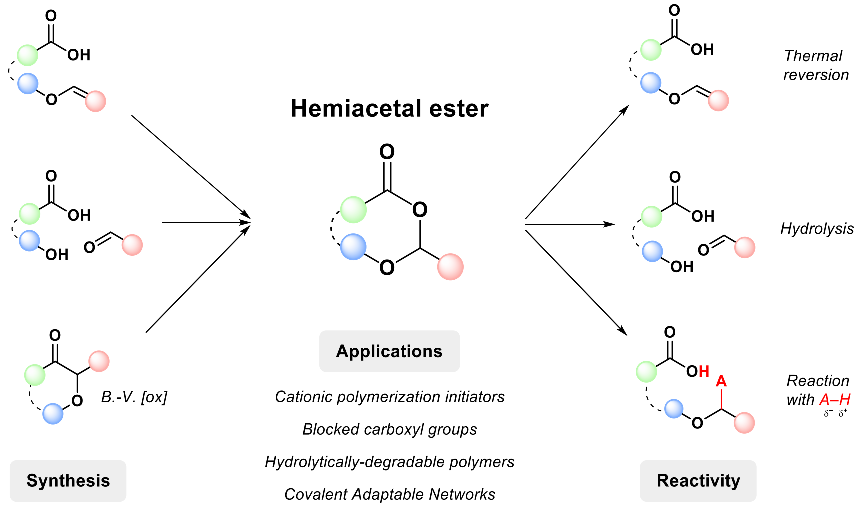
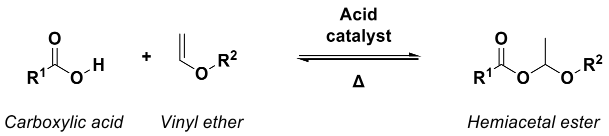


Figure 1: Hemiacetal esters - synthesis, reactivity and applications.

1. HAE synthetic routes

HAE functions are often simply obtained by the nucleophilic addition of a carboxylic acid onto a vinyl ether, in the presence of a strong Brønsted acid as a catalyst and this constitutes the most common preparations of HAE monomers (Scheme 1).[11–14] Cationic polymerization of vinyl ether can sometimes be observed as a side reaction during this synthesis. However, *Nakane and Ishidoya* found that this undesired route could be avoided by a careful selection of the acid used as a catalyst.[15] By using a panel of catalysts such as hydrochloric, sulfuric, nitric, and phosphoric acids, they established that cationic polymerization of the vinyl ether occurs more easily with stronger acids, with a limit pKa value of 2 above which no cationic polymerization was observed. Some preliminary studies also describe the synthesis of HAEs by reaction between an α-halo ether and salts of carboxylic acids which does not require any acid catalyst.[16–19]

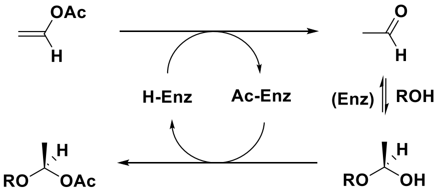


Scheme 1: Nucleophilic addition of a carboxylic acid onto a vinyl ether.[11–14]

Similarly, *Zhang et al.* recently described a three-component reaction of carboxylic acids, terminal alkynes, and *tert*-butyl hypochlorite (Scheme 2).[20] This very specific HAE synthetic route involves an excess of *tert*-butyl hypochlorite as a double Cl^+ donor, allowing the addition of the carboxylate and the *tert*-butoxide on the alkyne. The resulting HAEs were very stable towards acidic hydrolysis as they could be purified by silica gel chromatography, presumably stabilized by the electron-withdrawing chlorine atoms.[47]

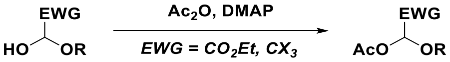
Scheme 2: Three-component HAE synthesis.[20]

An alternative method of synthesis consists in the use of lipases (enzymes).[21–27] A vinyl acetate is first converted into acetaldehyde by a lipase, that cleaves and retains the acetate. The released acetaldehyde is then converted, by reaction with an alcohol, into a hemiacetal group, which is subsequently acetylated by the acetyl-lipase (Scheme 3). This enzyme-mediated reaction is therefore enantioselective but this complex method only affords low yields, which could be explained by the sensitivity of HAEs towards hydrolysis and alcoholysis that will be described in the second part of this review.



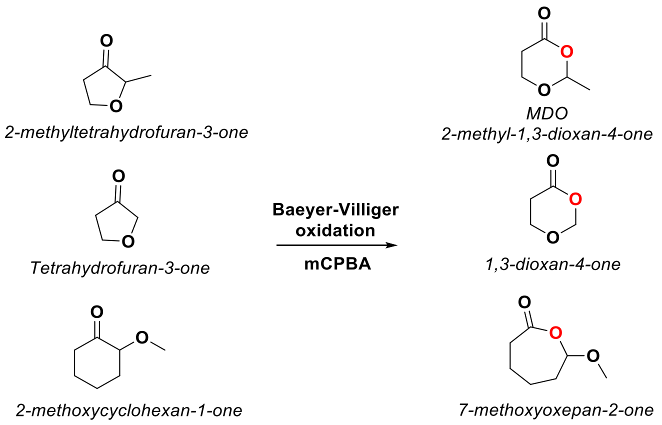
Scheme 3: Lipase-mediated HAE synthesis.[21,22]

An additional, but less general approach to synthesize linear HAEs can also be mentioned. Traditional esterification methods are not appropriate for HAE synthesis except for the condensation between anhydrides and exceptionally stable hemiacetal species. Indeed, hemiacetals derived from highly electrophilic aldehydes such as di- or trihaloacetaldehydes, or alkyl glyoxylates, react easily with alcohols to furnish a stable hemiketal intermediate that can be acylated under standard conditions (Scheme 4).[28–30]



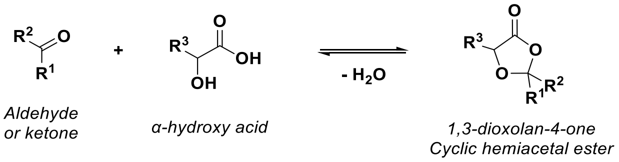
Scheme 4: HAE synthesis by acetylation of a stabilized hemiacetal.[28–30]

Besides acyclic molecules, HAE functions have often been embedded into 5-membered (or larger) rings.[9,10,31,32–39] Two distinct synthetic routes have been explored for the preparation of such cyclic compounds. The first one is based on the Bayer-Villiger oxidation of dihydrofuran-3-ones (or larger rings) (Scheme 5) .[9,10,32–36] This route has therefore been used only for the formation of 6-membered (or larger) rings and many substrates for cationic ring expansion polymerization with vinyl ethers have been prepared this way (*vide infra*).



Scheme 5: Baeyer-Villiger oxidation leading to cyclic HAEs, examples from the literature.[9,32–36]

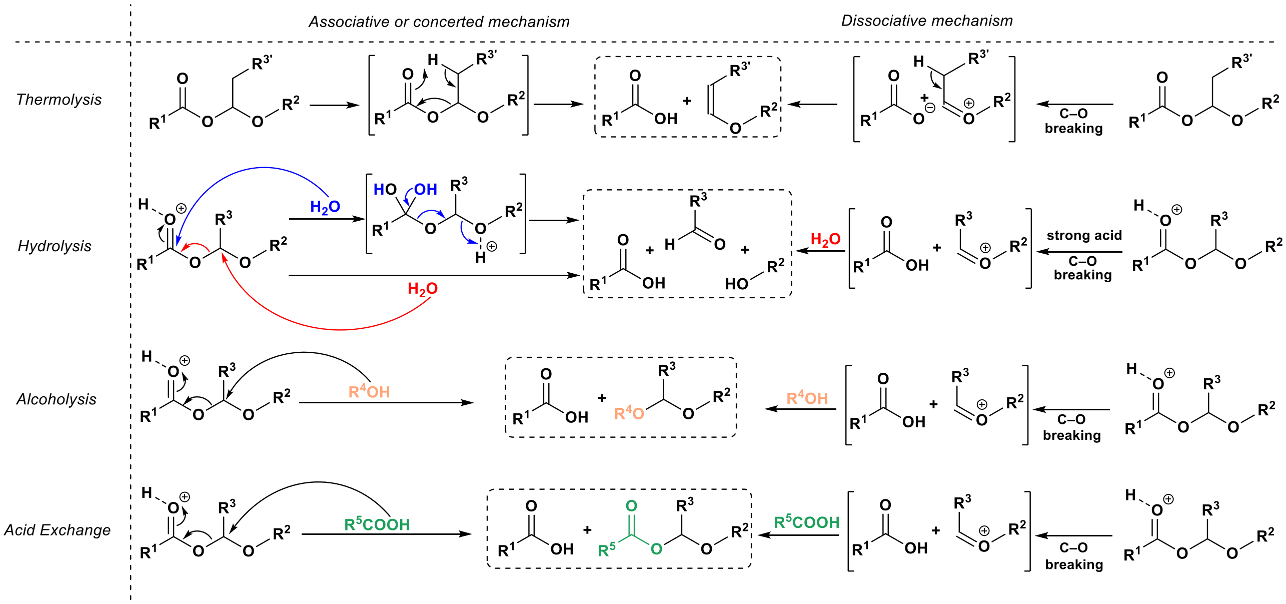
The second strategy allows the preparation of 6-membered and, more frequently, 5-membered cyclic HAEs and is based on the reaction between a β- or α-hydroxy acid, such as lactic acid, with a ketone or an aldehyde (Scheme 6).[31,37–39] The traditional synthesis of acetals (condensation of an aldehyde with alcohol molecules) cannot be applied to HAEs (condensation of aldehyde with an alcohol and an acid) as it would only provide the corresponding acetal due to its better stability and to the higher nucleophilicity of alcohols. However, in the case of the reaction between an aldehyde and a β- or α-hydroxy acid, the intramolecular reaction between the acid and the hemiacetal intermediate is favored over the intermolecular second addition of an alcohol and therefore provides the corresponding cyclic HAE. This condensation is usually catalyzed by a Bronsted or Lewis acid (PTSA, H_2SO_4, $BF_3.Et_2O$, …) and requires a dehydrating reagent (P_2O_5, …) or a water-removal technique.[40–44] The addition of trimethyl orthoformate to form a transient methoxy-substituted HAE appeared as an improved method to prepare a sterically hindered HAE derived from pivalaldehyde.[45] This approach also constitutes a very popular preparation of HAE monomers for various polymerization reactions (vide infra).



Scheme 6: Reaction of α-hydroxy acids with aldehydes or ketones to form cyclic HAEs.[37]

2. Reactivity of HAEs

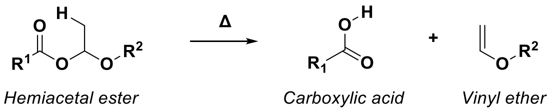
The applications that will be detailed in the following section, mainly in the polymer chemistry field, stem from several main reactivity pathways that are illustrated in the following scheme. Depending on the conditions (temperature, pKa, solvent) and the presence of weak nucleophiles (water, alcohols, or acids), HAEs can undergo thermal reversion (only if a β-proton can eliminate), hydrolysis/alcoholysis and exchange reactions according to different mechanistic pathways (Scheme 7).



Scheme 7: Mechanisms of HAE thermolysis, hydrolysis, alcoholysis and exchange reactions.

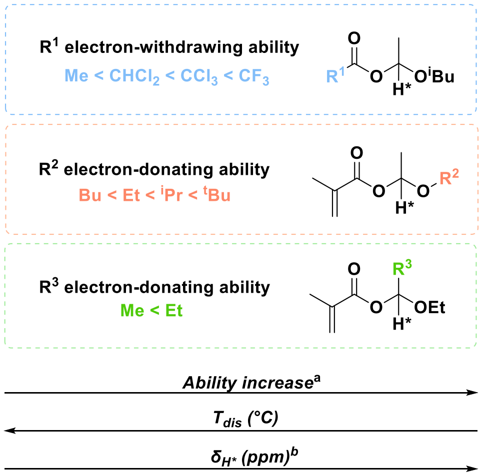
Thermal and ionic dissociation

The dissociation (or thermal reversion) of HAEs upon heating, leading to the release of the initial carboxylic acid and vinyl ether (Scheme 8), was first suggested by *Gallucci and Going*,[11] and used for the conversion of acetals into vinyl ethers through a transient HAE species.[46] This has been further studied by *Endo and co-workers* who highlighted, by thermogravimetry, the influence of the structure of the initial acid on the dissociation temperature of the HAE.[12] With aliphatic acids, the temperature required to trigger the dissociation increased with the length of the carbon chain. In contrast, switching from an aliphatic to a conjugated aromatic acid (*i.e.*, from a cyclohexane-1,4-dicarboxylic acid to a terephthalic acid) significantly reduced the dissociation temperature. A marked difference was also noticed between the dissociation temperatures of the HAE obtained from fumaric acid (*trans*, 145 °C) and maleic acid (*cis,* 190 °C), suggesting an effect of the *trans*/*cis* configuration of the acid on the dissociation energy. All these variations were explained by the authors by inductive and mesomeric effects induced by the increase of the chain length or the stabilization of the carboxylate group.



Scheme 8: Thermal dissociation of HAEs.[11]

In related studies, *Endo and co-workers* also investigated the influence of the vinyl ether structure on the thermal dissociation.[13,47] Several HAEs were prepared from methacrylic acid and different vinyl ethers and were then homopolymerized. The thermogravimetric analysis of these homopolymers unveiled an influence of the inductive effect of the R^2 group of the vinyl ether, the more electron-donating groups leading to lower dissociation temperatures (Figure 2, A). A similar influence on the dissociation temperature was observed by replacing the central methyl group (R^3 = Me) by a more electron-donating ethyl group (R^3 = Et). Indeed, *Endo and co-workers* demonstrated that the thermal stability was decreased by 20 °C with such a change, suggesting that electron donors in this position destabilize the HAE bond toward thermolysis.[47] Although a systematic study correlating HAE hydrolytic and/or thermal stability as a function of R^3 electronics is still outstanding, the fact that several groups were able to isolate HAEs with electron-withdrawing (EWG) R^3 substituents by column chromatography further suggests that EWG substituents in this position enhance the hydrolytic stability of these molecules. Along with these observations on the thermal stability, *Endo and co-workers* indicated a strong influence of the electron-donating ability of these substituents on the ^1H NMR chemical shift of the central hydrogen atom (highlighted in Figure 2).[13,47] Monitoring this chemical shift thus appears as a potential indicator of the relative stability of the HAE.

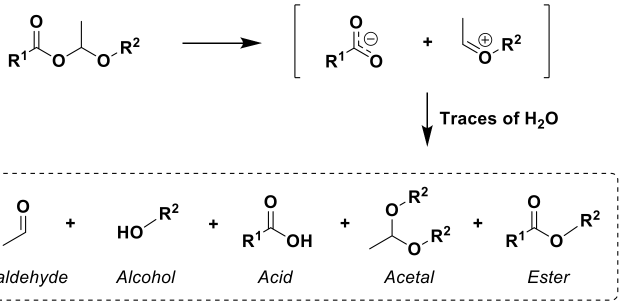


[a]Electron-donating or withdrawing ability of the highlighted group.
[b]Proton H* NMR chemical shift.

Figure 2: Influence of the inductive effect of the substituents on the HAE stability [7,13,47]

Besides the influence of the structure of the HAE, the effect of the polarity of the medium on the dissociation temperature was also investigated by *Endo and co-workers*.[48] The HAE resulting from the reaction of methacrylic acid with a vinyl ether (structure presented in Figure 2) was subjected to a radical copolymerization with monomers of various polarities and the thermal dissociation of the resulting materials was then studied by thermogravimetry. This study concluded that the polymers obtained from a polar comonomer had a lower dissociation temperature compared to the polymers obtained from an apolar comonomer. In addition, another investigation from the same group showed that the ratio between the HAE monomer and its comonomer also had an influence on the dissociation temperature of the resulting polymer.[49] Indeed, a decrease in the HAE monomer content led to an increase in the dissociation temperature, independently of the polarity of the comonomer. However, the polarity of the comonomer did have an influence on the extent of this variation. Indeed, this difference in dissociation temperatures between polymers with low and high HAE monomer contents ranged from 10 °C for polar comonomers to 50 °C for apolar comonomers. This would tend to indicate that apolar comonomers prevent the dissociation of HAEs. However, the authors also mentioned the potential influence of the steric hindrance displayed by the apolar comonomer (e.g., styrene) but could not determine which influence (polarity or steric hindrance) was responsible for their observations.

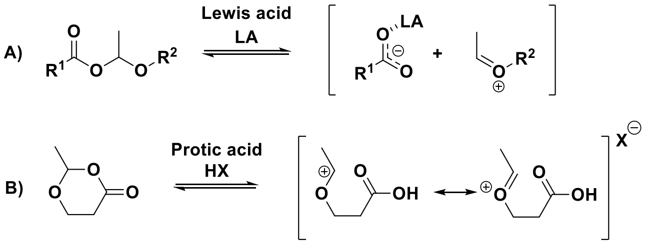
Although most studies agreed on the regeneration of the initial carboxylic acid during thermal dissociation of HAEs, only a few studies paid attention to the regeneration of the initial vinyl ether. Among them, *Gallucci and Going* observed, in their study of the dissociation of an HAE by distillation, that the vinyl ether was regenerated only when the released carboxylic acid was extracted from the reaction medium.[11] Otherwise, degradation products such as acetaldehyde, alcohol, acetate, ester, and carboxylic acids were identified (Scheme 9). *Gallucci et al.* hypothesized that the absence of vinyl ether might be due in part to the fast reassociation of the acid with the vinyl ether but would most likely be caused by the catalyzed degradation of the vinyl ether in the presence of carboxylic acid. *Endo and co-workers* studied the dissociation of HAEs obtained from the reaction between acetic acid or di-/trihaloacetic acid and *iso*-butyl vinyl ether (Figure 2, B) and could not detect as well the starting vinyl ether after dissociation.[7] They suggested that the reaction might proceed through a polar dissociation leading to a carboxylate and an oxonium cation (thermolysis – dissociative pathway in Scheme 7), rather than the direct concerted elimination to carboxylic acid and vinyl ether (thermolysis – concerted pathway in Scheme 7). In later publications, the same group reported the detection of the released vinyl ether when polymers featuring HAE groups were subjected to a thermal treatment in pressurized flasks.[47,48] This report thus differs from the study of *Gallucci and Going* which stated that the vinyl ether was degraded if the released acid was not extracted from the medium.[11]



Scheme 9: Degradation products obtained from the HAE thermolysis.[7,11]

Nakane and Ishidoya studied the acid-catalyzed dissociation of HAEs and observed that, under the same conditions (120 °C, 30 min), the dissociation was increased from 25 (in the case of the uncatalyzed reaction) to 75-95% in the presence of sulfonic acid or of a Lewis acid ($BF_3{\cdot}OEt_2$, zinc 2-ethylhexanoate).[15] The impact of the Lewis acid strength on the dissociation temperature of a network prepared by the reaction between Meldrum acids and bisphenol A diglycidyl ether (DGEBA) was also examined by *Gonzales et al*.[50,51] Using three different Lewis acids and thermogravimetric analysis, they concluded that the strength of the embedded Lewis acid had a significant impact on the network degradation caused by the dissociation of the HAEs. In the presence of ytterbium triflate, this degradation was observed at a lower temperature than with weaker Lewis acids such as lanthanum triflate or boron trifluoride-monoethylamine complex. The authors reached the somehow expected conclusion that stronger Lewis acids induced a decrease in the HAE dissociation temperature. However, two aspects of this study appear extremely surprising in light of the knowledge on the stability of HAE molecules and polymers. First of all, the dissociation temperatures announced in this work (200-300 °C) are way above the usual degradation temperatures observed for such materials. Then, these high degradation temperatures are even more surprising when the chemical structure proposed for these polymers is taken into consideration. Indeed, the HAE substituted by two methyl groups resulting from the initial polymerization reaction should be extremely labile and easily decompose to release acetone, as it is often observed in reactions involving the ring-opening of Meldrum's acid.[52] One can wonder if the polymers prepared from Meldrum's acid and DGEBA are not simple polyesters (resulting from ring-opening and acetone release of the first monomer), which could explain their high resistance to a thermal treatment in the presence of strong Lewis acids. The authors claim that the chemical structure was proved by IR spectroscopy, but this analytical technique does not seem appropriate and precise enough to distinguish a polyester from the proposed structure.

The dissociation in the presence of Lewis acids has been presented in most studies as an exclusively ionic phenomenon that can happen even at 0°C and lead to the formation of an ion pair (a carboxylate and an oxonium, Scheme 10, A), rather than a thermal phenomenon that can proceed by a concerted elimination.[15,53–55] This proposed mechanism is in line with the work of *Endo and co-workers* who also suggested such an ionic dissociation.[7] More recently, *Hillmyer and co-workers* suggested that the use of a protic acid (diphenyl phosphate, "DPP") could also lead to a polar cleavage of the C–O bond, giving rise to a carboxylic acid and an oxonium ion (Scheme 10, B).[33]



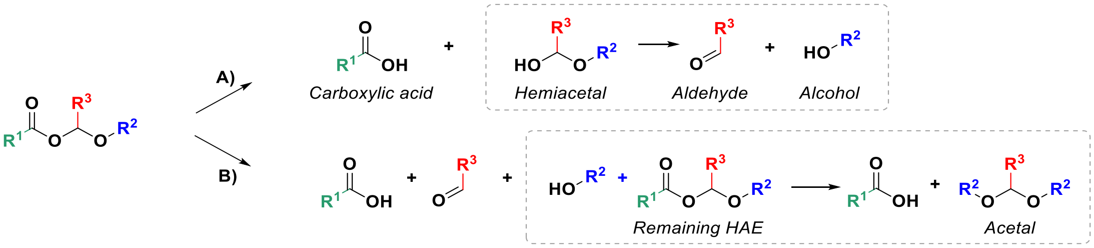
Scheme 10: HAE ionic dissociation in the presence of A) Lewis acid,[15,53–55] and B) protic acid.[33]

Hydrolysis and alcoholysis reactions

The moderate stability of HAEs is illustrated by their great reactivity towards hydrolysis and alcoholysis. An important point is that both reactions are generally promoted under moderately to strongly acidic conditions. The acid catalyst or promoter most probably protonates the carbonyl group of the ester residue which activates the HAE, either towards a direct addition of the nucleophile (associative or concerted pathways in Scheme 7) or to a dissociation of the HAE with acid release and oxonium formation (dissociative pathways in Scheme 7).

Regarding the alcoholysis reaction, an HAE can react with alcohols to yield the corresponding acetal and acid by substitution of the acetate group as first described by *Kruse et al*.[56] Such a reaction can thus serve as an access to asymmetric acetals.

This reaction with alcohol was later confirmed by *Gallucci and Going* in their seminal report on the HAE reactivity.[11] Indeed, as demonstrated in this study, water can substitute the ester of the HAE to release an acid and a hemiacetal, an unstable species which quickly dissociates into the corresponding alcohol and aldehyde.[56] The use of a large excess of water therefore leads to the complete hydrolysis of the HAE and the formation of these three constitutive molecules. However, a small amount of water can lead to a partial hydrolysis of the HAEs, inducing a reaction between the released alcohol and another HAE to provide the corresponding carboxylic acid and the symmetrical acetal (Scheme 11). Noteworthy, it has been demonstrated that an HAE was the transient intermediate in the deprotection of acetals with trifluoroacetic acid.[57]



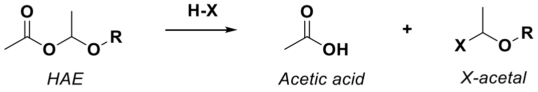
Scheme 11: HAE hydrolysis products in the case of A) excess of H_2O and B) sub-stoichiometric amounts of H_2O.[11]

Despite the standard conditions generally used for the hydrolysis of HAEs and the release of the carboxylic acid (dilute solutions of strong mineral acids), little information is known regarding the factors influencing their stability towards water. A mechanistic study of the hydrolysis of 1-aryloxyethyl alkanoates has been reported by *Hall et al*.[58] This study concluded that, under neutral or mildly acidic conditions, an associative mechanism involving hydration of the ester moiety ("A_{Ac}-2" mechanism, upper associative pathway Scheme 7) is operative, while strongly acidic media presumably followed a dissociative pathway through carboxylic acid release and oxonium formation ("A_{Ac}-1" mechanism, dissociative pathway Scheme 7). These authors also performed a kinetic study at basic pH and demonstrated that the hydrolysis was as fast as under strongly acidic conditions and proceeded through an associative "B_{Ac}-2" mechanism. An interesting feature is that the A_{Ac}-2 could potentially be at work in the alcoholysis reaction but would lead to an ester instead of an acid, which has never been mentioned to the best of our knowledge.

While the use of lipase has been presented as an enantioselective route to produce HAEs, it should be mentioned that some enzyme-catalyzed enantioselective hydrolysis/alcoholysis of HAEs were also reported. *Kirk et al.* demonstrated the enantioselective hydrolysis of 1,2,3,4,6-penta-O-acetyl-D-glucose with lipases of microbial origin, following some previous similar findings with porcine pancreatic lipase.[59] Similarly, *Villo et al*. exploited the lipase-catalyzed hydrolysis of cyclic HAEs in the course of the synthesis of enantioenriched deoxypyranose esters, as well as deoxyfuranose esters.[23–25] Regarding HAEs not derived from sugars, *Westermann and Krebs* reported the enantioselective alcoholysis of cyclopropanone hemiacetals esters with lipases of microbial origin.[60] Finally, *Chênevert et al.*, taking advantage of the high stability towards acidic hydrolysis of a chloral-derived HAE (central trichloromethyl group, position R^3 in Scheme 7 and Figure 2), described the highly enantioselective lipase-catalyzed hydrolysis of this compound.[61] In a similar fashion, *Fletcher and Rayner* reported the kinetic resolution of stable glyoxal-derived hemiacetal esters.[62] However, the ability of lipases to degrade HAEs is not limited to small molecules and was also successfully applied to the hydrolysis of poly(hemiacetal ester) by *Nuhn and co-workers*.[63]

Exchange reactions

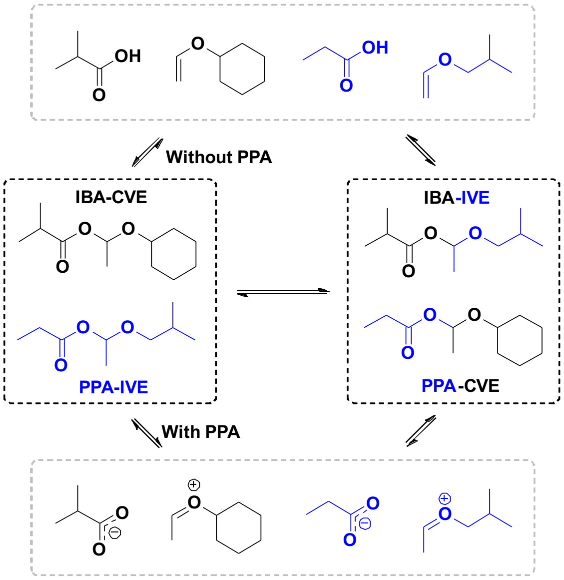
As for their thermal dissociation and their hydrolysis, the exchange reaction occurring between HAEs and acids has also been unveiled by *Gallucci and Going*.[11] The reaction of hydrochloric acid with the HAE derived from acetic acid and 2-phenoxyethyl vinyl ether resulted in the quick substitution of the acetic acid by the chloride, leading to the formation of an α-chloro-ether and the release of acetic acid (Scheme 12). The same substitution reaction was suspected by the authors to occur in the presence of trifluoroacetic acid but the attempt of isolation and identification of the reaction products did not succeed. However, in both cases, this reaction has been depicted by the authors as an irreversible substitution in which the stronger acid replaces the weaker one.



Scheme 12: Substitution of acetic acid by hydrochloric acid.[11]

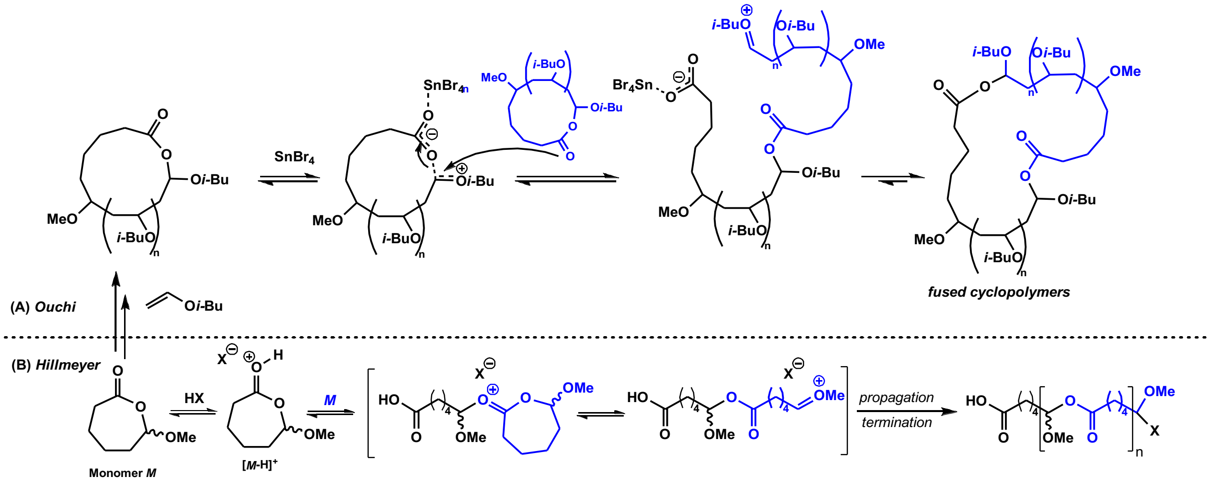
In 2020, our group reported the non-catalyzed HAE exchange reactions at ambient temperature.[64] This reaction occurred at ambient temperature when acrylic acid was added to an HAE obtained from butyl vinyl ether and nonanoic acid. The mixture was monitored by ^{1}H NMR spectroscopy and the detection of a signal characteristic of an HAE resulting from an exchange with acrylic acid was observed. At room temperature, no butyl vinyl ether release was observed and the rate of the exchange reaction was highly dependent on the acid concentration (initial rate doubled when the acid concentration was doubled). The rate-limiting step for a dissociative mechanism should be the dissociation itself and should therefore not depend on the acid concentration. The exchange at room temperature was thus assumed to follow an associative mechanism. However, the potential catalytic effect of acidic species on the HAE dissociation was not taken into account in this study,[15,33] and the exchange reaction using an excess of acid should be further investigated. Nonetheless, this exchange reaction was afterwards successfully applied to design a covalent adaptable material exhibiting vitrimer properties in a temperature range below the one required to trigger dissociation reactions at a significant rate.[65]

Feng et al. investigated an exchange reaction directly between two HAEs in an equimolar ratio. In this study, the first HAE was derived from isobutyric acid and cyclohexyl vinyl ether (named IBA-CVE) and the second one from propionic acid and isobutyl vinyl ether (PPA-IVE).[66] The tests were performed with and without a catalytic amount of propionic acid (Scheme 13). The exchange reaction was found to be faster and to require a lower temperature in the presence of free carboxylic acid (20 min at 200°C or 12h at 60°C, instead of 3h at 200°C without acid). In both cases, the exchange reaction reached an equilibrium between IBA-CVE/PPA-IVE and IBA-IVE/PPA-CVE. An experimental kinetic study suggested that the metathesis reaction between the two HAEs was of first order in each reagent and thermal treatment of IBA-CVE suggested its dissociation at high temperature. Therefore, the authors concluded that the exchange reaction was to proceed through a dissociative mechanism, the dissociation of each HAE being accelerated by the presence of an external acid. This hypothesis was supported by DFT calculations.



Scheme 13: Exchange reaction between two HAE groups.[66]

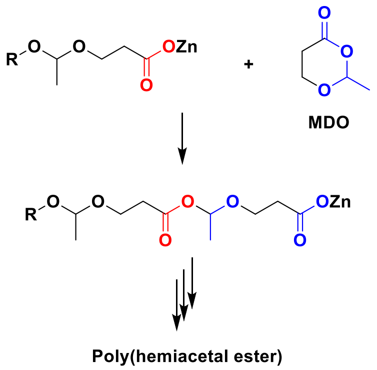
In a series of studies concerning the cyclopolymerization of a cyclic HAE with a vinyl ether, *Ouchi and co-workers* reported another adventitious exchange reaction between two HAE groups, this time in the presence of a Lewis acid.[8,34–36] Indeed, the controlled cyclopolymerization should provide cyclopolymers of similar molecular weights but, in some instances, different molar masses were observed. In contrast, the hydrolysis of the HAE function in these cyclopolymers provided linear polymers with unimodal molecular weights. This contradiction was attributed to the fusion of two or more cyclic polymers through an exchange reaction between two HAEs, providing larger cyclopolymers featuring more than one HAE within one ring. The mechanism of this exchange was suggested to proceed through a carboxylate exchange reaction between two HAEs. This could be made possible by the presence of Lewis acids, which results in the ionic dissociation of one HAE (as suggested in part 2.b.) followed by the nucleophilic attack of the HAE of another cyclopolymer. This results in the formation of a new HAE group and of an ion-pair which then reassociates to furnish a larger cyclopolymer featuring two HAE links (Scheme 14, A). This fusion was also demonstrated to be reversible by dilution and to be less likely to happen in low-polarity solvents. This last observation tends to confirm the protective effect of low polarity medium towards HAEs dissociation, as suggested by the work of *Endo and co-workers* previously discussed.[49]



Scheme 14: HAE self-condensation via the formation of an alkoxycarbenium ion : (A) Ring-fusion of cyclopolymers by *Ouchi and co-workers*,[8,34–36] and (B) Cationic polymerization by *Hillmyer and co-workers*.[10,33]

A similar mechanism of self-condensation of HAEs was reported by *Hillmyer and co-workers* for the cationic ring-opening polymerization of a cyclic HAE into poly(hemiacetal ester) [introduced by the authors of the original study as poly(esteracetal)], initiated at ambient temperature by protic acids.[10] If this reaction is not strictly an exchange since it is propagated in a polymerization reaction, it is however comparable to the one described above. Indeed, the identification of an alkoxycarbenium ion as the propagative species (by trapping with a phosphine and identification of the resulting phosphonium ion by ^{31}P NMR) suggested that the HAE function of the monomer could be activated by the acid catalyst in a similar fashion as with a Lewis acid, leading to the formation of an ion pair.[33] Another monomer can then react with this activated HAE via its ester carbonyl oxygen furnishing, after ring-opening, a new oxonium cation that can propagate the reaction. This mechanism, described in these two examples to explain a ring-fusion of two cyclopolymers and a cationic polymerization, can constitute a reasonable associative mechanism for an HAE exchange reaction in the presence of acids.

Another work by *Hillmyer and co-workers* can also be seen as an exchange reaction between an HAE and a carboxylate moiety. Indeed, a substitution reaction on an HAE was also implicitly at play in the Et$_2$Zn-promoted polymerization of 2-methyl-1,3-dioxane-4-one (MDO) into poly(hemiacetal ester) (Scheme 15).[9] In this polymerization, the propagating zinc-carboxylate opens MDO by substitution of the carboxylic moiety of the HAE function. However, these reactions suggesting that an exchange reaction is possible were not further discussed by the authors.



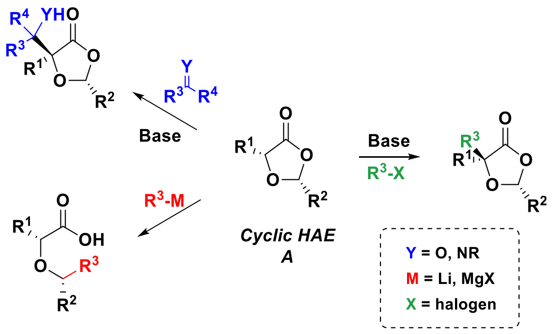
Scheme 15: Exchange reaction between an HAE (MDO) and a carboxylate during MDO polymerization.[9,33]

3. Applications in synthetic organic chemistry

As mentioned in the introduction, hemiacetal esters are less commonly exploited in synthetic organic chemistry than in polymer chemistry, most likely because of their poor hydrolytic stability which makes them difficult to handle. Carbohydrate derivatives such as 1-*O*-acetyl glycosides represent one major exception since these cyclic molecules exhibit a sufficiently high stability to make them the most common precursors of glycoside donors. More generally, 2-acetoxyfurans or larger rings have been used as oxonium precursors for nucleophilic additions.[67] This major role in glycoside chemistry will not be detailed in the present review since it would encompass decades of carbohydrate synthesis.[2]

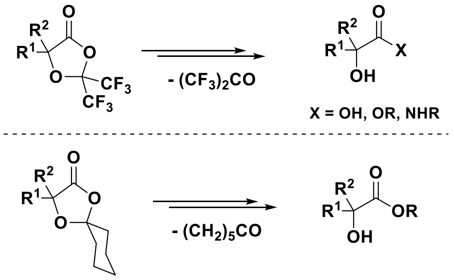
A second application in synthetic chemistry is their role as carboxylic acid protecting groups. Once again, and despite few exceptions as transient protecting groups,[4] this application is limited to exceptionally stable derivatives. The synthesis of 5-membered ring hemiacetal esters, more known as 1,3-dioxolan-4-ones, has already been mentioned in the synthesis and reactivity section and this role as an α-hydroxy acid protecting group is probably the most represented one as it also had implications in asymmetric synthesis.

Indeed, *cis*-2,5-disubstituted 1,3-dioxolan-4-ones such as **A** (Scheme 16), derived from lactic or mandelic acid and an aldehyde, are well-known as the Seebach and Fráter's chiral template and served as useful chiral platforms for Aldol-type reactions, Michael additions, nucleophilic ring-opening additions and other transformations.[43,44] Among these, the asymmetric alkylation of these chiral enolates stands as a very efficient reaction that has been applied in total synthesis for the preparation of stereodefined building blocks.[68,69]



Scheme 16: Examples of 1,3-dioxolan-4-ones functionalization and opening reactions.[43,44,68,69]

A more general application of such cyclic HAEs in organic chemistry is the simple use of 2,2-disubstituted 1,3-dioxolan-4-ones as protected β- or α-hydroxy acids. Indeed, their condensation with ketones such as acetone, cyclohexanone, and hexafluoroacetone blocks the two reactive OH at once and allows further synthetic elaboration. The cyclohexanone derivative is rather common in multistep synthesis, easily cleaved under acidic conditions or conveniently converted to the hydroxyester by reaction with an alkoxide.[40,41] The product obtained from hexafluoroacetone is less common but its higher reactivity allows a great variety of transformations once its use as a protecting group is fulfilled.[70] Indeed, the 2,2-*bis*(trifluoromethyl)-1,3-dioxolan-4-ones can be converted to the corresponding α-hydroxy acid, -ester or -amide (Scheme 17).[71]



Scheme 17: Examples of 1,3-dioxolan-4-ones ring opening reactions.[71]

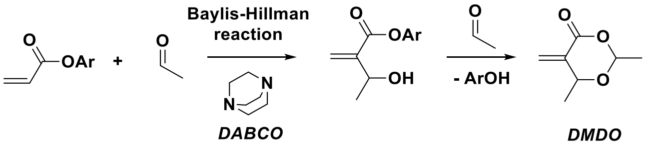
Overall, hemiacetal esters proved to be versatile and useful functional groups in organic synthesis, at least for stable cyclic structures. However, such species found a much wider use in polymer chemistry as demonstrated by the numerous applications described in the next section of this manuscript.

4. Applications in polymer synthesis

Reversible protection of carboxylic acids

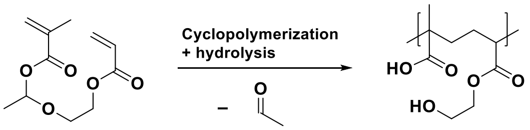
Thanks to their dissociative properties, HAE functional groups have often been used as a temporary protection of a carboxylic acid.[5,14,15] One of the earliest illustrations of such an application is a study from *Ruckenstein and Zhang* in which the acid function of a methacrylic acid was temporarily masked by reaction with a vinyl ether.[6] This protection allowed the sequential anionic block copolymerization of this monomer with styrene or methyl methacrylate by increasing their miscibility. The HAEs were then hydrolyzed, which released the carboxylic acids and endowed a hydrophilic character to the poly(methacrylic acid) blocks, and therefore yielded an amphiphilic copolymer.

On the same principle, *Kohsaka et al*. prepared a cyclic HAE through a Baylis-Hillman/cyclization sequence between an aryl acrylate and acetaldehyde (Scheme 18).[72] This acrylate was then submitted to radical and anionic polymerization and the HAE functions in the resulting polymers were hydrolyzed with an acidic solution. This hydrolysis step led to the formation of poly(2-(2-hydroxyethyl)acrylic acid), a polymer otherwise not accessible due to the lack of reactivity of 2-(2-hydroxyethyl)acrylic acid.



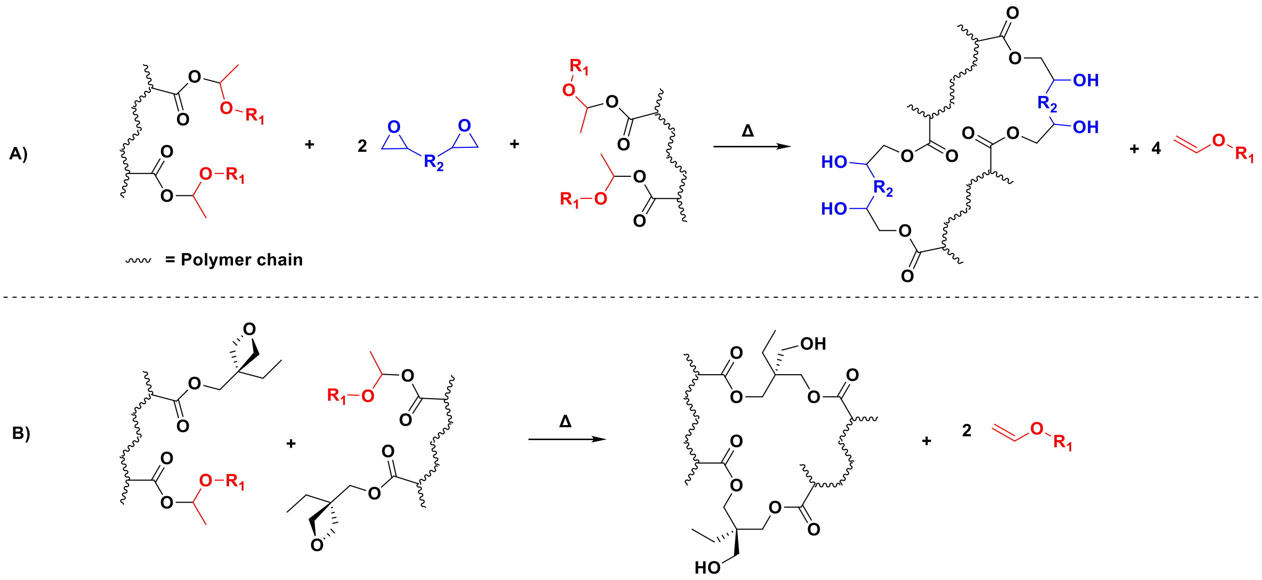
Scheme 18: DMDO synthesis by a Baylis-Hillman/cyclization sequence.[72]

In addition to homopolymers and block copolymers, *Ouchi and co-workers* demonstrated that HAEs could also be used for the synthesis of alternating copolymers.[73] An HAE was used to temporarily link a methacrylic acid and a hydroxyethyl acrylate, through the reaction of a methacrylic acid with a vinyl ether acrylate. The HAE acts as a tether between the two acrylate units that allows the cyclopolymerization of this substrate under ruthenium-catalyzed living radical polymerization. The final hydrolysis of the HAEs eventually led to a copolymer alternating methacrylic acid and hydroxyethyl acrylate units (Scheme 19).



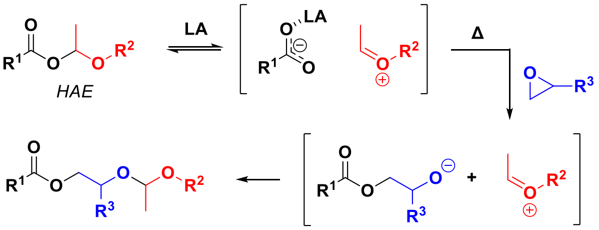
Scheme 19: Cyclopolymerization and hydrolysis performed by *Ouchi and co-workers* to prepare an alternating copolymer.[73]

Besides such preparations of well-controlled polymer structures, HAEs have been widely used for the on-demand reaction of acids with epoxides and oxetanes.[5,14,15,49,74–77] As such, HAE-protected methacrylic acids have been polymerized or copolymerized by *Komatsu et al*. under radical conditions.[49,74,75] After thermal dissociation of the HAEs and the release of the corresponding acids, the resulting polymer can react with epoxides either provided by a divalent cross-linker dispersed in the matrix (Scheme 20-A) or by one of the comonomers in the case of a copolymer (Scheme 20-B). This results in a time- or temperature-controlled post-curing of the polymer material and a longer shelf-life of this one-pot formulation.



Scheme 20: HAE-deprotection and polymer post-curing as described by *Komatsu et al.*[49,74,75]

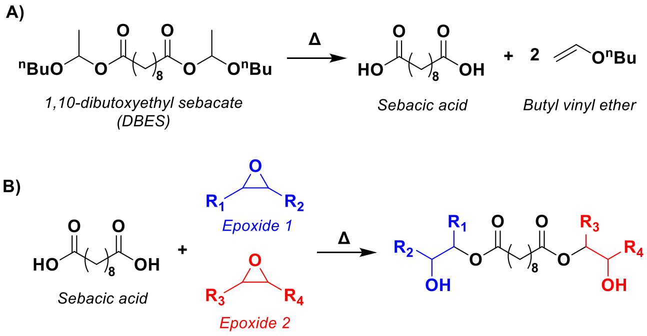
The low stability on storage of epoxy-acid formulations due to a slight reactivity of the acid with epoxides over time has been reported by several authors.[5,15] This reaction indeed occurs even at room temperature and results in an increase in the formulation's viscosity over time. In this context, *Yamamoto and Ishidoya* demonstrated that this issue could be circumvented by protecting the acid with an HAE group before being mixed with epoxides.[5] Due to its thermal reversibility, this protection did not affect the ability of the formulation to undergo thermal curing and was thus considered as a convenient approach to increase their storage. This protection was also beneficial for polyacids. Indeed, such compounds are usually solids with high melting points and are only soluble in polar and protic solvents such as alcohols. Consequently, the preparation of a homogeneous formulation by mixing them with epoxides is extremely difficult. In contrast, *Kovash et al.*[14] demonstrated that the conversion of carboxylic diacids into HAEs provided liquid compounds that could be homogeneously dispersed into an epoxy formulation. The thermal release of the diacids endowed such mixtures with the same curing ability as classical epoxy resins. This study also focused on the fate of the vinyl ether released during the dissociation/curing step promoted by DBU and demonstrated, via thermogravimetric analysis, that this compound evaporated during the curing step. In contrast, prior studies suggested that, in the presence of a Lewis acid, a reaction between the released oxonium cation and a hydroxy group resulting from the epoxy-acid reaction was occurring (Scheme 21).[5,15,49,74–78]



Scheme 21: Epoxy-acid reaction outcome in the presence of a Lewis acid.[5,15,49,74–78]

Nakane and Ishidoya indeed showed that, in the presence of a Lewis acid, the HAE is converted to a carboxylate/oxonium ion pair (see part 2.a.). The latter can react with the epoxide through a Lewis acidassisted ring-opening process to form a β-hydroxyester which can trap the oxocarbenium cation and yield a new HAE.[15] Since then, other studies focused on the screening of Lewis acids such as zinc complexes to accelerate the curing reaction of formulations containing HAE-protected acids and epoxides.[75–78]

The on-demand reaction of HAE-protected polyacids was also exploited by our group to bestow healing properties on a polymer matrix.[79] A protected diacid was introduced into an acrylated epoxidized oil formulation, which was applied onto a metallic substrate before being cured under UV. The introduction of this additive into the formulation was meant to allow an on-demand post-curing ability. After deprotection, the released diacid was able to react with the latent epoxide functional groups of the polyacrylate backbone (Scheme 22) and create new crosslinks. The electrochemical analysis of this coating demonstrated that the thermal treatment increased the protective properties of the coatings and allowed the protective properties of defective coatings to be partially recovered, indicating a repairing effect induced by the post-curing.



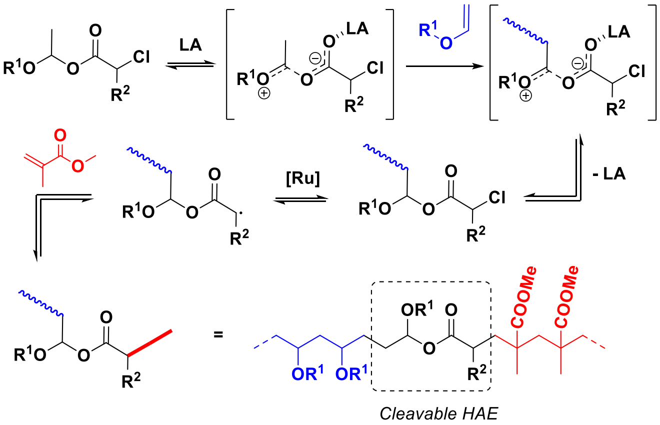
Scheme 22: (A) Thermal dissociation of DBES and (B) Post-curing through epoxy-acid reaction.[79]

Polymerization initiator

The Lewis acid-mediated dissociation of HAEs into an ion pair prompted their prominent application in polymer chemistry as polymerization initiators. This has been exploited for the first time by *Higashimura*'s group to trigger the living cationic polymerization of isobutyl vinyl ether.[53] The dissociation of the HAE derived from isobutyl vinyl ether and acetic acid (iBEA) triggered by $EtAlCl_2$ (Lewis acid) led to a carboxylate/oxocarbenium ion pair able to initiate the vinyl ether homopolymerization. The molar mass of the resulting poly(vinyl ether) was proportional to the ratio $[\text{vinyl ether}]_0/[\text{HAE}]_0$ and the molar mass distribution was very narrow (<1.1) in the presence of ethyl acetate. This was explained by the stabilization of the propagative species by an added ester which prevents chain transfer, termination or side reactions. Later, the same group observed a strong dependency between the strength of the carboxylic acid from which the HAE is obtained (substituted benzoic acids: 2,4-di-NO_2 > 3,4-di-NO_2 > *p*-NO_2 > *p*-CF_3 > *p*-Cl > *p*-H > *p*-CH_3 [54]; and substituted acetic acids: CF_3 > CCl_3 > $CHCl_2$ > CH_2Cl > CH_3 [55]) and the speed of the living polymerization, stronger acids leading to faster polymerizations and a better control of molar masses.[54,55] They also confirmed that the stabilization of the carboxylate-carbocation ion pair was an important parameter for a living polymerization process to take place. In 2021, *Imbrogno et al.* described similar living cationic homopolymerizations of alkyl and oxyethylene substituted-vinyl ethers in the presence of the same Lewis acid and an HAE initiator.[80]

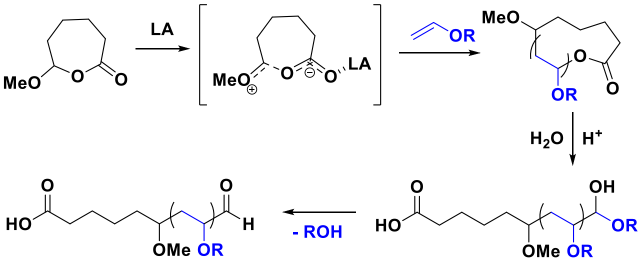
The cationic polymerization of vinyl ethers from an HAE initiator can also be triggered using a thermal stimulus instead of a Lewis acid as it was reported by *Endo and co-workers*.[7] The NMR monitoring of the thermal dissociation of HAEs (obtained from isobutyl ether and substituted acetic acids) in toluene suggested that this step did not lead to the recovery of the initial acids and vinyl ethers. Instead, the formation of an ion pair and the partial degradation into acid, ester, alcohol, acetal, and acetaldehyde species were observed. Such a process opened the way to a cationic living polymerization and this reaction was indeed observed in a sealed tube containing the HAE and an excess of vinyl ether. The structure of the acid constituting the HAE was shown to affect the temperature at which the vinyl ether polymerization was observed (which can be related to the influence of the structure on the dissociation temperature discussed in part 2.b.). This allowed a temperature-controlled polymerization through the choice of the initiator structure, in contrast with the instantaneous Lewis-acid-triggered polymerization. However, this approach led to the formation of two populations of molar mass. This was explained by the authors through the equilibrium between associated and dissociated HAE species, which might lead, on one hand, to early termination reactions leading to an HAE-terminated low molar mass polymer (poorly reactive under thermal conditions) and, on the other hand, to their gradual degradation during the propagation step. The authors also hypothesized that such a polymerization could be triggered by protic species like carboxylic acids.

HAEs have also been exploited by *Ouchi and co-workers* to prepare cleavable diblock copolymers using an HAE initiator obtained by the reaction between (2-chloro-2-phenyl)acetic acid and isobutyl vinyl ether.[81] The resulting difunctional HAE initiator was able to trigger both the cationic living polymerization of vinyl ethers in the presence of Lewis acid via HAE dissociation and the ruthenium-catalyzed ATRP of acrylates/methacrylates from its chloroalkyl terminus. This was exemplified by the preparation of a poly PMMA-*b*-PiBVE diblock copolymer featuring a cleavable HAE group between blocks. (Scheme 23).



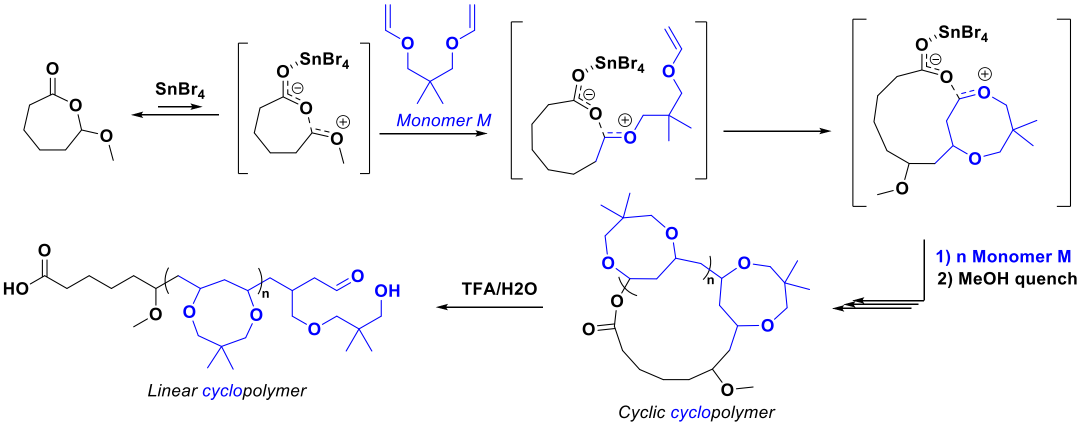
Scheme 23: Synthesis of a diblock-copolymer featuring a labile HAE junction according to *Ouchi and co-workers*.[81]

In addition to linear polymers, HAE-initiators have also been used to prepare cyclic polyvinyl ethers by cationic living polymerization. This has been introduced by *Ouchi and co-workers* using an HAE-containing cyclic initiator prepared by the Baeyer-Villiger oxidation of 2-methoxycyclohexanone.[34] As for acyclic initiators, the presence of a Lewis acid led to the formation of an ion pair with a strong interaction between the carboxylate and the propagative cationic species, which triggered the cationic living polymerization of isobutyl vinyl ether (IBVE). However, in that case, the cyclic nature of the initiator induced a ring-expansion process that led to the formation of cyclic homopolymers (Scheme 24). Yet, the presence of HAEs in the structure of the polymer allowed the easy transformation of the cyclic structures into a linear polymer by simple HAE hydrolysis. Under optimized conditions, this conversion was demonstrated to be sufficiently controlled to produce finely tuned block copolymers, although some ring fusion was detected at high initiator concentrations.[35] This ring fusion was explained by the occurrence of an exchange reaction between two HAE groups, leading to cycles with several HAE groups, and was demonstrated to be reversible, through intramolecular rearrangements, by a simple dilution of the cyclic polymer.[8,34–36,82]



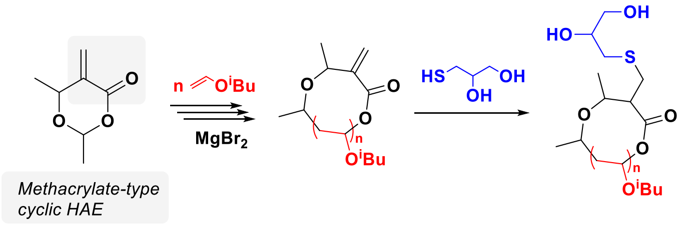
Scheme 24: Cationic ring expansion from a cyclic HAE initiator and hydrolysis of the homopolymer.[8,34–36]

The glass transition temperature of the cyclic polymers proved to be significantly higher than their linear counterpart, as well as to be less influenced by their molar mass.[36] This phenomenon, explained by the absence of chain ends for cyclic polymers, is also described for other polymers such as cyclic and linear polystyrene studied by *Li and co-workers*.[83] Finally, these rings were presented as entirely customizable, as numerous vinyl ether structures are available.[8] As a confirmation of this statement, this process was further exploited by the same group to synthesize linear and cyclic cyclopolymers.[84] This was made possible through the use of di-vinyl ethers for which the two functions were connected by a three-carbon spacer. A narrower dispersity was observed when the 2,2-dimethylpropane spacer was used (Scheme 25), which has been explained by a Thorpe–Ingold effect. In addition, the polymerization was better controlled under diluted conditions as cross-linking reactions were avoided. Surprisingly, the cyclic cyclopolymers prepared via this process showed lower glass transition temperature than the linear cyclopolymers of an equivalent degree of polymerization. In addition, their glass transition decreased with increasing the degree of polymerization, which is quite unusual for polymers and was explained by the authors by the large free volume and high rigidity induced by the chain topology.



Scheme 25: Synthesis of linear and cyclic cyclopolymers as described by *Ouchi and co-workers.*[84]

More recently, *Ouchi and co-workers* performed this ring expansion cationic polymerization using $MgBr_2$ instead of conventional tin catalysts such as $SnBr_4$.[82] In addition to its lower toxicity, magnesium bromide is much more reactive towards HAEs, which resulted in an increase in ring fusions. $MgBr_2$ is also able to dissociate a wider range of cyclic HAEs, including a methacrylate-type cyclic HAE, allowing post-polymerization modifications (Scheme 26).

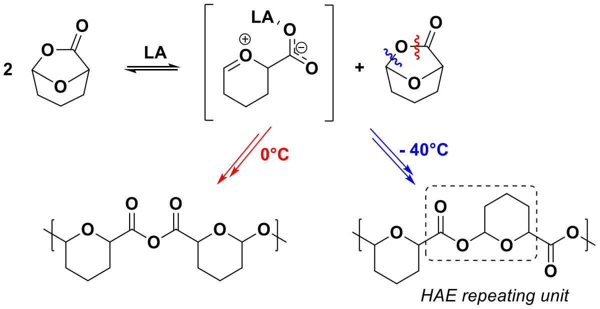


Scheme 26: Methacrylate-type cyclic HAE described by *Ouchi and co-workers*.[82]

The same year, *Ouchi and co-workers* described another kind of post-polymerization modifications, by synthesizing new cyclic initiators featuring between two and six HAEs, starting from dicarboxylic acid and divinyl ether units. The spacers of these HAE units featured functional groups that allowed post-polymerization modifications, such as crosslinking between polymer rings.[85]

Ring-opening polymerization

Beyond their use as polymerization initiators, cyclic HAEs have also been used as monomers. In a series of studies, *Okada et al*. examined the cationic ring-opening polymerization 6,8-dioxabicyclo[3.2.l]octan-7-one, a bicyclic HAE.[39,86–88] Depending on the temperature, two different products were observed. At 0 °C, the repeating unit of the resulting polymer features two tetrahydropyran rings linked by an acid anhydride group and an acetal function. In contrast, cyclic oligomers (with degrees of polymerization of 2, 4 and 6) composed of tetrahydropyran rings linked by HAE functions were obtained at –40 °C (Scheme 27). The initiator concentration was reported to have no influence on the yield or the composition of the oligomers, but the dilution of the reaction medium led to the conversion of hexamers and tetramers into dimers. This result is to be compared with the work of *Ouchi and co-workers* discussed in part 4.a.II.,[8,34–36] which reported the intermolecular exchange reaction of HAEs leading to the formation of cyclic polymers with sizes depending on the dilution ratio.



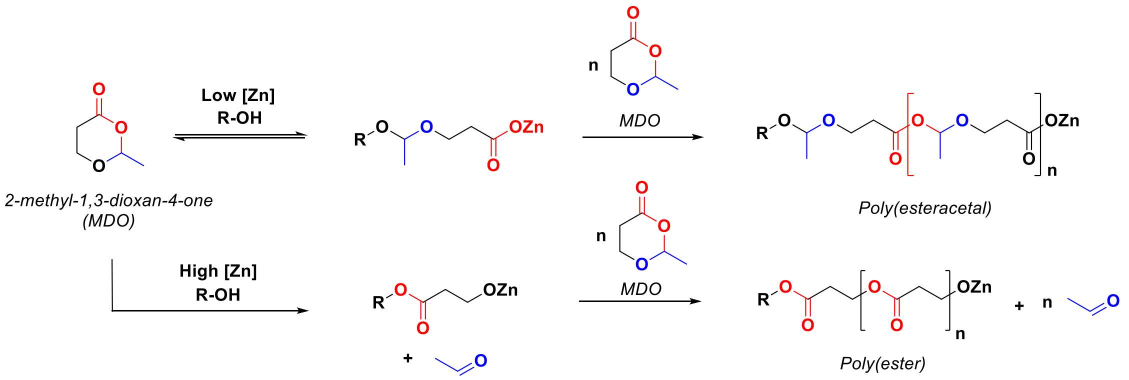
Scheme 27: 6,8-dioxabicyclo[3.2.l]octan-7-one polymerization products at -40°C and 0°C, from Okada et al.[39,86–88]

A cyclic HAE was also exploited by *Hillmyer and co-workers* as a monomer in a Et_2Zn-catalyzed polymerization.[9,10,33] In the first study, the authors unveiled the strong influence of the amount of Et_2Zn

on the polymerization.[9] At higher concentrations of Et_2Zn, the reaction produced a polyester with a polymerization rate that is second order in zinc catalyst concentration. The mechanism proceeds through the ring-opening of the HAE to release the corresponding alkoxide and a molecule of acetaldehyde (Scheme 28). This alkoxide then propagates through the same ring-opening reaction to yield the final poly(ester). This route was recently used by *Wei's group* for the copolymerization of MDO with lactones, producing poly(esters) copolymers with adjustable thermal properties and low dispersity.[89] In contrast, the use of lower concentrations of Et_2Zn resulted in a different mechanism and a different reaction outcome. Indeed, the polymerization rate was this time first order in zinc catalyst concentration and produced a poly(hemiacetal ester) as the major product. The initial ring-opening of MDO proceeds this time through an attack of benzyl alcohol on the acetal carbon atom, which releases a zinc carboxylate bearing an acetal function at the other end.[9,33] The zinc carboxylate propagates the polymerization through a similar ring-opening reaction of MDO, which releases a linear HAE and another zinc carboxylate. This work thus suggests that, depending on the reaction conditions, a cyclic HAE can be ring-opened from two different reaction sites.

In a second study, Brønsted acids were used as catalysts instead of diethylzinc. In particular, the use of diphenyl phosphate as a catalyst, at room temperature, led exclusively to the formation of poly(hemiacetal ester) whether benzyl alcohol is used as an initiator or not.[33] However, the mechanism and control of the polymerization reaction were reported to be significantly dependent on the presence or absence of an alcohol initiator. In the absence of initiator, MDO, protonated by the Brønsted acid catalyst, is ring-opened by another MDO molecule from its carbonyl oxygen atom, resulting in the formation of a new dioxacarbenium ion (acting as the propagative species) with a carboxylic acid end group. Since MDO is a poor nucleophile and the propagative species highly reactive, the initiation step is relatively slow in comparison to the propagation (active chain-end mechanism, ACE). This difference in reactivity resulted in poor polymerization control and the production of polymers of high molar masses. In the presence of an alcohol initiator, the latter ring-opens MDO (activated by the Brønsted acid catalyst) to form a propagating carboxylic acid with a benzyl acetal end group. In this route, the polymerization follows preferentially an activated monomer (AM) mechanism leading to a better control of the polymerization. However, even in the presence of an alcohol, the ACE mechanism is not entirely suppressed and poly(MDO) of different architectures and with different end groups can be produced under these conditions.

Kohsaka et al. studied the ring-opening homopolymerization of 2,6-dimethyl-5-methylene-1,3-dioxan-4-one (DMDO) catalyzed by diphenyl phosphate in toluene, in the presence of benzyl alcohol at 25, 50 and 80°C.[90] Surprisingly, in this work, the formation of poly(hemiacetal ester) was never observed and polymerization occurred only above 50 °C to yield exclusively a polyester with the release of acetaldehyde. The difference in reactivity observed with MDO was attributed to the presence of the double bond which presumably favored the alcohol addition onto the ester. Indeed, the formation of poly(hemiacetal ester) was restored using the BDDMO monomer (resulting from the addition of benzyl mercaptan to DMDO) despite a very poor reactivity of this substrate.

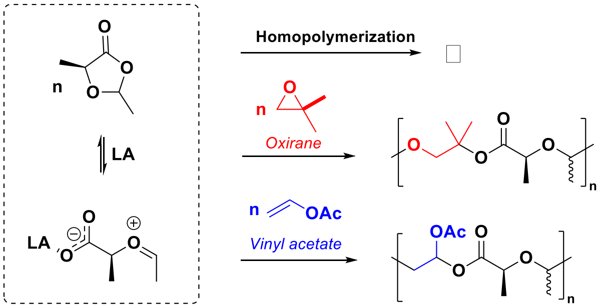


Scheme 28: Impact of the catalyst loading onto the ROP of a cyclic HAE initiated by alcohols.[9]

Hillmyer and co-workers also studied the ring-opening homopolymerization of 7-methoxyoxepan-2-one (MOPO) initiated by HCl.[10] In a similar fashion to MDO, polymerization was initiated by the addition of MOPO to another monomer activated by the acid (see Scheme 14, B) and was propagated through the same active chain-end ("ACE”) mechanism. The termination was achieved by counterion collapse between an oxonium and Cl^- when HCl was used as initiator, or by proton elimination to yield a vinyl ether chain end. The use of triflic acid as a catalyst disfavors this counterion collapse due to the weaker nucleophilicity of the triflate anion. This results in higher conversions for the polymerization process and termination yielding exclusively vinyl ether chain ends. In addition, this study demonstrated the possibility of performing cationic RAFT polymerization of MOPO through the use of a dithiocarbonyl chain-transfer agent and a photo-initiator. The copolymerization of MOPO with vinyl ethers through a simple photo-initiated cationic RAFT polymerization was also described.

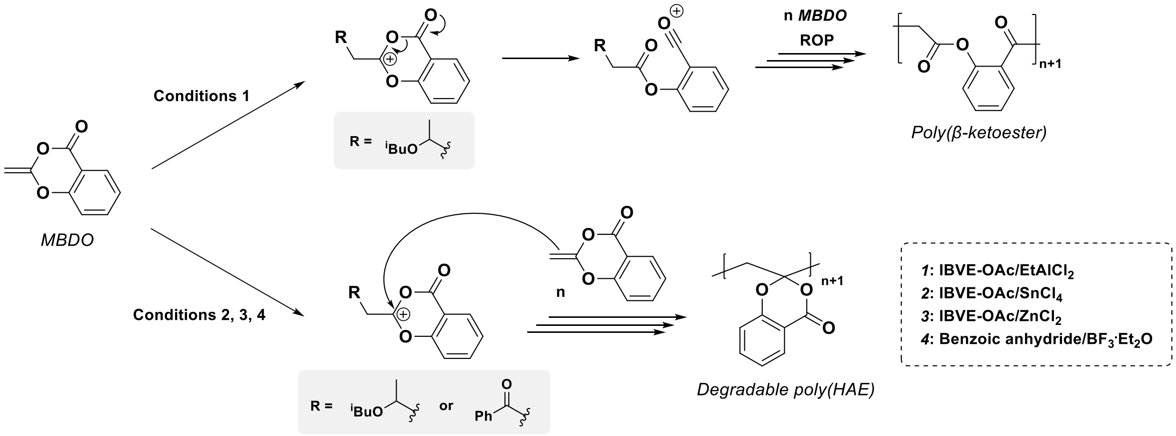
Ring-opening polymerization can also be performed from five-membered ring monomers such as 1,3-dioxolan-4-ones (DOLOs).[37,38,91] These bio-based and inexpensive monomers are prepared from the reaction between ketones or aldehydes with α-hydroxy acids (such as lactic or mandelic acids). Homopolymerization and copolymerization with cyclic esters (e.g. ε-caprolactone or β-butyrolactone) were reported to follow a ring-opening mechanism leading to the formation of polyesters and the release of formaldehyde or acetone in the presence of salen, DBU, TBD or $ZnEt_2$ catalysts.[37,38] Regarding homopolymerization, the salen-catalyzed reaction led to the formation of an isotactic bio-degradable polyester, which had so far been synthesized only through a very expensive and toxic process (ROP of O-carboxy anhydrides using stoichiometric amounts of phosgene).[38] The ring-opening polymerization was also reported to be better controlled with salen catalysts than with the other catalysts. However, when the polymerization proceeded in a sealed environment, the release of formaldehyde led to the formation of very low molar mass polymers due to extensive chain transfer reactions through the Tishchenko reaction.

The homopolymerization and copolymerization of 1,3-dioxolan-4-one with oxirane and vinyl ether[31] or vinyl acetate[92] via cationic polymerization in the presence of a Lewis acid were studied by *Aoshima and co-workers*. If the homopolymerization and copolymerization of 6- or 7-membered-ring cyclic HAEs with vinyl ethers were demonstrated by *Hillmyer and co-workers*,[9,10,33] *Aoshima and co-workers* reported that homopolymerization was not possible with 1,3-dioxolan-4-ones without extrusion of acetaldehyde and therefore loss of the acetal function in the final polymer. This reactivity was ascribed to the low ring strain of the monomer and to an inefficient addition of another DOLO molecule to the oxocarbenium obtained from a first monomer. However, the copolymerization of 1,3-dioxolan-4-ones with oxirane and vinyl acetate was observed, because the propagative species derived from these comonomers react preferentially with DOLOs. Since DOLO does not homopolymerize, these copolymerizations led to alternating copolymers of polyester type (Scheme 29). In the absence of an alcohol initiator, the authors suspected that the polymerization was initiated by the reaction of the HAE with adventitious water or by direct interaction with the Lewis acid catalyst.[31]



Scheme 29: Homopolymerization and copolymerization of a 1,3-dioxolan-4-one with vinyl acetate and oxirane.[31]

Finally, the choice of the Lewis acid was shown to impact the polymer structure obtained from the cationic polymerization of MBDO.[93,94] While the $ZnCl_2$-, $SnCl_4$- and $BF_3.Et_2O$-initiated cationic polymerization of MBDO led to a polymer containing HAE functions in the main chain, in a similar fashion to the one obtained under radical polymerization,[93] the use of $EtAlCl_2$ produced a polyester featuring β-ketoester units (Scheme 30). Once again, this study demonstrated that the versatility of HAE functional groups allows the obtention of very different final products depending on the conditions of polymerization.[94]

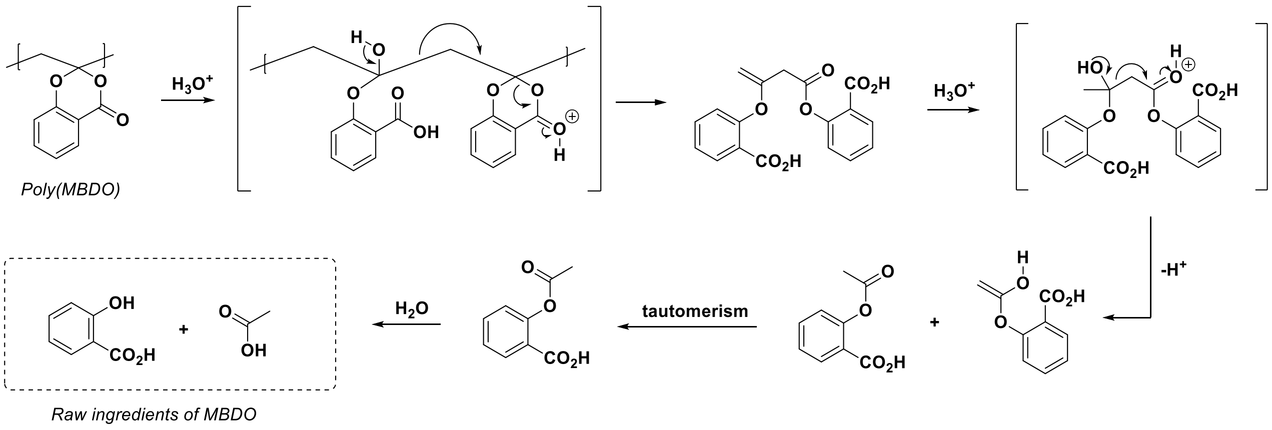


Scheme 30: MBDO cationic polymerization with different Lewis acids as initiators.[94]

5. Applications to the development of degradable or sustainable materials

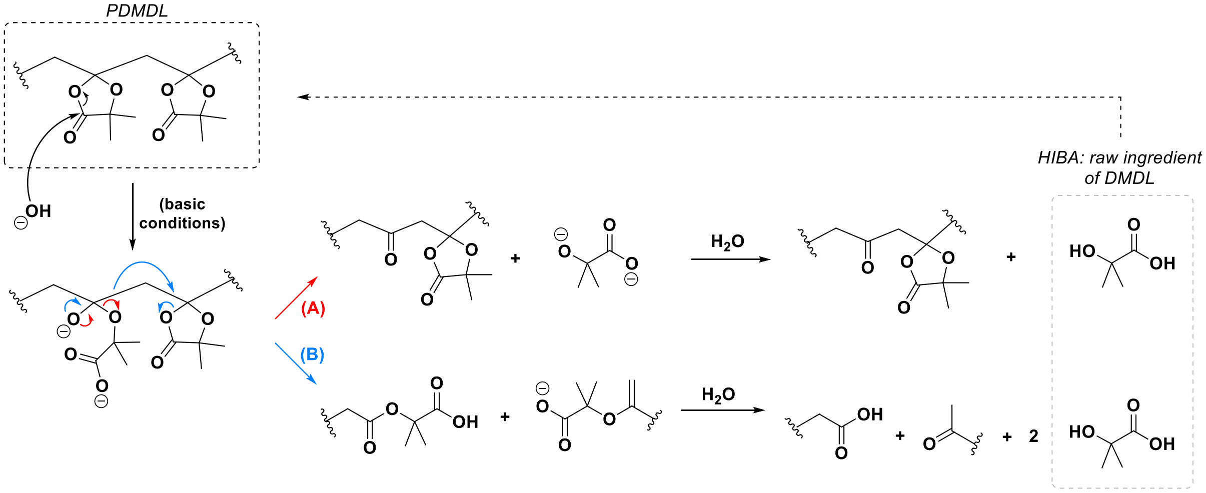
Degradable polymers

The presence of HAEs in the backbone of a polymer has been reported to provide degradation properties to such materials, either through thermal activation or via hydrolysis/solvolysis. This property could be applied to the recovery of the initial monomers as reported by *Otsuka and Endo*. Indeed, the linear polymer prepared by the reaction of difunctional vinyl ethers with diacids could be thermally degraded to release the initial reagents, which could be recycled for further syntheses.[12] In their work already described in part 4.b.iii, *Hillmyer and co-workers* reported that poly(hemiacetal ester) was completely hydrolyzed (HCl 1M) and converted to carboxylic acid and alcohol molecules.[10] Supposing that these molecules could be isolated, they might be potentially reused for further syntheses. Following a similar idea, *Kazama and Kohsaka* synthesized a linear polymer from 2-methylene-4H-benzo[d][1,3]dioxin-4-one (MBDO) and reported that its acidic hydrolysis released acetic acid and salicylic acid, demonstrating the sustainable character of this material (Scheme 31).[93]



Scheme 31: Hydrolysis mechanism of poly(MBDO).[93-94]

Oh et al. recently described the radical polymerization of two other cyclic ketene acetal esters: DMDL (4,4-dimethyl-2-methylene- 1,3-dioxolan-5-one) and PhDL (5-methyl-2-methylene-5-phenyl-1,3-dioxolan-4-one).[95] The resulting polymers were shown to be degradable by saponification, producing the α-hydroxy acids (HIBA) used as starting materials for the monomer synthesis (Scheme 32).



Scheme 32: Postulated mechanisms of degradation of PDMDL by saponification. (A) side-chain cleavage, (B) main-chain cleavage.[95]

The degradability of HAEs presents other advantages beyond the sustainable aspects. For instance, *Nuhn and co-workers* proposed a potential drug delivery application for an amphiphilic poly(hemiacetal ester) block copolymers,[63] produced through the activated monomer (AM) mechanism previously described by *Hillmyer and co-workers*.[33] This amphiphilic copolymer was made possible by replacing the alcohol initiators of the initial studies by a poly(ethylene glycol) chain containing one hydroxyl end-group. The resulting amphiphilic copolymer could self-assemble into monomodal micelles. Nile Red (drug model) was shown to be successfully loaded in these micelles and to be released through degradation of the polymeric chain under acidic, basic, or enzymatic treatment.

Shirai and co-workers exploited the degradability of HAEs in a series of studies using a monomer obtained through the nucleophilic addition of acrylic acids onto a divinyl ether.[96–99] The presence of two acrylates allowed the UV-promoted radical homo- and copolymerization of the monomer, while the two HAEs provided biodegradability to the resulting crosslinked network. In these publications, the crosslinked material was used as a sacrificial mold for the production of polymeric pieces with nanostructured surfaces by photolithography and was hydrolyzed to release the final piece. This hydrolysis reaction also released a polyacrylic acid that could be reused for other applications.

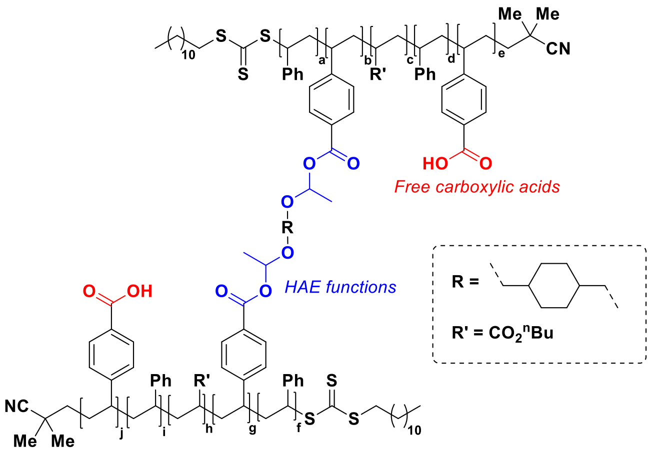
The hydrolysis reaction was exploited to produce star-shaped polymers, using a difunctional initiator prepared by the reaction of bromoisobutyric acid with ethylene glycol divinyl ether.[100] The bromine atoms allowed the synthesis by ATRP of E-grad-M-grad-D-I-D-grad-M-grad-E (E=poly(ethylene glycol dimethacrylate), M= poly(methyl methacrylate), D= poly(dimethylaminoethyl methacrylate), I = the difunctional HAE-containing initiator) co-networks by sequential monomer additions. The HAE groups in these co-networks were then hydrolyzed to prepare star-shaped amphiphilic block copolymers.

The polymers reported by *Shaver and co-workers* [37,38] and *Hyoi et al*.[31] can be mentioned, although they do not feature HAE moieties. Indeed, the HAE monomer used by *Shaver and co-workers* led to a degradable isotactic polyester otherwise obtained via an expensive process.[37,38] Similarly, the copolymerization of 1,3-dioxolan-4-ones with oxiranes reported by *Hyoi et al*. also led to degradable polymers through hydrolysis of the acetal groups inserted in their backbone.[31]

Finally, the degradation of HAEs was exploited by *Sato et al.* to develop dismantlable adhesives.[101] For this purpose, a 1-isobutoxyethyl acrylate (acrylate featuring an HAE function) was copolymerized with 2-ethylhexyl acrylate and 2-hydroxyethyl acrylate to form an adhesive which was used to apply polyethylene terephthalate films to steel. Exposed to boiling water, or under UV treatment in the presence of a photoacid generator, copolymers containing 70% or more of 1-isobutoxyethyl acrylate were shown to spontaneously detach from the surfaces, due to the hydrolysis or the trans-acetalization reactions of HAEs.

Covalent adaptable networks (CANs)

The carboxylic acid substitution in HAEs, observed in different studies described previously, is assimilable to an exchange reaction which has been exploited for the first time by our group to develop covalent adaptable network (CAN) or vitrimers based on carboxylic acid exchanges.[65] These CANs are cross-linked materials that can be reprocessed upon heating without loss of connectivity, due to a dynamic exchange between covalent linkages. In this work, a styrene copolymer network containing carboxylic acid moieties and HAE crosslinkers was synthesized by RAFT polymerization of styrene, vinylbenzoic acid and a dimer prepared from the reaction of 4-vinylbenzoic acid with a divinyl ether (Scheme 33). The use of HAEs as an exchangeable functionality led to a material presenting interesting properties. The fast exchange reaction, which is observed as low as 25°C, combined with a low glass transition (T_g) of the material allowed a relatively fast reprocessing that could be performed at a moderate temperature (90 min at 90°C). The carboxylic acid groups were not only at work in the topological rearrangement of the network but also generated hydrogen bonding that contributed to freeze the network under 80°C. This freezing of the network prevented undesirable deformation of the material under 80°C. Above 120°C the thermal dissociation of the HAEs became significant and led to the loss of the vitrimer-like properties. Finally, between 80°C and 120°C the material presented an Arrhenian behavior (linear evolution of the viscosity with temperature), which is the behavior expected from vitrimer materials. This observation, and the conclusion of a probable associative mechanism for the acid exchange drawn from a previous study,[64] suggest that this network is a vitrimer. However, the authors admit that the actual exchange mechanism should be studied more thoroughly to reach a definitive conclusion.



Scheme 33: Covalent adaptable network containing HAE cross-linkers and free carboxylic acid functions.[65]

A similar study was then carried out by *Feng et al.*, who replaced vinyl benzoic acid and styrene with methacrylic acid and methyl methacrylate respectively, considered greener synthons.[66] In this work, the successful reprocessing took place at 200 °C and exploited the thermal dissociation/reassociation of HAEs to introduce mobility. A deterioration of the mechanical properties of the material was however observed after reprocessing, which could easily be related to a partial evaporation or degradation, at 200 °C, of the divinyl ether involved in the HAE cross-linker.

6. Conclusion and outlook

This short review summarizes the literature involving hemiacetal esters, illustrates the potential of this functional group and tries to identify new paths of development. The use of HAEs in organic chemistry is widespread in the field of glycoside chemistry as glycosylacetates are standard glycoside donors. Another important field of application consists in the temporary protection of carboxylic acids and the use of chiral 1,3-dioxolan-4-ones as an asymmetric synthesis platform. Polymer chemistry has granted HAEs with even much more attention. This functional group was exploited in polymerization processes as a protecting group for the stabilization of epoxy-acid formulations, as an initiator of cationic polymerization, or as a monomer for ring-opening polymerization. The lability of this functionality towards hydrolysis, associated with the aforementioned reactivity in polymerization reactions, was often used to prepare hydrolyzable/degradable/depolymerizable polymers. Finally, the reactivity of HAEs in exchange reactions unveils a potential for the development of covalent adaptable networks, as it has recently been reported by our group.

A striking feature emerging from this literature is the diversity of usage of HAE functional groups, either as building blocks, initiators, protecting groups, exchangeable bonds or splitable connections. However, the versatility of this function might also be its biggest flaw. Despite the promising properties of the HAEs within the field of covalent adaptable networks, namely their low energy and fast exchange reaction, their sensitivity to hydrolysis or thermal dissociation represents a major drawback. Future paths of research in this field could aim at decreasing this sensitivity while maintaining the ability of HAEs to undergo exchange reactions. A first path in this direction can be found in the studies investigating the effect of electron-withdrawing or electron-donating groups in different positions of the HAE functional group. Although these effects have already been discussed, we believe such structural variations would gain to be expanded and more thoroughly investigated, and the hydrolysis sensitivity and exchangeability of the resulting structures to be carefully characterized. In particular, a very narrow range of structural variation was performed on the central substituent of the HAE (R^3 group in scheme 7 and figure 2), while preliminary evidence suggests that the presence of an electron-withdrawing group in this position significantly and positively impacts the hydrolytic stability of HAEs. An additional path, which would go beyond the sole scope of HAEs, would be to investigate the exchangeability of similar functional groups in which the oxygen atom would be replaced by another heteroatom, as this modification may positively impact their stability and/or reactivity.[102–104]

While our present discussion mainly focuses on covalent adaptable networks, increasing the stability of the HAEs embedded in polymer structures may be beneficial in many fields of application. This would imply better durability and increased lifetime of materials engineered to be exposed to standard atmospheric conditions (presence of humidity). Materials could then be designed to depolymerize/dissociate only under specific conditions, generating polymers for which the degradation process is finely controlled. Finally, a recent paper from *Nuhn and co-workers* proposed the use of HAEs for drug delivery applications.[63] Since the body contains around 70% of water, which could lead to early degradation of HAE bonds and drug-release, developing highly stable HAEs presenting an enzyme-specific degradation process could also be of significance in this field.

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