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# Polyether synthesis: From activated or metal-free anionic ring-opening polymerization of epoxides to functionalization

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## ABSTRACT

Epoxide derivatives constitute a broad family of monomers which are able to be polymerized by anionic or related nucleophilic ring-opening mechanism. The main synthetic strategies developed are reviewed in terms of polymerization rates, side reactions, and possibilities for controlling such polymerizations. Ring-opening polymerization of ethylene oxide and substituted epoxides utilizing alkali metal derivatives or other initiating systems in conjunction or not with activating systems are discussed. Emphasis is also given on the use of organic initiators or catalysts to trigger the metal-free ring-opening polymerization of epoxides. Functionalization of polyethers is also described, which includes the use of functional initiators, post-chemical modification of reactive functions carried by the polyether backbone, or functional-monomer insertion. A focus is particularly given on the preparation of polyethers bearing hydroxy, amine, allyl, azide and other reactive groups, at the chain ends or in the chains.

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## 1. Introduction

In the last 40 years, efforts in polymer science were directed toward several aspects, from “tailor-made” macromolecular synthesis to materials manufacturing. Technological needs, often in tandem with an increasing demand of our modern society, force researchers to explore alternatives and solutions. Both the control of the selectivity of propagating reactive species, in order to induce the so-called “controlled/living” polymerization method, and the processes optimization, are necessary. A precise control of the structure, topology and functionality of polymeric chains enables the design of macromolecular scaffolds that may find applications in high added-value domains. Polyethers like poly(ethylene oxide) and poly(propylene oxide) – often referred to as poly(ethylene glycol) and poly(propylene glycol) respectively and obtained by polycondensation of alcohols – are produced worldwide in several million tons per year in commodity or high performance applications. These polymers are mainly used as precursors for polyurethanes, surfactants and lubricants, but also in biomedical or cosmetic domains.

The chemistry which enables their synthesis is mainly based on the ring-opening of epoxides by ionic or coordination mechanism. The focus will be given here on anionic polymerization due to its efficiency in terms of control of molecular features (molar mass, dispersity. . .). Initiation is a bimolecular nucleophilic substitution that forms alkoxide species the reactivity of which depends mainly on the nature of the counter-ion. The alkoxide acts as a nucleophile and attacks a new epoxide molecule enabling the propagation step. A preliminary complexation of the monomer by specific additives can be considered as an anionic-related mechanism. Epoxide reactivity and polymerization kinetics are predominantly influenced by their polymerization enthalpy and ring strain, but also by electronic and steric factors associated with the nature of the ring substituent as well as reaction conditions like temperature and solvent. The ability of epoxide monomers to be activated by complexation with an electrophile can also strongly facilitate nucleophilic ring-opening. Based on this chemistry as well as organic synthetic tools, many substituted epoxide monomers are able to be polymerized, opening pathways for well-defined polyether structures and functionalities and allowing for the preparation of materials with various properties.

After a brief overview of conventional anionic ring-opening polymerization, this review article highlights recent advances in the field of synthesis of aliphatic

polyethers utilizing monomer activation on one hand, and using metal-free initiating systems on the other hand, as well as the various ways to prepare functional polyethers.

## 2. Overview of conventional anionic polymerization of epoxides

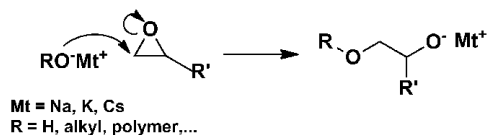
Flory observed in the 1940s that propagation may proceed without side reaction in anionic polymerization of ethylene oxide [1]. Alkali metal derivatives like hydrides, alkyls, aryls, amides, and mainly alkoxides of sodium, potassium, and cesium, represent the most common initiators used for the anionic ring-opening polymerization of epoxides (AROP) [2,3]. By conventional anionic polymerization we mean that initiation is triggered by such alkali metal derivatives. Lithium alkoxides do not conduct the polymerization of such monomers due to strong aggregation between lithium species after insertion of the first epoxide unit. Polymerizations initiated by alkali metal alkoxides are generally carried out in aprotic and apolar media or in coordinative solvents like dimethylsulfoxide (DMSO) or dimethylformamide (DMF) in order to dissociate active species. The reaction temperature plays also an important role. The driving force for a ring-opening reaction is the relief of the strain energy of the epoxide ring. At low temperature, below  $-20^{\circ}\text{C}$ , the most reactive epoxide named ethylene oxide is not reactive toward potassium-based initiators and can be used as solvent of the anionic polymerization of methyl methacrylate for instance [4]. High temperatures are usually needed for the AROP of long-chain alkylene oxides.

The different steps of conventional AROP of epoxides are shown in Scheme 1. The initiation step consists of a nucleophilic substitution  $-S_N2$  type-of the alkoxide species leading to the formation of new alkoxide species able to further attack monomer molecules resulting in polyether chains with an atactic structure. The termination step is achieved by addition of an acidic compound with labile hydrogen. Alcohols and water are the most commonly used termination agents in order to obtain hydroxyl end-groups. Transfer to monomer is observed with most of the initiating systems when substituted epoxides are polymerized. It will be discussed in a following paragraph.

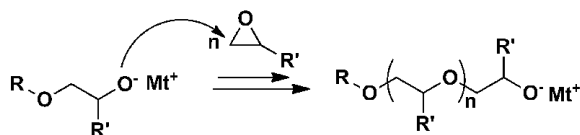
### 2.1. Ethylene oxide

Alkali metal derivatives are efficient initiators for the polymerization of ethylene oxide (EO). Anion radicals such as sodium naphthalene react by direct addition of the anion-radical to monomer [5]. It involves the addition of

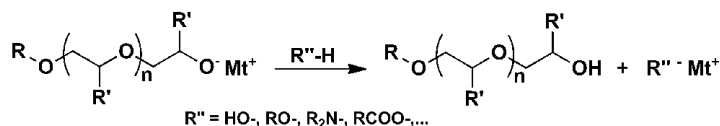
## Initiation Step



## Propagation Step

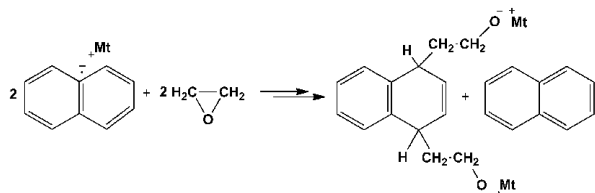


## Termination Step



Transfer: see paragraph 2.2, schemes 8 and 9

**Scheme 1.** Anionic ring-opening polymerization (AROP) of epoxides initiated by alkali metal alkoxides.



**Scheme 2.** Initiation of ethylene oxide polymerization by naphthalene alkali metal salts.

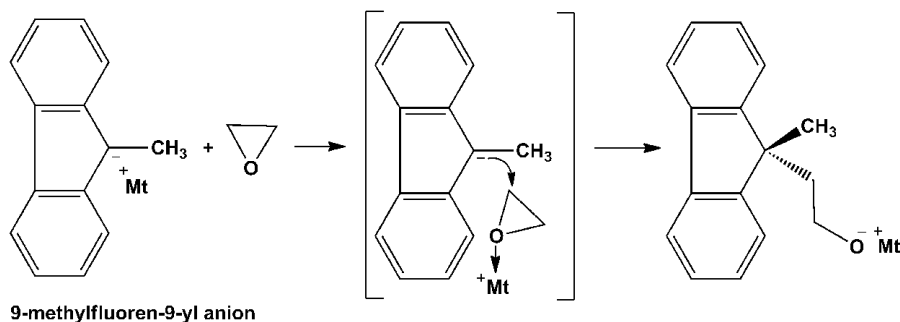
two monomer molecules on half of the initial naphthalene molecules, yielding bifunctional initiation (Scheme 2).

Alkali metal salts of carbanions, e.g. polystyryl ( $\text{PS}^-$ ), cumyl ( $\text{C}^-$ ), fluorenyl ( $\text{Fl}^-$ ) [6,7], and of nitranions, e.g. carbazyl ( $\text{N}^-$ ) and dibenzocarbazyl ( $\text{DBN}^-$ ) derivatives [8] were also used as initiators of ethylene oxide. Free ions were more reactive than ion-pairs due to the weak delocalization of anions, i.e.,  $\text{PS}^-$  or  $\text{N}^-$ . Opposite result was observed for more delocalized anions ( $\text{Fl}^-$  and  $\text{DBN}^-$ ). For instance, the rate of ring-opening of EO by alkali salts of 9-methylfluoren-9-yl decreases from tight ion-pairs to solvated ion-pairs and free ions. It was suggested that

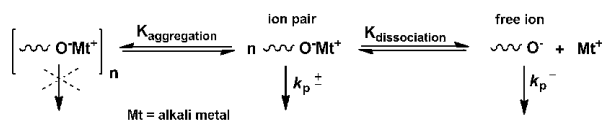
electrophilic activation of the epoxide by the metallic counter-ion contributes to the ring-opening reaction that overcomes the energy required for ion-pair dissociation (Scheme 3). For more localized  $\text{PS}^-$  or  $\text{N}^-$  anions, interaction of the anion with the cation is stronger and the energy required to separate the charges lowers the reactivity of ion-pairs compared to free ions.

Initiation of ethylene oxide polymerization by alkali metal alkoxides was also investigated in detail due to the fact that the structure of these derivatives is similar to the one of propagating species. In aprotic solvents with low to medium polarity, i.e., ethers, alkali metal alkoxides exhibit a strong tendency to aggregate and yield complex reaction kinetics. This is particularly significant for small metals such as lithium or sodium. If the reaction follows a monomer order of 1, the order in alkoxide propagating species varies according to counter-ion and solvent. This can be related to the presence of aggregates, ion pairs and free ions of different intrinsic reactivity (Scheme 4). EO polymerization with alkoxide aggregates is extremely slow and negligible in most cases.

Previous studies of EO polymerization in ethereal solvents dealt with initiating systems involving alkali metal



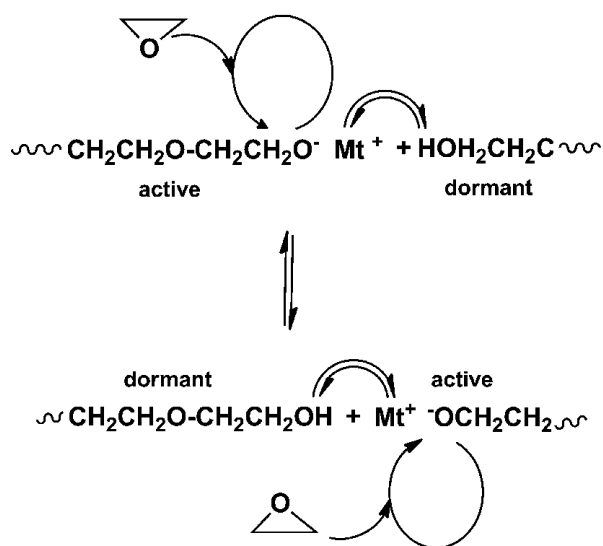
**Scheme 3.** Mechanism of initiation of ethylene oxide by alkali salts of 9-methylfluoren-9-yl.



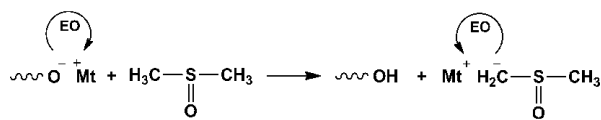
**Scheme 4.** Aggregates, ion pairs and free ions in EO polymerization and their capacity to contribute to propagation.

alkoxides,  $\text{RO}^-\text{Mt}^+$ , associated with their parent alcohol ROH to improve their solubility and limit the aggregation phenomenon [9]. Indeed, these systems are composed of two types of chains, the growing ones with an alkoxide-end and the dormant ones having a  $-\text{CH}_2\text{CH}_2\text{OH}$  terminus. Since alcohols act as efficient chain transfer agents, true living PEO is not formed in these conditions. However the reversibility of the transfer process, resulting from rapid exchanges between the two chain ends, and  $k_{\text{exch}} \gg k_p$ , ensured the growth of both chains allowing control of PEO molar mass,  $M_n = [\text{EO}]/([\text{RO}^-\text{Mt}^+] + [\text{ROH}])$ . Propagation and reversible transfer reactions are illustrated in Scheme 5. Today, this would be referred to a “degenerative transfer” (but already reported by Flory in the 1940s). The presence of alcohol in the medium leads to a reduction of the apparent polymerization rate [10,11]. It was proposed that the hydroxy-terminated chains contribute to lower the rate by hydrogen bonding interactions with alkoxide ends.

The combination of alkoxide with the parent hydroxy compound was used to initiate EO polymerization in various media like THF or DMSO. This was used for the preparation of multibranching PEO's. Typically, a polyhydroxy compound is partially deprotonated by addition of 0.2–0.8 molar equivalent of an alkali metal derivative to be used as a multifunctional initiator [12,13]. It limits aggregation between alkoxide species and preserves solubility, thus allowing a better control of the initiation and propagation of EO polymerization, but to the detriment of reaction kinetics.



**Scheme 5.** Exchange reactions between active and dormant species in ROMt/ROH polymerization systems.



**Scheme 6.** Formation of dimsyl ion through transfer to dimethylsulfoxide.

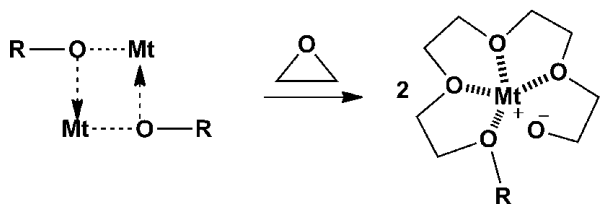
Kinetics of EO propagation reactions were investigated in media of varying polarities. The reaction rates were found to be first order in monomer, zeroth order with respect to sodium alkoxide and between zero and one with respect to potassium alkoxide in hexamethylphosphoramide (HMPA) ( $\epsilon = 30$  at  $20^\circ\text{C}$ ) [14]. These values were explained by the association of alkoxide chain ends as evidenced by different viscometric measurements between living and terminated polymerization systems. With cesium as counter-ion ( $\text{Cs}^+$ ), aggregates are absent and the propagation rate constant is a linear function of  $1/[\text{propagating species}]^{1/2}$ , indicating that propagation proceeds by ion pairs and free ions [15]. Although free ions are present in very low proportion, they are of much higher reactivity [9]. At  $40^\circ\text{C}$ ,  $k_p^-$  is approximately 100 times higher than  $k_p^\pm$  of Cs ion pairs.

In dimethylsulfoxide (DMSO), the use of potassium *tert*-butoxide as initiator was reported to yield living PEO's with molar masses controlled by the ratio  $[\text{monomer}]/[\text{initiator}]$  [15–17]. Formation of a dimsyl ion resulting from transfer to the solvent, Scheme 6, was considered by some authors as the main polymerization initiator [18,19]. With  $\text{K}^+$  and  $\text{Cs}^+$  salts, EO polymerization in DMSO proceeds almost exclusively by free ions [17] in agreement with a higher dissociation constant in this solvent ( $K_d = 9.4 \times 10^{-2} \text{ mol L}^{-1}$  at  $50^\circ\text{C}$  for Cs counter-ion), in line with a high DMSO permittivity ( $\epsilon = 48$  at  $20^\circ\text{C}$ ). With  $\text{Na}^+$  as counter-ion, both ion pairs in equilibrium with a small proportion of free ions contribute to the propagation [17]. A much higher propagation rate constant is observed in HMPA as compared to DMSO. A ratio of about 1800 is observed between  $k_p^-$  values in the two solvents. This difference is attributed to stabilization of free anions via hydrogen interaction with DMSO.

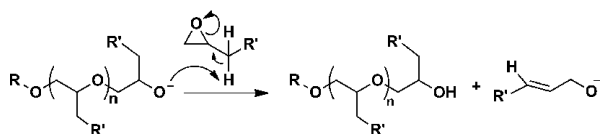
In tetrahydrofuran (THF) ( $\epsilon = 7.6$  at  $25^\circ\text{C}$ ) and in the presence of sodium, potassium and cesium naphthalene as initiators, a living polymerization takes place [20,21], the rate of propagation increases with respect to the size of the counter-ion [2]. Kinetics are however complicated by strong association of alkoxide end-groups, reflected by the low fractional kinetic order of reactants, i.e., 0.25 for Na alkoxide and 0.33 for K and Cs salts [20]. Dissociation constants are very low. In general, the presence of an acceleration period at the beginning of the polymerization in ethereal solvents was interpreted by the increasing solvation of alkoxide aggregates by the polyether growing chain, until chain reaches up to 4–6 EO units (Scheme 7) [21].

## 2.2. Mono-substituted epoxides

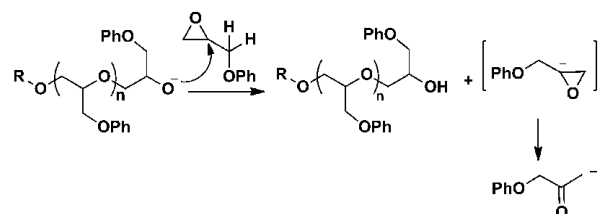
Although alkali metal derivatives are efficient initiators for ring-opening polymerization of ethylene oxide, they are much less efficient for mono-substituted epoxides,



**Scheme 7.** Solvation of the alkoxide propagating species by a polyether growing chain.



**Scheme 8.** Usual transfer to monomer observed during anionic polymerization of propylene oxide initiated with metal alkoxides.



**Scheme 9.** Transfer to monomer occurring in the anionic ring-opening polymerization of glycidyl phenyl ether.

e.g. propylene oxide, glycidyl ethers. ... Indeed, alkoxide species are relatively strong bases causing the abstraction of monomer substituents proton. This side reaction leads to the formation of polyether chains initiated by an allyloxy group (Scheme 8). This transfer reaction limits strongly the molar masses of polyethers up to 6000 g/mol [22,16].

Another type of transfer to monomer occurs particularly during the polymerization of glycidyl phenyl ether as mentioned by Stolarzewicz [10]. This side reaction may also occur with propylene and styrene oxides. The proton of the methine group of the ring can be abstracted by the alkoxide species and thus new active species are formed (Scheme 9).

Solvents were also reported to induce transfer reaction [23]. Specifically in DMSO, a proton of a methyl group can be removed by the attack of alkoxide species terminating the growing chains and giving new active species. The main consequence of these transfer reactions is indeed the loss of polymerization control.

Similarly to ethylene oxide, the size of the counter-ion and the temperature were shown to influence the polymerization rate of mono-substituted epoxides. The active species are thus more dissociated by increasing the size

of the counter-ion which increases the polymerization rate. Faster polymerizations occur with cesium counter-ion. Moreover, increasing temperatures increase the rate [22,24] with the time frame being generally in the magnitude of several hours or days to reach high yields. In the presence of potassium as counter-ion (*t*-BuOK as initiator) the reactivity of racemic propylene oxide in HMPA at 40 °C is about four times lower than that of EO on the basis of overall polymerization rates [23]. The reactivity of other mono-substituted epoxides depends on both electronic and steric factors associated with the substituent attached to the epoxide ring [25]. For instance, the reactivity of 2,2-dimethyloxirane (DMO) is 10 times lower than that of POx, whereas glycidyl ethers such as *tert*-butyl glycidyl ether (*t*-BuGE) are more readily polymerized than POx [23].

In this review we highlight two important factors that dictate aliphatic polyether synthetic strategies: better control (less transfer reactions) and rapid polymerization kinetics. The following chapter will focus on advancements concerning the aforementioned factors.

### 3. Systems for activated epoxides polymerization

#### 3.1. Alkali metal derivatives associated to crown-ether

Addition of complexing agents to alkali metal cations, such as crown ethers or cryptands (Scheme 10), was shown to drastically increase ethylene oxide propagation rate in ethereal solvents [8,26,27]. They allow reducing the aggregation of alkoxide polymer ends and increase the proportion of free ions. For example, the dissociation constant of PEO<sup>-</sup> K<sup>+</sup> at 20 °C in THF is 1700 times higher when K<sup>+</sup> is complexed by cryptand 222. In this system, the reactivity of free ions is about 60 times higher than that of cryptated ion-pairs. Surprisingly, the reactivity of the cryptated ion-pairs was found close to – or even lower than – that of the corresponding non-complexed ion-pairs, though the charges are more separated [26]. A similar tendency was reported for cryptated cesium [27]. It was explained by partial insertion of oxygen anion in the cavity of the complexing agent [2,28].

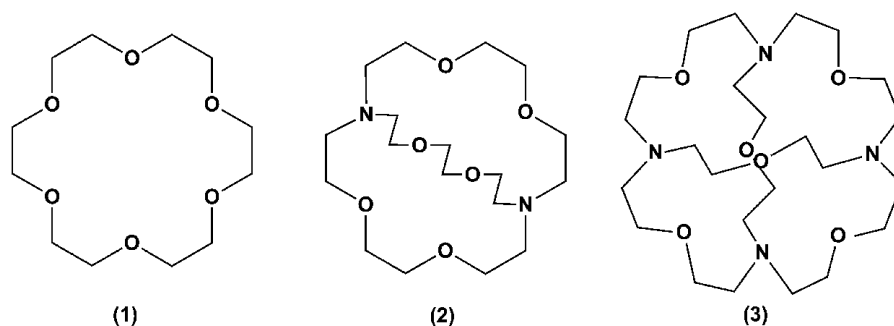
For mono-substituted epoxides, 18-crown-6 was also shown to increase the reactivity, as indicated by a multiplication factor of the propagation rate constant up to 14 times at 25 °C (Table 1). One can notice that bulk conditions at 60 °C were required to get a similar factor increase for propylene oxide. Again, aggregates are reduced and a larger charge separation of ion-pairs accompanied by an increase in ion dissociation constant was proposed.

In line with the acidic character of hydrogen on the  $\alpha$ -carbon of the monomer, nature of epoxide substituent

**Table 1**

Effect of addition of crown-ether 18C6 on the polymerization rate constant of propylene oxide (POx), phenyl glycidyl ether (PGE) and *tert*-butyl glycidyl ether (*t*BuGE).

Monomer	Initiator	[18C6]/[I]	Solvent	T (°C)	Time (h)	Conv. (%)	$k_{p(18C6)}/k_p$	Reference
POx	MeOCH <sub>2</sub> CH(CH <sub>3</sub> )OK	1.5	Bulk	60	92	95	13	[29,30]
PGE	<i>t</i> -BuOK	1	THF	25	7	81	14	[10]
<i>t</i> -BuGE	<i>t</i> -BuOK	1	THF	25	6	95	7	[29]
<i>t</i> -BuGE	<i>t</i> -BuOK	2	THF	25	6	95	13	[31]



**Scheme 10.** Crown Ether 18C6 (1), Cryptand 222 (2) and Sphere (3) used to complex alkali metal cations in ethylene oxide polymerization.

plays an important role in the chain transfer process [10,29–31]. For instance, the anionic polymerization of long-chain alkylene oxides initiated by potassium and cesium alkoxides is much less subjected to chain transfer processes than alkoxides deriving from POx. However, relatively high temperatures were needed to reach reasonable polymerization times, which caused residual side reactions limiting molar masses. The breakthrough of using the additive 18C6 was associated with a decrease of polymerization temperatures, minimizing transfer reaction to monomer. This is reflected by the obtainment of higher molar masses of poly(2-butyloxirane) obtained at 20 °C [24] (Table 2).

The polymerization temperature of 2-butyloxirane and of higher 2-alkyloxiranes like 2-hexyloxirane and 2-octyloxirane could even be reduced below 0 °C. It allowed the elimination of side reactions almost completely (Table 3). However, very long reaction times were required, i.e., 4–8 days, and non-complete conversion was observed. The best results were obtained with potassium alkoxides and 18C6 in toluene in the range of –10 to –23 °C. Poly(2-butyloxirane) (PBOx) and poly(2-hexyloxirane) (PHOx) homopolymers with molar masses up to 50,000–100,000 g/mol, close to theoretical values, and  $D < 1.1$  were synthesized applying this synthetic strategy [24].

Alkali metal hydrides were also used in conjunction with 18C6 as initiator for the AROP of glycidyl butyl ether [25,32]. Polyethers with molar masses lower

than 5000 g/mol and low dispersity were thus obtained. Polymerization time was considerably reduced, from several days to a few hours, as well as transfer reactions for this range of molar masses. Interestingly,  $\alpha$ -, $\omega$ -dihydroxytelechelic polyethers were also prepared. The authors mentioned that polymerization proceeded at the surface of the solid phase of potassium hydride as the latter reactant was not soluble in THF used as polymerization solvent, despite the presence of crown-ether. However, the release of one molecule of hydrogen with formation of one polymer chain initiated via potassium hydroxide resulting from reaction between potassium hydride and residual water might be suspected.

### 3.2. Calcium-based systems

The association of two metals was also proposed in 1980 to polymerize ethylene oxide [33]. A calcium amide/alkali metal alkoxide initiating system was used at high temperature in order to produce poly(ethylene oxide)s with high molar masses. EO polymerization involves monomer coordination at the catalyst active site via  $\sigma$  bond formation between the monomer heteroatom and the catalyst metal atom. It is followed by a nucleophilic attack of the alkoxide active group [34]. Tsvetanov and coworkers investigated this combination for the synthesis of poly(propylene oxide) and miscellaneous copolyethers [35–39]. The authors explained that calcium derivatives

**Table 2**

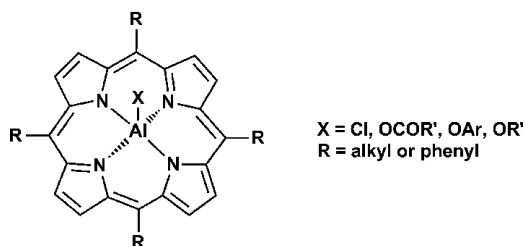
Polymerization conditions and characteristics of poly(2-butyloxirane) synthesized in presence of K or Cs *tert*-butoxide in toluene with or without crown ether 18C6 (Molar ratio 18C6/Metal = 3).

Counter-ion	$T$ (°C)	Time (h)	Conv. (%)	$\bar{M}_n$ , th. (g/mol)	$\bar{M}_n$ , exp. (g/mol)	$D$
K	80	40	96	14,700	11,200	1.15
Cs	80	18	97	14,800	11,700	1.11
K/18C6	20	19	92	47,000	43,600	1.11
Cs/18C6	20	68	81	39,600	28,000	1.13

**Table 3**

Polymerization of 2-butyloxirane (BOx), 2-hexyloxirane (HOx) and 2-octyloxirane (OOx) in presence of K *tert*-butoxide with crown ether 18C6 (Molar ratio 18C6/K = 3).

Monomer	$T$ (°C)	Time (h)	Conv. (%)	$\bar{M}_n$ , th. (g/mol)	$\bar{M}_n$ , exp. (g/mol)	$D$
BOx	20	19	92	47,000	43,600	1.11
HOx	20	92	99	67,800	52,500	1.18
HOx	–23	187	84	56,500	52,700	1.09
OOx	–23	189	73	61,600	50,000	1.09
OOx	–14	187	98	51,300	48,900	1.05



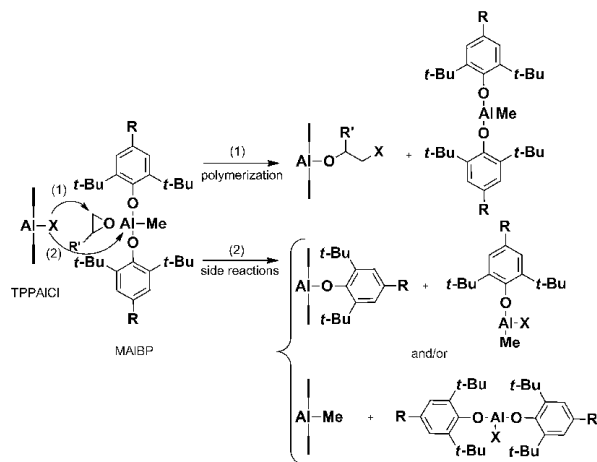
Scheme 11. Aluminum-based porphyrin structure.

are much weaker than other metals, like aluminum or zinc, in the formation of oxiranes complexes. As a result Ca–EO complexes are more readily formed in comparison with substituted epoxides where low-rate polymerizations are observed. In addition, the polymerization takes place under heterogeneous condition as the calcium-based initiator is not soluble in the solvents used. As an example, the synthesis of an amphiphilic poly(ethylene oxide)-*b*-poly(alkylglycidyl ether) copolymer with a molar mass up to  $10^6$  g/mol and a high dispersity (5–8) was achieved in relatively short times (several hours, but not days) at  $97^\circ\text{C}$  [37].

Coordination organometallic polymerization can be considered as borderline to anionic polymerization processes since epoxide ring-opening involves monomer coordination on a metal atom of a catalyst and nucleophilic attack of a weakened metal-X bond of the same – or another one – catalyst. High molar mass, as well as stereoregular and/or optically active polyethers, are specific characteristics of this coordination catalytic chemistry applied to epoxides [40–46]. For detailed informations see the review of Kuran [47] and C. Williams dedicated to  $\text{CO}_2$ /epoxide copolymerization [48]. Nevertheless, some introductory part on metalloporphyrin or double metal cyanide catalysts will be discussed in the following parts in order to better understand specificities of the AROP of epoxides by monomer activation and the functionalization of polyethers.

### 3.3. Aluminum systems: From bulky to simpler compounds

In the 1980s, Inoue et al. used metalloporphyrin as catalyst, in particular aluminum-based porphyrin, for the polymerization of methacrylates [49,50], lactones [51] and epoxides [52] (Scheme 11). The equimolar combination between diethylaluminum chloride and  $\alpha,\beta,\gamma,\delta$ -tetraphenylporphyrine (TPPAICl) led to a high catalytic activity in the polymerization of propylene oxide. The covalent nature of the Al–Cl bond suggests a polymerization via a coordination mechanism. Synthesized polyethers, by

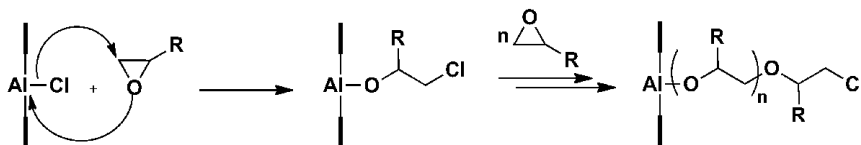


Scheme 13. Mechanism of epoxide polymerization initiated by aluminum porphyrin (TPPAICl) in presence of bulky Lewis acid (MAIBP).

the so-called “immortal” polymerization, reached molar masses up to 70,000 g/mol with a narrow distribution [53]. A monomer molecule is first inserted between the Al–Cl bond of the initiator (Scheme 12). Aluminum porphyrin, due to its nucleophilic character, was used as initiator enabling coordination with epoxide. Under such conditions, transfer reactions were considerably decreased, allowing the synthesis of a series of block copolymers, including Poly(POx-*b*-EO), poly(1,2-butene oxide-*b*-POx), poly(POx-*b*-epichlorohydrin), poly(lactones-*b*-POx), poly(lactones-*b*-EO)... [54,55]. Although EO polymerization could be achieved rapidly (reaction half-time is about 30 min at room temperature for  $[\text{EO}]/[\text{TPPAICl}] = 400$  in dichloromethane), other epoxides exhibited a lower reactivity. In similar conditions, several hours were required for the polymerization of POx and 1,2-epoxybutane [52], in order to reach complete conversion, whereas for styrene oxide or 1,2-epoxy-2-methylpropane conversions did not exceed 15% after 8 days of reaction [53].

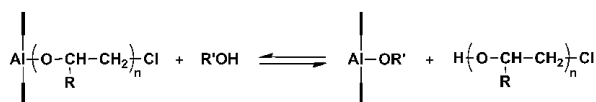
In order to increase polymerization rate, aluminum porphyrin was used in association with a bulky Lewis acid for either methacrylates [56–58] or propylene oxide [56,58,59]. For instance, methylaluminum bis(2,4,6-*tert*-butylphenolate) (MAIBP) was used to coordinate the epoxide and to activate the monomer substrate toward a nucleophilic attack (Scheme 13). As compared to the previous system, the catalytic species and the initiator are independent, i.e., employed as a bi-component initiating/activating system. There is no interaction between these two aluminum derivatives due to their bulkiness.

Polymerization rates of propylene oxide and 1,2-butene oxide were strongly increased due to the presence of



Scheme 12. Polymerization mechanism of epoxides initiated by an aluminum porphyrin.





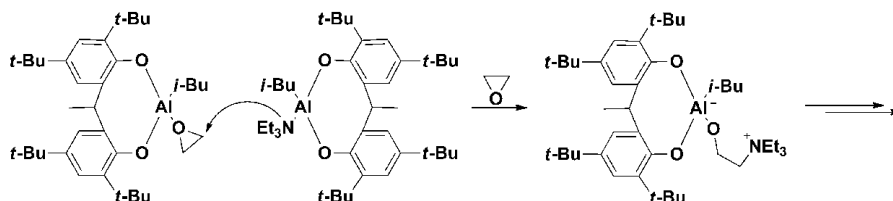
**Scheme 14.** Reversible chain-transfer (exchange) reaction between growing species initiated by an aluminum porphyrin and a protic agent.

the bulky Lewis acid [56]. Only 0.25% of MAIBP, with respect to propylene oxide concentration, was added to increase the polymerization rate by a factor of 460. With a [MAIBP]/[TPPAAlCl] ratio equal to 0.5, 3 min were enough for propylene oxide to be polymerized with 86% conversion, leading to a PPOx with a molar mass up to 12,000 g/mol. Without MAIBP, in 7 h, the conversion is around 20% and molar mass reached 3300 g/mol. The Lewis acid alone did not initiate the polymerization under similar conditions. The “living” nature of the polymerization could be demonstrated by the successful formation of block copolymers based on propylene oxide and 1,2-butene oxide, though complete conversions could not be obtained.

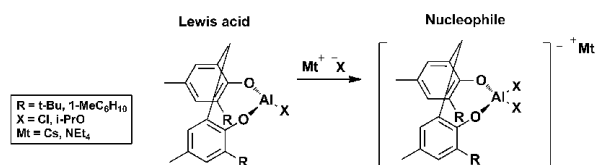
Protic chain-transfer agents (ROH) can be introduced into the medium to obtain a high-speed “immortal” polymerization of epoxides, when initiated with aluminum porphyrin in presence of an organoaluminum compound (i.e., MAIBP) as activator and to limit the amount of aluminum metal [60]. Growing species, the alkoxides of aluminum porphyrin, react reversibly with the alcohol leading to polymerization from all initiator and alcohol molecules (Scheme 14) [61]. The exchange reaction was estimated to occur 10 times faster than the propagation one. Resulting polymers exhibited controlled molar masses with narrow distributions.

Based on a similar system, Inoue et al. employed aluminum complexes of phthalocyanine, tetraazaannulene and Schiff bases as initiators, in conjunction with bulky Lewis acid such as MAIBP, in order to polymerize propylene oxide [59]. Comparatively, polymerization rates increased strongly with aluminum porphyrin and aluminum of tetraazaannulene exhibited the higher reactivity. Some limitations appeared however in the control of synthesized polyethers molar masses.

Recently, mixtures of trialkylaluminum and highly hindered di- or tetraphenol compounds have been also investigated as catalytic systems for the polymerization of ethylene and propylene oxides [62]. Ligands featuring four phenol groups formed particularly active catalysts when combined with an excess of triisobutylaluminum (2 equiv.) and triethylamine (1 equiv.) as initiator. A bimetallic activation was proposed as shown in Scheme 15. Highly regioirregular structures, observed with some of these



**Scheme 15.** Activated ring-opening of epoxide by a triethylamine/hindered aluminum system.



**Scheme 16.** Initiating aluminum complexes with their neutral Lewis acid precursors.

catalytic systems as well as high molar masses with dispersity around 2, suggested that the involved mechanism differs from the nucleophilic one so far described.

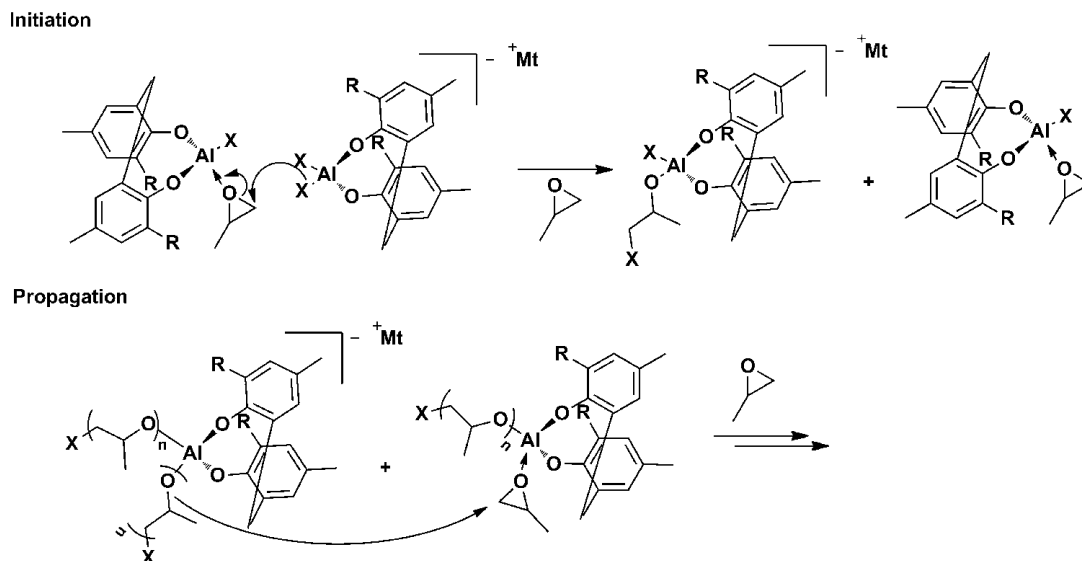
This “living” and “high speed” method, developed by Inoue et al., and its usefulness for the polymerization of some alkylene oxides appears as a breakthrough despite drawbacks, especially for industrial purposes, like the cost of reactants and the coloration of polymers due to aluminum porphyrin.

In 2003, Braune and Okuda proposed the synthesis of new porphyrin-free aluminate complexes for the polymerization of propylene oxide activated by their neutral Lewis acid precursors (Scheme 16) [63]. The nucleophilic species were easily obtained by reaction of a bulky Lewis acid based on diphenoxyaluminum compounds, with a cesium alkoxide or an ammonium salt.

The ring-opening polymerization proceeds under the synergic interaction of a phenolate–aluminium–oxirane complex forming an activated monomer with the corresponding “ate” complex which initiates the reaction (Scheme 17). Ring-opening takes place by transfer of an alkoxy group from the “ate” complex, regenerating an aluminate able to activate a new monomer. In contrast with aluminum porphyrins, the bulky Lewis acid alone cannot initiate, on its own, the polymerization. The synthesis of poly(propylene oxide)s with molar masses up to 4 000 g/mol was reported following an anionic or coordinative mechanism because of exclusive head-to-tail linkages.

Using relatively similar systems based on quaternary ammonium and quaternary phosphonium halides associated with sterically hindered methyl(diphenoxy) aluminum, a less-reactive four-membered ring oxetane, e.g. 1,3-propylene oxide, was polymerized according to a coordinated-anionic mechanism, as a result of strong monomer activation by complexation with the aluminum derivative [64].

Tsvetanov reported in 1985 the polymerization of ethylene oxide initiated by sodium tetrabutylaluminate [65]. PEO were prepared in toluene in the range 15–70 °C with a high order of the kinetic equation with respect to the initiator. The polymer chain growth was explained by the



**Scheme 17.** Initiation and propagation steps of propylene oxide polymerization initiated by bulky aluminum complexes.

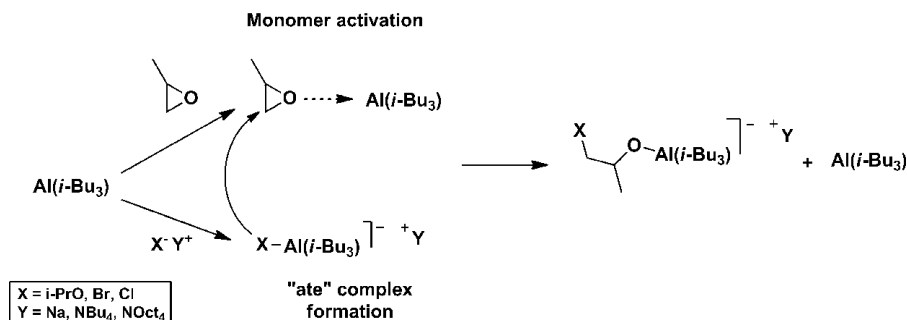
presence of aggregates of  $\text{NaAlBu}_4$ , predominantly trimers of the “ate” complex. Interaction between the oxygen atom of EO and the alkali metal, as well as EO and aluminum to a lesser degree, were shown, in line with some activation of the epoxide.

Playing with “ate” complexes and their stoichiometry, Carlotti and Deffieux developed the “Retarded Anionic Polymerization” of styrene and dienes enabling their anionic polymerization in bulk conditions and at high temperature [66]. Moving to epoxide monomers and using combinations of a Lewis acid (typically a trialkylaluminum) and alkali metal alkoxides or onium salts [67–72], efficient polymerizations were achieved. An excess of Lewis acid with respect to the initiator was required. The formation of an “ate” complex, which was able to ring-open the activated epoxide by the excess of activator, was observed (Scheme 18).

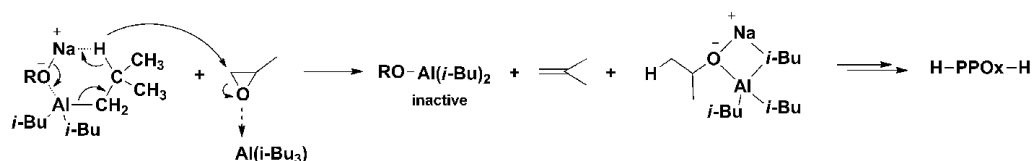
Propylene oxide polymerization, based on a monomer-activated anionic polymerization, occurs at room or lower temperature. Control over the polymerization strongly depends on the nature of the counter-ion. Sodium and potassium enable the polymerization inversely to lithium. A few hours allow obtaining controlled poly(propylene

oxide) chains, up to 20,000 g/mol, but some residual transfer reactions were observed, i.e., transfer to monomer leading to allyloxy groups in the  $\alpha$ -position and transfer to triisobutylaluminum ( $i\text{-Bu}_3\text{Al}$ ) which generates initiation by a hydride group coming from an isobutyl group (Scheme 19). Ammonium salts were more successful in the sense that much higher molar masses could be achieved in a controlled manner, especially at  $-30^\circ\text{C}$ , yielding polyethers of low dispersity (e.g.  $D=1.34$  for  $M_n=170,000$  g/mol) (Fig. 1) [70]. The strong decrease of transfer reactions was explained by the decrease of basicity of the active bi-component complex. The exclusive preparation of regioregular polymers (head-to-tail) was indicative of an anionic/coordination type mechanism.

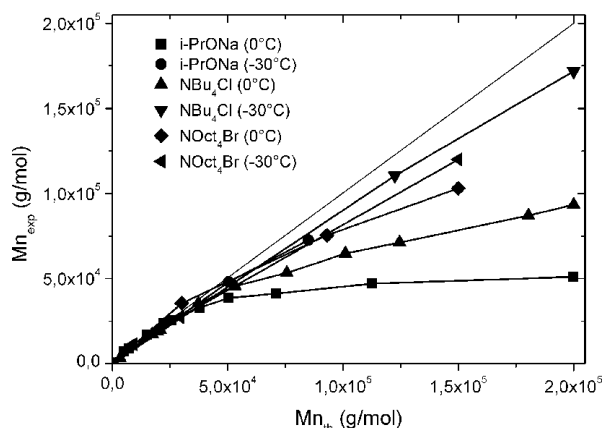
Polymerization proceeds at  $[\text{Al}]/[\text{Initiator}]$  ratio higher than unity, indicating that only complexed POx molecules are susceptible to ring-open, thanks to significant electron-withdrawing effect that makes the ring carbon atoms much more electrophilic. Increasing trialkylaluminum concentration, at constant monomer and initiator concentrations, was shown to yield a drastic increase in polymerization rate whereas the number of PPOx chains remained unchanged. This increase was also strictly dependent on the nature of



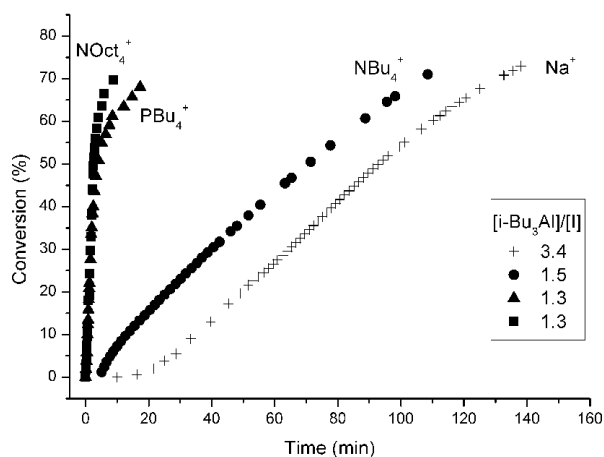
**Scheme 18.** Nucleophilic attack of sodium alkoxide or ammonium salts/triisobutylaluminum on activated propylene oxide.



**Scheme 19.** Transfer reaction with sodium alkoxide: initiation by a hydride coming from  $i\text{-Bu}_3\text{Al}$ .



**Fig. 1.** Experimental and theoretical molar masses of poly(propylene oxide) initiated by sodium *iso*-propoxide and ammonium salts in presence of triisobutylaluminum in toluene [70].



**Fig. 2.** Conversion versus time curves of POx polymerization initiated by *i*-PrONa (+),  $\text{NBu}_4\text{Cl}$  (◆),  $\text{NOct}_4\text{Br}$  (■) and  $\text{PBu}_4\text{Cl}$  (▲) in presence of  $i\text{-Bu}_3\text{Al}$  at  $0^\circ\text{C}$  in cyclohexane [70].

the counter-ion complexed with the Lewis acid, as shown in Fig. 2.

These initiating systems were next applied to the polymerization of a broad family of epoxides including several alkylene oxides and glycidyl ethers, epichlorohydrin (ECH). Compared to conventional alkali metal initiators, the tetraoctylammonium bromide/ $i\text{-Bu}_3\text{Al}$  initiating system strongly enhanced the rate of ethylene oxide polymerization, while retaining the living character of the reaction [73]. At a ratio  $[i\text{-Bu}_3\text{Al}]/[\text{NOct}_4\text{Br}] = 1.5$ , the synthesis of PEO of 20,000 g/mol was completed within 2 h at room temperature in dichloromethane. By changing the

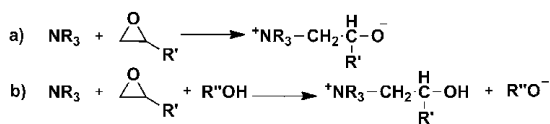
ammonium salt by an alkylaluminum, a PEO of 10,000 g/mol was synthesized at low temperature and in non-polar media, e.g. toluene [74]. The presence of trialkylaluminum used in excess with respect to the lithium initiator permits disaggregation of lithium alkoxides species by forming lithium/aluminate complexes which are able to ring-open the  $\text{AlR}_3$ -complexed EO molecules. However, ligand exchanges in the lithium/aluminate complex lead to slow deactivation of the propagating species during the polymerization which limits the access to high-molar-mass PEO.

Monomer-activated anionic polymerization of epichlorohydrin (ECH) utilizing similar conditions was also described. In contrast to conventional anionic polymerization, aluminate species that ensures propagation in  $\text{AlR}_3$ /onium systems selectively react with activated ECH ring, leaving the chloromethyl function untouched [75]. Syntheses of poly(glycidyl methyl ether) (PGME) [76], linear poly(2-ethoxyethyl glycidyl ether) (PEEGE) and poly(*tert*-butyl glycidyl ether) (PtBuGE) [77] with narrow chain distribution and controlled molar masses were also reported. The amount of Lewis acid required to trigger the reaction and achieve quantitative monomer conversions was shown to increase with the number of oxygen atoms in the monomer.

This anionic living/controlled polymerization employing onium salt/triisobutylaluminum systems involving a monomer-activated mechanism was applied to the synthesis of a series of random and block copolymers. For instance, EO/PPOx random copolymers with a gradient structure, molar masses up to 70,000 g/mol and narrow dispersity were prepared [73]. PPOx-*co*-PECH [75] and amphiphilic poly(alkylene oxide-*co*-glycidol) were also synthesized via the synthesis of PPOx-*co*-PEEGE and PBOx-*co*-PtBuGE copolymers [77], after deprotection of hydroxyl groups under acidic conditions. Despite the determining role of the monomer complexation in this polymerization process, the copolymerization ratios remain close to those reported for conventional anionic copolymerization.

Different diblock and triblock copolymers of various compositions and lengths were prepared by sequential monomer addition. Synthesis of PEO-*b*-PPOx-*b*-PEO triblock copolymers with  $\text{NOct}_4\text{Br}/i\text{-Bu}_3\text{Al}$  initiating system was first achieved [73]. PPOx-*b*-PECH block copolymers with molar masses ranging from 6000 g/mol to 30,000 g/mol and with various PPOx and PECH block lengths were also prepared by sequential addition of the two monomers [75]. The re-initiation efficiency was shown to be quantitative, no matter the order of addition of the two monomers.

Finally, block copolymerization of EO initiated with lithium derivatives was also lately described [74]. Although



**Scheme 20.** Possible initiation steps for the epoxide polymerization in presence of tertiary amines.

it is known that EO polymerization could not proceed properly when lithium alkoxide species are involved [78,79], it was shown that living polystyryllithium and polyisoprenyllithium chains can play the role of a macroinitiator for EO polymerization in presence of trialkylaluminum. Block copolymers polystyrene(or polyisoprene)-*b*-poly(ethylene oxide)s were obtained in hydrocarbon within a few hours with a PEO block molar mass up to 10,000 g/mol and re-initiation efficiency of about 80%.

In summary, various systems such as metals associated to crown ethers or metallic activators as well as combinations or organic initiators associated to organometallic compounds have been used to polymerize epoxides and afford control and fast kinetics. Nowadays, complementary challenges concerns metal-free systems which are able to fulfill all criteria so far discussed.

## 4. Towards organic initiating systems

### 4.1. Tertiary amines

Amines were essentially used for the anionic polymerization of di- and polyepoxides, mainly diglycidyl ether of bisphenol A and its derivatives as well as glycidyl phenyl ether which is used as model monomer [80]. Reaction with amines leads to slow polymerization rates, long induction periods and to the formation of short chains due to transfer reactions. Benzyltrimethylamine, pyridine, triethylamine, 4-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) are the most common amines used as initiators. Ammonium salts and imidazoles are also employed to open epoxides by anionic polymerization. The main drawback of these compounds is the limitation in terms of molar masses although the initiation mechanism is not well established, two pathways are generally considered [81,82] (Scheme 20). The addition of alcohol decreases induction periods and increases polymerization rates but limits molar masses

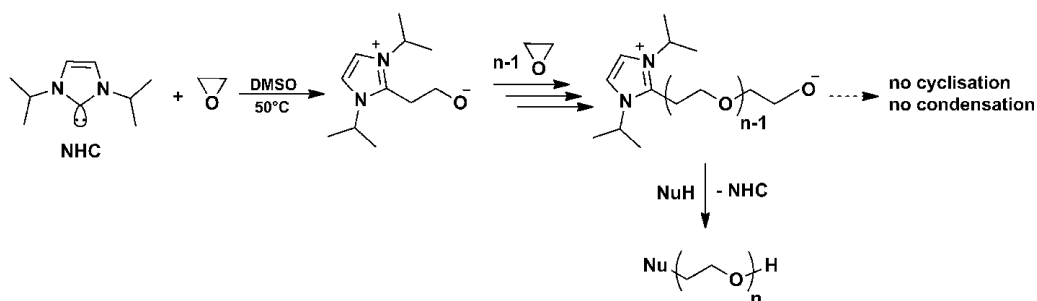
[80]. The alkoxide formed by the second way (Scheme 20b) is more reactive than species resulting from usual initiation step (Scheme 20a). Williams et al. succeeded to decrease the time of initiating step by using DMAP thanks to its conjugated structure with a negative charge on nitrogen of the cycle and a positive charge on tertiary amine [82]. The molar masses were about 1000 g/mol at 80 °C.

The initiation with amines leads to many side reactions. Their using leads to colored polymers which can be a real drawback for some applications.

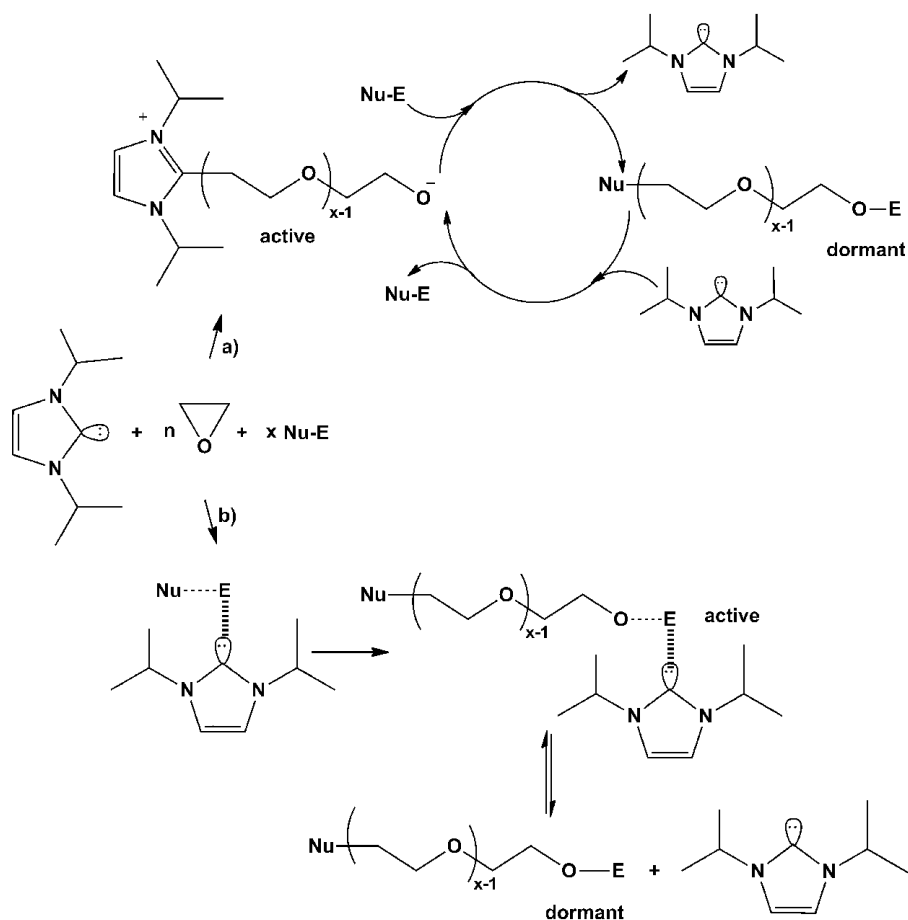
### 4.2. N-heterocyclic carbenes

N-heterocyclic carbenes (NHCs) can be used as ligands of transition metallic complexes [83], but also as organic catalysts for various metal-free reactions [84]. NHCs have been also employed to trigger polymerization reactions including ROP of lactide [85] and some epoxides [86–88] as well as group transfer polymerization of (meth)acrylates [89,90]. Taton et al. showed that 1,3-bis-(diisopropyl)imidazole-2-ylidene is able to initiate ethylene oxide polymerization according to a zwitterionic mechanism [86] (Scheme 21). NHC plays in this case the role of initiator controlling PEO molar masses and forming zwitterionic imidazolium. It can be released by attack of functionalizing terminators added to the medium. Polymerizations were performed at 50 °C in DMSO and required long times, i.e., several days. Molar masses up to 13,000 g/mol were obtained with narrow distribution and good agreement between theoretical and experimental molar masses, in line with a good control of the polymerization. This approach was less effective for the polymerization of propylene oxide due probably to transfer reactions to monomer. Poly(propylene oxide) oligomers with a relative low dispersity were prepared [88].

Controlled EO polymerization was found to proceed also with a catalytic amount of NHC, in DMSO at 50 °C and in presence of a variety of chain regulators, e.g. benzyl alcohol, propargyl alcohol or trimethylsilyl azide. They possess a nucleophilic part and an electrophilic one (Nu-E), typically in molar proportions [NHC]/[Nu-E]/[EO] = 0.1/1/100 [87]. In this case PEO molar masses match the [EO]/[Nu-E] ratio. Two possible mechanisms were considered (Scheme 22), a nucleophilic attack of the NHC catalyst onto EO and the formation of a zwitterionic intermediate (a) or activation by the NHC of the electrophilic moiety followed by EO polymerization initiated by the nucleophilic one (b). Reversible exchanges with Nu-E molecules, involving the formation of



**Scheme 21.** Proposed mechanism for ethylene oxide polymerization initiated by N-heterocyclic carbenes.



**Scheme 22.** Proposed mechanism for ethylene oxide polymerization in presence of catalytic amount of N-heterocyclic carbenes and additives constituted of nucleophilic and electrophilic parts.

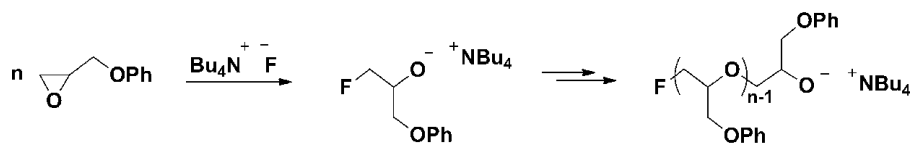
active and dormant chains, yield  $\alpha$ -Nu- $\omega$ -E-poly(ethylene oxide) opening a way for chain-ends functionalization.

#### 4.3. Ammonium, phosphonium and phosphazene bases

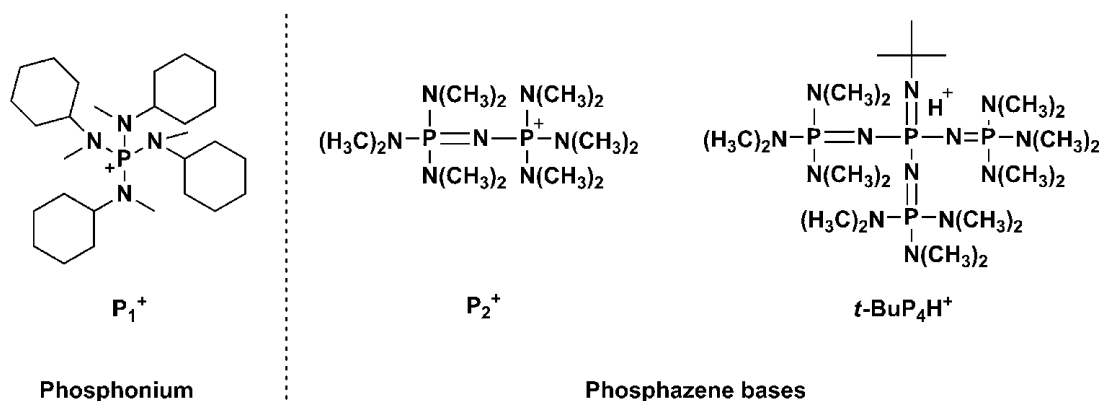
Ammonium salts were first used by Hemery, Ganachaud et al. for the AROP of glycidyl phenyl ether (GPE) in miniemulsion [91]. Didodecyldimethylammonium hydroxide was used as an inisurf (initiator-surfactant) exhibiting both surface-active properties and the ability to initiate polymerization of this epoxide. Average molar masses increased with conversion and were dependent on the initiator concentration. A critical polymerization degree of 8 was reached. Using a similar initiator, i.e., tetrabutylammonium fluoride, in solution polymerization, Endo achieved the synthesis of poly(glycidyl phenyl ether)

oligomers with controlled molar masses up to 4000 g/mol (Scheme 23) [92].

As already mentioned, the size of the counter-ion has a preponderant role in epoxides polymerization, in particular on the kinetics. As a result of their bulky size, some phosphonium and phosphazene derivatives arising from strong Brönsted phosphazene bases, developed by Schwesinger, revealed potential as counter-ions in order to limit aggregation phenomena (Scheme 24) [93,94]. Several of these commercially available bases were used as organic deprotonating agents of -OH (-CH, -SH, or -NH) containing initiators, to polymerize epoxides like ethylene oxide [95-100], propylene oxide [101-103], butene oxide [104], styrene oxide [105], as well as ethoxy ethyl glycidyl ether [104,106,107], a protected form of glycidol, affording homopolymers, copolymers [108,109], and grafted block copolymers as well [100,110].



**Scheme 23.** Polymerization of glycidyl phenyl ether initiated with tetrabutylammonium fluoride.



**Scheme 24.** Main phosphonium and phosphazene bases used in anionic polymerization of epoxides.



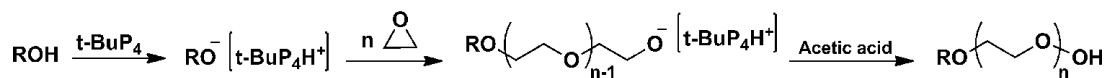
**Scheme 25.** Equilibrium between alcohol and phosphonium alkoxide.

As reviewed by Boileau and Illy [94], phosphonium and phosphazene bases were handled according to two different strategies: either with an alcohol to form a protonated counter-ion, or with organolithium initiators to complex lithium. In the first case, the strong and bulky base is directly used to deprotonate alcohols below stoichiometry. A bulky cation is formed, which prohibits the aggregation of alkoxide species and allows the nucleophilic attack of the monomer. When a phosphonium alkoxide  $\text{RO}^- \text{P}_1^+$  is used in default as compared to an alcohol (down to 5 mol%), rapid exchange equilibrium occurs between active and dormant chains leading to a better control of molar masses (Scheme 25). The alcohol/alkoxide complex is more active than the alkoxide alone due to separation of alkoxide ion pairs by the complexation phenomenon [111].

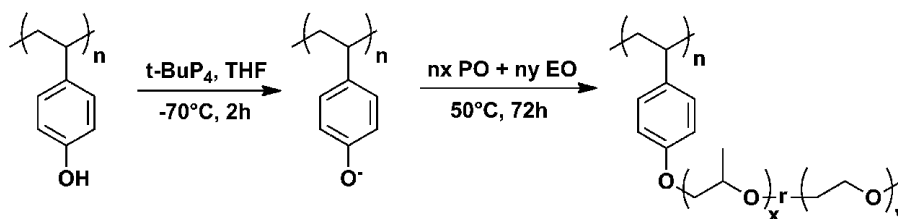
The use of  $t\text{-BuP}_4\text{H}^+$  enables an increase of the polymerization rate of propylene oxide by a factor of 44 as compared to an initiation with potassium as counterion, and allows the preparation of polymers with molar masses up to 4000 g/mol. However, the presence of chains

bearing double bonds at one extremity shows that transfer reactions to substituted monomers still occur. Polymerization rates increase when the positive charge is delocalized into the molecule, which is due to better ion separation [99,100]. The following rate order was observed:  $\text{Bu}_4\text{P}^+ < \text{K}^+ < \text{P}_1^+ < \text{P}_2^+ < t\text{-BuP}_4\text{H}^+$ .

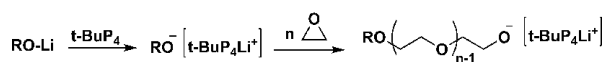
Ethylene oxide could also be polymerized from partially deprotonated alcohols (Scheme 26). Eßwein and Möller prepared well-defined linear PEO's using mono-alcohols, as well as graft copolymers containing PEO chains starting from a polyfunctional initiator, i.e., poly(ethylene-co-vinyl alcohol) [96]. Polystyrene with PEO or PPOx-PEO side chains were also synthesized by Pispas and Zhao [112,113] using the "grafting-from" technique with a polyfunctional initiating system generated by  $t\text{-BuP}_4$  and phenolic hydroxyl groups on the backbone of poly(hydroxystyrene) (Scheme 27). A similar methodology was also used to synthesize poly(ethylene carbonate-co-ethylene oxide) starting from 1,3-dioxolan-2-one as monomer [114] or poly(N-isopropylacrylamide)-poly(ethylene oxide) graft copolymers [100]. Schlaad, Antonietti and co-workers used also terpene alcohols in the presence of catalytic amount of  $t\text{-BuP}_4$  to initiate EO polymerization and to obtain biohybrid polymers with tunable compositions [99]. Macroinitiators like  $\omega$ -Hydroxy polyisobutylene [109] and  $\omega$ -hydroxy poly(ethylene-co-butylene) [108] enabled the polymerization of EO generating homogeneous porous materials by self-assembly.



**Scheme 26.** Ethylene oxide polymerization initiated by a  $t\text{-BuP}_4$  partially deprotonated alcohol.



**Scheme 27.** Preparation of brush copolymers with PPOx-PEO random copolymer side chains.



**Scheme 28.** Ethylene oxide polymerization initiated by lithium alkoxide in the presence of phosphazene base.

Additionally, phosphazene bases were also utilized in order to complex lithium alkoxides allowing the (co)polymerization of ethylene oxide and 1-ethoxyethyl glycidyl ether with lithium derivatives (Scheme 28) [95,98,104,106,107,115], which is generally not possible because of strong aggregation between lithium alkoxides except when a trialkylaluminum is added [74]. The base behaves as a cryptand for  $\text{Li}^+$  ions via polar amino and imino groups located inside the globular molecule and the outer shell is formed by alkyl substituents. The equilibrium between complexed lithium alkoxide ion pairs and reactive free anions is thus shifted towards the latter species allowing polymerization. Copolymers based on polystyrene and polyethers were prepared without the need of cation exchange. The presence of residual transfer reactions and an induction period resulting from the slow disaggregation of the lithium alkoxide ends complicated, however, the epoxide polymerization [98].

A broad range of polyethers can be synthesized leading to an important class of materials used in many applications. Controlled structures and dimensions as well as easy, inexpensive, and rapid polymerizations remain the major challenges to be addressed. One can add to this short list the preparation of functional polyethers used as reactive precursors. This is discussed in the next part of this review.

## 5. Functionalization of polyethers prepared by anionic ring opening polymerization

Functionalization of polyether chains can take place either to chain ends or along the polymer backbone. In the first case, a functional initiator and/or a termination agent is employed. Polymers are called “telechelic” when the functions to the ends are the same and “heterotelechelic” when they are different. Further polymerization or other reactions can be conducted from the as-introduced functional groups. The functionalization into the chains is carried out by the use of functional monomers. Hydroxy, amine, epoxide, carbonate, thiol, azide, as well as double and triple bonds are the most commonly used functions in order to obtain a versatile range of functional polymers for many applications. Frey et al. has reviewed in 2011 and 2012 main properties and applications of various functional polyethers like (temperature dependent) water solubility and reactivity for biomedical applications [116,117]. Riffle and co-workers discussed in detail the synthesis and applications of heterobifunctional poly(ethylene oxide) oligomers, featuring, for instance, the obtaining of

carboxylic acid, amine, thiol and maleimide chain ends for a use in the biomedical field [118].

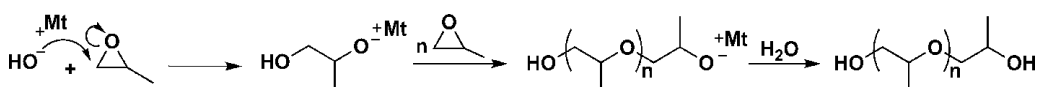
In this part, the focus will be given on synthetic aspects of the introduction of reactive functions in various polyethers, obtained by AROP.

### 5.1. Functional polyethers by initiation

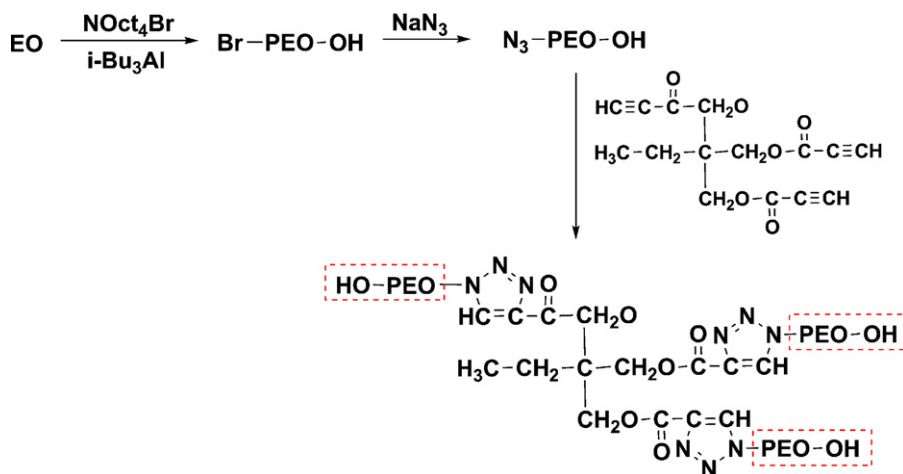
#### 5.1.1. Telechelic polyethers

**5.1.1.1. Hydroxy telechelic polyethers.** Low molar masses polyether polyols are mainly used as precursors of polyurethanes [119]. The majority of hydroxy telechelic polyethers are synthesized by AROP initiated by potassium or cesium hydroxide [22]. Initiation by a hydroxy group followed by termination reaction using water or an alcohol yields  $\alpha,\omega$ -dihydroxy polyethers (Scheme 29). As shown previously, this approach is efficient for ethylene oxide but much less with monosubstituted epoxides. Cesium hydroxide used as initiator leads to PPO's having molar masses limited to 6000 g/mol, due to transfer reactions to monomer [82,120]. The use of di- or polyalcohols as initiators enables the increase of hydroxyl groups in alpha position of linear chains, but limitations in length still exists, e.g. 2,4-dimethylhexane-2,4-diol [121]. Branched and star polyethers were synthesized from tri-, tetra-, penta-, and octa-alkoxides of potassium with molar masses close to 5 000 g/mol and a relatively broad dispersity [122–129]. With a similar approach and using hyperbranched polyglycerol initiators, P. Lutz, Frey et al. prepared functional multiarm star PEO [12]. Fan et al. [130] synthesized tri-hydroxy telechelic PEO by coupling reaction between a trialkyne issued from trimethylolpropane and three  $\alpha$ -azido,  $\omega$ -hydroxy PEO obtained by activated anionic polymerization of EO initiated by an ammonium bromide in presence of trialkylaluminum [70]. The bromine was replaced by an azido group by reaction with sodium azide (Scheme 30). Glycerol phosphate calcium salt hydrate associated to cesium hydroxide or potassium *tert*-butoxide was also used for the synthesis of dihydroxy telechelic poly(propylene oxide) (Scheme 31) [131]. Reactions were performed in DMSO at 120 °C with a pressure of 3 bars of propylene oxide. A monomodal population was obtained with dispersity varying between 1.5 and 2 and  $\overline{M}_n$  up to 5000 g/mol. The main interest of this approach based on conventional ring-opening polymerization by alkali metal alkoxides is to introduce a phosphate group in a reactive polyether to improve the flammability resistance of the final material.

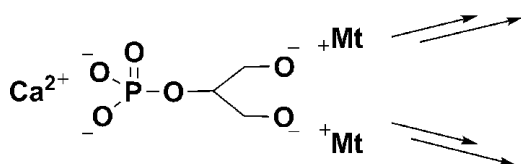
Bulkier counter-ion like phosphazene bases were used as deprotonating agents with dipropylene glycol as initiator showing some decrease of usual transfer reactions [101]. Using the monomer activation methodology [70], di-, tri- and penta-hydroxy telechelic poly(propylene oxide)s were obtained in very short times (hours) at room temperature in hydrocarbon solvents with molar



**Scheme 29.** Synthesis of dihydroxy telechelic polyethers by hydroxide initiation (Mt = potassium or cesium).



**Scheme 30.** Synthetic route to three-arm poly(ethylene oxide)s.



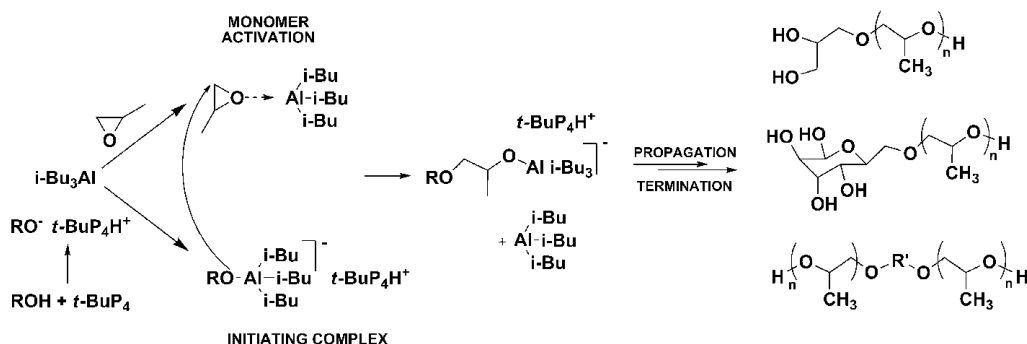
**Scheme 31.** Cesium or potassium glycerol phosphate calcium salt as initiator of propylene oxide.

masses up to 80,000 g/mol with a relatively low dispersity [132]. Alcohols bearing one or several protected hydroxyl groups, namely 1,2-isopropylidenglycerol and 1,2:3,4-di-O-isopropylidene-D-galactopyranose, were deprotonated with a phosphazene base and used as initiator of propylene oxide in presence of triisobutylaluminum (Scheme 32). A final step of deprotection released the terminal  $-OH$  groups. This step could be avoided using, for instance, complexed and deprotonated poly(propylene glycol) as macroinitiators, giving dihydroxy telechelic poly(propylene oxide) of high molar masses in a few hours.

Using an organo-catalysis approach described previously (Scheme 21), Taton et al. reported that N-heterocyclic carbenes (NHC) could lead to  $\alpha$ - $\omega$ -dihydroxy poly(ethylene oxide) using water as terminating agent. Hydroxide ( $OH^-$ )

was shown to behave as a nucleophile that displaces the  $\alpha$ -imidazolium moiety from PEO chains, thus releasing the NHC, whereas the terminal alkoxide was transformed into an  $\omega$ -hydroxy function [87].

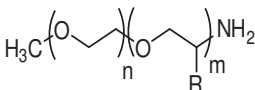
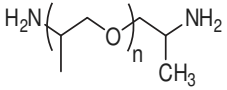
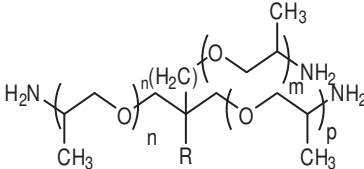
Poly(propylene oxide) polyols were also synthesized by double metal cyanide catalysts (DMC) obtained by the reaction of potassium hexacyanocobaltate(III) ( $K_3[Co(CN)_6]_2$ ) and zinc chloride ( $ZnCl_2$ ) in presence of *tert*-butanol as complexing agent [133–136]. Compared to conventional anionic systems, a low level of unsaturations, resulting from transfer to monomer, and narrow molar mass distributions, were generally obtained in the range of low molar masses. Through a coordination mechanism, the presence of some regioirregular sequences seemed to indicate the occurrence of cationic active sites [134]. While DMC catalysts offer significant advantages compared to KOH, they required long activation time, which increased polymerization cycles. The activation should be carried for over 2 h prior to the continuous addition of epoxide into the reactor at high temperature ( $>100^\circ C$ ). Usually, a polyol initiator was added to the catalyst and the system was heated under vacuum prior to the addition of a small proportion of monomer [137]. Heating the catalyst for a prolonged period, at temperature above  $100^\circ C$ , reduced its activity or deactivated it completely [138].



**Scheme 32.** Combination of phosphazene base and triisobutylaluminum for the synthesis of polyhydroxy telechelic poly(propylene oxide).



**Table 4**  
Structure of primary commercial polyetheramines (Jeffamines®).

Monoamine (R = H (EO) and CH <sub>3</sub> (POx))		$600 < \overline{M}_w < 2000 \text{ (g mol}^{-1}\text{)}$
Diamine		$230 < \overline{M}_w < 2000 \text{ (g mol}^{-1}\text{)}$
Triamine (R = H (EO) and CH <sub>3</sub> (POx))		$440 < \overline{M}_w < 5000 \text{ (g mol}^{-1}\text{)}$

Hydroxyl functions can also be introduced after post-modification of other reactive functions introduced via initiation. An amino function can lead to an OH group after reaction with a molecule of ethylene oxide [139]. The synthesis of  $\alpha$ -amino,  $\omega$ -hydroxy poly(ethylene oxide) will be discussed further. Use of tetrabutylammonium acetate as initiator proved efficient to introduce acetate-end groups to poly(glycidyl phenyl ether) [140]. Hydroxyl functions were obtained after an acidic treatment by hydrolysis. A narrow molar mass distribution and molar masses up to 4000 g/mol were obtained in this way.

**5.1.1.2. Amine-functionalized polyethers.** Jeffamines® represent the most industrially produced polyetheramines. Such polyamino telechelic polyethers cannot be directly obtained by initiation and termination steps. They are synthesized from hydroxytelechelic random copolymers of ethylene oxide and propylene oxide via reaction between hydroxyl functions and ammoniac gas at 300 °C. Some commercial structures are shown in Table 4. Considering the nature of the polymerization, only polyetheramines with low molar masses can be prepared. They are thermo-responsive possessing a lower critical solubility temperature around 30 °C in water. Amino end groups are mainly used as curing agents in epoxy resins [141,142] and as chain extenders for polyurethane applications [143,144].

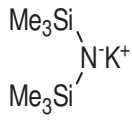
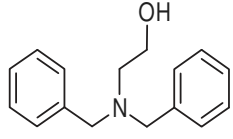
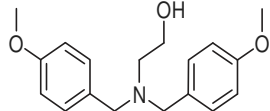
### 5.1.2. Heterotelechelic polyethers

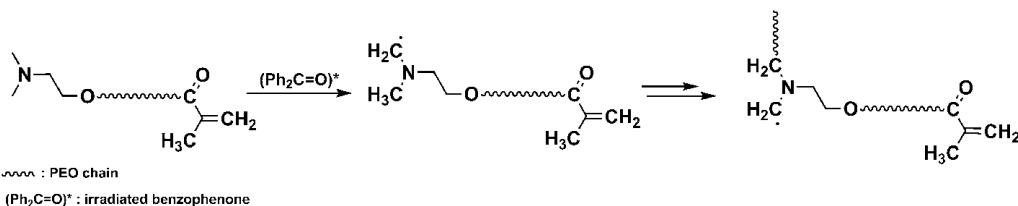
Heterotelechelic systems were developed with various functions like -OH, -NH<sub>2</sub>, -COOH, -CHO, -SH, and even more. Riffle and co-workers published a detailed review in 2008 on the synthesis and applications of heterobifunctional poly(ethylene oxide) oligomers, either by direct synthesis or by end group modification [118]. These polymeric materials can be used as hydrophilic, flexible and biocompatible spacers connecting two moieties. They also have the potential to increase drug potency by prolonging circulation in vivo due to a better solubility in aqueous media and by attaching drugs to targeting moieties [145,146].

**5.1.2.1. Amine-functionalized polyethers.** The introduction of amino groups at the head of polyethers chains is

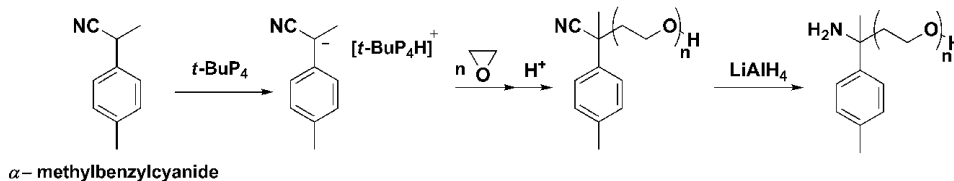
generally carried out using an initiator bearing a primary amine function and another function, more reactive, i.e., an alcohol, which enables the initiating step. Aminoalcohols can be used to polymerize ethylene oxide by an anionic mechanism [139]. In basic media, both metal alkoxide and amide are formed and the equilibrium is driven towards the formation of alkoxide by increasing the size of the counter-ion. Molar masses of  $\alpha$ -amino- $\omega$ -hydroxy functional polyethers reached 1000 g/mol. Transfer and termination reactions occur due to the hydrogen of amino groups. Protection of the primary amino group by a tertiary one was considered to overcome those limitations (Table 5). Molar masses increased up to 6000 g/mol and required long times, i.e., 150 h [147]. Tertiary amino function can be also of interest. Indeed, potassium dimethylamino alkoxide was used as initiator of EO polymerization and subsequently terminated by a methacryloyl moiety in order to obtain a macroinimer (Scheme 33). The tertiary amino group permits the formation of radicals via H-abstraction, which initiates its photopolymerization and crosslinking [148]. Radicals generated by UV irradiation of

**Table 5**  
Protected amines used as initiator for the conventional anionic epoxide ring-opening polymerization and their deprotection.

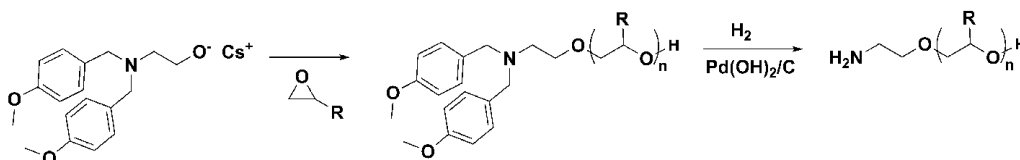
Amine	Deprotection	Reference
	HCl (acetic acid/THF)	[139]
	H <sub>2</sub> , Pd	[150]
	H <sub>2</sub> , Pd(OH) <sub>2</sub> /C	[151]



**Scheme 33.** Synthesis of PEO network from a PEO macroinimer bearing a tertiary amine introduced via the initiation step.



**Scheme 34.** Synthesis of  $\alpha$ -amino, $\omega$ -hydroxy poly(ethylene oxide) from  $\alpha$ -methylbenzyl cyanide and *t*-BuP<sub>4</sub>.



**Scheme 35.** Synthesis  $\alpha$ -amino, $\omega$ -hydroxy poly(ethylene oxide) from *N,N*-dibenzyl-2-aminoethanol and cesium hydroxide.

benzophenone were scavenged by HTEMPO (4-hydroxyl-2,2,6,6-tetramethyl-1-piperidinyloxy) moiety forming a PEO macroinitiator able to polymerize styrene [149].

Difunctional initiators, such as allyl alcohol, where the hydroxyl group is aimed at initiating the polymerization and the double bond at post-reacting with thiol derivatives, were used to polymerize ethylene oxide. The synthesis of  $\alpha$ -amino PEO was achieved [152], as well as the preparation of diblock copolymers like poly(ethylene oxide-*b*-methylidene malonate 2.1.2) forming micelles by self-assembly for the “transportation” of bio-active molecules [153].

Schlaad used  $\alpha$ -methylbenzyl cyanide as a CH-acidic compound to obtain  $\alpha$ -cyano, $\omega$ -hydroxy poly(ethylene oxide) with controlled molar masses up to 2500 g/mol with narrow distributions [97]. The cyanide function was then reduced in  $-\text{NH}_2$  group by  $\text{LiAlH}_4$  (Scheme 34).

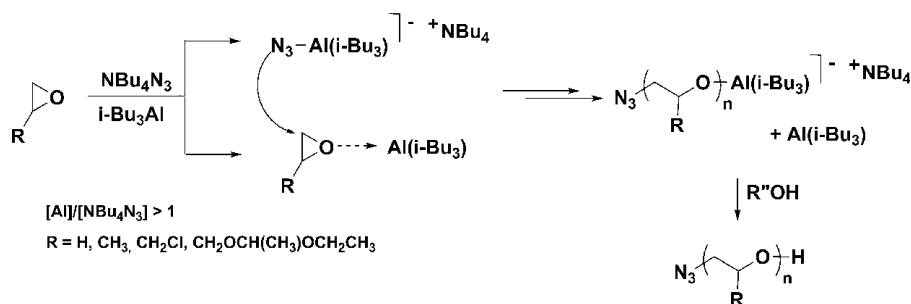
Linear PEO-based random copolymers were synthesised with one single terminal amino group from *N,N*-dibenzyl-2-aminoethanol deprotonated by cesium hydroxide as functional initiator (Scheme 35) [151]. A primary amine function was then released after  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2/\text{C}$  charcoal treatment.

The hydroxyl terminus was also subjected to a chemical modification. At first, this function was activated for nucleophilic displacement by reaction with toluene-4-sulfonyl chloride to yield PEO-tosylate. The tosyl group was then reacted with potassium phthalimide and afterwards the introduced phthalimide end group was finally removed by reaction with hydrazine hydrate [154]. Titrations indicated a degree of amination up to 92%.

**5.1.2.2. Alcene-functionalized polyethers.** Double bonds are known to be stable towards anionic ring-opening

**Table 6**  
Initiators used for anionic polymerization of ethylene oxide leading to allyl head groups.

Alcene-functionalized initiator		Reference
$\text{CH}_2=\text{CH}-\text{C}_6\text{H}_4-\text{CH}_2-\text{OH}$	<i>p</i> -vinylbenzyl ether	[158]
$\text{CH}_2=\text{CH}-\left(\text{OCH}_2\text{CH}_2\right)_2-\text{OH}$	diethylene glycol vinyl ether	[158]
$\text{CH}_2=\text{CH}-\text{O}-\left(\text{CH}_2\right)_4-\text{OH}$	Tetramethylene glycol vinyl ether	[158]
$\text{CH}_2=\text{CH}-\left(\text{CH}_2\right)_9-\text{OH}$	10-undecen-1-ol	[155]
$\text{CH}_2=\text{CH}-\text{CH}_2-\text{OH}$	Allyl alcohol	[153]



**Scheme 36.** Direct synthesis of  $\alpha$ -azido- $\omega$ -hydroxy polyethers using tetrabutylammonium azide/triisobutylaluminum initiating system.

polymerization conditions, but can be further easily modified into various functions which make them attractive. They can be introduced via initiation with an alcohol bearing such a function (Table 6). Allyl alcohol can be deprotonated, for instance, by naphthalene potassium, or 10-undecen-1-ol by sodium hydride. However, during polymerization, double bonds can be isomerized into propenyl group and form  $\text{CH}_3\text{CH}=\text{CHO}^-$  as initiating specie. To avoid this side reaction, polymerization has to occur between 15 and 20 °C, rather than high temperatures typically used with this chemistry [153]. As one example, thiol-ene reactions were applied to PEO oligomers initiated by 10-undecen-1-ol [155]. The synthesis of  $\alpha,\omega$ -diallyl PEO was achieved by reaction between  $\alpha,\omega$ -dihydroxy PEO, deprotonated with diphenylmethyl potassium, and allyl-bromide. Hydrogels were obtained by their post-reaction with octafunctional silsesquioxanes via hydrosilylation [156,157].

**5.1.2.3. Azide-functionalized polyethers.** Most of the PEO azidation routes reported in the literature involve the chemical modification of previously formed hydroxyl-terminated PEO [130,159–161]. Kataoka achieved the synthesis of azido-terminated heterobifunctional poly(ethylene oxide)s in a multistep process, involving ring-opening polymerization of ethylene oxide initiated by allyl alcohol, and subsequent transformation of R-allyloxy and  $\omega$ -hydroxy PEO end groups by a series of chemical reactions [162]. The azide group was introduced by mesylation of the hydroxyl terminus, followed by its subsequent substitution with sodium azide [163,164]. Indeed,

The monomer-activated approach allowed the direct synthesis of a broad series of heterofunctional polyethers bearing an azido head group, and an hydroxy-terminated chain-end, starting from tetrabutylammonium azide in presence of triisobutylaluminum (Scheme 36) [165]. Poly(alkylene oxide)s, protected polyglycidol and polyepichlorohydrin were obtained in this way with

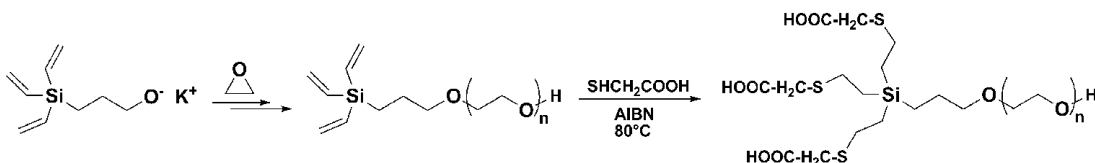
a high functionalization efficiency. Reduction reactions can lead to amine functionalization or Huisgen's coupling reaction with alkyne moieties can be applied [166]. For example, Matyjaszewski's group prepared, clickable PEO stars by combination of this methodology with aqueous AGET ATRP [167].

Using N-heterocyclic carbenes, the synthesis of  $\alpha$ -azido- $\omega$ -hydroxy poly(ethylene oxide) was achieved by termination with trimethylsilyl azide ( $\text{N}_3\text{SiMe}_3$ ) used either as a chain regulator or as a functionalizing quencher (Schemes 21 and 22) [87,88]. Propargyl alcohol was also used as chain regulator giving PEO and poly(propylene oxide) chains with an alkyne function which in turn may react with any kind of compounds bearing an azido group by Huisgen's coupling [88,89].

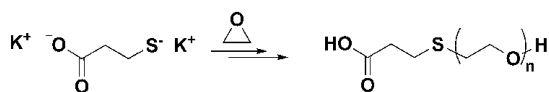
**5.1.2.4. Carboxylic acid-functionalized polyethers.** As discussed by Riffle et al. and demonstrated by other authors, activated carboxyl termini of PEO chains can react with amino groups to attach biological ligands through amide bonds and thus transport active substances [118,155,168–170].

Carboxylic acid groups were, for instance, introduced onto PEO from end-hydroxyl functions by the so-called Jones reactant [171], prepared from  $\text{CrO}_3$  and sulfuric acid, or with sodium chloroacetate in the presence of sodium hydride [155]. Termination of reaction with succinic anhydride can also produce carboxylic end groups [172].

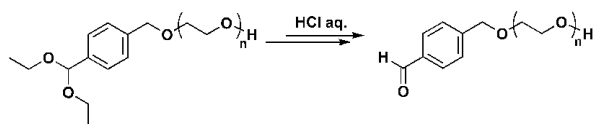
Regarding the functionalization via the initiation step, cyanomethylpotassium yielded carboxylate groups in  $\alpha$ -position by hydrolysis of the cyano moieties in a NaOH solution at 80 °C [154]. Vinylsilylpropanol initiators containing one to three vinyl groups allowed the synthesis of heterobifunctional PEO with 1–3 carboxylic acid groups on one chain end [173]. The chemistry was based on alkali metal alkoxides facilitated by reaction of alcohol initiator with potassium naphthalide. The vinylsilane moieties were



**Scheme 37.** Synthesis of  $(\text{COOH})_3\text{-PEO-OH}$ .



**Scheme 38.** Thiolate-initiated polymerization of ethylene oxide.



**Scheme 39.** Synthesis of  $\alpha$ -aldehyde, $\omega$ -hydroxy poly(ethylene oxide) from an acetal-based initiator.

then modified into carboxylic acid by thiol-ene addition with mercaptoacetic acid (Scheme 37).

The use of dipotassium-3-mercaptopropionate synthesized from 3-mercaptopropionic acid and two equivalents of potassium naphthalide allowed the direct synthesis of  $\alpha$ -carboxy,  $\omega$ -hydroxy poly(ethylene oxide) up to 25,000 g/mol with narrow distribution [174]. Only the thiolate was shown to react; the carboxylate did not participate in the polymerization (Scheme 38).

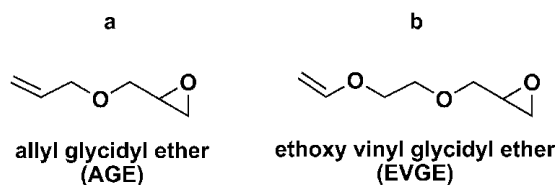
#### 5.1.2.5. Other heterotelechelic functionalized polyethers.

Aldehyde functions were introduced in  $\alpha$ -position using an initiator bearing a protected group, i.e., 4-(diethoxymethyl)benzyl alcohol [175]. After deprotonation with potassium naphthalene, EO polymerization, followed by deprotection by an acidic treatment, gave the benzaldehyde moiety (Scheme 39). Corresponding aldehyde groups were shown to react with primary amines under physiologic conditions leading to the formation of PEO derivatives featuring stable imine bound with biomacromolecules.

Epoxy functions can be introduced to chain extremities by reaction between hydroxy-end groups and epichlorohydrin [171]. Hyperbranched polyglycerol containing five-membered terminal cyclic carbonate groups were also prepared by reaction of their terminal vicinal hydroxyls with dimethyl carbonate, in the presence of potassium carbonate. They showed a reactivity with amine derivatives forming hydroxyurethane functions [176].

Hydroxy end-groups can be transformed into vinyl sulfonate moieties in order to favor reactions with amines, alcohols or amino-acids which can further interact with peptides and proteins [177]. They can also be reacted with maleimide which is interesting in the field of biosensors, targeted drug delivery and enzyme immobilization [178–181]. Reaction of vinylsulfonates with mercapto groups yields stable thioether linkages. A direct synthesis of maleimide-PEO-OH is generally prohibited due to the sensitivity of alcohol-based maleimide initiator to basic conditions. Nevertheless, a double metal cyanide complex catalyst was proved efficient to polymerize EO with retention of the maleimide functionality [134,182,183].

The method based on chemical modification of previously formed polyethers is the most common way to get various functionalized and reactive structures. In many cases a simple chemistry can be used which makes this way very attractive. But, in the other cases, the interest is much more limited particularly for an industrial application. The



**Scheme 40.** Reactive epoxides bearing double bonds.

recent advances in the control of the anionic polymerization of epoxide offer nowadays direct routes to prepare reactive and new polymers. The research and development of novel technologies will certainly contribute to an increasing use of such recent methods.

## 5.2. Functional polyethers by monomer insertion

The functionalization along the polyether backbone is achieved through the use of monomers bearing pendant reactive functions, followed or not by post-chemical modifications. The discussion will focus on the main reactive functions including alcohol, amine, double bonds and a few others, allowing the use of such polyethers as reactive precursors.

### 5.2.1. Synthesis of polyethers bearing pendant double bonds

Double bonds exhibit great interest as they can be post-modified easily. Monomers bearing allyl functions, like allyl glycidyl ether (AGE), can be directly used to synthesize polyethers with pendant double bonds (Scheme 40a). One way to synthesize poly(allyl glycidyl ether) (PAGE) by AROP is to use alkali metal alkoxides [25,184]. Generally, molar masses lower than 10 000 g/mol and long polymerization times are required. However, ammonium salts/trialkylaluminum systems [185] described above allowed getting controlled and high molar mass structures in a few hours. From potassium alkoxide/naphthalenide initiators Campos, Lynd and Hawker could also obtain molar masses up to 100,000 g/mol with low dispersity within 20–144 h [186]. Isomerization of the allyl side chain was observed and dictated by the polymerization temperature. A decrease of temperature lower than 40 °C, related with a time increase, allows the extent of isomerization to be reduced to essentially 0 °C under either in melt or solution conditions.

Allyl glycidyl ether is often copolymerized with other epoxides, in particular with ethylene oxide to increase the biocompatibility of PAGE in the field of biomedicine. Several copolymers prepared and their respective initiating systems are shown in Table 7.

The most commonly post-modification method used in order to obtain pendant reactive functions is thiol-ene reaction. It enables the introduction of functions such as  $-\text{NH}_2$  [187–189],  $-\text{COOH}$  [189],  $-\text{OH}$  [189], or specific groups like saccharide groups [191] and imidazole functions [193]. Hydroxyl groups were also obtained by oxidation of the double bonds. Cyclocarbonate functions were introduced using  $\text{CO}_2$  at low pressure [185]. Moreover, the formation

**Table 7**

Poly(allyl glycidyl ether)-based copolymers.

Copolymers	Initiator system	Reference
P(AGE-co-EO)	Diethylene glycol/KOH	[187,188]
P(AGE-co-EO)	CsOH	[189]
P(AGE-co-EEGE)/P(AGE-co-tBuGE)	t-BuOK	[184]
P(AGE-co-EO)	POE/NaH	[190]
P(AGE-co-EO)	POE monomethyl ether/NaH	[191]
P(AGE-co-EO)/P(AGE-b-EO-b-AGE)	CsOH	[192]
P(AGE-b-EO-b-AGE)	POE/NaH	[193]
P(AGE-b-ester)	2-ethyl-4methylimidazole	[194]
P(AGE-co-ECH)	NOct <sub>4</sub> Br/i-Bu <sub>3</sub> Al	[185]

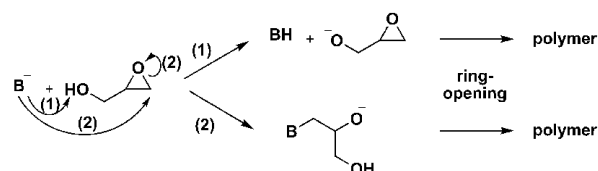
of crosslinked structures was induced by reacting double bonds under UV irradiation [190].

Another monomer, ethoxy vinyl glycidyl ether (EVGE) was shown to be selectively polymerized (Scheme 40b). EVGE was also copolymerized with ethylene oxide to give functional polyethers able to be post-modified [195].

### 5.2.2. Synthesis of polyethers-polyols

Pendant hydroxyl functions allow polymers to be soluble in water or to be post-modified. Due to the aforementioned characteristics, these polymers are very attractive for biological and medical applications [196]. Polyethers with hydroxyl pendant groups are predominantly synthesized from glycidol. This bifunctional monomer presents the advantages to contain both epoxy and hydroxyl groups and can be synthesized from glycerol which is a by-product of the transesterification of vegetable oils used for the production of biodiesel [197].

Direct reaction of glycidol with bases such as triethylamine, pyridine, alkali metal hydroxide, and sodium methoxide leads to two distinct initiation steps at room temperature (Scheme 41) [198–202]. The first way corresponds to a basic attack towards the hydrogen atom of the hydroxyl group, and thus an oxyanion bearing an epoxy group is formed. The second way is the attack of the base over the methylene of the epoxide leading to ring-opening. Hyperbranched polyethers with a high functionality in hydroxyl groups were achieved [203]. In the literature several uses for polymers are reported, in particular as highloading supports for substrates, reagents, and

**Scheme 41.** Initiation mechanisms of glycidol in presence of a base.

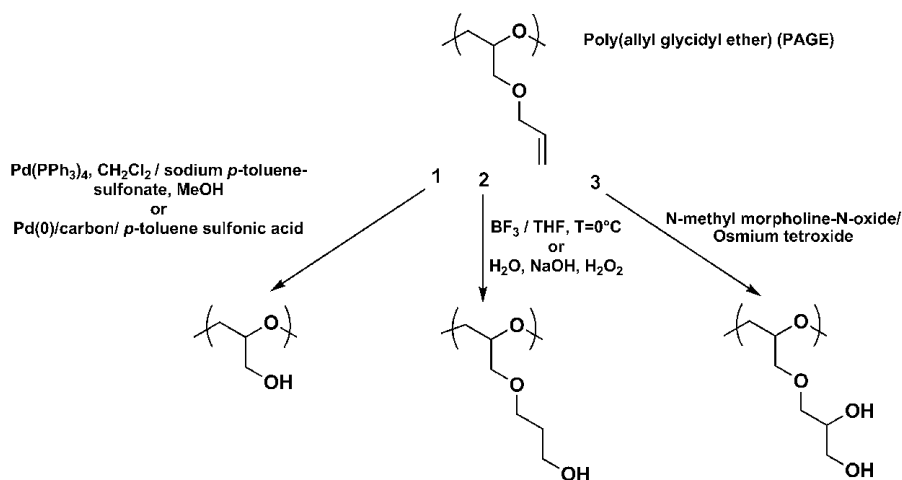
catalysts [204] as well as for storage or encapsulation of active molecules in medical field [205–208] or of silver nanoparticles [209]. Hyperbranched polyglycidol and PEO-based copolymers were also shown to mimic antifreeze properties of proteins [210].

In order to access to well-defined linear polyols derived from glycidol, hydroxyl functions of that monomer had to be protected. Representative protected monomers are given in Table 8. Deprotection of hydroxyl groups is performed by various acidic treatments. Noncommercial poly(ethoxy ethyl glycidyl ether) is easily modified in polyglycidol with diluted solution of hydrogen chloride in methanol or THF, at room temperature, in a few hours. Under similar conditions, the deprotection of commercial *tert*-butyl glycidyl ether demands longer periods of times and higher temperatures (70 °C). The use of trifluoroacetic acid accelerates deprotection. Such monomers can also be used as termination reagents of living PEO chains for instance, allowing the formation of 2 or 3 hydroxyl terminal groups [211,212].

**Table 8**

Monomers used for the synthesis of linear polyglycidol and its derivatives.

Hydroxy-protected glycidol		Reference
	Ethoxyethyl glycidyl ether (EEGE)	[77,177,213,214]
	<i>tert</i> -butyl glycidyl ether ( <i>t</i> -BuGE)	[77,184]
	Allyl glycidyl ether (AGE)	[184,215]
	Isopropylidene glyceryl glycidyl ether (IGG)	[213]



**Scheme 42.** Synthesis of polyethers polyols from chemical modification of poly(allyl glycidyl ether).

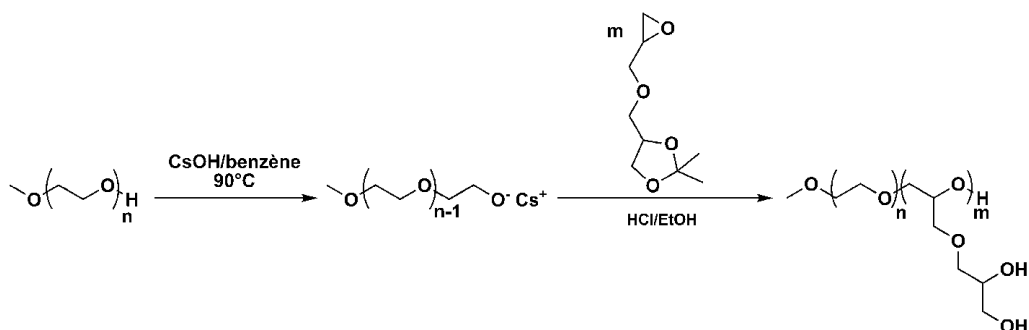
Dworak, Tsvetanov et al. [129,206,216–219] as well as Möller et al. [177,184,220] investigated the AROP of ethoxyethyl glycidyl ether using metal alkali alkoxides such as KOH, CsOH, and *t*-BuOK. These systems enabled the synthesis of linear polyols up to 30,000 g/mol. According to time, quantitative conversion was obtained between 17 and 48 hours, depending on targeted molar masses, and required high temperatures (up to  $120^\circ\text{C}$ ). Due to the initiating systems used, residual transfer reactions were observed, limiting somehow the control over the structures. Keul, Möller et al. studied in detail in 2009 the influence of temperature and of different initiating systems like 3-phenylpropanol/sodium 3-phenyl propanolate and *sec*-butyllithium/phosphazene base towards transfer to monomer reactions [107]. In all cases, basicity was responsible for the observed limitation. In 2010, linear polyglycidols with molar masses up to 85 000 g/mol, starting from ethoxyethyl glycidyl ether (EEGE) were obtained using  $\text{NOct}_4\text{Br}$ /triisobutylaluminum as initiating system at room temperature and in a few hours [77]. The formation of an initiating and propagating “ate” complex of weak basicity was proposed to explain the decrease of side reactions.

With allyl glycidyl ether as monomer, several ways can be used to obtain polyethers polyols. For instance, polyglycidol was obtained by release of the allyl group, Scheme 42

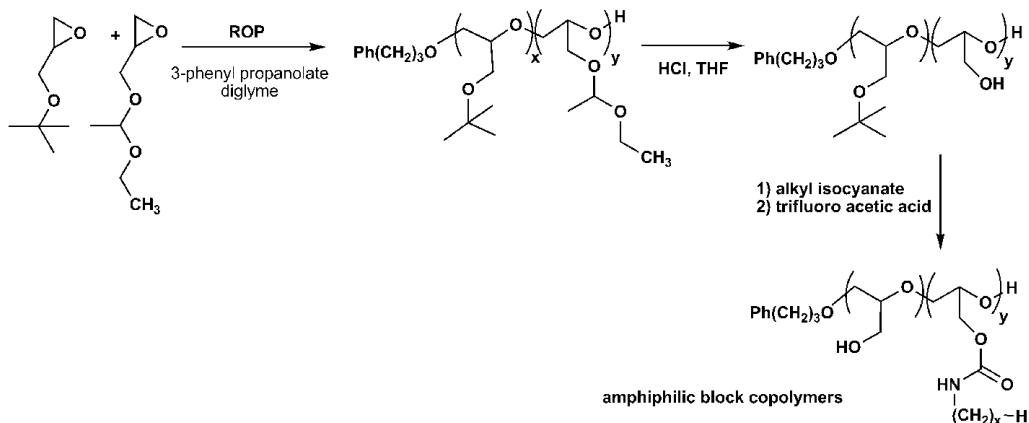
route 1. Double bonds were also chemically modified giving one or two pendant hydroxyl functions per monomer unit, Scheme 42 routes 2 and 3 respectively [129,184].

Isopropylidene glyceryl glycidyl ether (IGG) was also used as a protected form of glycidol. Each unit of IGG enables the formation of two hydroxyl groups after deprotection with hydrogen chloride [151,221]. The synthesis of poly(ethylene oxide-*co*-isopropylidene glycerol glycidyl ether) with molar masses up to 10,000 g/mol was achieved (Scheme 43) [151,184]. Due to many pendant –OH functions, such type of polyethers are of great interest for applications in biomedical area like encapsulation, storage, transport of bio-active molecules. . .).

Various binary block copolymers based on protected glycidol and allyl glycidyl ether with molar masses up to 5000 g/mol were obtained using 3-phenyl propanolate as initiator. By selective removal of the protective group of EEGE and subsequent functionalization of the free hydroxyl groups, followed by a second deprotection of the second block, well-defined functional block copolymers were achieved. As a first example, propargyl moieties were introduced after deprotection of one block and reaction of –OH groups with propargyl bromide to further conduct Huisgen’s coupling. The second block was then deprotected under different conditions providing additional



**Scheme 43.** Synthesis of poly(ethylene oxide) polyols using isopropylidene glyceryl glycidyl ether.



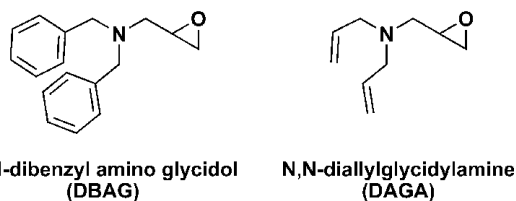
**Scheme 44.** Synthesis of amphiphilic block copolymers from protected polyglycidol.

-OH groups in the copolymer structure [184]. In a second example, starting with P(*t*-BuGE-*b*-EEGE) copolymer, Keul, Möller et al. selectively deprotected EEGE units and reacted hydroxyl groups with isocyanate ones bearing different alkyl chains. *t*-BuGE units were then deprotected by trifluoroacetic acid. Copolyethers having hydrophilic (polyglycidol) and hydrophobic (alkyl-urethane) segments with specific thermo properties were formed with molar masses up to 10,000 g/mol (Scheme 44) [222]. In a similar way, Dworak and Walach worked up amphiphilic block copolymers, namely poly(*t*-BuGE-*b*-glycidol) starting from pentaerythritol [216]. The synthesis of four arms polymers with controlled lengths could be achieved.

Thus, glycidol is polymerized with various epoxides, i.e., ethylene and propylene oxides to get statistical [223] or block [224–226] copolymers. Hydroxyl groups are modified by utilizing various organic reactions such as substitutions, transesterifications and others in order to introduce common reactive functions like carboxylic acid, azide, allyl or thiol moieties [226].

### 5.2.3. Synthesis of polyethers bearing pendant amino groups

Polyethers bearing primary amino groups are generated by using initiators with protected amines. Tertiary amines are known to protect primary amines. Frey and co-workers described synthesis of *N,N*-dibenzyl amino glycidol (DBAG) or *N,N*-diallylglycidylamine (DAGA) (Scheme 45) prepared from epichlorohydrin and *N,N*-dibenzylamine or *N,N*-diallylamine respectively [227,228]. The synthesis of copolymers based on EO and DBAG or DAGA was next performed using cesium alkoxide as initiator giving controlled



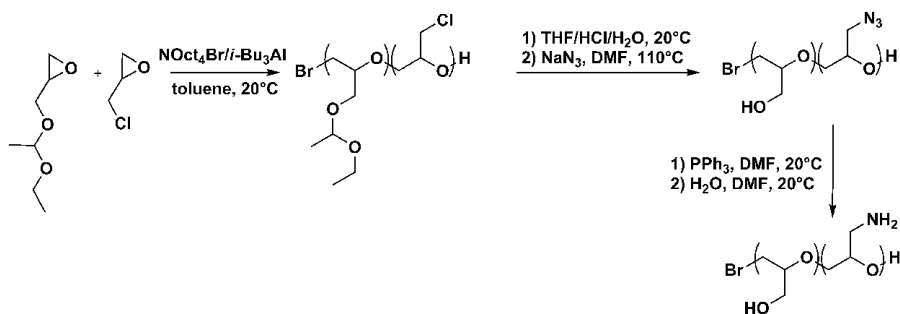
**Scheme 45.** Co-monomers for the synthesis of amino-functional poly(ethylene oxide).

copolyethers with molar masses up to 10,000 g/mol. If the “DBAG approach” was shown to be relatively “heavy”, the DAGA one possesses major advantages for the preparation of multiamino-functional PEOs via protected glycidylamines. Indeed, the monomer can be obtained in a facile one-step procedure on a large scale, time for deprotection is reduced from 1–8 days to 4 h using a two-step one-pot procedure via isomerization of allylamine to enamine moieties and subsequent acidic hydrolysis. Finally, yields were improved from 30–50% to over 85%. The obtained primary amines were derivatized using acetic anhydride, in a model reaction, proving accessibility for coupling reactions.

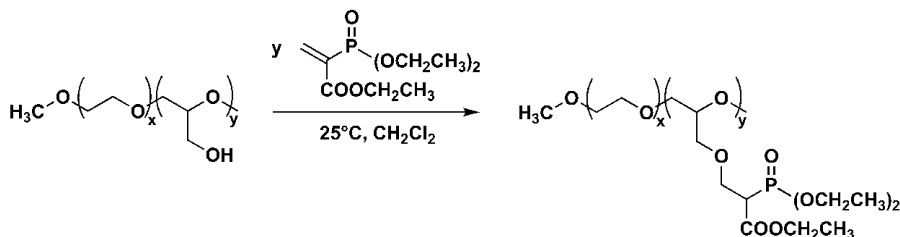
Pendant amine functions can also be introduced from chlorine atoms. Statistical or block copolyethers, made by  $\text{NOct}_4\text{Br}/i\text{-Bu}_3\text{Al}$  systems and having both hydroxy and amine pendant groups, were brought, respectively, by ethoxyethyl glycidyl ether (protected glycidol) and epichlorohydrin monomers (Scheme 46) [229]. Chlorine atoms were subsequently transformed into azido groups using sodium azide. Consequent reaction with triphenylphosphine enables quantitative formation of amino groups. Such type of copolymers was proposed to enable selective electrophilic reactions due to the difference of reactivity between -OH and -NH<sub>2</sub> functions.

### 5.2.4. Other functionalized polyethers

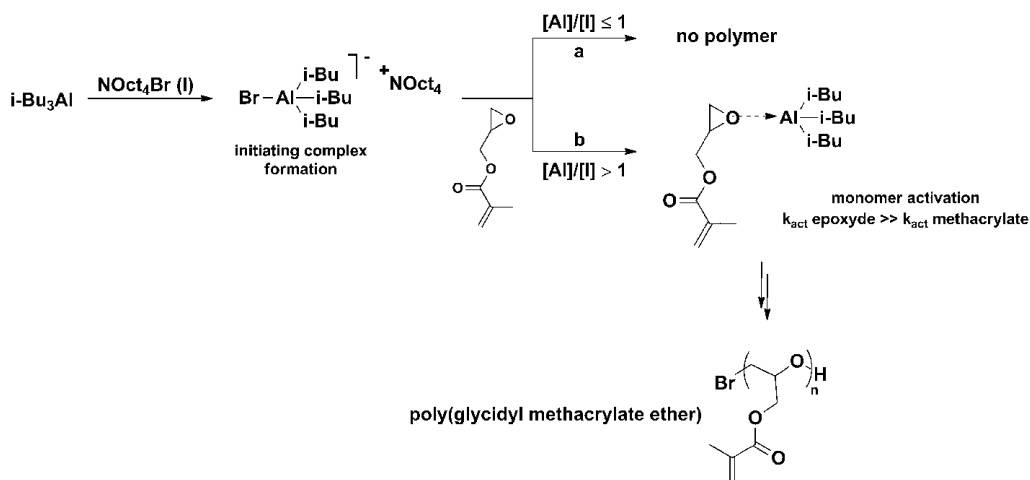
Phosphonic acids are known to be efficient anchoring groups for the formation of self-assembled monolayers on a wide range of metal oxides [230] due to strong mono-, di- or tri-dentate binding to the surface [231–233]. They are also known to reduce corrosion of steel in water purification or to promote adhesion [234,235]. They can be obtained by hydrolysis of phosphonate moieties. Penczek reacted 2-diethyl phosphonate ethyl acrylate with alcohol groups of poly(ethylene oxide-*b*-glycidol) block copolymers prepared from the cesium alkoxide chemistry (Scheme 47). A dealkylation reaction followed by a hydrolysis allowed the formation of a dihydrophilic ionic-nonionic diblock copolymer with -PO(OH)<sub>2</sub> and COOH functions at the same carbon atom. A straightforward method was proposed for the partial introduction of pendant phosphonate groups into linear polyglycidol. A Michael-type addition



**Scheme 46.** Synthesis of poly(glycidol-co-glycidyl amine) from protected glycidol and epichlorohydrin units.



**Scheme 47.** Addition of 2-diethyl phosphono-ethyl acrylate on poly(ethylene oxide-co-glycidol) copolymers.



**Scheme 48.** Polymerization of glycidyl methacrylate initiated by tetraoctylammonium bromide/triisobutylaluminum system.

under alkaline conditions permits to react hydroxyl functions with non-activated diethyl vinyl phosphonate [236]. Remaining  $-OH$  groups can be used to introduce additional functionalities to prepare tailor-made polymers carrying phosphonic acid for covalent binding to different surfaces.

Selective polymerization of the epoxide function of glycidyl methacrylate (GMA) was achieved by the monomer activated anionic approach, using tetraoctylammonium bromide/triisobutylaluminum initiating system in toluene at  $20^{\circ}C$ . Quantitative and controlled synthesis of poly(glycidyl methacrylate ether) (PGMA), up to 20 000 g/mol, with pendant methacrylate functions, was achieved by opening of the epoxide (Scheme 48). The copolymerization of GMA with glycidyl methyl ether (GME) in similar conditions gave copolyethers with lower critical solubility

temperature depending on the ratio  $[GME]/[GMA]$ . Cross-linked structures could be obtained after heating or UV irradiation [237].

## 6. Conclusion

Epoxide derivatives constitute an interesting and rich family of monomers that are readily prepared by epoxidation of olefins or issued from renewable resources like glycerol. Functional oxiranes and/or functionalities that can be introduced into a poly(ethylene oxide) backbone put nowadays more values to the polyethers synthesized. Due to the recent advances in their controlled ring-opening polymerization, functional and reactive polyethers as well as block copolymers of various epoxides can now readily



be obtained, opening opportunities to use those as precursors in the formation of new and complex macromolecular architectures and in applications in plethora of domains, i.e., biomedicine, surfactants. Tuning the basicity of the active species and activating the monomer by metallic additives enable to decrease side reactions, which increase the molar masses obtained, and to increase kinetics. The use of organic initiators or catalysts to trigger the metal-free ring-opening polymerization of epoxides still suffers from strong limitation and might be a forthcoming challenge.

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