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Systematic investigation of alkyl sulfonate initiators for the cationic ring-opening polymerization of 2-oxazolines revealing optimal combinations of monomers and initiators

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ABSTRACT

A systematic kinetic investigation of the living cationic ring-opening polymerization (CROP) involving 2-ethyl-2-oxazoline, 2-methyl-2-oxazoline, and 2-phenyl-2-oxazoline employing a series of alkyl sulfonate initiators with variation of the alkyl initiating fragment (methyl, ethyl, *iso*-propyl) and the leaving group/counterion (tosylate, nosylate, triflate) is reported. The study reveals that the initiation and propagation reactivity increases in the order tosylate < nosylate < triflate. Slow initiation is observed for EtOTs, while EtONs is a sufficiently fast initiator even for 2-phenyl-2-oxazoline. It is thus recommended to avoid the use of alkyl tosylates, except MeOTs, as initiators for the CROP of 2-alkyl-2-oxazolines. Although triflates are generally the best initiators, the use of the more stable and easier synthesizable nosylates provides a suitable alternative for the design of functional initiators for the CROP of 2-alkyl-2-oxazolines.

1. Introduction

The living cationic ring-opening polymerization (CROP) of 2-substituted-2-oxazolines was first described in the mid 1960s by four independent research groups [1–4]. The resulting poly(2-oxazoline)s, which can be regarded as pseudo-polypeptides, have received considerable attention in recent years for biomedical applications [1,2] and as thermoresponsive materials [3]. Telechelic poly(2-oxazoline)s can be synthesized utilizing functional initiators or terminating agents [4]. As illustrated in Scheme 1, the CROP of 2-oxazolines, selecting 2-ethyl-2-oxazoline as representative monomer, is initiated by an electrophile that reacts with the endocyclic nitrogen atom of the oxazoline ring to form an oxazolinium cation. Propagation occurs via nucleophilic attack of the monomer on the oxazolinium species, resulting in ring-opening and the formation of an amide by isomerization. Typical initiators are alkyl or benzyl halides including chlorides [5], bromides [5] and iodides [6] or alkyl sulfonates such as *p*-toluenesulfonates (tosylates) [7], *p*-nitrobenzenesulfonates (nosylates) [8] and trifluoromethanesulfonates (triflates) [9].

To obtain well-defined polymers with narrow molar mass distributions and to gain good control over the polymerization, initiation should be quantitative and fast with respect to propagation (initiation rate coefficient, $k_i \gg$ propagation rate coefficient, k_p). These requirements can be fulfilled using a simple electrophilic initiator such as methyl tosylate. When employing a functional initiator, which opens the path to more complex macromolecular architectures, however, this task becomes more challenging. For example, slow initiation has been reported for

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dodecyl and oleyl tosylate [10,11], 2-(*p*-toluenesulfonato)ethyl methacrylate [12] as well as tosylated poly(dimethylsiloxane-co-methylhydrosiloxane) macro-initiators [13]. This issue of slow initiation could be partially resolved by the use of the respective nosylates [11,12] or triflates [10,14]. The importance of careful selection of the alkyl group was clearly demonstrated by the comparison of butynyl and propargyl tosylate where only the latter one exhibited a sufficiently fast initiation [15]. Despite the aforementioned experimental studies there is still a lack of a systematic investigation of initiators for the CROP of 2-oxazolines with variation of both the alkyl group and the sulfonate leaving group, acting as counterion during the polymerization. Nonetheless, based on three independent reports on using sulfonate esters of pentaerythritol for the preparation of star-shaped poly(2-oxazolines) [16–18] it may be suggested that nosylates and triflates are better initiators than tosylates.

In this work, a systematic kinetic investigation of the CROP of 2-ethyl-2-oxazoline (EtOx), 2-methyl-2-oxazoline (MeOx) and 2-phenyl-2-oxazoline (PhOx) is presented employing a series of alkyl sulfonate initiators with variation of the alkyl initiating fragment (methyl, ethyl, *iso*-propyl) and the leaving group/counterion (tosylate, nosylate, triflate). Alkyl sulfonates are chosen because it was previously shown that with such initiators the CROP proceeds exclusively via the cationic species shown in Scheme 1. A mixture of covalent and ionic species is thus avoided and, therefore, we favor these initiators over halide initiators that often lead to combined cationic and covalent propagating species [5,19]. The propagation rate coefficients are calculated from the linear first-order kinetic plots in case of fast initiation while possible slow initiators are identified based on non-linear first order kinetic plots for which regression analysis was used to determine initiation and propagation rate coefficients.

2. Experimental section

2.1. Materials and instrumentation

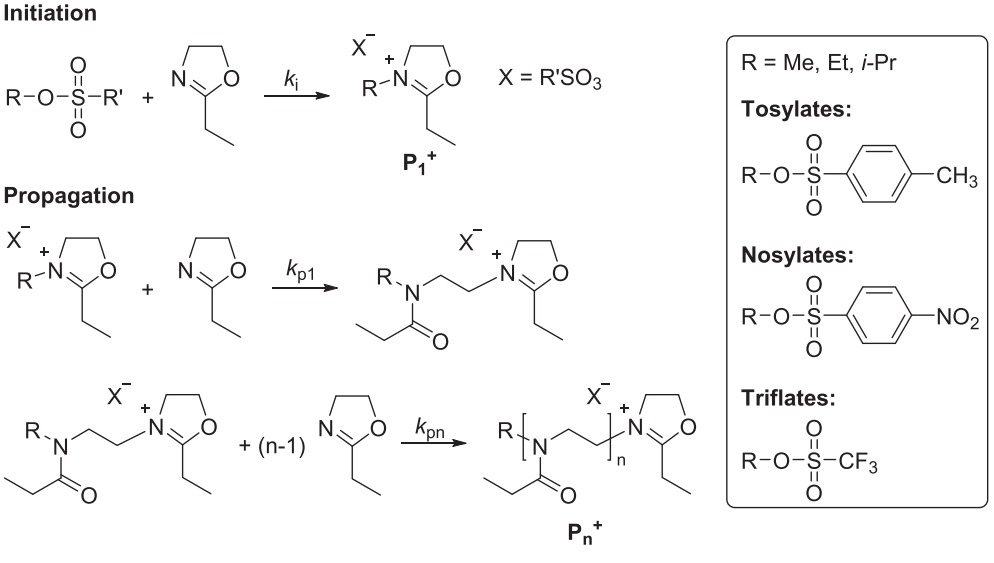
Acetonitrile (Aldrich) was dried in a solvent purification system (JC Meyer) before use as a polymerization solvent. 2-ethyl-2-oxazoline (EtOx), 2-methyl-2-oxazoline (MeOx) and 2-phenyl-2-oxazoline (PhOx, Aldrich) were distilled over barium oxide and stored under argon. Methyl tosylate, ethyl tosylate, methyl triflate and ethyl triflate (Aldrich) were distilled and stored under argon. Methyl nosylate [20], ethyl nosylate [21], and *iso*-propyl nosylate [22] were synthesized according to literature procedures, recrystallized twice from ethanol, dried under high vacuum and stored under argon. All other chemicals were used as received.

All polymerizations were performed in capped vials in a microwave reactor (Biotage) equipped with an infrared (IR) temperature sensor.

Gas chromatography (GC) was performed on a 7890A from Agilent Technologies with an Agilent J&W Advanced Capillary GC column (30 m, 0.320 mm, and 0.25 μm). Injections were performed with an Agilent Technologies 7693 auto sampler.

Size exclusion chromatography (SEC) measurements were performed on an Agilent 1260-series equipped with a 1260 ISO-pump, a 1260 Diode Array Detector (DAD), a 1260 Refractive Index Detector (RID), and a PSS Gram30 column in series with a PSS Gram1000 column inside a 1260 Thermostated Column Compartment (TCC) at 50 °C using dimethylacetamide (DMAc) containing 50 mM of LiCl (flow rate of 0.59 mL min^{-1}) as solvent. Molar masses were measured against poly(methyl methacrylate) standards.

Matrix assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) was performed on an Applied Biosystems Voyager De STR MALDI-TOF



Scheme 1. Left: Schematic representation of the mechanism of the CROP of 2-oxazolines initiated by alkyl sulfonates; 2-ethyl-2-oxazoline is selected as representative monomer. The chemical structures of the investigated initiators are shown on the right.