Unlocking the potential of poly(ortho ester)s: A general catalytic approach to the synthesis of surface erodible materials.

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Abstract: Poly(ortho ester)s, POEs, are well established as displaying surface eroding properties and hence present unique opportunities for controlled release and tissue engineering applications. Their development and wide spread investigation has however been severely limited by challenging synthetic requirements *via* unstable intermediates and is therefore highly irreproducible. Herein, we present the first catalytic method for the synthesis of POEs using air and moisture stable vinyl acetal precursors. The synthesis of a range of POE structures is demonstrated including those that are extremely hard to achieve by other synthetic methodologies. Furthermore, we demonstrate that the application of this chemistry to efficiently install functional groups *via* ortho ester linkages to an aliphatic polycarbonate.

The use of biodegradable polymers for controlled drug release and tissue engineering represents one of the most important advances in biomedicine.[1-3] The ideal material would display a surface erosion profile in which hydrolysis occurs faster than water ingress into the materials and results in the sequential erosion of the surface layers.[4,5] Such profiles enable idealized zero order release profiles and predictable materials properties throughout degradation.[7] Despite this, the paucity of easily accessible surface eroding materials have led to the extensive study of bulk eroding materials such as poly(lactic acid) and poly(ε-caprolactone),[6-8] in which water diffusion into the material occurs at a comparable or faster rate to hydrolysis. This results in a non-linear mass loss over time, amplified by autocatalysis from trapped degradation products, which in turn lead to non-linear release of encapsulants, significant burst effects and uncontrolled loss of mechanical stability.

Despite the clear potential advantages of surface erodible polymers, examples are limited to only a few families such as poly(anhydride)s[9,10] and poly(ortho ester)s, (POEs).[11,12] The milder degradation products present POEs as a potentially more attractive choice for *in vivo* applications and, indeed, POE types III and IV (Figure 1) have shown significant promise in ocular[11-14] as well as gene delivery.[11,12] Typically however, their synthesis involves either step-growth polymerization of the highly air and moisture sensitive diketene acetal (3,9-bis(ethylidene-2,4,8,10-tetraoxaspiro[5,5]undecane (DETSOU, Scheme 1) with a diol[15] or the transesterification between a triorthoester and triol,[16] both of which present significant synthetic challenges to produce repeatable polymer characteristics, likely resulting from the high reactivity of ketene acetal monomers that compromises the high levels of purity required for successful step-growth polymerization. More recently, some success has been achieved by the preparation of ortho ester-containing monomers by multi-step syntheses to create poly(ortho ester amide)s and poly(ortho ester urethane)s.[17] Despite these advances, the further development of general routes to POE-based materials that overcome the challenging synthetic procedures that are required to access them would greatly enable their wider study.

Herein, we present a facile, catalytic methodology for the synthesis of POEs *via* easy to access, air and moisture stable intermediates. Furthermore, we show this unique approach to be the only general synthetic pathway that can yield POEs of types II, III and IV, is suitable to increase the range of potential feedstocks as well as to functionalize other materials. The development of a more general and simple synthetic methodology to access POEs will more readily enable their wider study and hence potentially address some of the outstanding problems that face the current biomedical industry including enhanced control over release rate and increase efficiency of delivery systems.

Inspired by the wealth of ruthenium-based double-bond migration catalysis in the literature,[18,19] including for the synthesis of ketene acetals,[20,21] we postulated that a 1,3-dihydride shift of a vinyl acetal with catalysts such as $[RuHCOCl(PPh_3)_3]$ (**2**)[20] and $[RuHCl(PPh_3)_3]$[18] (**3**) would enable *in situ* olefin isomerization catalysts in the presence of alcohols without the need to isolate the highly sensitive ketene acetal intermediate. Initially, model reactions focused on the *in situ* isomerization of the commercially-available 5,5-dimethyl-2-vinyl-1,3-dioxane, thus avoiding isolation of the highly reactive DETSOU monomer (Scheme 1). With excess 1,6-hexanediol it was found that while **2** catalyzed the formation of the diorthoester to 99.7% conversion at 45 °C in 6.5 h, using analogous catalyst loading **3** only gave similar conversion at the same rate when carried out at 85 °C (See ESI). Moreover, no side-products/side-reactions could be observed by ^{1}H and ^{13}C NMR spectroscopic analysis of the model reaction crude mixture and only the expected product was formed.

The optimal conditions found for each catalyst from the model reaction were then applied to the step-growth polymerization of the difunctional monomers **1** and 1,6-hexandiol (Scheme 1). It is noted that **1** is obtained in a straightforward one-step reaction in 56% yield while DETSOU was obtained *via* a difficult two-step

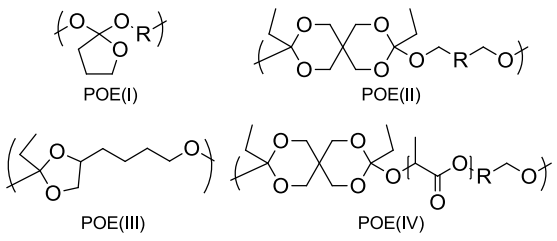

Figure 1. Types of poly(ortho ester), POE.

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[†] This manuscript is dedicated to the memory of Mr. Jack Everson, a former undergraduate student who contributed to the project (deceased 16/09/2012).

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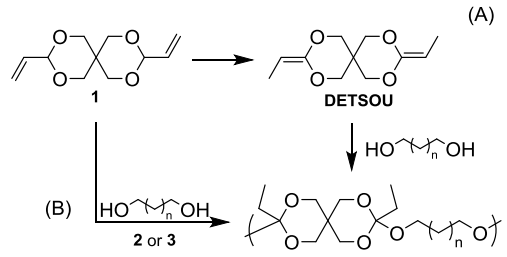


Scheme 1. Synthesis of POE(II) from **1** and diols (A) via DETSOU; (B) using catalytic synthesis (**2** = $[RuHCOCl(PPh_3)_3]$; **3** = $[RuHCl(PPh_3)_3]$).

synthetic procedure in ~40% overall yield.[15] Initially, the polymerization was attempted using catalyst **2**. While **2** was active at a lower temperature and hence limited the chance of polymer degradation, only oligomers were isolated (<1 kDa as determined by size-exclusion chromatography (SEC) analysis in $CHCl_3$). Interestingly, POE(II) of significantly higher molecular weight was only achieved when catalyst **3** was employed at an increased temperature. Monitoring the reaction by SEC analysis revealed that the molecular weight of the polymer plateaued after *ca.* 4 h, reaching a weight-averaged molecular weight, M_w of 9.5 kDa (Figure S2). The generality of the approach was demonstrated by the polymerization of **1** with 1,10-decanediol under comparable conditions and yielded a polymeric material that displayed M_w = 8.1 kDa (Figures S3 and S4). Thus POE(II) type materials were accessible without the requirement of the synthesis and isolation of the DETSOU intermediate.

In order to display that this methodology could be extended to a wider range of POE structures and to take advantage of the relatively low molecular weights, we sought to extend our studies to the polymerization of monomers that would yield POEs of type III. At low molecular weights, the inherently flexible polymer backbone means that POE(III) are typically semi-solids with low glass transition temperatures (T_g) which can be conveniently mixed with a drug without heating and/or a processing solvent, a property particularly important for incorporation of sensitive therapeutics.[12,22] Despite offering numerous advantages, the potential to use them is again limited by the difficulty in polymer synthesis and the reproducibility of the materials which led to development of POE(III) largely being ceased in the late 1990s.[11,12] We postulated that our methodology could be applicable across all POE platforms and sought to investigate this further.

Preparation of bifunctional, A-B, monomers (**7** - **9**) that consist of both the cyclic vinyl acetal and alcohol moieties was achieved in two simple steps (Scheme 2). Following success with POE(II) from **1**, initially, we focused on the retention of the 6-membered ring precursors. Firstly, the triols (**4 - 6**) were synthesized by simple esterification between bis-hydroxymetholpropionic acid (bis-MPA) and corresponding bromoalkanol in DMF. This reaction reached maximum conversion at *ca.* 85% (with 15% bis-MPA starting material). The crude mixture was ring-closed directly in the subsequent reaction with acrolein to yield the bifunctional monomers **7** – **9**. The ^{1}H NMR spectra of the bifunctional monomers (Figure S5 – S7) showed the appearance of vinyl protons (δ = 5.89 - 5.26 ppm) which indicates a successful ring closure. Notably, as a consequence of the existence of two chiral centres in the 1,3-dioxane ring, two diastereomers were observed in each case, evident by the occurrence of two distinct sets of vinyl signals and dioxane ring proton resonance. Polymerization of the bifunctional monomers was undertaken with the optimized conditions for catalyst **3** (Table 1). All materials were characterized by ^{1}H NMR spectroscopy (Figures S9, S11 and S13) and SEC (Figures S10, S12 and S14) which demonstrated that the polymers displayed M_w in the range of 8 to 11 kDa. The formation of *endo* and *exo* isomers of the ortho ester unit by addition of the alcohol function above or below the planar ketene acetal function is evidenced by the splitting of the hydrogen atom signals of the 1,3-dioxane ring in the ^{1}H NMR spectra of the polymers. Each polymerization was repeated to demonstrate reproducibility, in stark contrast to typical POE(III) by transesterification which cannot be reproducibly prepared.[11,12]

Table 1. Synthesis of POE(III) (P7 – P14) from bifunctional monomers 7 - 14.[a]

	M_w (kDa)[b]	M_n (kDa)[b]	$Đ_M$[b]	T_g (°C)[c]	T_m (°C)[c]
P7	8.0	5.2	1.53	18	-
P8	10.5	7.2	1.47	-23	-
P9	11.0	6.8	1.62	-39	-
P10	21.2	12.1	1.75	-32	-
P11	23.1	10.0	2.32	n.d.	-
P12	28.8	15.3	1.88	-57	41
P13	43.2	24.6	1.75	-59	51
P14	48.8	21.3	2.28	-59	61

[a]conditions: Catalyst **3**, 1,4-dioxane or toluene, 85 °C, 7 - 48 h; [b]Determined by SEC ($CHCl_3$ or THF against PS standards); [c]Determined by DSC analysis

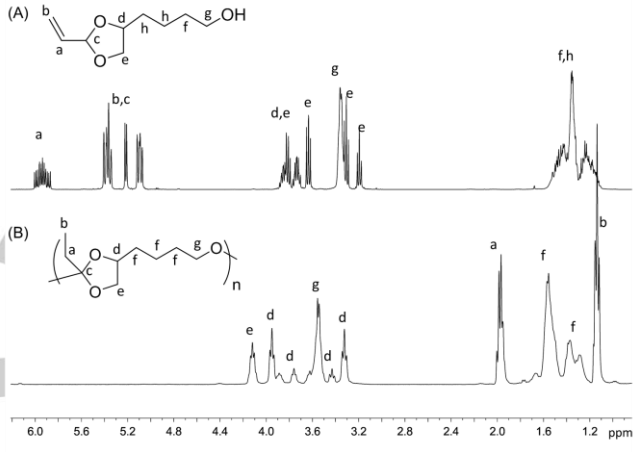
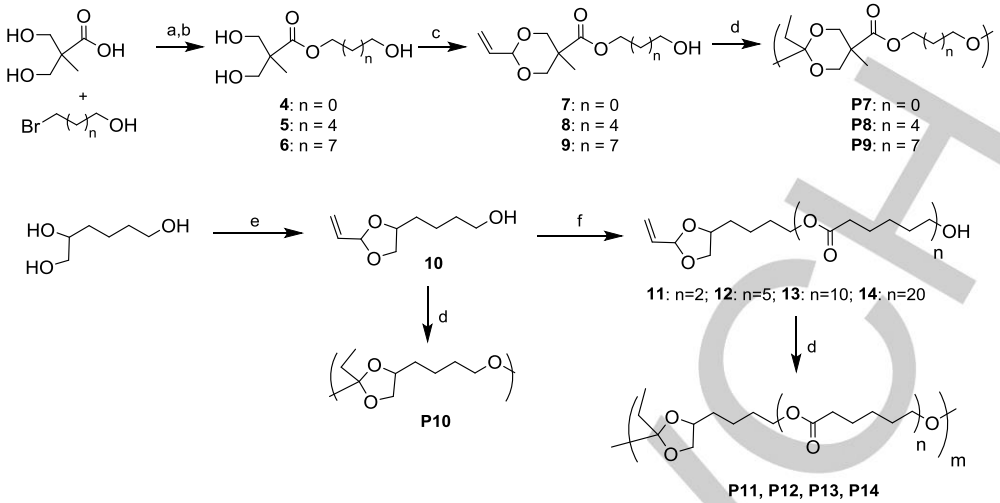


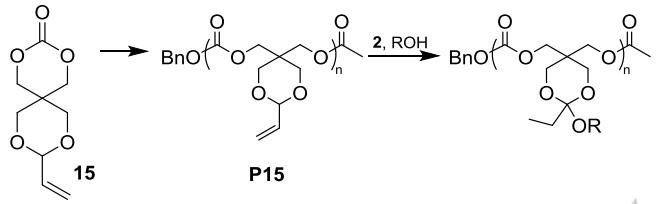
Figure 2. ^{1}H NMR spectra of **10** (A) and **P10** (B) in C_6D_6 (400 MHz, 25ºC).

The ability to apply air stable vinyl acetal potentially allows access to a wide range of novel materials that would be otherwise inaccessible by traditional routes. Most notably, the instability of ketene acetal precursors to excipient nucleophiles, such as water, increases as the ring size is contracted from six to five.[23,24] To further demonstrate the utility of this method for the synthesis of new materials, the five- membered vinyl acetal-containing ring bifunctional monomer (**10**) was isolated directly from the commercially available 1,2,6-hexanetriol (Figure 2a).[25] The subsequent *in situ*-generated ketene acetal was able to undergo successful step-growth polymerization (Figures 2b & S15-16) to yield polymer with M_w up to 21 kDa.

The powerful and mild catalytic methodology presented herein was further applied to access novel materials. Specifically, the preparation of oligo(ε-caprolactone)-based poly(ortho ester)s (Scheme 2) was undertaken using the bifunctional monomer **10** as initiator for the ROP of ε-caprolactone (CL) in the presence of the magnesium catalyst $Mg(BHT)_2(THF)_2$[26] previously reported for the controlled ROP of lactones.[27] The new bifunctional macromonomers **11**-**14** containing oligo(ε-caprolactone) (from 2 to 20 CL units) were obtained in good yield (60-70%) after 3 &



Scheme 2. Synthesis and polymerizations of bifunctional monomers 7 - 14. (a) KOH, DMF, 100 °C, 2 h; (b) 50 °C, 48 h; (c) acrolein, $MgSO_4$, *p*TSA, acetonitrile, 65 °C, 1.5 h; (d) **3** (1 mol%), 1,4-dioxane or toluene, 85 °C, 7 - 48 h; (e) acrolein, *p*TSA, benzene, reflux, 1h; (f) ε-caprolactone, $Mg(BHT)_2(THF)_2$, THF.



Scheme 3. Functionalization of PVDC. Conditions: 2, 45 °C, dioxane, 12 h.

purification (Figures 3 & S18-S25, Table S1). Macromonomers **13** and **14** were obtained with good control over molecular weight (M_n = 1.63 to 3.21 kDa) and dispersity ($Đ_M$ = 1.42 to 1.45). As expected, the synthesis of the shorter oligomers, **11** and **12** (2 and 5 eq. of CL), led to higher dispersity ($Đ_M$ ~ 2). Monomers **11** - **14** were polymerized in the presence of **3** to yield poly(ortho ester)s **P11** - **P14**. The polymerization proceeded and polymers were produced reproducibly (see Table S2) with M_w up to *ca*. 50 kDa for the higher molecular weight oligomers (**14**) with lower M_w poly(ortho ester)s when the molecular weight of the PCL macromonomer was lower (Figures S26-S36). Poly(ortho ester)s **P7** - **P10** are amorphous and don't show any melting peak by DSC analysis. By contrast, the oligo(ε-caprolactone)-based poly(ortho ester)s, **P12** - **P14**, showed a melting point (T_m = 40 to 61 °C) that results from the presence of the oligo(ε-caprolactone) segments in the polymer (Figures S30, S33, S36).

Finally, the mild nature of the process has been further demonstrated by the side-chain functionalization of a novel degradable aliphatic polycarbonate. The application of ortho esters as pH-responsive side chains[21,28] has received increased interest over the past few years, While cyclic ketene acetals have been applied for the functionalization of hydroxyl-containing polymers (or monomers thereby derived), the application of such methodology to degradable polymers would require protection-deprotection strategies to be employed to overcome incompatibilities of functional groups with polymerization methods typically required in their synthesis.

To this end, we synthesized a vinyl acetal-functional, degradable carbonate polymer, **P15**, *via* ROP of the corresponding cyclic carbonate monomer, 9-vinyl-2,4,8,10-tetraoxaspiro[5.5]undecan-3-one, **15** (Scheme 3). Monomer **15** was prepared in two simple steps starting from pentaerythritol and acrolein to form 2-vinyl-1,3-dioxane-5,5-diyldimethanol

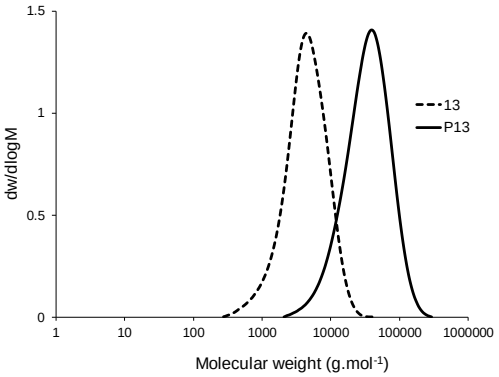


Figure 3. Size exclusion chromatograms of **13** (solid line) and **P13** (dashed line)

(Figure S37) that was subsequently ring-closed with ethylchloroformate to form **15** in good yield (74%, Figure S38). ROP of **15** was achieved using 1,8-diazabicycloundec-7-ene (DBU) with a thiourea cocatalyst,[29] initiated from benzyl alcohol to realize a polymer with a molecular weight close to that predicted by the monomer:initiator ratio with narrow dispersity. The vinyl acetal-functionalized polycarbonate was subsequently end-capped with acetic anhydride to form **P15** with an ester end-group to prevent undesired crosslinking reactions in the subsequent steps (Figure S39).

The vinyl acetal side chains of **P15** were functionalized with 1-hexanol and benzyl alcohol as model alcohols (Scheme 3). Initial application of catalyst **3** at the higher temperatures required for it to operate led to degradation of the polycarbonate backbone. However application of catalyst **2** which is highly active at lower temperatures, was shown to result in the polycarbonate with pendant hexyl or benzyl moieties linked through an ortho ester respectively. The successful functionalization was evident from the ^{1}H NMR spectrum (Figure S40), showing distinct upfield shift of the proton resonances from the vinylic (δ = 5.85 - 5.25 ppm) to alkyl regions (δ = 1.72 and 0.92 ppm) and the appearance of the signal (δ = 3.38 ppm) indicative of the attachment of hexyl groups on the side chain of the polycarbonate backbone. SEC analysis (Figure S41) revealed a single distribution with a comparable dispersity to that of the original **P15** which indicates that no observable degradation of the polycarbonate backbone occurred. this is the

first report to our knowledge of generating an ortho ester functional group *via* addition of alcohol. In turn this presents a much more versatile method to generate side chain substituents linked to a polymer backbone by an ortho ester.

In summary, the application of $RuHCl(PPh_3)_3$ as catalyst for the synthesis of surface erodible poly(ortho ester)s was reported for the first time by a simple and accessible *in situ* 1,3-(di)hydride shift of stable (di)vinylacetal moieties in di(bi)functional monomers. In addition, application to bifunctional monomer systems enabled the preparation of POEs that would be extremely difficult, or impossible to prepare in a consistent manner by any other method. As with typical POE(III), the semi-solid nature of **P7 – P10** means that these materials may be useful as injectable materials for biomedical applications where viscosity can be easily tuned within a wide range of T_g (-39 to 19 ˚C) simply by varying the lengths of the alkyl chain in the bifunctional monomers. We have also demonstrated the versatility of this method by functionalizing an aliphatic polycarbonate *via* formation of ortho ester linkages. The facile nature of this synthetic procedure and the stability of the monomers (compared to other synthetic methodologies) provide a simple synthetic route to further research into these interesting and highly applicable materials. Our work can potentially open new avenues of research to access hitherto unprecedented surface erodible materials to potentially enhance the efficacy and control of the current drug delivery systems which relies on bulk degrading materials.

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Keywords: poly(ortho ester) • vinyl-acetal monomer• olefin isomerization • step-growth polymerization

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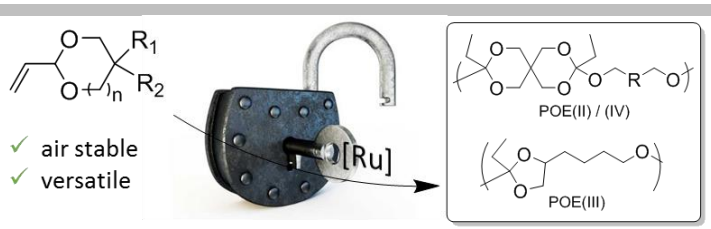

Poly(Ortho Esters) Revived: A catalytic method to access poly(ortho ester)s from air and moisture stable vinyl acetal precursors is reported. This mild and efficient methodology is versatile with respect to monomer and allows access to novel materials and side chain functionalization of sensitive degradable backbone. In turn, it enables the facile synthesis of these valuable but almost forgotten polymers.

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