Design of biomaterials through direct ring-opening metathesis polymerisation of functionalised cyclic alkenes

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Design, System, Application

Ring-opening metathesis polymerization (ROMP) utilizing olefin metathesis reaction has emerged as a powerful approach for synthesizing polymers with complex architectures. In this review, we demonstrate the synthesis of functionalized polymers by ROMP, which has potential applications in biomaterials that require the introduction of complex functional groups. In ROMP-based functionalized polymer synthesis, the synthetic pathway involves the synthesis of functionalized monomers, followed by their polymerization to obtain the desired polymers. In the synthesis of functionalized polymers using ROMP, any functional group can be used with few limitations, as long as the chemical structure can coexist with the catalyst used and does not hinder the reactivity of the alkene in the molecule. However, contrary to the versatility and convenience of metathesis catalysts, the synthesis of functionalized monomers often requires difficult multi-step reactions. Additionally, in the biomaterials field, where contact with living organisms is necessary, metal residues can have an adverse effect, and it requires to heed residual transition metal complex catalysts. Catalysts with higher activity, functional group tolerance, and selectivity are continuously being developed, and ROMP will become a versatile tool in the synthesis of functionalized polymers, comparable to radical polymerization methods in the future.

REVIEW

Design of biomaterials through direct ring-opening metathesis polymerisation of functionalised cyclic alkenes

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Ring-opening metathesis polymerisation (ROMP) has become a popular method for synthesising complex functional polymers owing to the high functional group tolerance of metathesis catalysts. In recent years, ROMP has emerged as an indispensable approach for the design and synthesis of polymeric biomaterials, allowing for precise control of polymer structure and introduction of complex polar functional groups that are challenging to access through conventional polymerisation methods. In this review, we present examples of precision polymer synthesis with polar functional groups and their utilisation as soft-biomaterials in biotechnology and biomedical fields. Specifically, we focus on two approaches: the underexplored ROMP of functionalised monocyclic alkenes and the dominant methods of synthesising biomaterials using functionalised norbornene.

1. Introduction

Since the discovery of polymeric materials, their chemical modification has been of particular interest. Specifically, chemical modification by the introduction of functional groups with the desired function and the application of the materials as advanced materials have attracted much attention in recent years. Although there are various well-established methodologies for obtaining functionalised polymers, they can be broadly classified into two types. The first type is the modification of a pre-synthesised polymer into a functionalised polymer with the desired functional group through a post-polymerisation modification reaction. The second one involves the synthesis of monomers that have desired functional groups, which are then (co)polymerised in an appropriate polymerisation system to obtain functionalised polymers. (Figure 1)

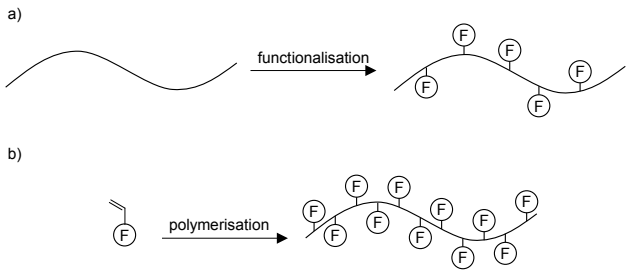

Figure 1. Synthetic pathways to access functionalised polymers. a) Post-polymerisation functionalisation and b) Polymerisation of functionalised monomer. F represents the functional group.

The first method is relatively simple and is frequently used, especially for surface modification of materials in a component member.[1] This direct functionalisation of polymers does not require sophisticated polymerisation techniques and is a more practical approach than the second method because functional groups are incorporated stoichiometrically and randomly to the treated surface. However, it is not the most suitable functionalisation method for the study of polymer properties and functions, particularly in terms of precision of the obtained polymer structure and due to the unambiguous control of the functionalisation efficiency. The second method has the potential to produce polymers with a well-defined primary structure. However, there are significant limitations on the applicable polymerisation active species and polymerisation systems depending on the type of functional group to be introduced. In particular, in the application of functionalised polymers in the biomedical field, attempts have been made to introduce quite complex and diverse biologically active substances, e.g., polypeptides, sugar chains, fluorescent dyes, nucleotides, and drugs.[2-5] In the synthesis of polymers with bioactive substances, it is important to select polymerisation active species with functional group tolerance that can coexist with polar functional groups such as amides, esters, carboxylic acids, hydroxy groups, amino groups and zwitterions in the substances. When introducing these functional groups in polymerisation systems with anionic and cationic active species, it is necessary to perform tedious protection-deprotection processes.[6,7] Radicals, the active species in radical polymerisation, can coexist with a wide range of functional groups, except for highly reactive groups such as thiols.[8] This has facilitated the widespread use of radical polymerisation for polymer synthesis, which requires the introduction of complex functional groups.[9] Since its development, readily available living radical polymerisation under relatively mild conditions, such as atom transfer radical polymerisation[10,11] (ATRP) and reversible addition-fragmentation chain-transfer[12] (RAFT) polymerisation, has been recognised as the most preferred

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polymerisation approach in this field. However, over the past two decades, a new reaction known as ring-opening metathesis polymerisation (ROMP) has made remarkable progress in the synthesis of functionalised polymers. This approach utilises the olefin metathesis reaction.[13-15] Owing to the commercial availability of metathesis catalysts that are highly functional group tolerant, ease of handling in air, and extremely high activity, metathesis polymerisation is now firmly established as a significant polymer synthesis method that allows easy synthesis of functionalised polymers. In addition, ROMP as a chain polymerisation approach enables the synthesis of polymers with more complex structures similar to general vinyl polymerisation methodologies. A wide variety of polymer synthesis methods have been reported for obtaining polymers with complex architectures, including block copolymers, graft copolymers, comb-like copolymers, and star-shaped copolymers.[16] ROMP can be applied to monomers such as cyclic compounds in which the double bonds involved in the olefin metathesis reaction are incorporated in the ring. Because ROMP is usually driven by the release of ring strain energy to produce polymers, cyclic compounds must have a strained ring structure. The ring structure of monomers can be composed of carbon chains or other heteroatoms or functional groups. However, in the synthesis of functionalised polymers using olefin metathesis reactions, the most widely used cluster of monomers are those whose ring structures are composed of hydrocarbon chains. (Figure 2)

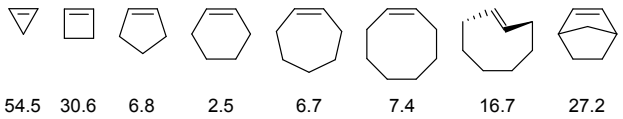

Figure 2. Chemical structure of cyclic alkenes and their corresponding ring strains (kcal/mol).[17]

Therefore, this study reviews the synthesis of functionalised polymers using ROMP of monomers classified as monocyclic alkenes and bicyclic alkenes, as well as studies that have reported applications of the resulting polymers in the biotechnology field.

2. Ring-opening metathesis polymerisation: overview of reaction and catalysts

Olefin metathesis is a catalytic process in which the scission/recombination of two intra- or intermolecular carbon-carbon double bonds occurs. This reaction is essentially an equilibrium reaction that includes ring-closing metathesis (RCM), ring-opening metathesis (ROM), acyclic diene metathesis (ADMET) polymerisation, and ring-opening metathesis polymerisation (ROMP) (Figure 3).

Polymeric products can be produced by two reactions, ADMET polymerisation and ROMP. ADMET polymerisation is a step-growth polycondensation that can be performed with α,ω-dienes as the monomer. It has the same characteristics as general polycondensation and yields polymers with broad molecular weight distribution. Additionally, it is difficult to obtain high molecular weight polymers by this reaction unless very high reaction conversion occurs.[18] Although ADMET polymerisation also synthesises functionalised polymers by polymerising functionalised monomers, it will not be covered in detail in this review. For details, readers can refer to the reviews and articles by Wagener et al. who are an authority on ADMET polymerisation.[19-23]

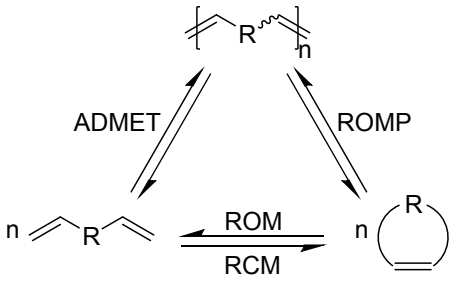

Figure 3. Reaction variations in the equilibrium of olefin metathesis.

In contrast, ROMP is a chain-growth polymerisation approach that can be performed with cyclic alkenes. ROMP utilises the release of ring-strain energy associated with cyclic monomers as the driving force, leading to the thermodynamically favourable product, linear polymer. A notable advantage of ROMP is the ease of producing high molecular weight polymers. Moreover, appropriate reaction conditions can yield polymers with "living polymerisation" characteristics.

Up until the development of highly functional-group tolerant olefin metathesis catalysts, the monomers used in polymer synthesis utilising metathesis reactions were limited to relatively simple unsaturated hydrocarbon compounds that lacked functional groups. This was because the previously reported catalysts, which had early transition metals such as Ti,[24] Nb,[25,26] Ta,[25-27] W,[25,28-30] and Mo[30,31] as active centres, were highly sensitive to oxygen and protic solvents, making it difficult to coexist with polar functional groups. However, despite this limitation, metathesis polymerisation with transition metal carbenes as active species continued to be studied with the aim of exploring the possibility of coexisting with functional groups. In particular, Schrock catalyst[15,32-35] with molybdenum or tungsten as the metal centre was widely used in the field of polymer synthesis until the late 1990s, resulting in numerous reports on precision polymer synthesis, including stereo-regularity control and living polymerisation.[33] However, although these catalysts exhibit extremely high metathesis activity, the metal complexes have low acceptability of functional groups. In addition, the catalysts are unstable to water, protic compounds, and air, making the catalysts difficult to handle.

Grubbs catalysts[14,36-39] with ruthenium as the metal centre was first reported in the mid-1990s. They were considered as highly functional-group tolerant catalysts and later became widely known worldwide as the first-generation Grubbs catalyst.[40] The second-generation Grubbs catalysts with *N*-heterocyclic carbene (NHC) as a ligand also exhibits extremely high functional group tolerance and can be handled relatively easily even in an environment where air and water coexist.[41] This led

to the fabrication of subsequent catalyst systems using ruthenium as the central metal; these catalysts were widely used in the synthesis of functionalised polymers. With the development of functional group-tolerant catalysts, such as second-generation Grubbs catalysts, researchers began to focus on the synthesis of functionalised polymers for both ADMET polymerisation[23] and ROMP.[42,43] In recent years, these catalysts have been increasingly used in polymer synthesis that require the introduction of complex functional groups, in the same manner as radical polymerisation. The fundamental reaction mechanism of ROMP is not also described in detail in this review and more about the mechanism can be covered in the treatises and reviews.[16,44-46]

Most functional group-substituted cyclic monomers have asymmetric structures with some exceptions. In ROMP using asymmetric monomers, linear polymers with head-to-tail, head-to-head, and tail-to-tail repeating units are obtained depending on the mode of ring insertion, and a regio-mixture is usually obtained. Considering the microstructure control over the double bond geometric isomerism and the stereoregularity control of substituents, there are a wide variety of reports on the control of the primary structure; for more details, other articles and textbooks can be refered.[16,44,46,47]

Currently, the most commonly used catalysts in this polymerisation reaction are a group of commercially available catalysts as shown in Figure 4. G1, G2, G3, and HG2 are a group of catalysts developed by Grubbs with ruthenium as the central metal, and G1, G2, and G3 are termed the first-,[40] second-,[41] and third-generation[39] Grubbs catalysts, respectively. HG2 is a catalyst developed by Hoveyda and is a modified version of G2.[48,49] Mo1, a phenylimido bisalkoxide complex,[50] and Mo2, a monoaryloxide pyrrolide (MAP) imide complex,[51] are catalysts developed by Schrock with molybdenum as the central metal and is available with different ligands. Tungsten catalyst W1 will be available in the near future.

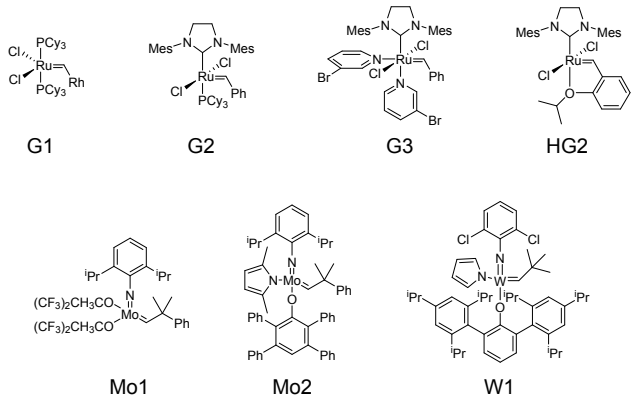

Figure 4. Commercially available catalysts for ROMP. (Mes = −2,4,6-trimethylphenyl; ^{i}Pr = −isopropyl; Ph = phenyl; Cy = cyclohexyl)

Metathesis catalysts based on Mo or W exhibit high reactivity towards olefins and often produce polymers with high primary structural regularity. However, their functional group tolerance is inferior to that of Ru catalysts. Therefore, they are less commonly used in the synthesis of functionalised polymers, which is the focus of this paper. The following sections will mainly introduce synthesis examples utilising the high functional group tolerance of Ru-based Grubbs catalysts.

3. Polymers from monocyclic alkenes

The difficulty in preparing functionalised monocyclic alkenamers can be attributed in part to the availability of starting monocyclic alkenes and the stability of the compounds themselves. For example, cyclopropene, cyclobutene, and their derivatives are often unstable due to their very high ring strain energy,[17] and there are very few reported examples of monocyclic compounds. In addition, cyclopentene and cyclohexene and their derivatives have very low ring strain, and there are few reports on the synthesis of homopolymers, especially from cyclohexene. Cyclopentene and its derivatives are relatively easy to synthesise, and several reports have been found in recent years. Although cycloheptene has relatively high polymerisability, the 7-membered ring is difficult to obtain and is rarely used except when special sequences are desired to be constructed. 8-Membered rings, cyclooctene and 1,5-cyclooctadiene, have sufficient ring strain and stability for ring-opening polymerisation. This is a group of monocyclic alkenes that are most frequently used in the synthesis of monomers with functional groups and polymer synthesis by ROMP. Monocyclic compounds with more than 9-members also have sufficient ring strain energy[52-54] that enables ring-opening polymerisation; however, there are only few reported cases due to the difficulty in obtaining and isolating *cis*- and *trans*-isomers of the double bond, as well as low ring strain energy.

	–	–	+	–	+	+
G1	high yield if • and • are: Me, Me or Me, Ph	•: low yield, •: no reports found	•: moderate yield at low temp. •: low yield	••: negligible yield	••: moderate yield •: low yield, HT biased	••: high yield •: low yield, HT biased
G2	++	++	++	–	+++	+++
	•: high yield with substitution via alkylene, must have Me at either • or •	•: high yield, low PDI •: moderate yield,	•: moderate yield, •: low yield, HT biased	•: AROMP with strained monomers	•••: high yield, •: regioselective	•••: high yield •: regioselective
G3	+++	++	++	–	+++	+++
	•: high yield with substitution via alkylene, must have Me at either • or •, low PDI	•: high yield, low PDI •: moderate yield, regioselective,	•: moderate yield, •: low yield, HT biased	•: AROMP with strained monomers	•••: high yield, •: regioselective	•••: high yield •: regioselective
HG2	•••: no reports found	+++	+++	–	++	++
		•: high yield, low PDI •: moderate yield, HT biased	•: moderate yield, •: low yield, regioselective with bulky substituents	•: AROMP with strained monomers	•••: high yield, •: regioselective	•••: high yield •: regioselective

Figure 5. Application table of ruthenium-based catalysts for ROMP of functionalised monocyclic alkenes and their product characteristics. The colour-filled circles on the monomer structure indicate the positions where functional groups can be introduced; blue for rare, green for occasional, and red for general. The reactivity of the monomer and the recommended/appropriate level of the catalyst are evaluated in the following four-level ratings: +++ for very high; ++ for high; + for moderate; – for low (this pair should be avoided).

Although entropy-driven ROMP has been reported recently,[55,56] there are only a few reports on the ROMP of cyclic alkenes which remains essentially a polymerisation reaction driven by the release of ring strain energy. Monocyclic alkenes with functional groups are less frequently used as monomers than multicyclic alkenes with high strain energies. However, they are useful for model copolymer synthesis of ethylene and polar vinyl monomers. Thus, they are frequently used especially in the field of functionalised polyethylene synthesis and in the study of changes in polymer properties due to the introduction of side-chain functional groups. Figure 5 presents a table summarising the general polymer yield and characteristics obtained from the ROMP of functionalised monocyclic alkenes, using ruthenium-based catalysts with high functional group tolerance. The color-filled circles on the monomer structure indicate the positions where functional groups can be introduced, with blue for rare, green for occasional, and red for general. In brief, G1 is preferred for relatively high ring-strain and stable monomers, but its use has become infrequent nowadays. G2 is suitable for a broad range of functionalised monomers, but its use with highly strained 3- and 4-membered ring monomers is rare. G3 is widely used due to its high tolerance for functional groups and fast initiation rate, while HG2 is particularly useful for reactions low-temperature reactions or for monomers with low electron-deficient double bonds.

The following sections deal with examples of the introduction of polar functional groups using monocyclic alkenes and provide an overview of functionalised polymers considered for application as biocompatible polymer materials.

3.1 Cyclopropenes

Cyclopropene is the most strained cyclic alkene with the smallest ring members, and its strain energy (54.5 kcal mol^{-1})[17] exceeds that of norbornene, which will be described below later. Due to their very large ring strain, cyclopentenes and its derivatives have been used extensively since the advent of transition metal metathesis catalysts to investigate reaction mechanisms and catalyst synthesis. For example, Grubbs et al. reported the reaction of 3,3-diphenylcyclopropene with chloro(pentamethylcyclopentadienyl)ruthenium(II) tetramer[57] and ruthenium chloride complexes with triphenylphosphine ligands in 1992.[58] The reaction afforded a ruthenium carbene

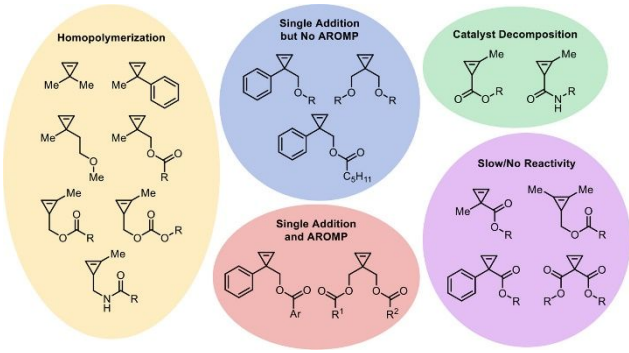

Figure 6. Scope of cyclopropene monomers for ROMP investigated by Xia et al.[64] Reprinted with permission from ref. 64. Copyright 2021 American Chemical Society.

complex that is stable in the presence of protic solvents, and this complex catalyses the ROMP of norbornene.

Schlock et al. also reported in 2006 the living ROMP of disubstituted cyclopropene derivatives with a substituent at the 3-position using a molybdenum imide alkylidene complex in a highly oxidised state, yielding polymers with controlled molecular weight and very narrow molecular-weight distribution.[59] They had successfully conduct the ROMP of a monomer with a 2-methoxyethyl group, which was a polymer with a glass transition temperature at −42 °C. Schrock subsequently reported *Z*-selective ROMP of 3-methyl-3-phenylcyclopropene with monoaryloxide pyrrolide (MAP) catalysts in 2010.[60]

Until now, there have been very few reports on the synthesis of polymers from functionalised cyclopropenes; however, in recent years, Xia et al. made major contributions to this area of study.[61-65] (Figure 6) In their reports, relatively stable 1,2-disubstituted or 1,1-disubstituted cyclopropene derivatives were used as monomers, and ROMP of cyclopropene derivatives with diverse structures were studied. The pyridine-ligated G3 catalyst has been commonly used in their report, and they successfully obtained alternating copolymers and chain-end functionalised polymers. Very recently, living polymerisation[65] and block copolymer synthesis[63] have also been reported, expanding the scope of monomer structures and introduced functional groups. Although the number of reports is currently limited, there is significant potential for the future development of this polymerisation technique.

It has been challenging to use cyclopropenes as monomers for the synthesis of biocompatible polymers due to stability issues caused by the high strain energy. To address this problem, diallyl-substituted cyclopropenes have been synthesised as monomers, and polar functional groups such as esters, amides, alcohols, and carbonates have been achieved by ROMP. Unfortunately, these polymers have not yet been observed to have applications as biocompatible polymers. However, the repeating unit structure of these polymers is different from that of polymers obtained by vinyl polymerisation. With future reports on physicochemical properties, there is potential for these polymers to have applications as biocompatible polymers.

3.2 Cyclobutenes

Cyclobutene and its derivatives are compounds with a large ring strain (30.6 kcal mol^{-1}),[17] similar to the cyclopropene derivatives, and are a group of monocyclic alkenes that have been underutilised in ROMP research. Prior to the development of highly functional-group tolerant metathesis catalysts, investigations mainly focused on substituted monomers with hydrocarbon chains such as methyl groups, as the repeating units of polymers obtained by ROMP of cyclobutene derivatives are structurally similar to those of 1,4-polydienes (e.g., butadiene and polyisoprene). However, the use of derivatives with mono- or di-hydrocarbon chains at the 3-position or polar functional group at the 1-position has been avoided due to the complexity of their synthesis, as most substituted cyclobutenes require multiple steps for their preparation (Figure 7).[66]

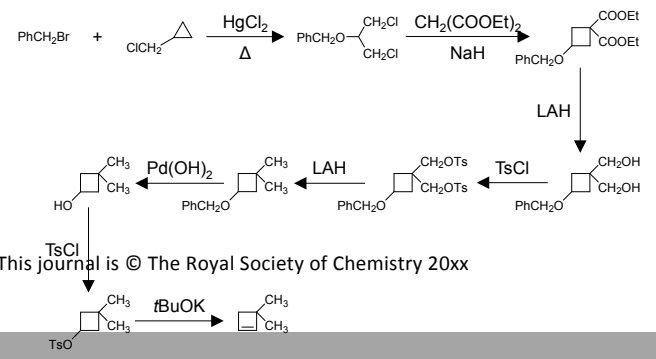

Figure 7. Synthesis of 3,3-dimethylcyclobutene reported by Grubbs et al.[66]

Dall'Asta et al., in 1972, reported that Ziegler-Natta catalysts afforded ring-opening polymerisation products from cyclobutene-based monomers.[67] Katz et al. also reported in 1976 that (phenylmethoxycarbene)pentacarbonyl tungsten complexes could produce ring-opened polymeric products from cyclobutene.[68] Grubbs et al. reported in their early work on polymer synthesis that the polymers produced by ROMP of 3-methylcyclobutene and 3,3-dimethylcyclobutene are analogs of polyisoprene and poly(ethylene-*alt*-isobutene).[66,69,70] Subsequently, in the mid-1990s, reports emerged of ROMP of cyclobutene derivatives with polar functional groups. For example, Novak et al. reported that polymerisation with a Schlock-type molybdenum imide alkylidene complex, ROMP of cyclobutene derivative with 3,4-disubstituted structure, proceeds in a living polymerisation manner (Figure 8).[71] Fontaine et al. also reported ROMP of 3,4-bis(acetyloxymethyl)cyclobutene with G1 as a catalyst, showing that the polymerisation proceeds living polymerisation.[72] They have reported a number of polymer syntheses by ROMP utilising 3,4-bis(hydroxymethyl)cyclobutene[73] as the modular monomer unit, primarily using G1, G2, and G3 as catalysts.[74]

In 2006, Sampson et al. first reported the ROMP of cyclobutenes with functional groups such as amides and esters derived from cyclobutene-1-carboxylic acid, and have been continuously developing their chemistry since then.[75-80] They demonstrated the synthesis of a polymer by ROMP using cyclobutene-1-carboxamide modified with methoxy-esterified glycine as the monomer and G3 as the catalyst.[75] Microstructural analysis of the resulting polymer revealed regio/stereoselective

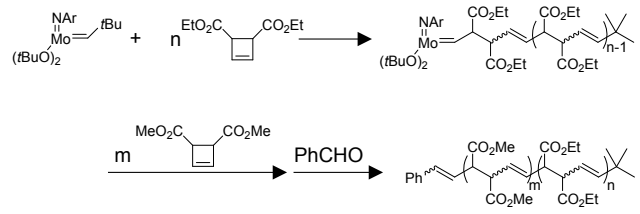

Figure 8. ROMP of 3,4-difunctionalised cyclobutenes reported by Novak et al.[71]

polymerisation that led to the formation of a highly regio/stereo-regulated *cis*-head-to-tail polymer. However, increasing the amount of monomer relative to the catalyst and polymerising under heating resulted in broadened molecular weight distribution when attempting to obtain high molecular weight polymers. They aim to apply this technique to the synthesis of peptide-modified polymers, which are expected to

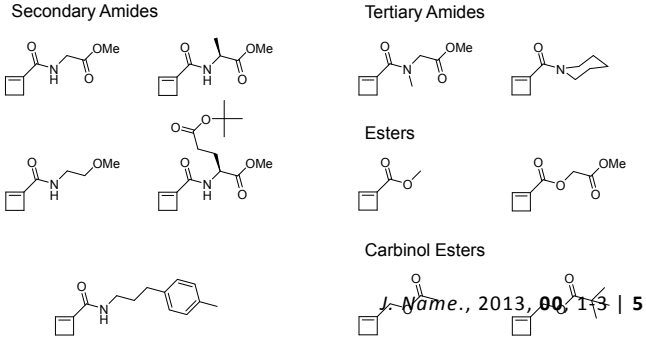

Figure 9. 1-Substituted cyclobutenes investigated by Sampson et al.[77] Secondary amide monomers exhibit an optimal level of reactivity and generate regio and stereoregular polymers.

be evaluated in bio-relevant chemistry. Furthermore, they have conducted a detailed study of the functionalisation of the 1-position of cyclobutene and the ROMP reactivity of this monomer with a ruthenium-catalyst. The ROMP of secondary amide, tertiary amide, ester, and carbinol ester type monomers was reported, and polymers were obtained from the monomers modified with secondary amide and ester.[77] (Figure 9) In addition, alternating copolymers of 1-cyclobutene carboxylate and cyclohexene derivatives were synthesised.[78] Synthesis of functionalised polymers with quaternary ammonium salts introduced at the side chain termini, by alternating copolymerisation by ROMP of cyclobutene and cyclohexene, followed by subsequent functional group transformation was successfully carried out.[79] These functionalised polymers can be combined with hydrogels for drug delivery and cell adhesion experiments, and used as biocompatible polymers. Moreover, they exhibit antimicrobial activity, and the relationship between their primary structure and the expressed functions has also been reported. Further details will be discussed below in a later section on cyclohexene.

3.3 Cyclopentenes

Due to its low ring strain (6.8 kcal mol^{-1}),[17] cyclopentene has not extensively studied as monomer for ROMP, as its ring-closed state is more thermodynamically favourable than the ring-opened polymeric product at high temperatures. However, conducting the ROMP of cyclopentene at low temperatures can shift the equilibrium towards the formation of polymers, and its temperature dependence is highly significant. Recently, this thermodynamic features of the ROMP of cyclopentene has been utilised for polymer synthesis.[81] As monocyclic alkene with this ring members are stable and readily accessible, there has been a significant increase in number of reports on the ROMP of cyclopentenes.

Since the report by Grubbs et al. in 2005 on the relationship between strain energy and ring-opening reaction of substituted cyclopentenes, several suitable structures for ROMP have been identified, and the number of reports has been gradually increasing since then.[82] In 2004, they also reported the successful synthesis of a model polymer of polyvinyl alcohol from functionalised cyclopentene, where the ring strain energy of the functionalised monomers was estimated by DFT calculations.[83] Calculations have been performed for various substituted cyclopentenes for the introduction of hydroxy groups, and 3-cyclopentene-1-ol was found to have slightly greater ring strain energy than unsubstituted cyclopentene. The polymerisation of this monomer with HG2 produced a polymer with low molecular weight, the introduction of substituents at the allyl position of cyclopentene results in smaller ring strain energy compared to bare cyclopentene. For example, Hillmyer et al. reported G2-catalysed ROMP of a monomer with an acetoxy group at the allyl position; however, the polymeric product could not be obtained.[84] There are also examples of introducing substituents at the allyl position of cyclopentene and studying the ROMP behaviour, especially the primary structure control of the resulting polymers.

Since 2016, Kennemur et al. have maintained a continuous interest in polymer synthesis through ROMP using substituted cyclopentenes,[85-87] with a particular focus on regioregular polymer synthesis from asymmetrically substituted monomers with a silyl-protected hydroxy group at the allyl position.[88, 89] For instance, they prepared four monomers in which the hydroxy group introduced at the 3-position of cyclopentene was protected by trimethylsilyl (TMS), triethylsilyl (TES), *tert*-butyldimethylsilyl (*t*BDMS), and triisopropylsilyl (TIPS) groups, and performed ROMP using HG2. (Figure 10) The

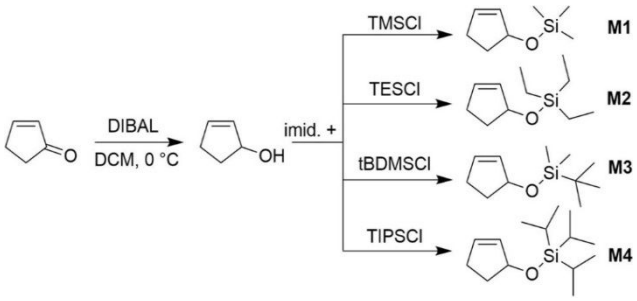

Figure 10. Synthesis of various allylic-substituted trialkylsiloxy-cyclopentene monomers.[88] Reprinted with permission from ref. 88. Copyright 2019 Elsevier.

polymerisation behaviour and microstructure of the generated polymers were studied in detail; among the obtained polymers, the one obtained from the monomer protected with a TIPS group demonstrated the highest regio/stereoregularity, with HT content over 99% and trans-double bond content of 95.5%.[88] They also studied the model synthesis and application of ethylene-styrene copolymers using monomers with a phenyl group at the 4-position of cyclopentene.[90-93]

ROMP of monomers derived from 3-cyclopentene-1-carboxylic acid by esterification yields model copolymers of ethylene and acrylates. Several reports have been made on the synthesis of functionalised polymers by this method.[94,95] For example, in 2017, Fan et al. performed ROMP with HG2 for eight different monomers with varying alkyl chain lengths from 1 to 16 carbons, followed by hydrogenation to obtain model ethylene-acrylate copolymers.[95] The obtained polymers had a number-average molecular weight up to 80k and a molecular weight distribution of approximately 1.7. The glass transition temperature of the polymer decreased with increasing side chain length, and the polymers became crystalline at chain lengths above 12 carbons. Although reports on ROMP using cyclopentene derivatives have been published in recent years, there has been little evaluation of polymer properties with respect to biomedical applications.

3.4 Cyclohexenes

Cyclohexene and its derivatives have the lowest ring strain energy (2.5 kcal mol^{-1})[17] among the monocyclic alkenes, making them unsuitable monomers for ROMP. The ring-closing product is more thermodynamically favourable than the ring-opening product, which limits its use for polymer synthesis.[45,85,96,97] Although it is not completely inert to olefin metathesis reactions,[98] its polymerisation in ROMP is rare due to the difficulty of the process. As a result, there have been few reports on homopolymerisation of cyclohexene derivatives and

applications of the resulting polymers.[98] However, it has been used in methods to construct highly alternating sequences by copolymerisation with other high-strain monomers.[76,78-80,99-104]

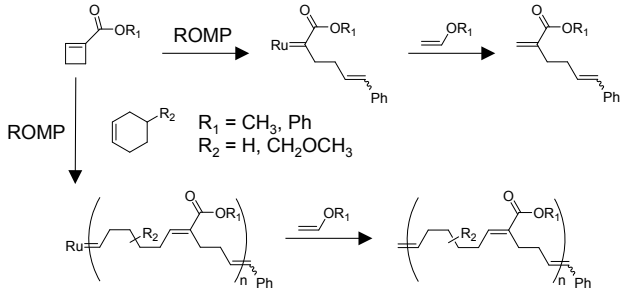

Figure 11. Synthesis of polymers containing a cyclohexene unit by alternating ring-opening metathesis polymerisation (AROMP) reported by Sampson et al.[76]

For example, Sampson et al. described several methods for obtaining alternating copolymers by copolymerising highly strained cyclobutene 1-carboxylic acid ester derivatives with cyclohexene.[76,78-80,99-103] (Figure 11) This approach utilises two monomers that cannot be polymerised individually but are active in metathesis, and is carried out with a large excess of low-strain monomers such as cyclohexene to obtain the polymeric product. The range of high-strained monomers that can be used in this system has now been expanded to include bicycloalkenes, enabling the synthesis of polymers with unique structures.[80,100,101,103] These polymers have been investigated for applications in the biomedical field, and the synthesis and evaluation of antimicrobial polymer materials have been reported. The authors synthesised a variety of polymers with quaternary ammonium cations at the side chain termini by ROMP of alkyl halide functionalised monomers, followed by the reaction with trimethyl amine.[79] They also synthesised different polymers with varying side chain spacings by copolymerising substituted cyclobutene derivatives and cycloalkenes with different number of ring members. The structure-function relationship of the antimicrobial properties exhibited by the resulting polymers was investigated. Interestingly, cyclobutene-cyclohexene alternating copolymers with a regular side chain spacing of 10 Å exhibited higher antimicrobial properties than homopolymers obtained from a cyclobutene derivative with side chain spacing of 4 Å.

3.5 Cycloheptenes

Cycloheptene is a compound with sufficient strain energy (6.7 kcal mol^{-1})[17] to be used as a monomer for ROMP, comparable to that of cyclopentene (6.8 kcal mol^{-1}). In 2005, Grubbs et al. reported on the ruthenium-catalysed ROMP of functionalised monomers with small ring strain and showed that the ROMP of cycloheptene is possible with first- to third-generation Grubbs catalysts, and that the polymeric product can be obtained from the system.[82] However, the ROMP of cycloheptene monomers has not been reported very often, probably because of the difficulty of obtaining cycloheptene itself. Even in recent years, this group of compounds has rarely been used as ROMP monomers, except in the field of metathesis polymerisation catalysts development and polymerisability studies.[105-109,110,111]

Nevertheless, there are reports that investigate functionalised cycloheptene as a monomer; for example, Hillmyer et al. reported the ROMP of a cycloheptene derivatives[112] in which an acetoxy group was introduced at the allyl position, and the resulting polymer was highly HT-biased (95.9% HT).[84] Matson et al. reported the ROMP of 1,4-dioxaspiro[4,6]undec-8-ene with G1, followed by hydrogenation and deprotection to obtain precision polyketones with regular ketone spacing.[113] The polyketone with a regularly placed functional group exhibited a melting point at 160 °C, 30 °C higher than that of an irregular polymer.

Only a few reports have investigated ROMP using cycloheptene derivatives and their biocompatibility, including Kobayashi et al.[94,114] They reported on the ROMP of cycloheptene derivatives in which 2-methoxyethoxycarbonyl and 2-dimethylaminoethoxycarbonyl groups were introduced at the allylic position of the ring. Polymerisation of this monomer proceeded regio-selectively, as seen in a series of reports,[94,114-117] producing polymers with very high HT regularity (97% and 96%, respectively). (Figure 12) After the obtained polymers

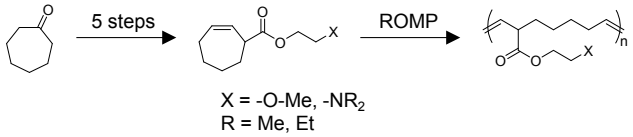

Figure 12. ROMP of functionalised cycloheptenes reported by Kobayashi et al.[94,114]

were subjected to hydrogenation reactions to create model copolymers of polar monomers and ethylene, platelet adhesion and protein adsorption tests were conducted to evaluate biocompatibility. However, they found that the blood-compatibility was low, probably due to the low density of side chain functional groups.

3.6 Cyclooctenes

Cyclooctene and its derivatives are most commonly used in polymer synthesis with monocyclic alkenes as the monomer of ROMP.[118] This is due to their high stability, easy handling, and the relative ease of synthesising functionalised monomer. Substituted cyclooctenes with a *cis*- double bond (7.4 kcal mol^{-1})[17] are typically used due to their sufficient ring strain, but those with trans- (16.7 kcal mol^{-1})[17] can also be used as monomers. In the case of *trans*-cyclooctene, the ring strain is quite high, and the equilibrium of the reaction is strongly biased toward the ring-opening product. This greatly increases the polymerisation rate, and if the polymerisation system is appropriately selected, living-like polymerisation can occur, as seen in the norbornene system.[119] The remaining double bonds in the main chain can be converted to saturated bonds by hydrogenation,[120-122] resulting in structures that can be regarded as copolymers of ethylene and polar monomers.[43,84,94,112,114,116,117,123-126] The introduction of a polar functional group into cyclooctene is often achieved using 1,5-cyclooctadiene or *cis*-cyclooctene as a starting material.[43,118] For example, a hydrogen halide addition reaction can be performed

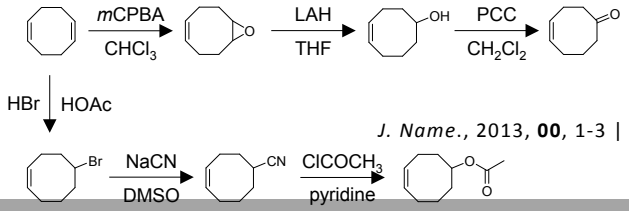

Figure 13. Synthesis of functionalised cyclooctenes reported by Hillmyer et al.[43]

on a double bond of 1,5-cyclooctadiene to obtain cyclooctene with a halogenated 5-position, which is then react with a nucleophilic reagent. Alternatively, the double bond can be treated with a peroxide to form an epoxide, which can then be converted to alcohol by ring-opening to serve as the starting point for the subsequent reaction. (Figure 13) Additionally, a halogen or other functional group can be introduced at the allylic position of cyclooctene, which has a relatively high reaction activity.

Polymerisation of allyl-substituted cis-cyclooctenes using ruthenium-based catalysts with bulky NHC ligands results in highly head-to-tail regioregular polymers.[115] This method has been widely studied since Hillmyer et al. first report in 2011. Various studies have utilised this allyl functionalised monomer,[94,114,116,117,125,127-132] and it is also effective for Schrock-type catalysts. Grubbs-type ruthenium catalysts yield polymers with trans-double bonds, while Schrock-type catalysts produce polymers with cis-double bonds.[133,134]

Hillmyer and Cramer et al. have investigated the mechanism of this ruthenium-catalysed system and found that regioregularity is mainly due to the smaller repulsive interaction between the NHC ligand and the substituent located distal to the metal centre.[135] This method can be applied when a functional group that can coexist with the catalyst is introduced, but polymerisation does not proceed for bulky substituents such as the tert-butyl group, and the rate is significantly reduced for substituents such as the i-propyl group.[136] Regardless, ROMP proceeds even in cases where the bulky substituent is linked to the allyl position[137,138] Kobayashi et al. have continuously reported on the synthesis and functional control of regioregular polymers.[94,114,116,117] Recently, they have also attempted to apply this method to monomers with other ring members, and they reported the synthesis of polymers with controlled side chain spacing.[94] The hydration state and biocompatibility of these polymers can be tuned by controlling the side chain spacing[94,114,139-141] and changing the chemical structure of the side chains.[142-167]

In 2016, Tao et al. reported the ROMP of monomers with ethylene glycol (EG) chains with 0 to 4 different numbers of EG units for the substituted carboxyl groups at the 3- or 5- positions of cyclooctene in order to tune water-related functions.[129] (Figure 14) Glycine act as a linker between EG and cyclooctene carboxylic acid, and some of the resulting polymers are crystalline. The authors successfully synthesised polymers with

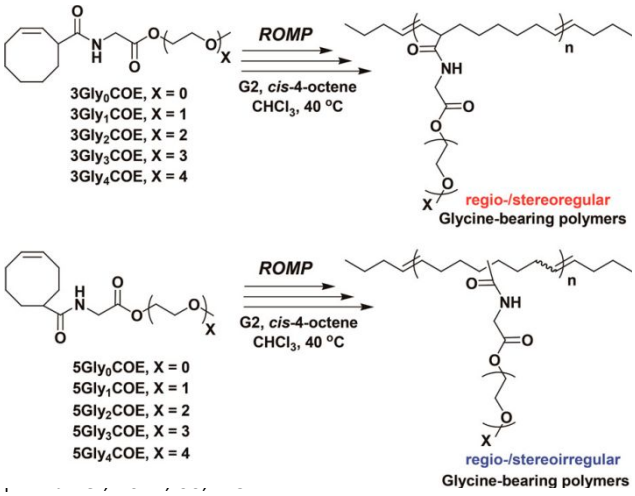

Figure 14. ROMP of EG functionalised cyclooctenes reported by Tao et al.[129] Allyl substituted cyclooctenes afford highly *trans*-head-to-tail regio and stereoregular polymers. Reprinted with permission from ref. 129. Copyright 2016 American Chemical Society.

different regularities of side chain spacing by altering the substituent position of the functional group, and these polymers displayed crystallinity, hydrophilicity, and LCST that are aligned with changes in the microstructure. They suggest that this polymer synthesis approach presents not only an attractive strategy for the production of precise amino acid-containing polymers, but also provides a wealth of information for correlating structure-property relationships in biomimetic materials.

In 2017, Sampson et al. reported the ROMP of monomers substituted with *L*-fucose, *D*-mannose, *N*-acetyl-*D*-glucosamine (*D*-GlcNAc), and *D*-glucose for carboxylic acids introduced at the 4-position of cyclooctene.[168] (Figure 15) Acetoxy-protected monomers were polymerised using G3, and polymers with narrow molecular weight distribution and sufficiently high molecular weights up to 77k. In a separate study, they also examined the polymerisation of monomers with a similar

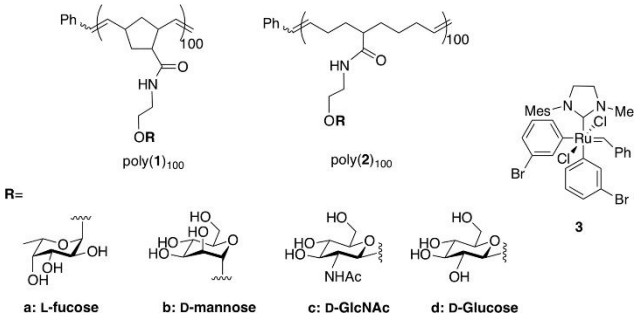

Figure 15. Monosaccharide bearing polymers synthesised by Sampson et al.[168] Poly(1)$_{100}$ and Poly(2)$_{100}$ were prepared from acetoxy-protected monomers of functionalised norbornene and cyclooctene, respectively. Reprinted with permission from ref. 168. Copyright 2017 American Chemical Society.

modification to 5-norbornene-2-carboxylic acid.[169] They used monosaccharide-modified polynorbornene derivatives and polycyclooctene derivatives to compare the functionality of the two polymers with different main chain flexibilities. They synthesised these polymers since the process by which sperm acrosomal vesicles fuse with the plasma membrane and release acrosomal contents is induced by the binding of multiple sugar residues to sperm receptors. The study identified that polynorbornene derivatives induce acrosomal epithelialisation (AE) more efficiently than polycyclooctene derivatives, indicating that the AE-inducing effect of polymers modified with monosaccharides may be enhanced by using relatively rigid polymers that can stabilise the receptor complex for signalling.

PEGylation is a commonly used technique for imparting hydrophilicity to hydrophobic polymers.[116,170-172] In 2002, Emrick et al. reported the ROMP of PEGylated COEs synthesised by a coupling reaction between 5-hydroxy-1-cyclooctene and PEG using succinic acid[171] or by anionic polymerisation of ethylene oxide using 5-hydroxy-1-cyclooctene as an initiator.[172] They polymerised the monomers using Grubbs catalysts and obtained copolymers of the PEGylated monomer with cyclooctene. In 2014, Yin et al. also synthesised copolymers from cyclooctene and the derivatives with methoxy-terminated ethylene glycols having different chain lengths.[170] Toluene diisocyanate was used to couple 5-hydroxy-1-cyclooctene and

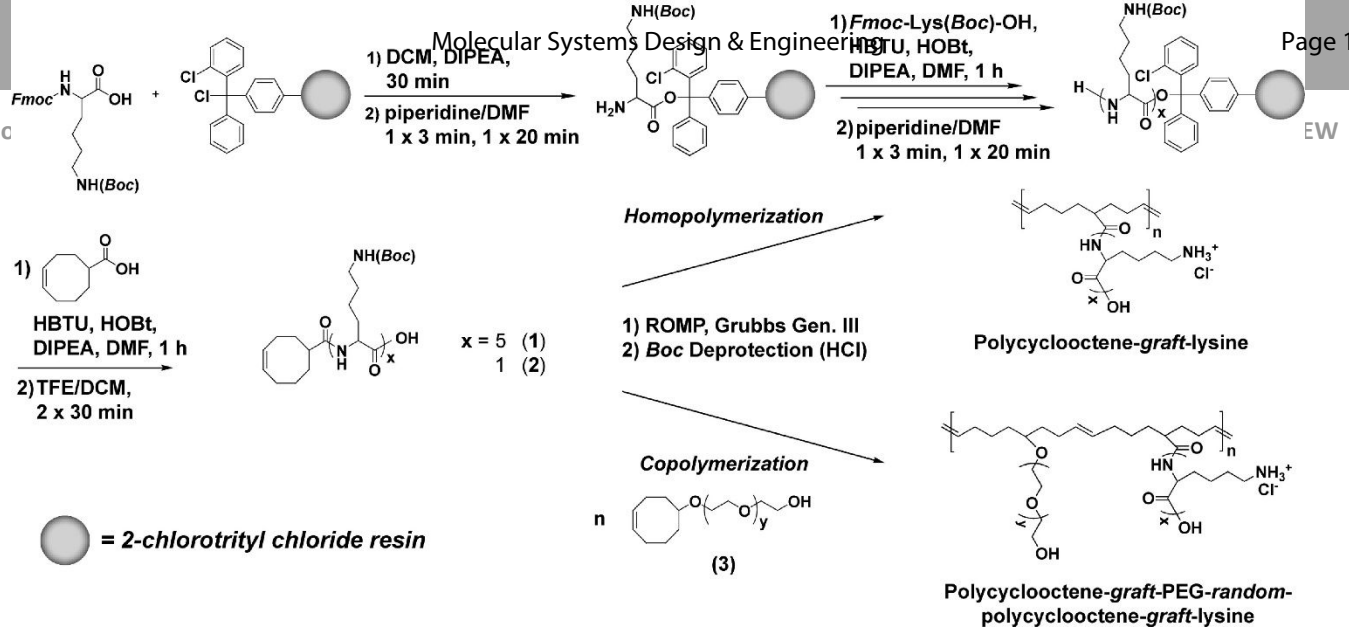

Figure 16. PEG- and oligopeptide-functionalised polyolefin reported by Emrick et al.[173] Reprinted with permission from ref. 173.Copyright 2017 American Chemical Society.

PEG in this case. They performed ROMP with G2, and the properties of the obtained polymer were evaluated. The hydrophilicity of the resulting polymers increased as the PEGylated comonomer content increased. The highest platelet adhesion inhibition was observed when the comonomer content was about 60%. The adsorption behaviour of BSA to the polymer surface was evaluated. The amount of adsorption was minimal when the chain length of PEG was 750 g/mol. Both studies suggested that this amphiphilic polymer could be used as a coating material for biomedical applications such as implants, and biomedical coatings.

Emrick et al. reported a series of cyclooctenes that were modified with peptides and betaines for ROMP.[173-177] For peptide modification, they synthesised monomers of 1-cyclooctene-5-carboxylic acid amide, which were linked with *t*Boc-protected lysine and pentalysine, as well as copolymers with PEGylated monomers.[173] (Figure 16) The catalyst employed was G3. The solution behaviour of the resulting polyelectrolytes, obtained after deprotection, was evaluated and fine-tuned by altering the peptide graft length and density. The polymers exhibited aggregation structures depending on the ionic strength. The copolymer synthesised by copolymerising the pentalysine-modified monomer and 30 mol% of the PEGylated COE formed aggregates, while the pentalysine-modified polymer was capable of forming complexes with DNA and varied in size from 60 to 200 nm depending on the mixing ratio. The polymer produced a complex with plasmid DNA pZsGreen1-N1 and can be used as a transfection reagent.[174] These polyplexes have been reported to effectively transfect COS-1 and HeLa cell lines while maintaining very high cell viability. Emrick et al. further obtained betaine-modified polymers by ROMP of cyclooctene derivatives with phosphobetaine[175] and sulfobetaine.[177] In particular, they copolymerised the sulfobetaine-functionalised monomer with the above mentioned tetralysine-modified monomer. They varied the sulfobetaine monomer content and evaluated the efficiency of DNA transfection in terms of experiments and simulations. Both the results showed that the binding strength between the polymer and DNA decreases as the sulfobetaine content in the polymer increases. The simulation results showed that the sulfobetaine groups are distributed throughout the polyplex, thus maintaining a positive charge, which allows for high gene expression levels in living cells. They stated that the simulation- and experiment-based results are findings that demonstrate the effectiveness of incorporating zwitterions into polyplexes and allow for the design of effective gene delivery vectors.

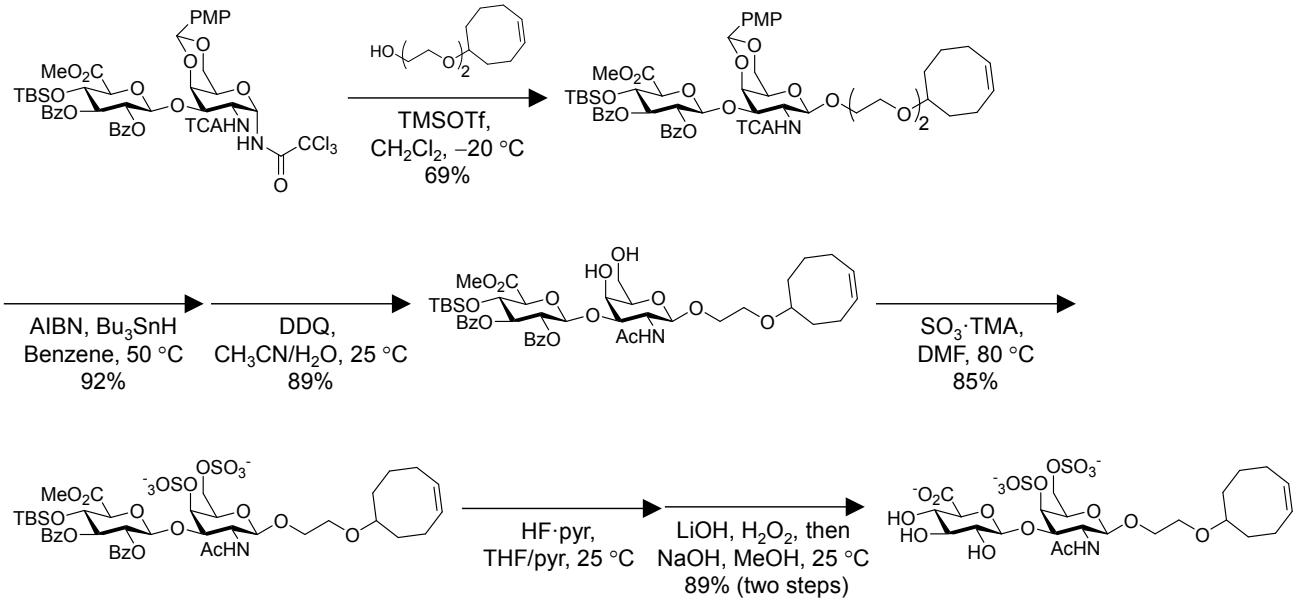

Figure 17. Synthesis of sulphated disaccharide bearing cyclooctene reported by Hsieh-Wilson et al.[178] The monomer was subjected to ROMP by G3 in methanol.

In 2008, Hsieh-Wilson et al. reported the ROMP of cyclooctene modified with chondroitin sulphate mimetic oligosaccharide.[178] Chondroitin sulphate (CS), a glycosaminoglycan, has significant applications in various biological processes. CS has a sulphated structure with a repeating sugar chain of two different sugars, *D*-glucuronic acid (GlcA) and *N*-acetyl-*D*-galactosamine (GalNAc), and the synthesis of polymers modified with this sulphated polysaccharide is one of the most challenging polymer syntheses. They performed the ROMP of 5-(diethylene glycol)-1-cyclooctene modified with sulphated di-/tetra-saccharides with protected hydroxyl groups (Figure 17) using PEG-modified Hoveyda-Grubbs catalysts in an aqueous solution to obtain polymers with molecular weights up to 110k. The deprotected modified polymers were added to hippocampal neuron cells, and the effect was found to result in complete inhibition of neurite outgrowth. The polymers obtained from sulphated disaccharide-modified monomers mimicked the activity of natural polysaccharides and showed higher biological activity than the sulphated disaccharides themselves. The authors describe their results as a greatly simplified synthesis of complex glycosaminoglycans and provide synthetically accessible bioactive structures in programmable sulphated sequences.

4. Polymers from bicyclic alkenes

4.1 Norbornenes and oxanorbornenes

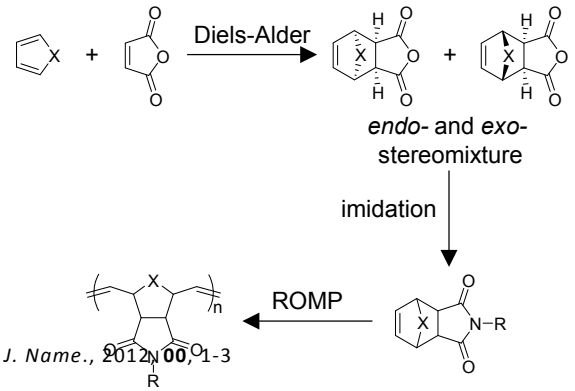

Figure 18. General synthetic pathway to achieve functionalised poly(oxa)norborneneimide via the Diels-Alder reaction. X = -CH_2- or -O-, and R = any substituent.

Norbornene and oxanorbornene exhibit high reactivity towards ROMP due to their very high ring strain energy (27.2 kcal mol^{-1} for norbornene).[17] Additionally, the functionalised variants can be easily synthesised by the Diels-Alder reaction with dienophiles using cyclopentadiene and furan as dienes. In particular, maleic anhydride as a dienophile can yields (oxa)norbornene-2,3-dicarboxylic anhydride, which can be easily converted to a norbornenimide monomer by reaction with amino-functionalised molecules. (Figure 18) Therefore, functionalised (oxa)norbornene derivatives are frequently used in the field of biomaterial applications that require the incorporation of a diverse range of physiologically active substances, to achieve complex polymer structures through ROMP.

In the case of (oxa)norbornene derivatives, those with carboxyl or hydroxymethyl groups at the 2- and 3-positions as a foothold for functionalisation are commercially available, and the starting materials are relatively easy to obtain compared to monocyclic alkenes. By combining norbornene derivatives with the appropriate condensing agents, molecules with complex structures can be readily introduced into monomers in good yield. Consequently, ROMP of norbornene derivatives is often used in functionalised polymer synthesis, particularly in biomaterial applications that require the incorporation of bioactive substances. Introducing substituents to 5-norbornene,

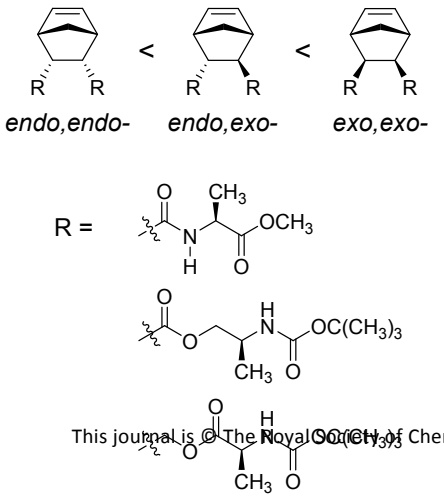

Figure 19. ROMP activity of 2,3-difunctionalised norbornene to G2 reported by Sanda et al.[179]

especially at the 2- and 3-positions, leads to *endo*- and *exo*-stereochemistry. The stereo structures of synthesisable norbornene derivatives are thus very diverse. Polymerisation behaviour has been investigated using monomers with *endo*, *endo*-, *endo*, *exo*-, and *exo*, *exo*- substituents at the 2- and 3-positions, with the polymerisation rate increases in the order of *endo*, *endo*- < *endo*, *exo*- < *exo*, *exo*-.[179-181] (Figure 19) This trend is speculated to reflect the steric hindrance caused by the bulkiness of the substituted functional groups and the stability of metallacyclobutane intermediate formed by the coordination of monomer.

In the ROMP of norbornene derivatives, polymers with various primary structures can be constructed by changing the type of catalyst used in the polymerisation. However, little attention has been paid to the primary structure with respect to application as a biocompatible polymer. The norbornene ring is highly strained and have very high strain energy. As a result, ring-opening metathesis proceeds extremely smoothly, allowing for the synthesis of polymers with high molecular weight. With the development of catalysts with fast initiation rates (e.g., G3 catalyst), it has become easier to achieve living-like polymerisation, enabling the synthesis of polymers with controlled molecular weight and narrow molecular weight distribution. The use of catalysts exhibiting fast initiation rates and high functional group tolerance facilitates the synthesis of polymers with "living-like" characteristics containing complex functional groups. Therefore, these catalysts have become indispensable for the ROMP of functionalised cyclic monomers. Figure 20 shows a diagram summarising the common structure of functionalised norbornene derivatives. It also summarises the features of ROMP using G1, G2, HG2, and G3 catalysts and the resulting polymers. HG2 and G3 and their derivatives are currently the most widely used for biomaterials synthesis, with their ligands being modified to impart water solubility.

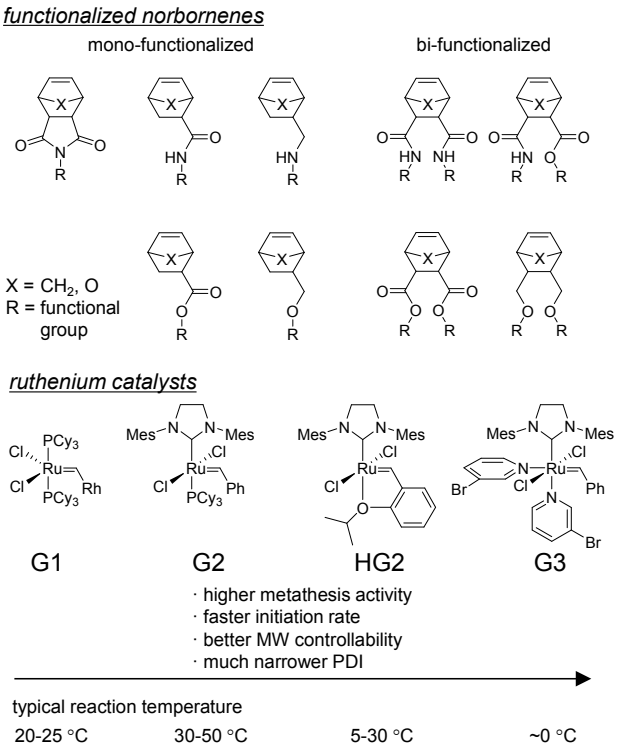

Figure 20. Representative structures of functionalised (oxa)norbornene derivatives and their characteristics in combination with ruthenium catalysts. 3-Bromopyridine, which is a ligand for G3, can be substituted with unsubstituted or PEG-modified pyridine. Modification can also be made to NHC ligands.

The advent of highly functional group-tolerant catalysts has enabled the polymerisation of not only monomers with polar functional groups such as PEG and betaine, but also monomers with bioactive substances. A wide range of polymers have been synthesised, including those modified with amino acids, peptides, nucleobases, sugars, and fluorescent molecules. There are no molecular weight restrictions on the substances that can be introduced, ranging from amino acids to polypeptides, nucleotides to DNA and RNA, and even sugars to polysaccharides. These polymer syntheses have been particularly active in the arena of biomaterials applications. Therefore, we have provided a summary of synthesising poly(oxa)norbornene derivatives modified with characteristic molecules.

4.2 Amino acids and peptides

Polypeptides, or proteins, are biopolymers that are obtained from amino acids as monomers, and they are the most attractive polymers among the biopolymers present in living organisms. As exemplified by enzymes and antibodies composed of proteins, they often exhibit extremely high biological activity. Therefore, many attempts have been made to modify synthetic polymers with amino acids and polypeptides using a wide variety of synthetic methods,[182,183] especially for application in the pharmaceutical and biomedical fields. This trend is particularly evident in the area of ROMP for the synthesis of poly(oxa)norbornene derivatives.

In 1999, Arimoto et al. focused on the functional group tolerance of G1 and discovered that polymers obtained from peptide-conjugated monomers could enhance the weak non-covalent bonding interaction of peptides through multivalency or cluster effects.[184] They performed the ROMP of a norbornenimide derivative conjugated with vancomycin, an antibiotic used in the treatment of infections caused by methicillin-resistant Staphylococcus aureus (MRSA). Since the chemical structure of vancomycin contains various functional groups such as amino, amide, hydroxy, and carboxylic acid groups, ROMP using G1, which has already been reported to be resistant to many polar functional groups, was chosen as the most suitable approach for the synthesis of such polymers. (Figure 21) The results confirmed the antibacterial activity of the resulting polymers against Staphylococcus aureus, enterococci, and vancomycin-resistant enterococci (VRE) and that the vancomycin-modified polymers exhibited 8- to 60-fold higher antibacterial activity than the monomer.

The binding of the sperm to the egg cell membrane is a crucial step in the fertilisation,[185,186] and fertilinβ, a membrane-bound protein present on the extracellular surface of sperm, mediates this binding. Peptides that mimic the binding loop of this fertilinβ can inhibit fertilisation in vitro. The Glu-Cys-Asp (ECD) tripeptide is the minimal recognition element necessary for the binding of fertilinβ to its egg receptor,[187,188] but monomeric ECD

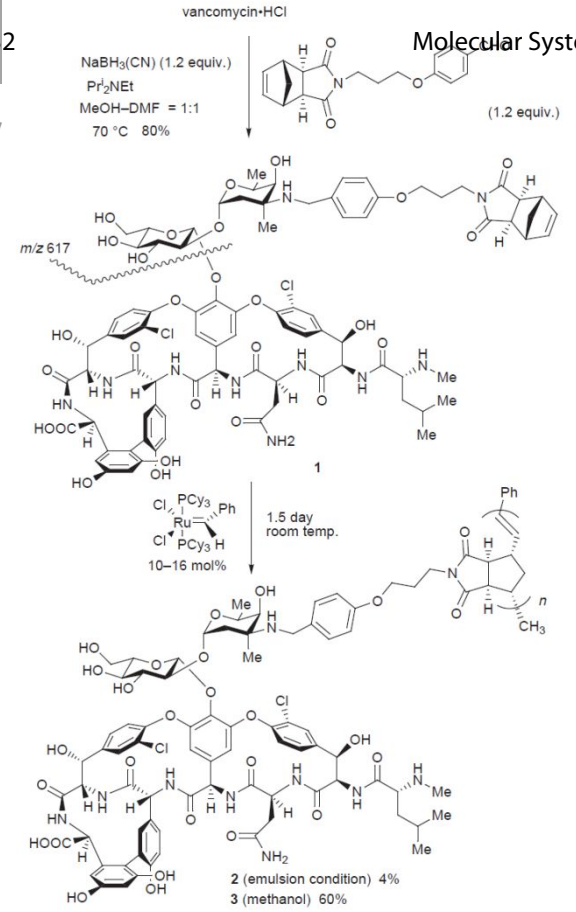

Figure 21. ROMP of vancomycin modified norborneneimide reported by Arimoto et al.[184] Reprinted with permission from ref. 184. Copyright 1999 Royal Society of Chemistry.

peptides are poor inhibitors, and multivalent presentations of ligands often improve their affinity.[189] Sampson et al., who were interested in fertilin since the late 1990s,[185,186,190,191] reported oligopeptide-modified polynorbornenes in 2003,[192,193] where they introduced the linear variant of Glu-Cys-Asp-Val-Thr-OMe (ECDVT) peptide into the side chain of polynorbornene to inhibit fertilisation. The resulting polymers exhibited higher fertilisation inhibition than the monomer due to the multivalency effect.[192] (Figure 22) They later developed their work using an even simpler binding sequence, ECD, and found that an 11-mer containing two ECD ligands at both termini, 4 to 5 nm separated by seven spacer monomers, is the most potent fertilineβ-derived fertilisation inhibitor.[194] In 2004, they obtained block copolymers from monomers in which 5-norbornene-exo-2-carboxylic acid was activated with N-hydroxysuccinimide and modified with oligopeptide.[195] The resulting polymers were fluorescently labeled with Oregon Green 488 via cadaverine, and the cellular uptake behaviour was evaluated. The ECDVT-modified polymers showed oligopeptide-dependent binding to the plasma membrane of zona-free oocytes, and they stated that peptide-modified polymers synthesised by this method can be used as probes for polymer-receptor interactions at the oocyte surface.

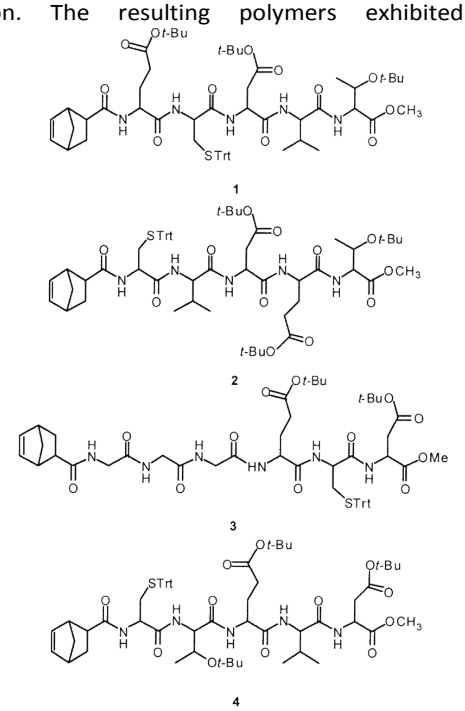

Figure 22. Oligopeptide-modified norbornene derivatives reported by Sampson et al.[192] Carboxylic acid and thiol were protected by the *tert*-butyl group (*t*-Bu) and trityl group (Trt), respectively. 1) - E(*t*Bu)C(Trt)D(*t*Bu)VT(*t*Bu)-OMe, 2) - C(Trt)VD(tBu)E(tBu)T(tBu)-OMe, 3) - GGGE(*t*Bu)C(Trt)D(*t*Bu)-OMe, and 4) - C(Trt)T(*t*Bu)E(*t*Bu)VD(*t*Bu)-OMe. Reprinted with permission from ref. 192. Copyright 2003 American Chemical Society

In 2009, Sanda et al. performed ROMP of norbornene derivatives modified with amino acids using G2 and reported the polymerisation behaviour and structure of the resulting polymers in detail.[179,196,197] They reported that the substitution of methyl group on the amino group improves polymerisation in the ROMP of monomers with unprotected amines for *L*-alanine and *N*-methyl-*L*-alanine-modified norbornene derivatives. They also reported that *t*Boc protection of the amino group is effective in improving polymerisation in ruthenium catalyst systems. Moreover, they obtained alternating copolymers for norbornene derivatives in which carboxylic acids and amines derived from amino acids were introduced. The monomers used in their study are of two types: one is a 5-norbornene-2,3-*exo*,*exo*-dicarboxylic acid to which a carboxy group derived from *L*-leucine is introduced, and the other is a 5-norbornene-2,3-*exo*,*exo*-dimethanol to which an amino group derived from *N*-methyl-*L*-phenylalanine is introduced. Alternating copolymerisation was found to proceed through an increase in local concentration due to acid-base interaction between the monomers coordinating to the metal carbene active centre.

In 2012, Grubbs et al. reported the use of polymers synthesised by ROMP in the field of biotechnology.[198] (Figure 23) They synthesised various monomers with PEG chains, linear and cyclic RGD peptides, and *t*Boc-protected amino groups on the imide nitrogen of norbornenimide and copolymerised them using G3 to produce polynorbornenimides with water solubility, cell adhesion, and crosslinking properties through post-modification reactions. The polymerisation of monomers proceeded in a living and quantitative manner without the influence of introduced functional groups, and the resulting polymers exhibited living characteristics with molecular weights ranging from 15k to 74k, molecular weight distributions around 1.1, and monomer contents as designed. The introduction of amino groups by a deprotection reaction, followed by a cross-linking reaction with bis(sulfosuccinimidyl)suberate, produces a hydrogel that can be used for cell culture. HUVECs were cultured on this gel, and it was found that cyclic RGDs are 100-fold more active than chain RGDs, and that the introduction of 1% cyclic RGDs results in extremely high cell adhesion and viability even in a serum-free culture.

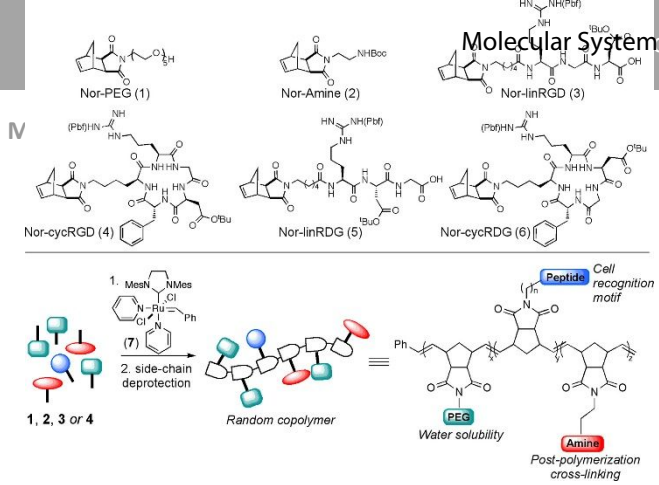

Figure 23. Cyclic- and linear- RGD modified norborneneimide monomers reported by Grubbs et al.[198] Reprinted with permission from ref. 198. Copyright 2012 American Chemical Society.

Polymers exhibiting a lower critical solution temperature (LCST) in aqueous media near room to body temperature have been investigated as thermoresponsive polymers for various biomedical applications.[199-202] Elastin-like polypeptides (ELPs) are one of the most extensively studied thermoresponsive polymers, consisting of a sequence of VPGXG (X is any amino acid except proline). The thermal or pH-triggered phase transition of ELP pentapeptides, which can be controlled by the type and concentration of the guest residue X, has been used for protein purification tagging,[203] drug delivery vehicles,[204] and tissue engineering scaffolds.[205]

In 2007, Setton et al. polymerised *exo*-5-norbornene-2-carboxylic acid with the VPGVGVPGKG sequence using G2.[206] (Figure 24) During the polymerisation process, K is protected with *t*Boc and G with *t*Bu, and the desired sequence is introduced into the polymer by deprotection with trifluoroacetic acid. The oligomers were fixed on aldehyde-modified glass substrates and cultured with porcine intervertebral disc-derived fibrochondrocytes, with the cells adhering, stretching, and proliferating well on the substrate coated with this polymer. By incorporating various cell adhesion peptides into the polymer by ROMP, it can be applied as a cell culture substrate with various functions.

The studies reported by Wu et al. from 2016 to 2018 utilised cell membrane-permeable peptide-modified polynorbornenes for tumour cell organelle-specific imaging.[207,208] They designed a modular approach to endow polynorbornene hydrophilicity, cell membrane permeability, and fluorescent staining properties. Specifically, they used *exo*-5-norbornene-2-carboxylic acid as the monomer building block and M_n = 550 PEG-modified monomers to impart hydrophilicity. They synthesised ternary copolymers from PEG-, peptide-, and fluorescent molecule-modified monomers. The peptides used for modification were TAT, a well-known cell membrane permeability peptide (CPP) derived from the human immunodeficiency virus (HIV) transactivator protein, SV40, a typical nuclear-localising sequence (NLS) peptide, and FxrFxK, a mitochondrial transmitting peptide sequence. Rhodamine B, dichlorofluorescein, and 9,10-dichloroanthracene were used as fluorescent molecules, designed to provide red, green, and blue staining. Polymerisation was carried out using G3 in chloroform at a monomer to initiator ratio of 100. The corresponding water-soluble peptide-modified polynorbornene derivatives were prepared and added to a culture system of the human

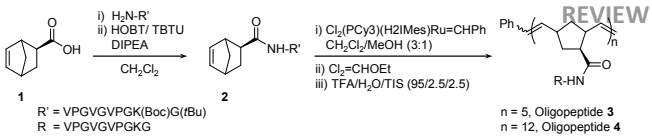

Figure 24. Elastin like oligopeptide modified norbornenes reported by Setton et al.[206] The amino group and carboxylic acid were protected by *tert*-butoxy carbonyl (*t*Boc) and *t*Bu, respectively. Reprinted with permission from ref. 206. Copyright 2012 American Chemical Society.

hepatocellular carcinoma cell line Bel-7402 for imaging, and the authors successfully achieved simultaneous multicolour imaging of intracellular lysosomes and mitochondria.

Peptides are used in the biomedical field, but their rapid digestion by endogenous proteases, rapid clearance from the kidney, and short activity duration are major issues. Proteases that degrade peptides are abundant in both serum and tissues, but the enzymatic degradation of proteins in the body has the potential to progress rapidly, with a half-life of less than a few minutes. In particular, proteases secreted from the pancreas and peptidases present in the brush border membrane are abundant in the small intestine, limiting the use of peptide and protein drugs. To utilise the inherent bioactivity of peptides for therapeutic and diagnostic purposes, there is a need to develop methods that protect active peptides from degradation and do not inhibit their functions. Particularly, for the application of peptide-modified polymers to biomedical applications, modification with PEG and zwitterionic polymers is used to provide stealth properties. However, modification with these polymers may also make the peptides themselves less likely to be recognised by their target receptors, ultimately facilitating the need for simpler and more efficient methods to protect peptides from proteolysis and achieve peptide delivery.

Gianneschi et al. synthesised a number of peptide-modified polymers using peptide-bearing *exo*-5-norbornene dicarboximides as a platform, and have continuously reported their functions.[209-220] Throughout their studies, they have found that peptide-modified polymers are more resistant to protein degradation than their monomer analogues. Therefore, they hypothesised that polymerised peptides might be protected from proteolysis, and that this may be a general feature of peptide-arrayed polymers that allows them to maintain their native biological functions. They conducted numerous experiments to investigate this hypothesis.

First, they polymerised norborneneimide monomers with 31 different pentapeptides by ROMP using G2. (Figure 25) They polymerised the monomers without introducing any specific protecting group, and found that polymerisation proceeded more efficiently when a spacer was introduced to keep the peptides away from the norborneneimide moiety. The polymers produced had an extremely narrow molecular weight distribution and a designed degree of polymerisation.[210] They also compared the trypsin cleavage behaviour of monomers and polymers modified with peptides containing lysin in the sequence. They discovered that higher molecular weight (20-mers) polymers were more resistant to cleavage. Additionally, they found that side-chain peptide sequences with lysines located closer to the main chain are more resistant to cleavage.

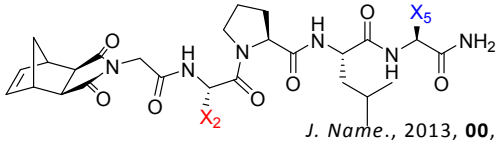

Figure 25. The norborneneimide monomer template with -Gly-X_2-Pro-Ile-X_5 peptide reported by Gianneschi et al.[210] X_2 and X_5 were systematically substituted for different amino acids.

Gianneschi et al. subsequently investigated the incorporation of a wide variety of peptides into the side chains of polynorbornenimides, with the GSGSG sequence serving as a control sequence.[211] This sequence is uncharged, water-soluble, and non-cell-penetrating. Additionally, they synthesised various peptides modified polymers, including cell-penetrating peptides (CPPs) such as Tat,[211] Arg8,[211] Arg appended peptide,[212,217] differentially charged matrix metalloproteinase-9 recognition sequence,[213] CPP30,[214] CPP44,[214] iRGD,[215] protease substrate of thermolysin, a zinc metalloproteinase,[218] tandem repeat sequence of Mefp1,[219] and other modified polynorbornenimides.[220] They continue to study the functions and applications of protein-like peptide brush polymeric materials and their usefulness.

For example, in 2014, they reported that high-density peptide brushes obtained by the polymerisation of norborneneimide monomers with the cell-permeable peptides Tat and Arg8 exhibit protease resistance while maintaining their cell-penetrating properties.[211] In this report, they further investigated the peptide cleavage rate by adjusting the peptide density through copolymerisation with OEG-modified monomers in order to elucidate the factors that lead to the development of protease resistance. The results indicate that the lower the density of peptide chains and the higher the OEG content, the faster the cleavage occurs. Additionally, the packing of peptides through high-density brushing or the stabilisation of peptides by other peptide-peptide interactions provides steric protection against enzymatic cleavage. The higher the amount of OEG introduced, the faster the cleavage occurs.

Pokorski et al. have also reported on the synthesis and application of peptide-modified polymers utilising ROMP.[221-226] Their synthesised polymer consists of a hydrophilic segment that is modified with PEG sidechains and a 5-norbornene-2,3-dicarboxylic acid anhydride segment that facilitates binding with peptides. Peptide modification of the anhydride segment can be carried out either at the monomer synthesis step or post ROMP. Notably, their report describes polymer synthesis in an aqueous medium using water-soluble metathesis catalysts. In addition to (oxa)norbornene imide derivatives modified with PEG, they have also used monomers modified with sidechains of sulfobetaine, biotin, FITC, and other functional groups.

As an example, they used a commercially available, water-soluble Hoveyda-Grubbs type catalyst called AquaMet to carry out the ROMP of norbornene introduced with lysozyme and Bacteriophage Qβ (Qubevirus durum) in buffer solution, followed by block copolymerisation with PEG- or sulfobetaine-modified monomers to synthesise protein-polymer conjugates (PPCs).[226] (Figure 26) Qβ is a 128 nm icosahedral virus-like particle (VLP), which is useful for verifying the effects of anti-PEG antibodies that have been recently pointed out. They performed immunoreactivity tests on Qβ-PPCs and reported that polynorbornene-based PPCs have lower immunogenicity than grafting-to PEG conjugates, and that replacing the PEG-modified segment with a sulfobetaine-modified segment avoided immunoreactivity from both protein-specific antibodies and PEG-specific antibodies.

4.3 Nucleic acids, nucleobases and polynucleotides

Synthetic polymers that can interact with DNA and RNA can serve as a fixation layer in chromatography to collect the target DNA. They are expected to be used as a tool for understanding the structure-activity relationship of biological macromolecules. DNA (or oligonucleotides) can be introduced into polymers as a side chain or as the terminal group (as in block copolymers), similar to the general method of introducing functional groups into polymers. This type of polymer can be synthesised through

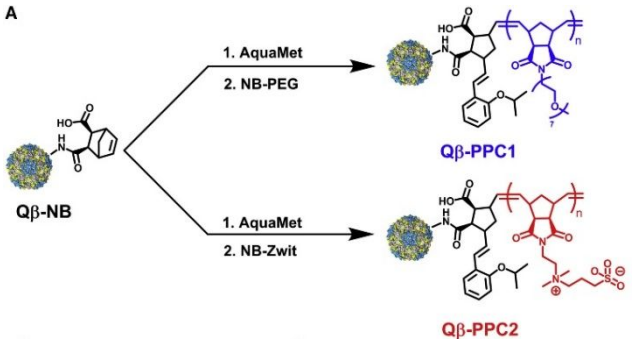

Figure 26. PNA synthesis reported by Pokorski et al.[226] Figure 5A was adapted from ref. 226 with permission. Copyright 2022 Elsevier.

ROMP by introducing nucleic acids into the monomer or through the later modification of polymers.

In 2001, North et al. reported the synthesis of monomers consisting of an ethylamino group as a linker on the nitrogen atom of norbornenimide, and modified the amino group with carboxymethylated nucleobases.[227] They performed ROMP on these monomers using G1, but the yield of the polymers was limited to only 10% to 20%.

Zhang et al. synthesised an ABA-type triblock copolymer by the block copolymerisation of 5-norbornene-2-carboxylic acid derivatives modified with *N*-hydroxysuccinimide (NHS) and PEG45 on the side chains.[228] They synthesised a hairpin DNA-polymer complex by modifying this triblock copolymer with an amine-modified DNA sequence. They have shown that this block copolymer formed worm-shaped nanostructures in 0.15 M NaCl solution. In addition, they obtained heterometallic DNA-polymer complexes by introducing a DNA sequence modified with amine and fluorescein, and a DNA sequence modified with thiol and Cy3 into triblock copolymers synthesised with three different monomers (NHS-activated monomer, PEG-modified monomer, and maleimide-modified monomer). They further reported that this polymer can be complexed with linker DNA to form a cross-linked network structure.

In 2014, Gianneschi et al. introduced single-stranded peptide nucleic acids (PNAs) sequences into norbornenimide monomers and reported polymerisation using G3.[229] (Figure 27) They also succeeded in synthesising block copolymers of PNA-modified monomers with three types of monomers: 1) phenyl group-modified monomers, 2) OEG-modified monomers, and 3) quaternary amino group-modified monomers. The block copolymers, especially those with hydrophobic phenyl group-modified monomers, were reported to form PNA-coated nanoparticles with a particle diameter of about 20 nm. Furthermore, they reported the synthesis of a polymer named locked nucleic acid (LNA)-polymer complex for the above hydrophobic block and DNA, namely LNA-polymer amphiphile (LPA) nanoparticles.[230] They synthesised antisense fluorescein-labeled LPA (AS-FL-LPA) nanoparticles containing a fluorescently labeled LNA sequence that is complementary to a 20-base region located in the second exon of survivin mRNA in HeLa cells. The uptake experiments showed that treatment with

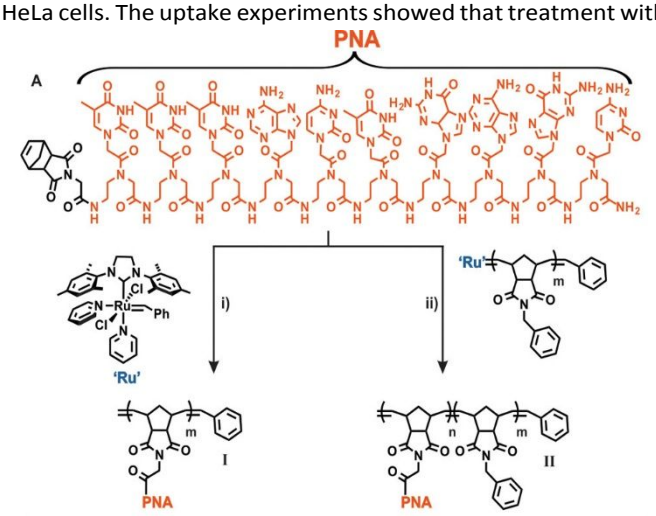

Figure 27. PNA synthesis reported by Gianneschi et al.[229] Figure 1A was adapted from ref. 229 with permission. Copyright 2014 American Chemical Society.

AS-FL-LPA nanoparticles efficiently and significantly depleted survivin mRNA levels compared to endogenous GAPDH mRNA transcripts. They also observed nanoparticles with a hydrophobic core of norbornenimide with phenyl groups, the surface of which was modified with a thrombin-binding DNA aptamer.[231] They found that the high density of aptamers as a corona of micelles was stable against degradation by nucleases in buffer solution and serum, and that the nanoparticles act efficiently as coagulation inhibitors in human plasma and are rapidly neutralised by the addition of complementary oligonucleotides. They also found that the particles showed the same or better effect than unmodified free aptamers in blood coagulation assays, and stated that the introduction of nucleobases into polymers could expand the potential for *in vivo* use.

4.4 Sugars and polysaccharides

The polysaccharides are biopolymers that comprise living organisms, along with proteins and nucleic acids. Glycans modified with proteins and lipids exist on cell membranes and play a crucial role in cell functions by acting as markers for cell identification and information exchange. Glycoproteins exist not only on the cell surface but also inside the cell, and they are involved in the expression of extremely diverse biological phenomena.

In 1995, Grubbs et al. demonstrated the utility of ROMP for the synthesis of sugar functionalised polymers. They used G1 and 5-norbornene-2-carboxamide modified with the monosaccharide D-glucopyranose as a monomer.[232] (Figure 28) They successfully polymerised monomers in which the hydroxyl group on glucopyranose is protected by acetoxy, benzyloxy, triethylsilyl, and trityl groups. For the unprotected monomers, they obtained polymers by polymerisation in an emulsion of dichloromethane dissolved in the catalyst and dispersed in water.

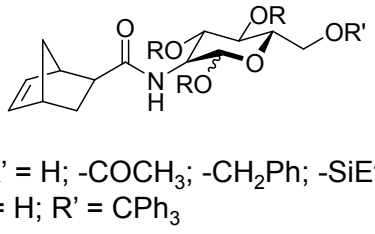

Figure 28. *D*-glucopyranose substituted norbornene reported by Grubbs et al.[232] This might be the first report on the ROMP of sugar functionalised norbornene using G1. Only the acetate-protected monomer (RR' = -$COCH_3$) could be polymerised.

Before the widespread use of highly functional group tolerant G2 catalyst with NHC as ligands, Kiessling et al. attempted to introduce mannose,[233,234] 3,6-disulfo galactose,[235,236] and galactose.[233,237] Multivalent sugar-modified polymers were synthesised by performing polymerisation in a dichloromethane/water emulsion or a mixed solution of dichloromethane/methanol, respectively.

For norbornene derivatives modified with monosaccharides, Sampson et al. in 2014 reported the ROMP of 5-norbornene-2-carboxamide monomers modified with mannose, glucose, galactose, fucose, *N*-acetylglucosamine, and *N*-acetylgalactosamine using G3.[169] (Figure 29) Both 10-mers and 100-mers were obtained with narrow molecular weight distributions. The hydroxyl group is protected in the form of an acetoxy group for all monomers. After polymerisation in dry dichloromethane, deprotection is carried out to convert the polymer into a multivalent sugar-modified polymer in which the desired sugar is introduced. The resulting polymers were used to study the process of cross-linking or aggregation of sperm membranous receptors by sugar chains on the mouse egg zona pellucida during the exocytosis step in the mouse sperm acrosome reaction (AR). They found that the 10-mers and 100-mers modified with mannose, fucose, and *N*-acetylglucosamine induce AR in a dose-dependent manner, with the 100-mers inducing AR more potently per monomer than the 10-mers. In addition, AR activated by the 100-mer was sensitive to guanine-binding regulatory protein (G protein), tyrosine kinase, protein kinase A, protein kinase C, and Ca^{2+} associated antagonists. Thus, they reported that the glycosylated polymers obtained here are able to mimic physiological AR activators, and that occupying at

least one of the three different receptor binding sites is sufficient to initiate AR.

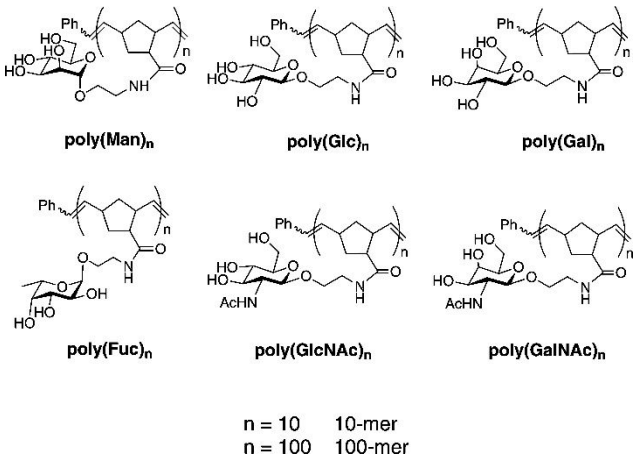

Figure 29. Monosaccharide-modified polynorbornenes reported by Sampson et al.[169] Monomers were synthesised via 4 to 7 step reactions. For details, see the supporting information of ref. 169. Reprinted with permission from ref. 169. Copyright 2014 American Chemical Society.

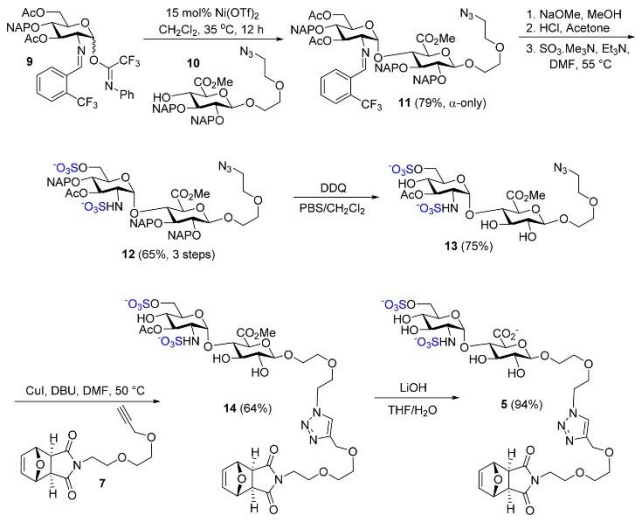

Figure 31. Stereoselective synthesis for monoantennary sulphate saccharide-modified oxanorborneneimide reported by Nguyen et al.[240] Reprinted with permission from ref. 240. Copyright 2017 American Chemical Society.

Sialic acids are negatively charged monosaccharides found on the non-reducing termini of glycans on the surface of cell membranes. They play a significant role in cell recognition. Glycoproteins rich in sialic acid are known to be expressed by cancer cells with high metastatic potential,[238] enabling them to leak into the bloodstream. In 2016, Olsen et al. conducted a study focusing on the infection process of influenza viruses,[239] focusing on hemagglutinin (HA) trimer present on the virus surface that binds to the sialic acid receptors, which can be inhibited by the presence of other sialyl-terminated oligosaccharides. It is also known that mucins present on the mucosal surface of the organisms contain large amounts of sialic acid and act as an effective antiviral barrier. Taking this into consideration, Olsen et al. synthesised mucin-like brush polymers via the "grafting-through" polymerisation of norbornenimide monomers modified with sialic acid residues at the terminus of the side chain. Using click chemistry, they introduced sialyllactose, which has a sialic acid attached to lactose, into the chain ends of norbornenimide monomers, and obtained polymers by ROMP using G3. (Figure 30) Further, they successfully synthesised copolymers with varying ratios of glycosylated monomers and polymers with different degrees of polymerisation. In addition, they obtained polymers with high molecular weights up to 400k and narrow molecular weight distributions at high conversion rates. Results of erythrocyte aggregation inhibition experiments using human influenza strain A/WSN/1933 (H1N1) indicated that the antiviral activity of the obtained brush polymer greatly depends on the molecular structure, and that the effect is greater with higher molecular weight. Additionally, it has been clarified that the shorter OEG spacers between sugar chains and main chains, the greater the effect. The resulting polymers were added in vitro on modified Madin-Darby canine kidney cells (MDCK-SIAT1-CMV-PB1), and their resistance to infection from GFP-labeled modified viruses was compared to that of mucin. The results showed that homopolymers with higher molecular weight

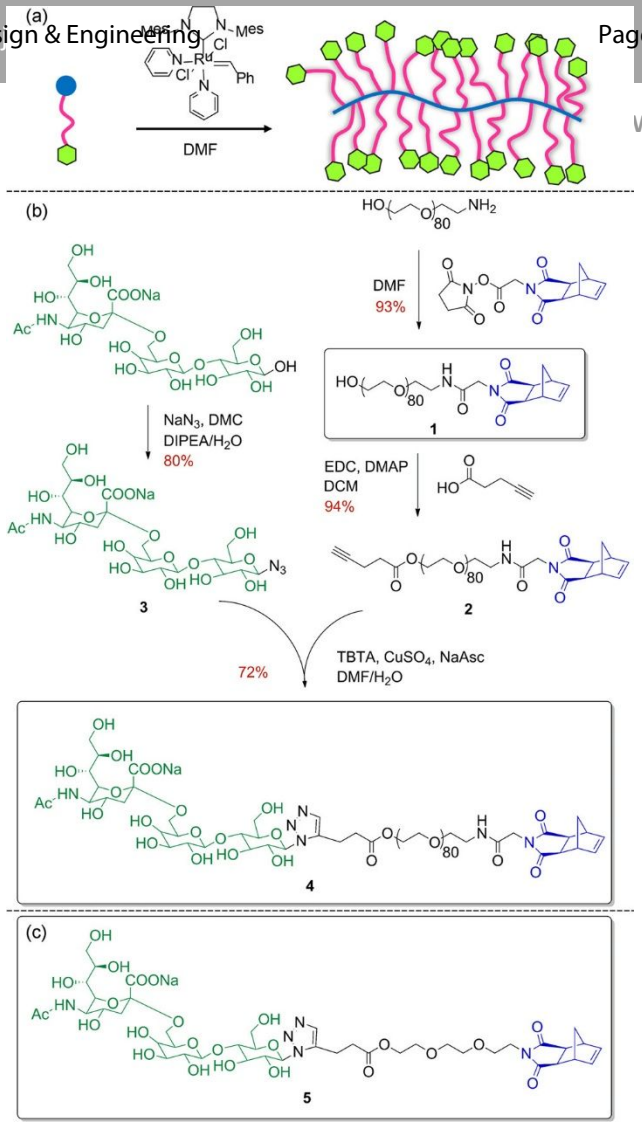

Figure 30. Synthesis of sialic acid functionalised polynorbornenimides reported by Olsen et al.[239] The monomers were synthesised by Huisgen cycloaddition using azidated sialyllactose and α -norbornenyl, ω-alkynyl PEG. Reprinted with permission from ref. 239. Copyright 2014 American Chemical Society.

derived from monomers with long OEG spacers exhibited a higher ability to inhibit infection due to the multivalency effect. The specific binding of proteins to sugars exhibits diverse biological functions through signal transduction in cell-cell adhesion, cell proliferation, and immune defense mechanisms. In most cases, sugar-binding proteins, i.e., lectins, often do not undergo major changes in their domain structure upon binding to sugar chains, and intracellular signal transduction is mainly caused by the interaction of lectins with multivalent sugar ligands, leading to multimerisation and clustering of the lectin receptor. This enhancement of the interaction by the "cluster glycoside effect" encourages research on the polymerisation of glycosylated monomers to mimic the structure of natural polysaccharides and realise their functions as synthetic multivalent sugar-functional ligands. Nguyen et al. focused on heparinase, a β-endoglucuronidase, which directs the cleavage site to the hydrolysis site of the enzyme when it degrades the GlcAβ(1,4)GlcN glycosidic bonds inside heparan sulphate proteoglycans using two highly positively charged domains (HBD-1 and NBD-2).[240] (Figure 31) They synthesised a monoantenna-type norbornenimide monomer modified solely with GlcNS(6S)α(1,4)GlcA disaccharide and a diantenna-type monomer introducing GlcNS(6S)α(1,4)GlcA disaccharide and

GlcNS(6S) monosaccharide, which were polymerised using G3 to obtain 5-mer to 18-mer and 8-mer, respectively. The inhibition results of heparinase with the obtained polymers showed that it exhibited 1000-fold stronger inhibition than the monovalent one. Moreover, in the case of enzymes such as heparanase, which have a degradation active site in deep positions, the addition of monosaccharides works against the inhibition of activity, and the steric interaction limits the amount of substrate that can enter the pocket for inhibition. Nguyen et al. also reported monoantennary and diantennary sugar-modified monomers, and performed the ROMP of norbornenimide-type monomers modified with the monosaccharides α-mannose and β-glucose [241] In this study, the ROMP of three monomers modified with one α-mannose, two α-mannoses, and α-mannose and β-glucose was performed to obtain polymers with degrees of polymerisation ranging from 137 to 195. The binding behaviour of each polymer to concanavalin A, which is known to bind α-mannose very strongly, was analysed by isothermal titration calorimetry. The results show that hetero-bifunctional and homo-bifunctional diantennary polymers exhibit equally high binding affinity for concanavalin A. It is suggested that the proximity of non-binding β-glucose and binding α-mannose may have facilitated the interaction of bound α-mannose with β-glucose.

After the development of G2, polymers were synthesised using the subsequently developed G3 and HG2. As a result, polymers modified with more complex oligosaccharides could be synthesised. Heparin is a glycosaminoglycan that has been used as a blood anticoagulant for over a century. It is a type of heparan sulphate, which is a polymer of β-*D*-glucuronic acid or α-*L*-isuronic acid and *D*-glucosamine polymerised by 1,4 linkage. Heparin is characterised by a particularly high degree of sulfation compared to heparan sulphate. Previous studies have analysed the anticoagulant activity fraction of heparin and found that the structure of the anticoagulant active domain contains pentasaccharides. Based on this finding, synthetic glycopolymers with heparin epitopes can be considered as an alternative anticoagulant drug option to naturally occurring glycan epitopes.

In 2013, Hsieh-Wilson et al. synthesised norbornene monomers with a sulphated disaccharide unit based on the structures of Arixtra and Org31550. These are known anticoagulants for blood; they investigated the anticoagulant activity of the polymer obtained by the ROMP of this monomer.[242] (Figure 32) Interestingly, it was reported that potent anticoagulant activity developed upon the introduction of a disaccharide rather than the identified minimum unit, the pentasaccharide. This glycosylated polymer inhibits serine proteases FXa and FIIa by enhancing anti thrombin III and has been found to exhibit ex vivo blood coagulation activity similar to that of heparin and aliquestra, which are used in clinical practice. In this regard, a disaccharide epitope is sufficient if it can be presented multivalently on the polymer scaffold, and the high-density introduction of the epitope is due to its improved binding affinity. They also showed that the anticoagulant activity can be finely tuned by changing the degree of the polymerisation of the polymer synthesised by ROMP and the degree of sulphation of

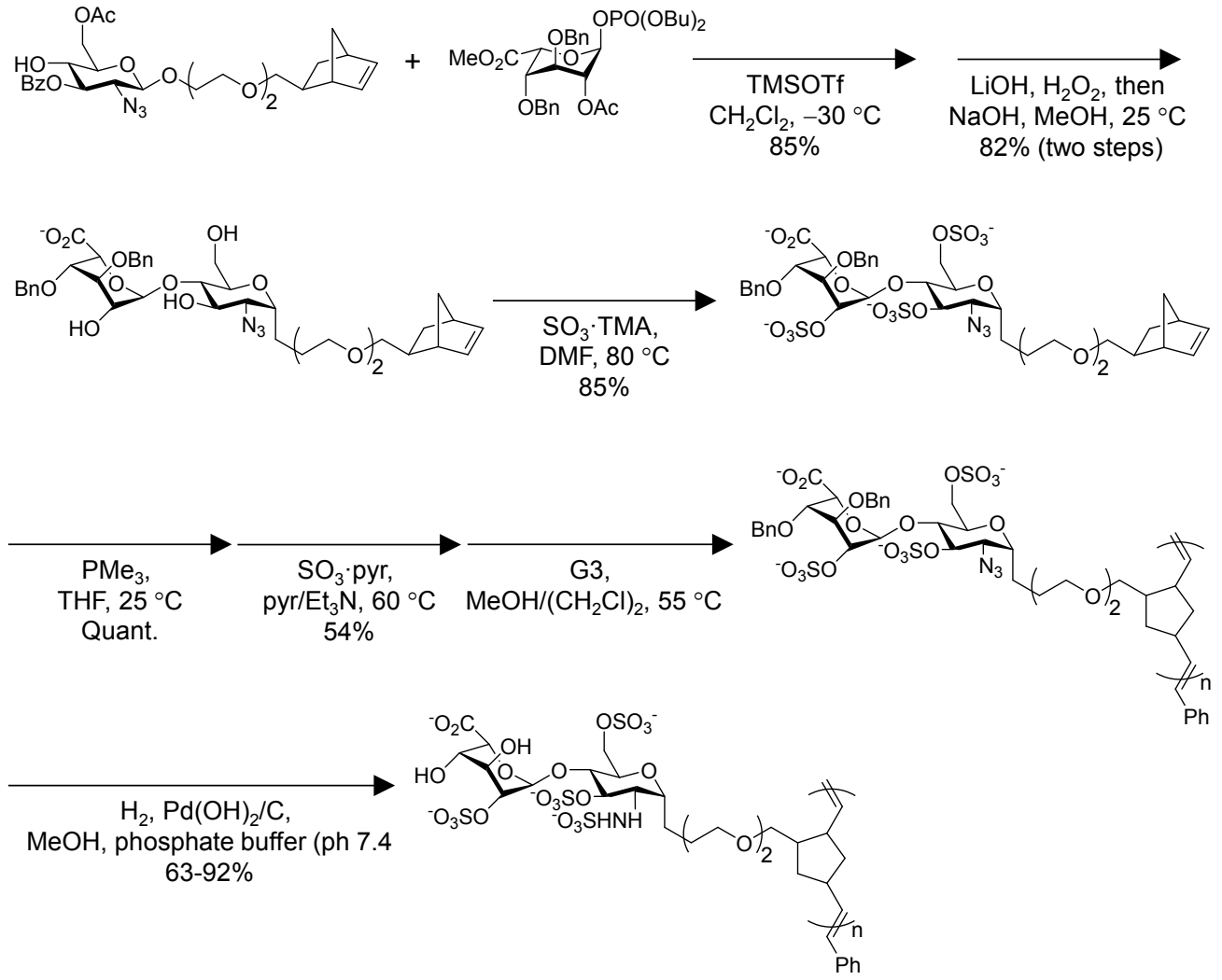

Figure 32. Synthesis of tetrasulphated disaccharide-modified polynorbornene reported by Hsieh-Wilson et al.[242] Pyridine ligated G3 was used for ROMP.

the sugar chains. They also reported the synthesis of heparan sulphate-mimetic polymers that allow the modulation of chemokine activity.[243] Focusing on the fact that heparan sulphate glycosaminoglycans have disaccharide subunits, four types of sulphated disaccharides with different degrees of sulphation have been prepared by synthesising disaccharide precursors from protected units of iduronic acid and glucosamine, and sulphating the precursors with pyridine-sulphur trioxide complexes after deprotection. The disaccharide was introduced as a side chain of norbornene and then polymerised by ROMP using G3, and the obtained polymer was used in subsequent evaluations. Among the polymers, the trisulphated sugar chains with the highest degree of sulphation bind to RANTES with nanomolar order affinity and CCR3-dependent cellular responses without affecting the components of the blood coagulation cascade. In other words, this polymer has the ability to antagonise various heparan sulphate-binding proteins that are clinically relevant, such as atherosclerosis, cancer, and autoimmune diseases.

4.5 Fluorescent dyes

Molecular labeling with fluorescent molecules is highly valuable for visualising the interaction between bioactive substances and cells. ROMP can be utilised to synthesise polymers labeled with various fluorescent molecules for use as polymeric biomaterials, which can be further employed for fluorescence microscopy imaging and fluorescence spectroscopy measurements. Visualisation of polymers by fluorescent labeling also allows us to track the microstructure of the polymer, the environment around the molecule, and in areas such as drug delivery systems (DDS), the uptake behaviour of the drug into the cells. Methods for modifying polymers with fluorescent probes include synthesising monomers with fluorescent molecules and copolymerising them with other monomers, introducing fluorescent molecules into initiators or terminators for the polymerisation, or introducing fluorescent molecules into polymers through polymer modification reactions. Although any of these methods can be used in polymer synthesis using ROMP, copolymerisation of fluorescently labeled monomers is the preferred method for synthesising fluorescently labeled polymers using norbornene derivatives. Various types of fluorescent molecules can be introduced, as long as they can coexist with the metathesis catalyst used, and their structure

does not interfere with the reaction activity of the monomer. For example, coumarin,[244] DABCYL, fluorescein,[208,236,245] EDANS, Anthracene, Rhodamine B,[207,208,244,246-248] 7-chloro-4-nitrobenzo-2-oxa-1,3-diazole (NBD),[244,249] Cy5.5,[250] Oregon Green,[251] indocyanine green,[195,252-254] perylene diimide,[255] 9,10-diphenylanthracene,[208] pyrene,[256] fluorene,[257] and near-infrared (NIR) fluorescent cyanine,[258] can all be used.

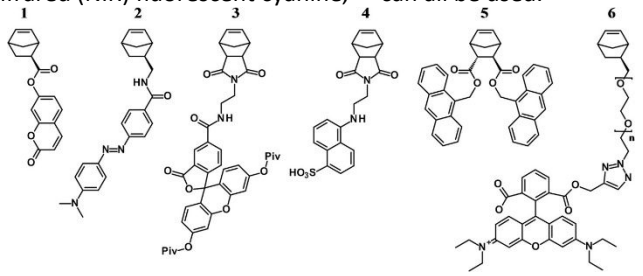

Figure 33. Fluorescent labeled ROMP monomers[244] 1) coumarin, 2) DABCYL, 3) fluorescein, 4) EDANS, 5) anthracene, and 6) rhodamine B. Reprinted with permission from ref. 244. Copyright 2013 John Wiley and Sons.

Lienkamp et al. synthesised derivatives of oxanorbornenimide and 5-norbornene-2-carboxylic acid amide, modified with nitrobenzofurazan, coumarin, and rhodamine B.[244] (Figure 33) They synthesised polymers that can be used as fluorescent probes in the biomedical field by copolymerising these fluorescently labeled monomers with oxanorbornene derivatives having sulfobetaine, *t*Boc-protected guanidine, or *t*Boc-protected amine. Although the polymers were not used for staining cells or tissues in this report, corresponding fluorescent polymers were found to cover the surfaces of the model-coated polyurethane foams.

The molecular labeling using fluorescent molecules as shown above has become a widely used technique. In addition to this, the use of nitroxide radicals as imaging labels can be introduced. Nitroxide radicals have a stable unpaired electron (radical) within the molecule and have been used as redox-responsive contrast agents for magnetic resonance imaging (MRI) and electron spin resonance (ESR) to visualise the redox dynamics of living organisms. Johnson et al. reported on ESR and MRI imaging using nitroxide radicals as a labeling agent in a series of studies using their bottle-brush polymer.[259-265] As an example, they introduced near-infrared fluorescent probe Cy5.5 and MRI probe spirocyclohexyl nitroxide (Chex) into a norbornene imide monomer and co-polymerised them to synthesise redox-responsive bottle-brush polymer.[262] (Figure 34) The fluorescence of this molecule, named dual-modality organic radical contrast agent (ORCAFluors), is partially quenched by surrounding nitroxides. However, when exposed to reducing molecules such as ascorbic acid or glutathione, the nitroxide is reduced and an increase in luminescence intensity is observed. In fact, in vivo and in vitro fluorescence emission was dependent on the concentration of ascorbic acid, particularly in vivo demonstrating the highest level of contrast among organic MRI contrast agents.

4.6 Antifouling and antimicrobial functional groups

Host defense peptides (HDPs), also known as antimicrobial peptides, are produced in all organisms including plants, insects, amphibians, and mammals, as a natural defense mechanism against pathogenic bacteria. More than 3400 types of antimicrobial peptides have been identified.[266] For example, Magainin II, isolated from the skin of the Xenopus laevis, is an oligopeptide consisting of 23 amino acids, with four positively charged lysine residues in the molecule, making the entire molecule positively charged. Similarly, most of the identified antimicrobial peptides are cationic peptides. Their mechanism of antimicrobial action is through interaction with negatively charged cell membranes, subsequent aggregation, and disruption through the cell membrane of pathogenic bacteria and microbes.[267]

Attempts to mimic this function using synthetic polymers have long been reported. For example, functionalised polymers with quaternary ammonium,[268] sulfonium,[269] or phosphonium[270] structures have been synthesised as cationic polymers, and their strong antimicrobial activity has been demonstrated. In order to endow polymers with cationic charges, active species that can coexist with the functional group to be introduced are selected in the polymer synthesis. Most polymers have been synthesised through the polymerisation of vinyl monomers bearing cationic charges with radicals as the active species. Although tolerance to unprotected amino groups still remains a challenge, polymer synthesis by ROMP has evolved into a powerful tool for the synthesis of cationic amphiphilic polymers with the advent of highly functional group tolerant metathesis catalysts.

In 2004, Tew and Coughlin et al. reported the synthesis of amphiphilic polynorbornene derivatives with tailored hemolytic and antimicrobial activities.[271,272] They synthesised four water soluble polynorbornenimide derivatives with ammonium cations in the side chains. These polymers have backbones with different branched alkylidene substituents and exhibit different hydrophobicities depending on the substituted alkylidenyl side chain. The average molecular weight of the resulting polymers can be tuned, and in all cases have a narrow molecular weight distribution. Although G3 was used in the polymerisation, amino-functionalised ¬*t*Boc protected monomers were used for polymerisation, and the obtained polymers were deprotected after polymerisation to convert them into water-soluble polymers with ammonium cations. They evaluated the hemolytic activity of the obtained polymers using erythrocytes and the antibacterial activity using Escherichia coli and Bacillus subtilis. They found that polymers without hydrophobic residues did not show strong antibacterial activity, and the activity changes with the length of side chains. In addition, the chain length also affects hemolytic properties, the longer the chain introduced into the polymer, the higher the hemolytic property. They also succeeded in obtaining a polymer with both antimicrobial activity and non-hemolytic properties. They subsequently reported similar studies[273] on the impact of the number of cations on the monomer unit,[274,275] hydrophobic residues,[276] and polynorbornene with different structural

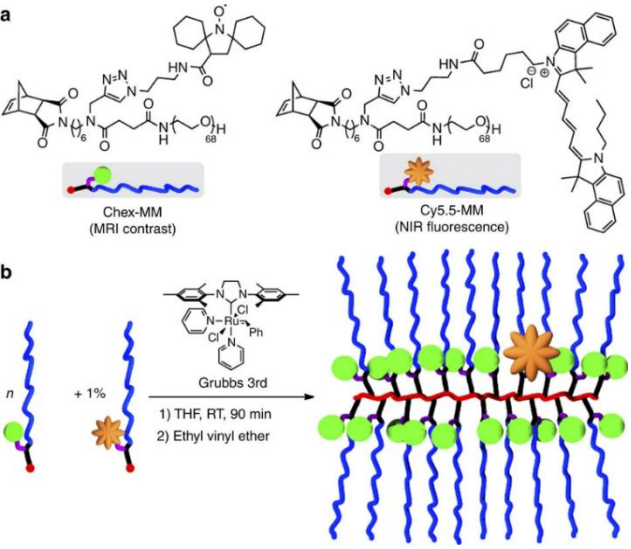

Figure 34. General procedure for the graft-through ROMP synthesis of ORCAFluor imaging agents reported by Johnson et. al.[262] Reprinted with permission from ref. 262. Copyright 2014 Springer Nature.

cations.[277,278] (Figure 35) Their findings indicate that an increase in the number of amino groups (i.e., number of cations) does

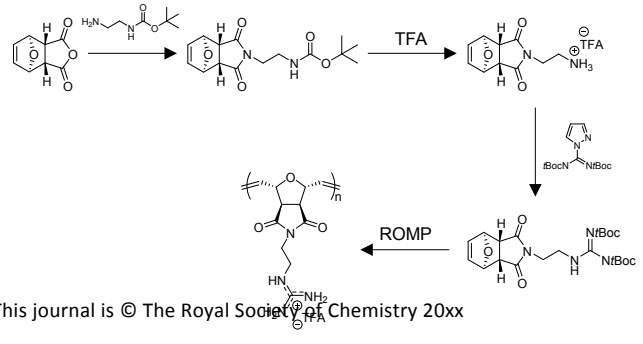

Figure 35. Synthesis of antimicrobial poly(guanidinium oxanorbornene) (PGON) reported by Tew et al.[278]

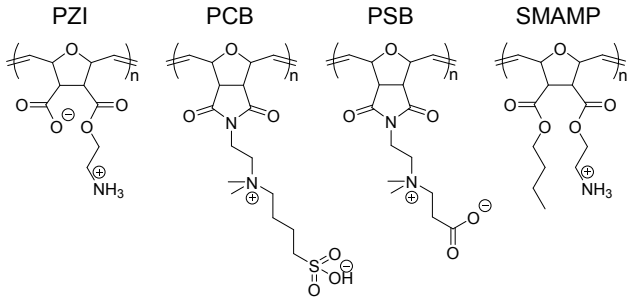

Figure 36. Functionalised polyoxanorbornenes reported by Lienkamp et al.[281] Monomers bearing zwitterion can be polymerised by G3 to produce PCB and PSB. Ammonium bearing polymers PZI and SMAMP were synthesised via the ROMP of *t*Boc protected monomers and a deprotection process.

not alter the antimicrobial activity, whereas polymers with guanidinium displayed remarkably high antimicrobial activity.

In addition to the introduction of cationic functional groups, the introduction of zwitterionic functional groups is often used to impart antimicrobial properties to polymeric materials. Zwitterionic polymers have long been studied as water-soluble (meth)acrylate polymers with functional groups such as phosphobetaine, sulfobetaine, and carboxybetaine on their side chains. Since these polybetaines are water-soluble, the polymers need to be fixed to the material surface. For example, they can be coated onto other materials by copolymerising them with a water-insoluble hydrophobic monomer, or they can be grafted onto the material's surface as a polymer brush by graft-to, graft-from, or graft-thorough methods. The resultant surfaces coated with polybetaines are known to exhibit extremely high antimicrobial and protein non-adsorption properties, commonly referred to as antifouling properties. (Oxa)norbornenedicarboxylic anhydride, which is often used as a starting material for the synthesis of functionalised monomers in ROMP, enables easy incorporation of an anionic charged carboxylic acid and a cationic charged functional group onto a single monomer unit.[279] For example, Lienkamp et al. obtained a monomer by the reaction of exo-7-oxabicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylic acid anhydride and *t*BOC protected ethanolamine.[280] This monomer can be polymerised using G3, followed by deprotection with hydrochloric acid to afford a poly(oxanorbornene)-based zwitterion (PZI), bearing both a carboxylic acid and an amine on a single oxanorbornene monomer unit. Since this polymer is water soluble, a solution containing the polymer and pentaerythritol-tetrakis(3-mercaptopropionate) was spin-cast onto a benzophenone-modified substrate, and then UV irradiated to obtain a cross-linked polymer film by a thiol-ene click reaction. They further synthesised polycationic polymers (synthetic mimics of antimicrobial peptides, SMAMP) with butyl esterified carboxylic acid of PZI,[280-283] and compared their functions with those of sulfobetaine (PSB)[281,282] and carboxybetaine (PCB)[281,283] in the side chains.[281,284] (Figure 36) They reported that PZI is a material with both antimicrobial and protein non-adhesive properties, whereas PSB shows protein non-adsorption but not antimicrobial properties. However, SMAMP has antimicrobial properties but not protein adsorption. Furthermore, PZI was found to kill Staphylococcus aureus and

Escherichia coli almost completely and reduce protein adsorption to below the detection level of surface plasmon resonance spectroscopy, effectively reducing the formation of biofilms. In addition, cell culture on the film showed that the polymer is compatible with human keratinocytes. Polymers possessing antibacterial, protein-repellent, anti-biofilm-forming, and cytocompatible properties are useful as coating materials for medical devices, wound dressings, and catheter coatings where biofilm control is necessary.

4.7 Drugs for Drug Delivery System (DDS)

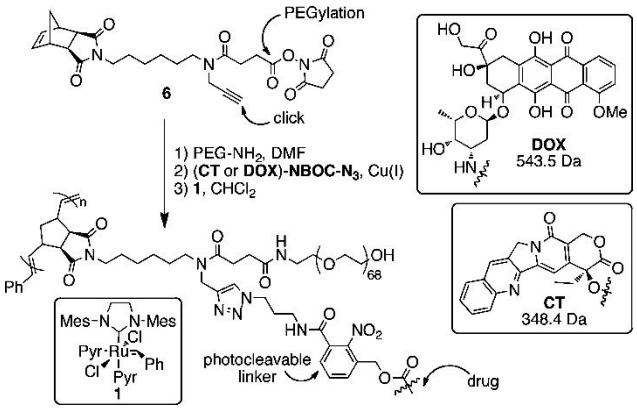

Figure 37. Synthesis and structure of poly(norbornene)-PEG brush polymers with DOX and CT reported by Grubbs et al.[285] Reprinted with permission from ref. 285. Copyright 2017 American Chemical Society.

Drug delivery systems (DDS) have been extensively studied owing to its potential to deliver drugs to the required site, in the required amount, and for the required time period. Various methods have been employed to load bioactive drugs onto synthetic polymers, including covalently bonding to the chain-ends or side-chains, encapsulating the drugs in micelles composed of amphiphilic block copolymers, and loading in cross-linked gel-like polymers.

In 2010, Grubbs et al. synthesised drug-loaded bottlebrush polymers by graft-through ROMP of bivalent norbornenimide macromonomers modified with a PEG chain and a drug.[285] (Figure 37) The anti-cancer drugs camptothecin (CT) and doxorubicin (DOX) were chosen, and the drug was bound to the monomer via a photodegradable nitrobenzyl group. This design allowed for controlled drug release upon UV light irradiation. G3 was used for ROMP, and polymers with molecular weights from 33k to 499k, ranging from 10- to 135-mers, were obtained. The obtained polymers were dissolved in an aqueous solution and added to human mammary carcinoma cells, MCF-7, to investigate the concentration dependence of viability with and without UV irradiation. The results showed that the drug conjugated brush-polymer was non-toxic to the cells, even at concentrations exceeding 10-fold those of free CT and DOX, and UV irradiation released the drug and exhibited anticancer activity. Although the use of UV light to cleave the linker for drug release presents challenges in terms of light penetration into tissues, the ROMP method has shown promise in the development of drug delivery systems.

Johnson, who developed the bivalent norbornene imide platform under Grubbs,[285,286] has continuously reported on the application of the above-mentioned method to polymer

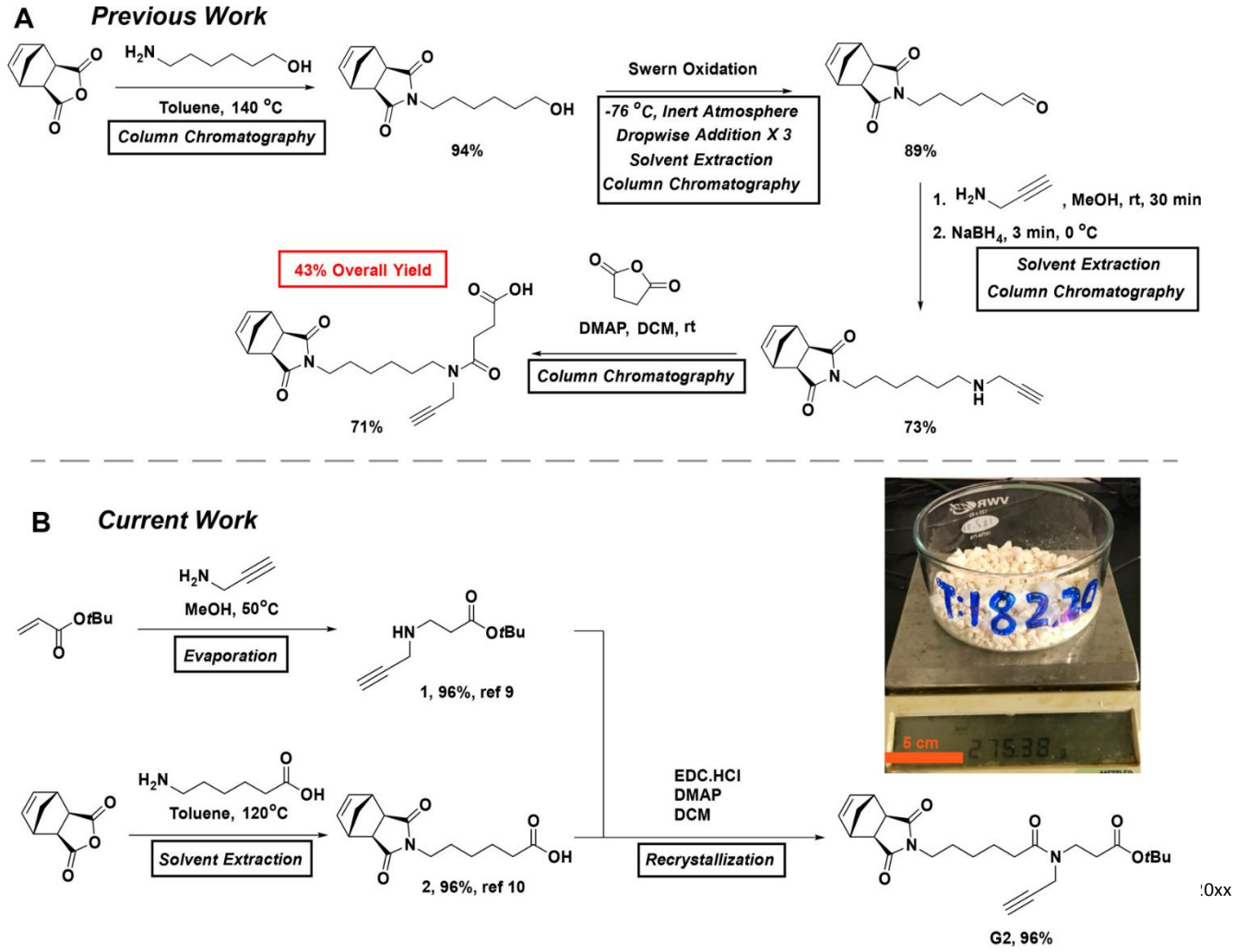

Figure 38. Synthesis pathway to give multivalent norbornene imide monomer reported by Johnson et al.[285,289] B) shows the improved synthetic route that attains exceedingly high yields. Reprinted with permission from ref. 289. Copyright 2018 American Chemical Society.

synthesis and biomaterials.[259,261-263,287,288] In 2018, Johnson et al. developed a straightforward monomer synthesis pathway (Figure 38) that affords multivalent norbornene imide in extremely high yield, high efficiency, and simplicity,[289] achieving the establishment of a modular, scalable, and well-defined bottlebrush prodrug (BPD) platform.[263-265,290-295]

Recently, they reported using this BPD platform to explore combinations of drugs for optimal cancer treatment effects.[295] In this report, they conducted a study aimed at treating multiple myeloma, and demonstrated that a monotherapy of BPD based on a proteasome inhibitor (bortezomib) can slow tumor progression in vivo. They also showed in vitro that a mixture of bortezomib, pomalidomide, and dexamethasone BPD exhibited synergistic, additive, and antagonistic effects, demonstrating a pattern distinct from that of the corresponding free drugs. BPDs carrying a statistical mixture of the three drugs in a synergistic ratio outperformed the free drug combination at the same ratio. Furthermore, the triplex PBDs exhibited superior performance even compared to the same ratio mixture of single-drug PBDs.

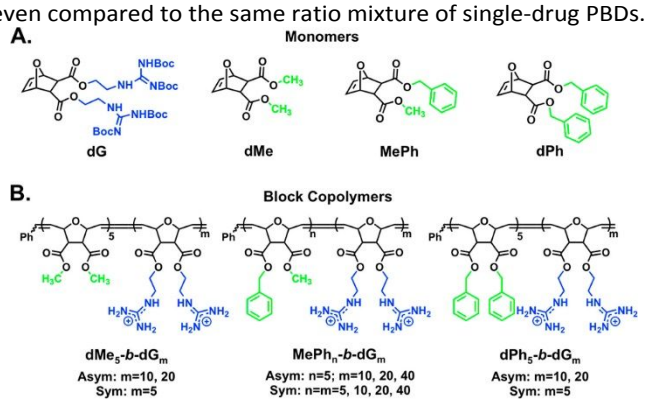

Figure 39. Monomer and polymer examples reported by Tew et al.[299] A) Monomer structures. B) Polymer structures. Blue represents cationic moieties, and green represents hydrophobic moieties. Reprinted with permission from ref. 299. Copyright 2016 American Chemical Society.

In 2005, Nguyen et al. performed the ROMP of doxorubicin-modified 5-norbornen-2-ols using G1.[296] They showed that the block copolymerisation of PEG-modified and DOX-modified norbornene resulted in a block copolymer with an average molecular weight of 13k and a molecular weight distribution of 1.3. The resulting block copolymer formed nanoparticles in water with a size of 230 nm. DOX was introduced and linked via a carbamate group, and the drug can be released by acid-cleavage of the bond. They have shown that DOX was released upon placing the particles in an environment of pH = 4 at room temperature. They further showed that by reducing the size of these particles to 65 nm and modifying the OEG chain terminus with 3'-amino oligonucleotides, the particles were able to promote uptake into SKOV-3 cells and exhibit high cytotoxicity.

Tew et al. reported a number of studies on the synthesis of guanidine-conjugated polyoxanorbornenes using ROMP.[297-301] Applications utilising the cationic properties of the resulting polymer have been investigated, and attempts have been made to apply the polymer to siRNA and protein drug delivery systems. The basic polymer synthesis method involves the reaction of oxanorbornene dicarboxylic anhydride with tBoc-protected 1,3-di-Boc-2-(2-hydroxyethyl)guanidine, followed by ROMP and deprotection to the guanidino group. Copolymers were prepared using monomers in which guanidino and phenyl groups are introduced into oxanorbornene, owing to the fact that amino acids constituting membrane-permeable proteins are composed of cationic and hydrophobic units, and various investigations were conducted. G3 has been exclusively used for ROMP, and in all cases, polymers with narrow molecular weight distribution and living characteristics were synthesised. Furthermore, the structure of optimal block copolymers for siRNA and protein internalisation was investigated, with valuable insights reported on the density of cationic functional groups in the guanidine-modified segment and the chemical structure of hydrophobic units in the hydrophobic segment. (Figure 39) In a recent study, the hydrophobic unit motif was sought from amino acids, and block copolymers of monomers with methyl (alanine), phenyl (phenylalanine), and indole (tryptophan) groups introduced as hydrophobic substituents and monomers modified with guanidino groups were synthesised to determine drug delivery efficiency by using green fluorescent protein and Cre recombinase. According to their report, the performance of the polymer as a DDS carrier cannot be predicted based solely on the function derived from the structure of the side chain. The hydrophobicity of the whole molecule dictates both internalisation and activity as a protein carrier. In addition, studies using Cre discovered carriers that exhibit high recombination efficiency despite having significantly low internalisation efficiency, leading to the

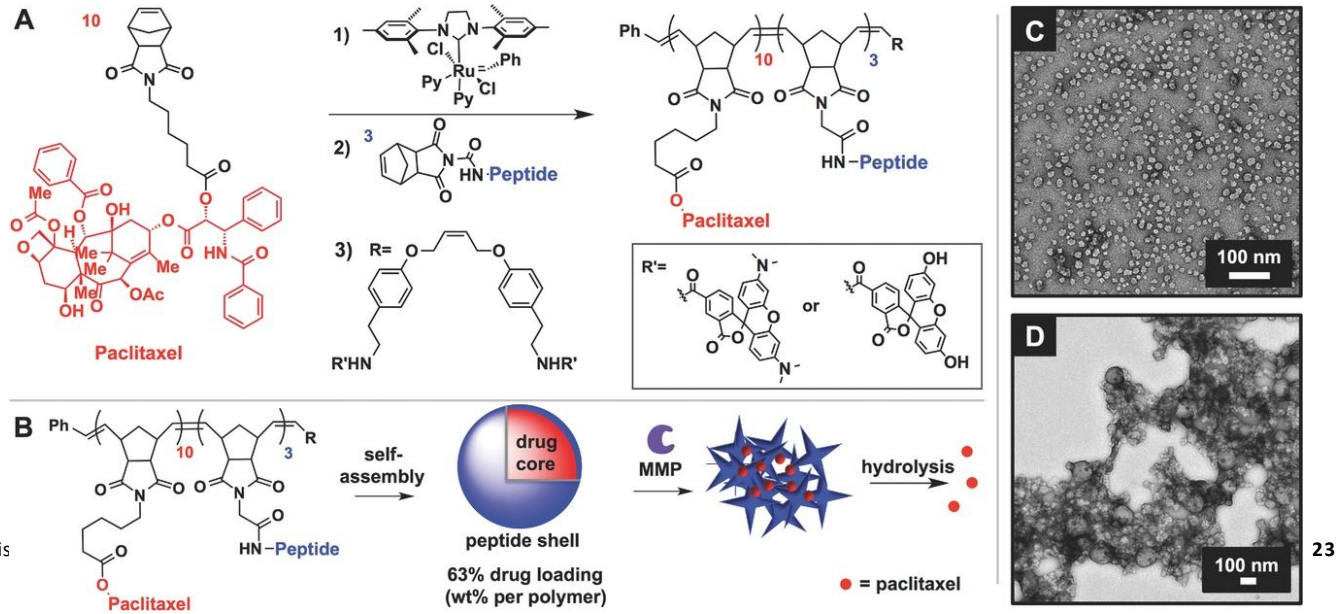

Figure 40. Synthesis of drug-loaded, enzyme responsive micellar nanoparticles reported by Gianneschi et al.[302] Reprinted with permission from ref. 302. Copyright 2015 John Wiley and Sons.

establishment of a measure of intracellular availability (IA) of a single molecule.

Gianneschi et al. investigated cancer-targeted DDS, and reported the synthesis of core-shell micellar anti-cancer drug carriers incorporating oxaliplatin, cisplatin, and paclitaxel.[302-304] They chose norbornenimide as the monomer's modular framework, a homopolymer from a paclitaxel-modified monomer or a random copolymer from a benzyl-modified monomer and oxaliplatin- or cisplatin-modified monomers were used for the hydrophobic core. Monomers modified with OEG or peptides were used for the hydrophilic shell. For example, in 2015, they reported 20 nm- diameter nanoparticles for DDS that can accumulate in tumours. They employed a peptide sequence that recognises matrix metalloproteinases (MMPs), tumour markers overexpressed in cancer cells, as the hydrophilic shell and a paclitaxel-incorporated segment as the hydrophobic core. (Figure 40) In addition, fluorescein or rhodamine is introduced at the chain end of this polymer, and it is designed in a manner that allows the tracking of the accumulation of particles by Förster resonance energy transfer (FRET). Nanoparticles synthesised from these polymers undergo morphological changes upon binding to MMPs, resulting in hydrolysis of the paclitaxel binding site to release the drug. In animal experiments using these nanoparticles, accumulation of the polymer in tumour sites was observed, and they reported that the growth of xenografted HT1080 cells was found to have been inhibited for approximately 2 weeks after administration. The nanoparticles obtained from the modified polynorbornene prepared by ROMP can encapsulate a variety of drugs and can be applied to other drug-carrying systems.

DDS based on polymer micelles composed of (oxa)norbornene derivatives with OEG-modified segments as the hydrophilic shells and drug-bearing segments as the hydrophobic core have been extensively investigated, and a wide variety of drug molecules have been introduced. Examples of such drugs include birabresib,[293] bortezomib,[295,305] camptothecin,[285,288] cisplatin,[288,306-308] coumarin,[309-312] DACH-platin,[250] dexamethasone,[295] doxorubicin,[261,285-288,296,313-318] folate,[253,254,256] isoniazid,[319,320] paclitaxel,[217,258,290,292,310,321-323] piplatine,[258] pomalidomide,[295] rifampicin,[319] retinol,[320,324] and vorinostat,[246] which have all demonstrated efficacy comparable to that of the introduced agent.

5. Conclusions

In this review, we have demonstrated the efficacy of polymer synthesis via ROMP of functionalised cyclic alkenes as an exceptionally powerful method of producing functionalised polymers. Although polymer synthesis using cyclic alkenes may face limitations such as difficulties in monomer preparation and low stability of highly strained monomers, ROMP has facilitated the synthesis of functionalised polymers that are challenging to prepare using other active species. Introducing functional groups into monocyclic monomers, especially those with 8-membered rings, is relatively straightforward and the resulting compounds exhibit adequate chemical stability and high reactivity towards ROMP. Among multicyclic compounds, functionalised monomers based on (oxa)norbornene are particularly well-suited for synthesising functionalised polymers as they offer a platform for realising living polymerisation, supported by the advent of highly active catalysts that can control the primary structure of the resulting polymer. To date, most polymers synthesised by ROMP for application to biomaterials have been primarily based on norbornene as a module, which is now a well-established methodology. Advances in metathesis catalysts will enable the production of previously unattainable biomaterials in the future.

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Notes

The authors declare no competing financial interest.

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Abbreviations

ADMET: acyclic diene metathesis
AE: acrosomal epithelialisation
ATRP: atom transfer radical polymerisation
AR: acrosome reaction
AROMP: alternating ring-opening metathesis polymerisation
*t*BDMS: *tert*-butyl dimethylsilyl
BSA: bovine serum albumin
COE: cyclooctene
COD: 1,5-cyclooctadiene
COSY: correlation spectroscopy
*m*CPBA: *m*- chloroperoxybenzoic acid
CPP: cell penetrating peptide
CS: chondroitin sulfate
CT: camptotecin

DABCYL: 4-{[4-(dimethylamino)phenyl]azo}benzoic acid
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCM: dichloromethane
DDQ: 2,3-dichloro-5,6-dicyano-p-benzoquinone
DDS: drug delivery system
DFT: density functional theory
DIPEA: *N,N*-diisopropylethylamine
DMF: *N*,*N*-dimethylformamide
DMSO: dimethyl sulfoxide
DNA: deoxyribonucleic acid
DOX: doxorubicin
EDANS: 5-[(2-Aminoethyl)amino]naphthalene-1-sulfonic acid
EG: ethylene glycol
ELP: elastin-like polypeptide
FRET: Förster resonance energy transfer
G1: first-generation Grubbs catalyst
G2: second-generation Grubbs catalyst
G3: third-generation Grubbs catalyst
GAPDH: glyceraldehyde-3-phosphate dehydrogenase
GFP: green fluorescent protein
GPC: gel permeation chromatography
HA: hemagglutinin
HBTU: hexafluorophosphate benzotriazole tetramethyl uronium
HDP: host defense peptide
HG2: Hoveyda-Grubbs second-generation catalyst
HH: head-to-head
HIV: human immunodeficiency virus
HOBt: 1-hydroxybenzotriazole
HT: head-to-tail
HUVEC: human umbilical vein endothelial cells
IA: intracellular availability
LAH: lithium aluminium hydride
LCST: lower critical solution temperature
LNA: locked nucleic acid
MAP: monoaryloxide pyrrolide
MMP: matrix metalloproteinase
MRSA: methicillin-resistant Staphylococcus aureus
NBD: 7-chloro-4-nitrobenzo-2-oxa-1,3-diazole
NHC: *N*-heterocyclic carbene
NHS: *N*-hydroxy succinimide
NLS: nuclear-localising sequence
NMR: nuclear magnetic resonance
OEG: oligo ethylene glycol
PBS: phosphate-buffered saline
PCB: polycalboxybetaine
PCC: pyridinium chlorochromate
PEG: polyethylene glycol
PGON: poly(guanidinium oxanorbornene)
PNA: peptide nucleic acid
PSB: polysulfobetaine
PZI: poly(oxanorbornene)-based zwitterion
RAFT: reversible addition-fragmentation chain-transfer
RANTES: regulated on activation, normal T cell expressed and secreted
RCM: ring-closing metathesis
RNA: ribonucleic acid
mRNA: messenger ribonucleic acid
siRNA: small interfering ribonucleic acid
ROM: ring-opening metathesis
ROMP: ring-opening metathesis polymerisation
SEC-MALS: size exclusion chromatography - multi-angle light scattering
SMAMP: synthetic mimics of antimicrobial peptides
TES: triethylsilyl
TFA: trifluoroacetic acid
TFE: trifluoroethanol
THF: tetrahydrofuran
TIPS: triisopropylsilyl
TMS: trimethylsilyl
TT: tail-to-tail
UV: ultraviolet
VRE: vancomycin-resistant Enterococci

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