Synthesis of penicillin derived polymers utilising ring-opening metathesis polymerisation methodology

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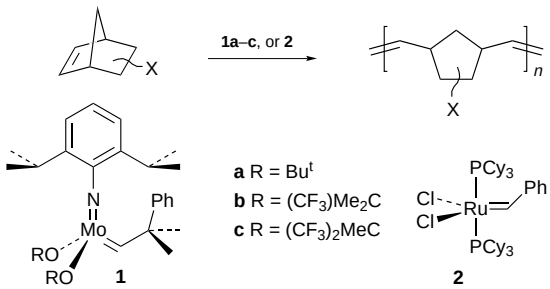
Penicillin functionalised poly(norbornene)s are synthesised *via* living ring-opening metathesis polymerisation using the ruthenium initiator {$RuCl_2(CHPh)[P(C_6H_{11})_3]_2$}.

There is currently much interest in the synthesis of new polymeric structures possessing unusual functionalities and/or molecular architectures. One of the most versatile approaches to the preparation of such polymers is the ring-opening metathesis polymerisation (ROMP) of strained ring systems, especially norbornenes, using well defined polymerisation initiators based upon molybdenum,[1] *e.g.* **1a**–**c**, or ruthenium,[2] *e.g.* **2**, as illustrated in Scheme 1. This process allows the preparation of polymers *via* a living polymerisation which gives excellent control of the molecular weight and polydispersity, and facilitates the synthesis of more complex polymer architectures such as block copolymers. The molybdenum based initiators **1a**–**c** also allow the alkene geometry within the polymer to be controlled, whilst ruthenium based initiator **2** is tolerant of a wide range of functional groups.

In recent reports, we have described the use of ROMP initiators **1a**–**c** and **2** to prepare polymers derived from amino acids[3] and from nucleic acid bases,[4] respectively. The synthesis of carbohydrate derived polymers has also been reported.[5]

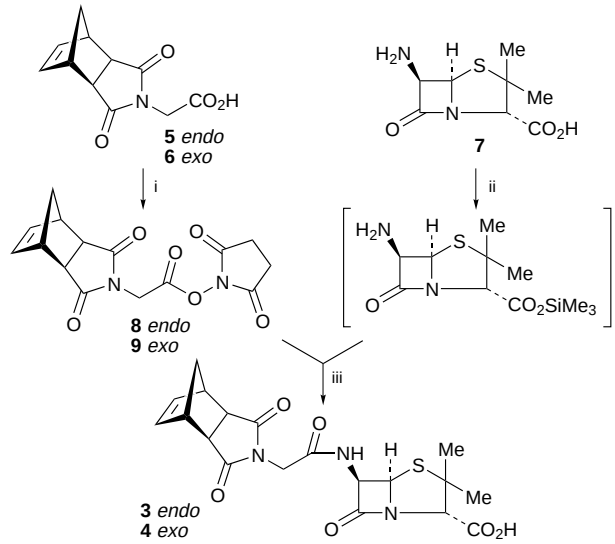
Here, we show how this methodology may be used to prepare polymers incorporating penicillin units. Penicillin was chosen as an archetypal, biologically active peptide, which is also susceptible to decomposition under a wide range of reaction conditions.[6] Thus the preparation of polymers incorporating this group would demonstrate both the ability to prepare polymers with potential biological activity, and illustrate the compatibility of the methodology with even the most sensitive of functional groups. Polymers derived from penicillin or other biologically active peptides have a number of potential applications: high molecular weight polymers may be suitable for the preparation of slow release capsules or bandages for the treatment of surface wounds, whilst low molecular weight oligomers may be able to deliver multiple copies of a drug to its site of action simultaneously, thus helping to circumvent problems of drug resistance. It should also be possible to prepare chromatography columns from polymers of this type, and to utilise these in isolating the biological receptors.



Scheme 1

The synthesis of the desired monomers **3** and **4**‡ was achieved as shown in Scheme 2, the preparation of *endo* and *exo* glycine derivatives **5** and **6** having been previously reported.[7] All attempts to couple activated derivatives (preformed acid chloride or *N*-hydroxysuccinimide ester) of acids **5** and **6** directly to (+)-6-aminopenicillanic acid (6-APA) **7** were unsuccessful, resulting in extensive decomposition of the penicillin ring. Eventually, we found that monomers **3** and **4** could be prepared by treatment of 6-APA first with bis-(trimethylsilyl)acetamide to protect the acid functionality,[8] followed, without isolation of the ester, by coupling with the *N*-hydroxysuccinimide esters **8** and **9**, and aqueous workup. Samples of monomers **3** and **4** prepared in this way contained silyl alcohol and/or silyl ether by-products which could not be removed without extensive decomposition, but were suitable for use in subsequent polymerisation reactions. So far, our polymerisation studies have focused on the *exo* derivative **4** which we have found to polymerise in a more controlled fashion than its *endo* isomer **3**.

Addition of initiator **2** to a stirred solution of **4** (10 equiv.) in acetone afforded a magenta solution which within a few minutes turned light brown and precipitated a beige solid. This suspension was stirred at room temperature for 22 h. The polymerisation was then terminated by addition of ethyl vinyl ether (50 μl) and the resultant solid collected and dried *in vacuo* for 2 h. It proved possible to follow the reaction of the closely related but more soluble silyl ester derivative of **4** by NMR spectroscopy in $CDCl_3$. The 270 MHz ^1H NMR spectrum of a sample containing the ruthenium initiator and 10 equiv. of Me_3Si-**4**, recorded a few minutes after mixing, is shown in Fig. 1. The sharp singlet resonance at δ 19.9 is attributable to the carbene hydrogen of unconsumed initiator, while the broadened resonance closeby is due to the carbene hydrogens of the [Ru]



Scheme 2 *Reagents and conditions*: i, DCC, *N*-hydroxysuccinimide; ii, $MeC(OSiMe_3)=NSiMe_3$; iii, H_2O

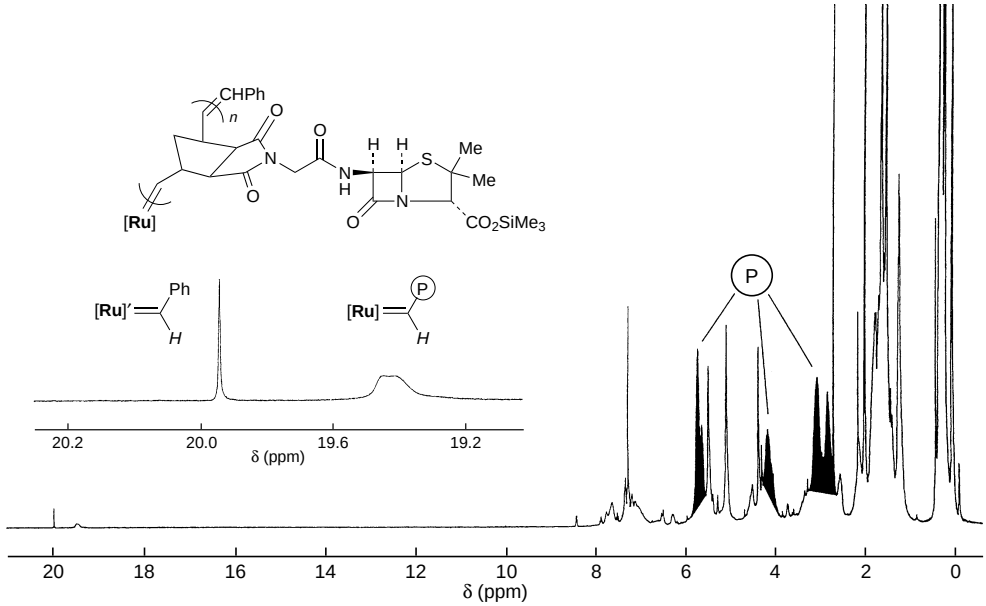


Fig. 1 270 MHz ^{1}H NMR spectrum ([^{2}H]chloroform) of the products arising from treatment of $\{RuCl_2(CHPh)[P(C_6H_{11})_3]_2\}$ with (Me_3Si-**4**) (10 equiv.); [Ru] = $[RuCl_2(PCy_3)]$, [Ru]′ = $[RuCl_2(PCy_3)_2]$

end-groups of the propagating polymer chains. The shaded resonances in the region δ 2–6 are attributable to protons attached to the hydrocarbon backbone of the ring-opened products. In the olefinic region (*ca.* δ 5.5–6.0) there are two principal resonances (shaded); the more intense signal is tentatively assigned to the vinylene hydrogens of the *trans* polymer, consistent with the predominantly *trans* products arising from polymerisations of other closely related glycine-functionalised monomers with this ruthenium initiator (typically 80–90% *trans*[9]).

An infrared spectrum on the isolated polymer shows that the penicillin ring system survives intact during the polymerisations; a characteristic high frequency absorption at 1770 cm^{-1} is observed for the β-lactam carbonyl. Attempts to further characterise the polymers by GPC were frustrated due to their insolubility in standard GPC solvents, and abnormal elution from the column when DMF was used as the GPC solvent. An approximate value for the number average molecular weight (M_n) could, however, be obtained from the ^{1}H NMR spectrum of living poly(Me_3Si-**4**); integration of the chain-end ruthenium carbene hydrogen resonance *versus* the olefinic hydrogens of the polymer backbone gave an approximate value for M_n of 11800, corresponding to *ca.* 24 repeat units.§ To date, unlike for thymine-functionalised poly(norbornene)s,[4] it has not proved possible to obtain good quality MALDI-TOF mass spectra on these polymers. Electrospray mass spectrometry on the other hand does give some, if limited, information on the molecular weight distributions of the resultant polymers. The negative ion electrospray mass spectrum in DMF–MeCN–H_2O of a polymer prepared from 10 equiv. of *exo*-monomer **4** and ruthenium initiator **2** shows molecular ion or fragment (loss of CO_2) peaks attributable to polymer chains containing 8–17 monomer units. The corresponding positive ion spectrum shows a series of fragment peaks attributable to consecutive loss of penicillin residues from the polymer chains. Thus, in addition to providing information on the molecular weights of the polymer chains, the mass spectra also provide corroborative evidence that the β-lactam ring survives intact.

In conclusion, we have shown that ROMP methodology using well-defined ruthenium initiators is compatible with the penicillin ring system. Our work on the synthesis of biomimetic polymers using ROMP methodology is continuing, and further results will be presented in due course.

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Footnotes

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‡ All new compounds were characterised by ^{1}H NMR, IR, specific rotation and mass spectrometry. *Selected data* for **3**: mp 64 °C, with decomposition; $[\alpha]_D^{21}$ + 103.6 (*c* 1, MeOH). For **4**: mp 75 °C, with decomposition; $[\alpha]_D^{21}$ + 163.8 (*c* 1, MeOH).

§ It is not possible to perform a similar end-group analysis on the isolated polymer due to overlap of the end-group resonances with the signals of other groups within the polymer.

References

1 See, for example: R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare and M. O'Regan, *J. Am. Chem. Soc.*, 1990, **112**, 3875; G. C. Bazan, R. R. Schrock, H.-N. Cho and V. C. Gibson, *Macromolecules*, 1991, **24**, 4495; G. C. Bazan, E. Khosravi, R. R. Schrock, W. J. Feast, V. C. Gibson, M. B. O'Regan, J. K. Thomas and W. M. Davis, *J. Am. Chem. Soc.*, 1990, **112**, 8378.

2 For leading references, see: D. M. Lynn, S. Kanaoka and R. H. Grubbs, *J. Am. Chem. Soc.*, 1966, **118**, 784; P. Schwab, M. B. France, J. W. Ziller and R. H. Grubbs, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2039; Z. Wu, S. T. Nguyen, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1995, **117**, 5503.

3 M. P. Coles, V. C. Gibson, L. Mazzariol, M. North, W. G. Teasdale, C. M. Williams and D. Zamuner, *J. Chem. Soc., Chem. Commun.*, 1994, 2505.

4 V. C. Gibson, E. L. Marshall, M. North, D. A. Robson and P. J. Williams, *Chem. Commun.*, in the press.

5 K. H. Mortell, R. V. Weatherman and L. L. Kiessling, *J. Am. Chem. Soc.*, 1996, **118**, 2297; C. Fraser and R. H. Grubbs, *Macromolecules*, 1995, **28**, 7248; K. H. Mortell, M. Gingras and L. L. Kiessling, *J. Am. Chem. Soc.*, 1994, **116**, 12053; K. Nomura and R. R. Schrock, *Macromolecules*, 1996, **29**, 540.

6 R. J. Simmonds, *Chemistry of Biomolecules; An Introduction*, The Royal Society of Chemistry, Cambridge, 1992, ch. 8.

7 S. C. G. Biagini, S. M. Bush, V. C. Gibson, L. Mazzariol, M. North, W. G. Teasdale, C. M. Williams, G. Zagotto and D. Zamuner, *Tetrahedron*, 1995, **51**, 7247.

8 P. D. Berry, A. C. Brown, J. C. Hanson, A. C. Kaura, P. H. Milner, C. J. Moores, J. K. Quick, R. N. Saunders, R. Southgate and N. Whittall, *Tetrahedron Lett.*, 1991, **32**, 2683.

9 M. R. Giles and V. C. Gibson, unpublished observations.

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