The synthesis and ring-opening metathesis polymerization of peptide functionalized norbornenes

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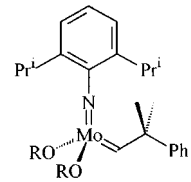
Norbornene monomers bearing two and three amino acid residues have been synthesized and the ring-opening metathesis polymerization of the monomers investigated using Mo(=CHCMe$_2$Ph)(=N-2,6-Pr$^i_2$C$_6$H$_3$)(OR)$_2$, [R = CMe$_3$ 1a, CMe$_2$CF$_3$ 1b, CMe(CF$_3$)$_2$ 1c].

The preparation of macromolecular biomimetic compounds requires careful control of the primary, secondary, and tertiary structures of the polymeric material. Typically, polymerization processes have failed to address these requirements due to lack of control over the polydispersity of the polymer which needs to be as near to monodisperse as possible, or due to the limited diversity of functional groups present in the final polymer.[1] Ring-opening metathesis polymerization (ROMP) using well-defined transition metal initiators, gives products with a narrow molecular weight distribution, and offers a high degree of control over the final molecular weight of the products. The latest generation initiators have also allowed the introduction of a wide range of functionalities within ROMP products. Furthermore, the living nature of the polymerization allows the preparation of block copolymers.[2]

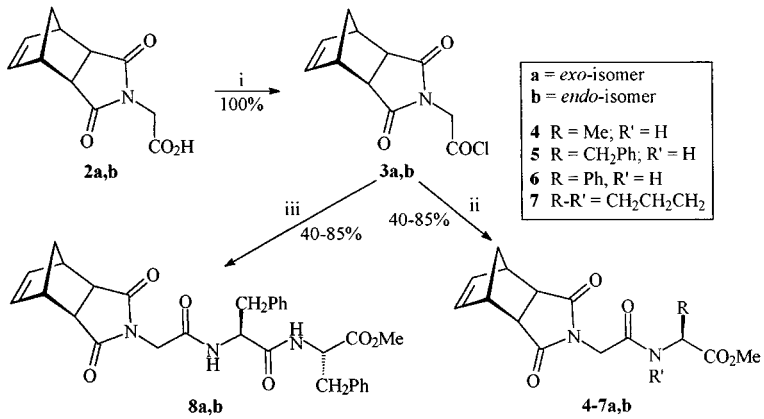
We have previously described the use of ROMP methodology in the synthesis of biomimetic polymers based upon amino acids,[3] antibiotics[4] and nucleic acids.[5] Other workers have also reported the preparation of carbohydrate derived polymers.[6] Here we describe our initial results towards the preparation of polymers incorporating peptide units. Our strategy was based upon the preparation of the monomers by coupling norbornene derivatives **2a**,**b**[7] to different amino acid and peptide moieties. This would allow the introduction of peptides chosen for their specific folding pattern (*e.g.* α-helical) and thus provide further control of the macrostructure of the polymer product. The well-defined initiators Mo(=CHCMe$_2$Ph)(=N-2,6-Pr$^i_2$C$_6$H$_3$)(OR)$_2$ [R = CMe$_3$ **1a**, CMe$_2$CF$_3$ **1b**, CMe(CF$_3$)$_2$ **1c**] developed by Schrock and co-workers[8] were employed for the ROMP reactions.



1a; R = Me$_3$C
1b; R = (CF$_3$)Me$_2$C
1c; R = (CF$_3$)$_2$MeC

Acids **2a**,**b** could be converted into the corresponding acid chlorides† **3a**,**b** by reaction with oxalyl chloride and DMF (Scheme 1). Compounds **3a**,**b** are crystalline solids and are convenient starting materials for the synthesis of the desired peptides **4**–**8a**,**b**. Thus, reaction of compounds **3a**,**b** with the methyl esters of alanine,‡ phenylalanine, phenylglycine, or proline gave monomers **4**–**7a**,**b** respectively, whilst reaction of **3a**,**b** with the dipeptide derivative phenylalanyl–phenylalanine methyl ester gave tripeptide derivatives **8a**,**b**.

Preliminary studies indicated that both the *exo*- and *endo*-isomers of monomers **4**–**8** could be polymerized by initiators **1a**–**c**. However, the polymerization of the *exo*-monomers was more facile (in line with previous reports of the ROMP of *endo*- and *exo*-norbornene derivatives[8]) and the isolated polymers were easily characterized, so monomers **4**–**8a** were selected for a more detailed study. The polymerization of each of monomers **4**–**8a** was then investigated as shown in Scheme 2, utilizing each of initiators **1a**–**c**, the results being given in Table 1. In each case, the polymerization was first carried out using 10 equiv. of monomer **4**–**8a** to allow the propagating alkylidene resonance to be detected by ^{1}H NMR spectroscopy, and the polymerization was then repeated using approximately 100 equiv. of the monomer to prepare a larger sample of the polymer. The initiators **1a**–**c** were tolerant of the amide bond(s)

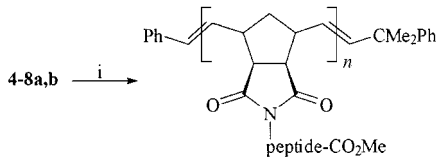


Scheme 1 *Reagents*: (i) (COCl)$_2$, DMF; (ii) Cl$^-$ H$_3^+$NCH(R)CO$_2$Me, Et$_3$N; (iii) Cl$^-$ H$_3^+$NCH(CH$_2$Ph)CONHCH(CH$_2$Ph)CO$_2$Me, Et$_3$N.

Table 1 Physical and selected spectroscopic data for the polymers derived from monomers **4a**–**8a**

Monomer	Catalyst	δ_H Mo=C*H*R	%*cis*[a]	T_g[b]/°C	M_n(calc)[c]	M_n[d]	M_w[d]	PDI[e]	$[\alpha]_D$[f]
4a	**1c**	12.48	60	133	15 300	12 000	14 700	1.22	−54
5a	**1a**	11.58	8	123	19 000	15 000	20 100	1.34	+79
	1b	11.99	44	161	19 000	18 600	29 000	1.56	+59
	1c	12.40	69	110	13 350	12 900	16 300	1.26	+63
6a	**1a**	11.56	13	165	9 950	6 900*	7 120*	1.03	+61**
	1b	11.97	57	150	18 400	17 800	24 700	1.39	+57**
	1c	12.44	74	149	16 200	7 100	7 400	1.03	+56**
7a	**1a**	11.60	9	179	13 360	21 600	25 200	1.17	−64
	1b	12.00	45	161	17 000	17 200	19 400	1.13	−56
	1c	12.60	71	154	18 700	29 500	32 700	1.13	−58
8a	**1a**	11.57	[g]	134	14 000	9 200*	9 500*	1.04	+24
	1b	12.20	[g]	120	17 400	7 000*	7 200*	1.03	+27
	1c	12.45	[g]	106	13 400	7 800*	8 100*	1.03	+19

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by TMA analysis. [c] Calculated from the monomer to initiator ratio. [d] M_n and M_w values were obtained by GPC using $CHCl_3$ as eluent, a differential refractometry detector, and two PLgel 10 μl mixed columns calibrated using polystyrene standards ranging in molecular weight from 1560 to 10^6 except where indicated by *. In these cases, the polymers were not soluble in $CHCl_3$, so molecular weight data were obtained by MALDI-TOF mass spectrometry. The experimentally determined M_ns are lower than M_n(calc) reflecting the tendency of MALDI-TOF to detect components of lower mass preferentially.[9] [e] Calculated as M_w/M_n. [f] Measured in $CHCl_3$ except where indicated by ** when DMSO was used as solvent. [g] Determination of the %cis alkenes in the polymer was not possible due to signal overlap.



Scheme 2 *Reagents*: (i) a, **1a**–**c**, CH_2Cl_2, b, PhCHO.

in monomers **4**–**8a**, even when the polymerizations were left for three days. However, the polymers derived from monomer **4a** using initiators **1a**,**b** were found to be insoluble in organic solvents and so could not be fully characterized. These polymers are therefore not included in Table 1. Monomer **4a** contains the two amino acids (glycine and alanine) with the least hydrophobic sidechains and this probably accounts for the poor solubility of polymers derived from this monomer, as all of the other monomers gave polymers which were soluble in at least some organic solvents.

The ^{1}H NMR results show the expected trend of increasing *cis*–*trans* ratio associated with using initiators possessing increased fluorination of the ancillary ligands.[2] This trend is also apparent in the glass transition temperatures (T_g), which decrease with increasing *cis* content. All of the polymers were optically active which suggests that the chirality of the amino acids has been preserved during the polymerizations as has previously been observed for amino acid derived monomers.[3] The fact that all of the polymers derived from the same monomer have similar specific rotations suggests that the chemical environment around the peptide chains is not significantly affected by changes in the stereochemistry of the polymer backbone. All of the polymers exhibited low PDIs, and in each case, a propagating alkylidene signal could be observed in the ^{1}H NMR spectrum, indicating that the polymers were formed by a living polymerization process.

In conclusion, we have shown that peptide derived norbornenes **4**–**8** are suitable substrates for ROMP using well-defined molybdenum-based initiators. It is possible to control the stereochemistry of the polymers by varying the structure of the initiator. Our work in this area is continuing and further results using peptides that are known to adopt preferred conformations will be reported in due course.

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Notes and references

† All new compounds exhibited satisfactory spectroscopic and analytical properties.

‡ All chiral amino acids discussed in this manuscript have the (*S*)-configuration.

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