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# *endo*-Selective (3+2) cycloaddition polymerizations of nitrone monomers with olefins utilising high pressure conditions

Glenn W. Goodall [a], Kevin Costick [b], Simon C. Richards [a], Wayne Hayes [a],*

[a] *Department of Chemistry, University of Reading, P.O. Box 224, Whiteknights RG6 6AD, UK*
[b] *INVISTA (UK) Ltd., P.O. Box 401, Wilton, Redcar TS10 4XY, UK*

## Abstract

A high pressure mediated (3+2) cycloaddition polymerization strategy has been employed to afford linear poly(isoxazolidine) architectures. Under these high pressure conditions this cycloaddition process was found to afford primarily *endo*-heterocycles which when translated to the polymerization should ultimately affect the tacticity and resultant properties of the polymer. The stereoselectivity occurred as a result of a lower volume of activation for the *endo*-transition state and the application of a 'type-I' regime ($HOMO_{Dipole}$–$LUMO_{Dipolarophile}$) cycloaddition process that features secondary orbital interactions within the extended molecular orbitals. A variety of linker segments were employed in an attempt to affect the physical properties of the polymeric cycloadducts such as $T_g$ and solubility in order to tailor these materials for use in coating applications.
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*Keywords:* Cycloaddition; Polymerization; Poly(isoxazolidine); Nitrone

## 1. Introduction

Pericyclic reactions such as the (3+2) cycloaddition are a convenient one-step route for the construction of a variety of complex heterocycles. Cycloadditions have been utilised [1] to access numerous poly-heterocyclic systems such as poly(arylene ethynylene)s, poly(triazole)s and poly(dithiafulvene)s. Notably, there has been significant interest recently in the application of the copper mediated cycloaddition between alkynes and azides – commonly referred to as 'click chemistry' – in order to prepare linear, hyperbranched polymers and dendrimers [1]. When nitrone moieties are combined with dipolarophiles such as styrene, acrylates or maleimides, isoxazolidine cycloadducts are generated in an efficient manner and with high regioselectively. Advantageously, the nitrone precursors to the desired isoxazolidines are stable under ambient conditions and moderate temperatures without degradation [2]. The addition of electron rich or deficient moieties to the dipolarophile leads to polarisation of the molecular orbitals of the double bond which in turn influences the frontier molecular orbital symmetry of the substrate in the transition state of the desired (3+2) cycloaddition

* Corresponding author. Tel.: +44 118 378 6491; fax: +44 118 378 6331.
  *E-mail address:* w.c.hayes@reading.ac.uk (W. Hayes).

reaction. These polarising effects influence the dominant interactions, $HOMO_{Dipole}$–$LUMO_{Dipolarophile}$ or $LUMO_{Dipole}$–$HOMO_{Dipolarophile}$ and thus the orientation of the dipole to the dipolarophile [3]. As a consequence, there is sufficient regioselective control of this cycloaddition process to allow the prediction of the formation of 1,3-substituted isoxazolidine ring systems. However, in contrast, the stereoselectivity of the cycloaddition process is controlled to a lesser extent as a consequence of the small energy difference between the *exo* and *endo* transition states [4], but favourable electronic interactions or thermodynamic effects can still influence this reaction.

High pressure reaction conditions [5] promote the formation of more compressed transition states during cycloaddition reactions. In order for pressurised conditions to accelerate the rate of an irreversible reaction, the volume of activation for the transition state for the reaction ($\Delta V^{\ddagger}$) must be negative – as observed in cycloaddition processes. The volumes of activation [5] for (3+2) cycloadditions are observed [6a] to range between −20 and −32 cm$^2$ mol$^{-1}$. Furthermore, if the volumes occupied by the *exo* or *endo* transition states are sufficiently different, the stereochemical outcome of a (3+2) cycloaddition can be influenced by pressurised reaction conditions [6]. Therefore, in the case of cycloaddition polymerizations, the application of high pressure conditions may allow the tacticity of resultant polycycloadducts produced in this manner to be controlled or influenced in a significant fashion.

Thermal cycloaddition polymerizations [1,7] of nitrone monomers have been used to produce poly(isoxazolidine)s. Ritter *et al.* have produced oligomers [7a] and poly(isoxazolidine)s [7b] with $M_w$ values up to 29 kDa. Unfortunately, several of these polymers possessed relatively low $M_w$ values (∼4 kDa) as a consequence of nitrone degradation at the elevated temperatures used in the polymerization process. These polymers do exhibit high thermal stability ($T_d > 200\,°C$) and good film forming abilities rendering them suitable for future coating and high temperature applications. Our interest in these polymers stems from the fact that isoxazolidine substituted heterocycles exhibit [8] anti-bacterial, anti-fungal and biological activities. It is not unreasonable to thus propose that poly(isoxazolidine)s could potentially exhibit similar biological activities and render these polymers useful in biomedical coatings.

This report summarises our synthetic studies to produce poly(isoxazolidine) architectures under high pressure reaction conditions. Model reactions were used optimise the high pressure conditions used for the subsequent polymerization and to also understand the discrete ratio of *endo* and *exo*-cycloadducts within the resultant polymers thus formed. The use of an ($A_2 + B_2$) polymerization strategy was employed in order to tailor the thermal and solubility properties of the resultant polymers through careful choice of spacer groups in an attempt to aid the processing of these cycloadduct materials.

## 2. Experimental

### 2.1. General experimental

All of the reagents were purchased from Aldrich Chemical Company, Lancaster and Acros Chimica and were used as received without any further purification. Melting points were determined on a Mettler FP61 digital melting point apparatus and are uncorrected. The $^{1}H$ NMR (250 MHz) and $^{13}C$ NMR (62.8 MHz) nuclear magnetic resonance (NMR) spectra were acquired using a Bruker AC250 spectrometer (using the deuterated solvent as lock or tetramethylsilane as an internal reference). Infrared (IR) spectroscopic analyses were performed on Perkin-Elmer (1720-X) Infrared Fourier Transform spectrometer using NaCl plates for the preparation of samples, unless otherwise stated. Gel permeation chromatography (GPC) was performed at 60 °C on a Polymer Laboratories PL-GPC 220 high temperature chromatograph equipped with PL Mixed Gel columns, using samples dissolved in GPC grade DMF, and calibrated with PL Easy-Cal Polystyrene and employing RI/LS detection. Differential scanning calorimetry (DSC) was performed on a Mettler Toledo DSC 20 differential scanning calorimeter. DSC was performed on *ca.* 4–6 mg of sample, under an atmosphere of nitrogen, by scanning from 25 to 250 °C at a rate of 10 °C min$^{-1}$. All of the thermal analysis data were analysed using Mettler Toledo Star systems software. High pressure reactions (1–19 kbar) were carried out using a simple piston and reinforced cylinder type pressurising apparatus (1–10 kbar) and a cylinder with two opposed pistons type apparatus (14–19 kbar) – each piston was equipped with Enerpac hydraulic rams and independent temperature control.

Using the method described [4c] by Heaney et al. benzyl nitrone **1** and N,N′-dimethyl-p-phenylenedi-

nitrone **2** were prepared. 1,6-Bis(maleimido)hexane **3** was prepared [9] as described by Cheronis et al. and *N,N′-m*-phenylenedimaleimide **4** was obtained from the Aldrich Chemical Company. The following acrylate monomers were prepared according to literature methods [10]: 1,6-hexanediol diacrylate **5**, 1,2-ethanediylbis(oxy-2,1-ethanediyl)diacrylate **6** and 1,4-bis-acryloyloxy-benzene **7**.

## 2.2. Model high pressure cycloaddition reactions to afford 2-methyl-3,5-diphenyl-dihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6aH)-dione

A solution of benzyl nitrone **1** (47 mg, 0.35 mmol) and *N*-phenylmaleimide (60 mg, 0.35 mmol) in solvent (1 mL) was placed into a PTFE reaction vessel which was then transferred into the high pressure reactor and exposed to various conditions: 1–6 kbar, 30–80 °C and for periods in between 24 and 216 h, in order to obtain the optimum reaction conditions. Upon completion of the reaction, the cycloadduct was purified by column chromatography (dichloromethane/ethyl acetate 15:1) to yield the desired cycloadduct as a white powder (64 mg, 60%); M.p. 173–175 °C; IR (Nujol) $v_{max}$/cm$^{-1}$ 1691.

*trans*-Isomer: ^{1}H NMR (250 MHz, CDCl$_3$) $\delta_H$ 7.47 (5H, m, ArH), 7.35 (5H, m, ArH) 5.05 (1H, d, $J = 7.5$ Hz, H5), 4.22 (1H, m, H4) 3.87 (1H, dd, $J = 3.5$, 7.5 Hz, H3), 2.53 (3H, br-s, NCH$_3$); ^{13}C NMR (62.8 MHz, CDCl$_3$) $\delta_C$ 174.6, 174.0, 133.6, 131.3, 129.9, 128.9, 128.6, 127.7, 126.0, 76.4, 75.6, 54.4, 42.6.

*cis*-Isomer: ^{1}H NMR (250 MHz, CDCl$_3$) $\delta_H$ 7.38 (10H, m, ArH), 5.02 (1H, d, $J = 7.5$ Hz, H5), 3.94 (1H d, $J = 8.5$ Hz, H3) 3.84 (1H, dd, $J = 7.5$, 8.5 Hz, H4), 2.70 (3H, s, NCH$_3$); ^{13}C NMR (62.8 MHz, CDCl$_3$) $\delta_C$ 172.2, 129.6, 129.4, 129.3, 129.1, 126.7, 76.9, 76.4, 56.3, 41.2. m/z (CI) (Calc(C$_{18}$H$_{16}$N$_2$O$_3$) 308.1161), 309.1239 (M+H$^+$).

## 2.3. Model cycloaddition polymerizations

Polymerizations of *N,N*-dimethyl-*p*-phenylenedinitrone **2** and 1,6-bis(maleimido)hexane **3** were carried out at various temperatures (either 40, 55 or 60 °C) over 72 h. Further studies were carried out at 72, 96, and 144 h under a constant temperature of 40 °C. *N,N*-Dimethyl-*p*-phenylenedinitrone (66 mg, 0.33 mmol) and 1,6-bis(maleimido)hexane (83 mg, 0.33 mmol) were dissolved in 1 mL of solvent (either dimethylformamide or dichlorometh-

ane), the solution was placed in a PTFE reacting vessel, and subjected to high pressure conditions (4.5 kbar). Upon completion, the reaction mixture was concentrated to dryness *in vacuo* to afford a white powdery polymer (141 mg, 95%). $T_m = 220$–232 °C, $T_d = \sim 250$ °C; IR $v_{max}$/cm$^{-1}$ 1707 (C=O), 1159 (N–O); ^{1}H NMR (250 MHz, CDCl$_3$) $\delta_H$ 7.28–7.19 (ArH), 4.94 (H-5), 4.88 (*trans* H-3), 3.83 (*cis* H-3), 3.72 (*cis* H-4), 3.55 (CH$_2$), 3.44 (*trans* H-4), 2.63 (*cis* NCH$_3$) 2.43 (*trans* NCH$_3$), 1.57 (CH$_2$) 1.30 (CH$_2$); ^{13}C NMR (62.8 MHz, CDCl$_3$) $\delta_C$ 176.0, 138.3, 129.4, 128.6, 125.7, 76.9, 55.0, 54.8, 43.1, 39.7, 30.1, 23.1; GPC (RI/LS), $M_n = 6300$, $M_w = 14,500$, polydispersity index = 2.3.

## 2.4. General cycloaddition polymerization: Poly(isoxazolidine) produced from N,N-Dimethyl-p-phenylenedinitrone (2) and 1,6-bis(maleimido)hexane monomers (3)

*N,N*-Dimethyl-*p*-phenylenedinitrone **2** (66 mg, 0.3 mmol) and 1,6-bis(maleimido)hexane **3** (83 mg, 0.33 mmol) were dissolved in dimethylformamide (0.9 mL), the solution was placed in a PTFE reaction vessel and subjected to high pressure (4.5 kbar) for nine days at 40 °C. Once complete the resultant solution was concentrated to dryness *in vacuo* to afford a pale yellow solid polymer (143 mg, 96%). $T_m = 224$ °C, $T_d = 250$ °C; IR $v_{max}$/cm$^{-1}$ 1707 (C=O), 1159 (N–O); ^{1}H NMR (250 MHz, CDCl$_3$) $\delta_H$ 7.28–7.19 (ArH), 4.94 (H-5), 4.88 (*trans* H-3), 3.83 (*cis* H-3), 3.72 (*cis* H-4), 3.55 (CH$_2$), 3.44 (*trans* H-4), 2.63 (*cis* NCH$_3$) 2.43 (*trans* NCH$_3$), 1.57 (CH$_2$) 1.30 (CH$_2$); ^{13}C NMR (62.8 MHz, CDCl$_3$) $\delta_C$ 176.0, 138.3, 129.4, 128.6, 125.7, 76.9, 55.0, 54.8, 43.1, 39.7, 30.1, 23.1; GPC (RI/LS): $M_n = 13,000$, $M_w = 27,900$, polydispersity index = 2.2.

### 2.4.1. Poly(isoxazolidine) produced from N,N-dimethyl-p-phenylenedinitrone (2) and 1,3-N,N-m-phenylmaleimide (4) monomers

The general procedure was followed (*vide infra*) using the following reactants: *N,N*-Dimethyl-*p*-phenylenedinitrone **2** (66 mg, 0.33 mmol) and 1,3-*N,N-m*-phenylmaleimide **4** (80 mg, 0.33 mmol) in dimethylformamide (0.9 mL) to afford a pink solid polymer (143 mg, 96%); $T_m = 212$ °C, $T_d = 255$ °C; IR $v_{max}$/cm$^{-1}$ 1725 (C=O), 1170 (N–O); ^{1}H NMR (250 MHz, DMSO-d$_6$) $\delta_H$ 7.45-7.11 (ArH), 5.15 (H-5), 4.03–3.99 (H-3), 3.79 (H-4), 2.63 (*cis* NCH$_3$), 2.51 (*trans* NCH$_3$); ^{13}C NMR (62.8 MHz, DMSO-d$_6$) $\delta_C$ 174.0, 162.7, 129.3, 128.6, 127.9,

125.7, 79.8, 74.5, 54.6, 42.8; GPC (RI/LS): $M_n = 4100$, $M_w = 8500$, polydispersity index = 2.1.

### 2.4.2. Poly(isoxazolidine) produced from N,N-dimethyl-p-phenylenedinitrone (2) and 1,6-hexanediol diacrylate (5) monomers

The general procedure was followed (*vide infra*) using the following reactants: *N,N*-Dimethyl-*p*-phenylenedinitrone **2** (66 mg, 0.33 mmol) and 1,6-hexanediol diacrylate **5** (68 mg, 0.33 mmol) in dimethylformamide (0.9 mL) to afford a yellow solid polymer (119 mg, 89%); $T_d = 172$ °C; IR $\nu_{max}/cm^{-1}$ 1732 (C=O), 1199 (N–O); $^1$H NMR (250 MHz, CDCl₃) $\delta_H$ 7.33–7.04 (ArH), 4.63-4.54 (H-5), 4.18 4.09 (CH₂), 3.80 (*cis* H-3), 3.66 (*trans* H-3), 2.90 (*trans* NCH₃), 2.65 (*cis* NCH₃), 2.61 (CH₂, H-4),1.60 (CH₂), 1.36 (CH₂); $^{13}$C NMR (62.8 MHz, CDCl₃) $\delta_C$ 171.6, 170.8, 138.3, 129.5, 127.9, 78.0, 76.0, 75.5, 68.5, 65.6, 54.8, 44.1, 43.5, 30.0, 25.8; GPC (RI/LS): $M_n = 3300$, $M_w = 7500$, polydispersity index = 2.2.

### 2.4.3. Poly(isoxazolidine) produced from N,N′-dimethyl-p-phenylenedinitrone (2) and 1,4-bis-acryloyloxy-benzene (6) monomers

The general procedure was followed (*vide infra*) using the following reactants: *N,N′*-Dimethyl-*p*-phenylenedinitrone **2** (64 mg, 0.33 mmol) and 1,4-bis-acryloyloxy-benzene **6** (74 mg, 0.33 mmol) in dimethylformamide (0.9 mL) to afford a yellow solid polymer (129 mg, 92%); $T_m = 195$ °C, $T_d = 215$ °C; IR $\nu_{max}/cm^{-1}$ 1738 (C=O), 1171 (N–O); $^1$H NMR (250 MHz, CDCl₃) $\delta_H$ 7.34–7.05 (ArH), 5.16–5.09 (H-5), 3.71 (*cis* H-3), 3.44 (*trans* H-3), 2.85 (*trans* NCH₃), 2.65 (*cis* NCH₃), 2.52 (CH₂ H-4); $^{13}$C NMR (62.8 MHz, CDCl₃) $\delta_C$ 170.1, 169.3, 139.5, 136.8, 129.2, 127.5, 124.3, 75.6, 74.0, 70.2, 56.2, 42.0; GPC (RI/LS): $M_n = 3300$, $M_w = 7500$, polydispersity index = 2.3.

### 2.4.4. Poly(isoxazolidine) produced from N,N-dimethyl-p-phenylenedinitrone and 1,2-ethanediylbis(oxy-2,1-ethanediyl)diacrylate monomers

The general procedure was followed as above using the following reactants: *N,N*-dimethyl-*p*-phenylenedinitrone **2** (66 mg, 0.33 mmol) and 1,2-ethanediylbis(oxy-2,1-ethanediyl)diacrylate **7** (64 mg, 0.33 mmol) in dimethylformamide (0.9 mL) to afford a yellow solid polymer (128 mg, 98%); IR $\nu_{max}/cm^{-1}$ 1737 (C=O), 1170 (N–O); $^1$H NMR (250 MHz, CDCl₃) $\delta_H$ 7.27–7.14 (ArH), 4.74–4.68

(H-5), 4.24 (OCH₂), 3.76–3.70 (H-3), 3.67 (OCH₂), 3.59 (OCH₂) 2.90 (*trans* NCH₃), 2.71 (*cis* NCH₃), 2.65 (CH₂ H-4); $^{13}$C NMR (62.8 MHz, CDCl₃) $\delta_C$ 171.8, 138.3, 135.2, 129.4, 128.6, 75.2, 74.6, 70.6, 68.8, 63.8, 54.7, 43.47, 39.07; GPC (RI/LS): $M_n = 9700$, $M_w = 18,900$, polydispersity index = 2.0.

## 3. Results and discussion

In order to optimise high pressure reaction conditions, benzyl nitrone **1** was reacted with *N*-phenyl maleimide under various pressurised conditions and temperatures (Scheme 1) utilising a piston and cylinder apparatus.

The model cycloaddition reaction between benzyl nitrone **1** and *N*-phenyl maleimide was carried out at room temperature, in various solvents (dimethylformamide, toluene, chloroform), over a period of 24 h and under 2–4 kbar of pressure, however, these conditions afforded the cycloadduct in poor yield (7–43%). However, upon extending the reaction time (up to 9 days) and increasing the reaction temperature (up to 50 °C), higher yields of the desired cycloadduct were achieved (up to 98%).

To improve our understanding of the stereochemical outcome of this cycloaddition reaction and the nature of the transition states involved, a detailed knowledge of the structure of the nitrone precursors was required. Therefore, $^1$H NMR spectroscopy nuclear Overhauser effect (NOE) experiments were employed to determine the *E*- or *Z*-configuration of the C=N double bond featured in the nitrone moiety. The benzyl nitrone **1** was irradiated at the resonance frequency of the protons of the *N*-methyl substituent. Upon irradiation of these specific protons, the resonance observed at 7.37 ppm was enhanced (by 3.3%, see Fig. 1) and assigned to the vinylic proton and not the *ortho*-aromatic proton thus confirming the *Z*-configuration of the C=N double bond. The *N,N′*-dimethyl-*p*-phenylenedinitrone **2** was also studied using the NOE technique – the resonant frequency of the protons of the *N*-methyl substituent were irradiated and in this case the resonance observed at 7.91 ppm was enhanced by 5.6% (Fig. 2) to also confirm the *Z*-configuration of the two C=N double bonds.

The stereoselectivity of the cycloaddition reaction of benzylnitrones and *N*-phenylmaleimides has been studied in detail – when carried out under thermal conditions *exo*- and *endo*-cycloadducts were observed (42/58% [4c] and 45/55% [8]). However, when the same cycloaddition reaction between ben-
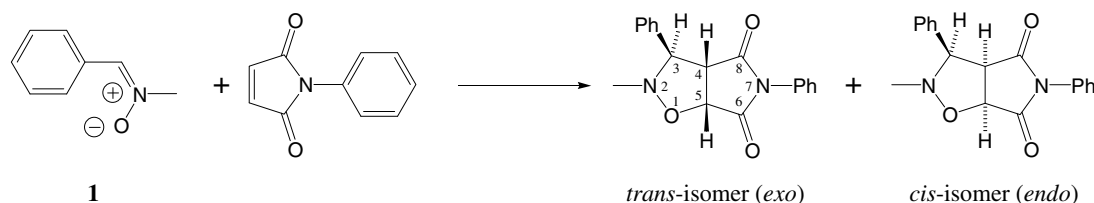
Scheme 1. The model (3+2) cycloaddition reaction between benzylnitrone and N-phenylmaleimide used to optimise the high pressure conditions for subsequent polymerizations and to study the ratio of endo- and exo-cycloadducts under those conditions.
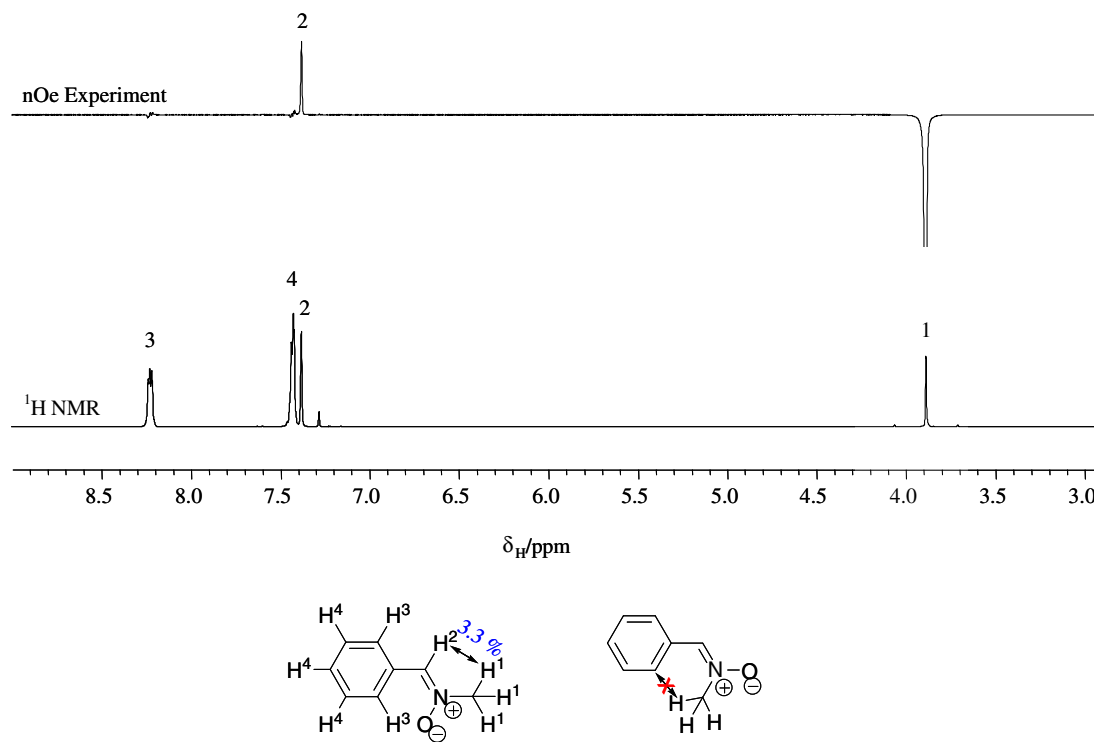


Fig. 1. NOE NMR spectroscopic analysis used to determine nitrone E- or Z-confirmation of benzylnitrone **1**.

zylnitrone and N-phenylmaleimide was carried out under pressurised conditions (4 kbar, 40 °C, 3 days) endo-selectivity (89%) was observed clearly as determined by ^{1}H NMR spectroscopic analysis. After chromatographic purification of the cycloadduct, ^{1}H NMR spectroscopic analysis revealed key resonances at 2.53, 3.87, 4.22 and 5.06 ppm, respectively, that were assigned [4c] to the trans-cycloadduct resulting from the exo-transition state and the protons at positions 4 and 5 of the isoxazolidine ring (Scheme 1). Furthermore, the resonance at 2.53 ppm corresponds [4c] to the protons of the N-methyl moiety of the isoxazolidine when the exo-bicycle was in the chair-like i-conformation –

this proton would resonate at ~2.7 ppm if the exo-bicycle was present in the boat-like o-conformation (Fig. 2). The trans-geometry was further identified by analysis of the ^{13}C NMR spectrum of cycloadduct which featured key resonances at 38.7, 65.9, 70.1 and 76.0 ppm that were assigned to central fused-bicyclic unit. The cis-cycloadduct produced from the endo-transition state in this high pressure reaction was confirmed by key resonances in the ^{1}H NMR spectrum of cycloadduct at 2.70, 3.84, 3.94 and 5.03 ppm, respectively, that correlated to the protons positions 2, 3, 5 and 4 (see Scheme 1) of the bicycloadduct. In addition, ^{13}C NMR spectroscopic analysis of endo-cycloadduct
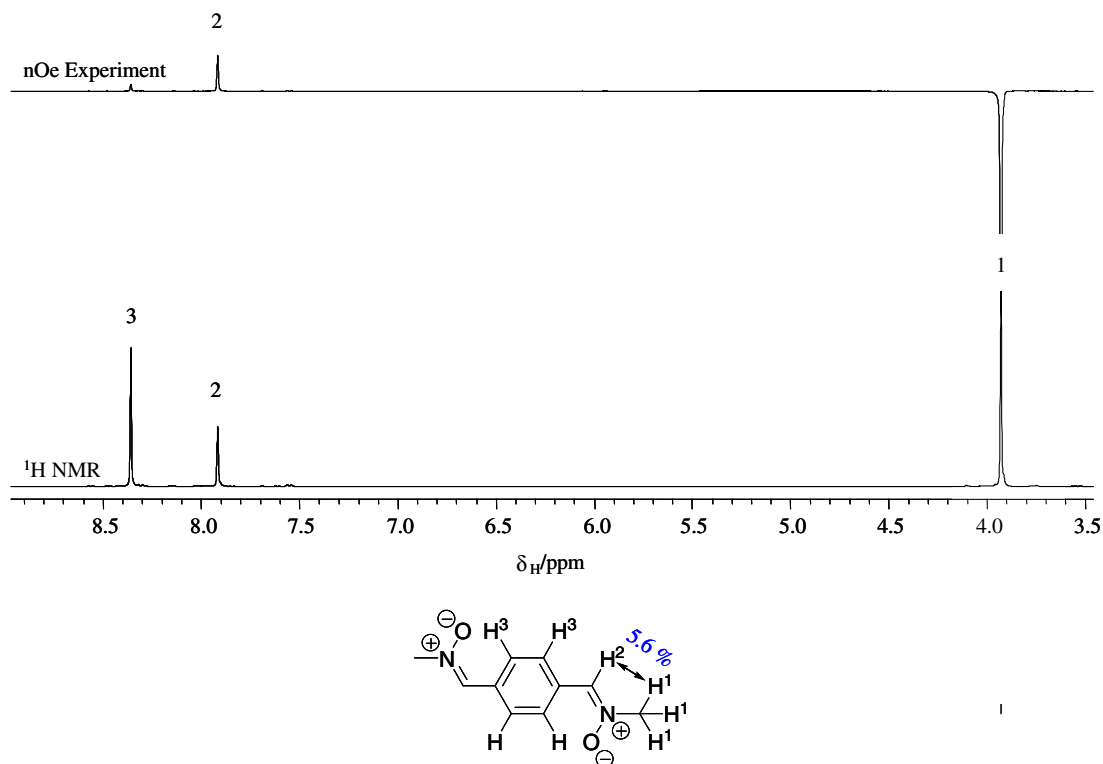
Fig. 2. NOE NMR spectroscopic analysis used to determine nitrone *E*- or *Z*-confirmation *N*,*N*′-dimethyl-*p*-phenylenedinitrone **2**.

featured resonances at 43.1, 54.8, 76.0 and 76.8 ppm, respectively, that were attributed to the carbon framework of the bicycloadduct in the *cis*-form.

The *endo*-selectivity was observed as a consequence of the lower volume of activation for the *endo* transition state when compared to the *exo* state. Furthermore, this selectivity could be attributed to the cycloaddition interaction 'type' [11] which dominates the reaction pathway under high pressure reaction conditions, and the potentiality for secondary orbital interactions within the extended molecular orbitals. Extended molecular orbitals and interaction 'type' have been shown [12] to influence *endo*/*exo*-selectivity. Cycloadditions involving nitrones have been observed to proceed via type-II frontier molecular orbital interactions, but can be influenced [3,13] to follow type-I ($HOMO_{Dipole}$–$LUMO_{Dipolarophile}$) or type-III ($LUMO_{Dipole}$–$HOMO_{Dipolarophile}$) using either electron rich or deficient dipolarophiles or even using Lewis acid catalysis. Within the *endo*-transition state of the reaction studied here, the extended

molecular orbitals of the carbonyl oxygen orbitals on the maleimide monomer are proximal under a type-I regime and are in phase with the aryl orbitals on the nitrone monomer. This proximity could a lead to secondary interactions that enhance the *endo*-selectivity of this reaction. In addition, there is also the possibility of aryl-aryl orbital interactions in the transition state. These secondary interactions are not possible within the *exo*-transition state under the type-I regime. This stereoselectivity under high pressure conditions should translate to the formation of stereochemical well-defined poly(isoxazolidine)s and thus will enable the thermal properties of these polymers to be 'tuned'.

### 3.1. (3+2) Cycloaddition polymerizations utilising high pressure conditions
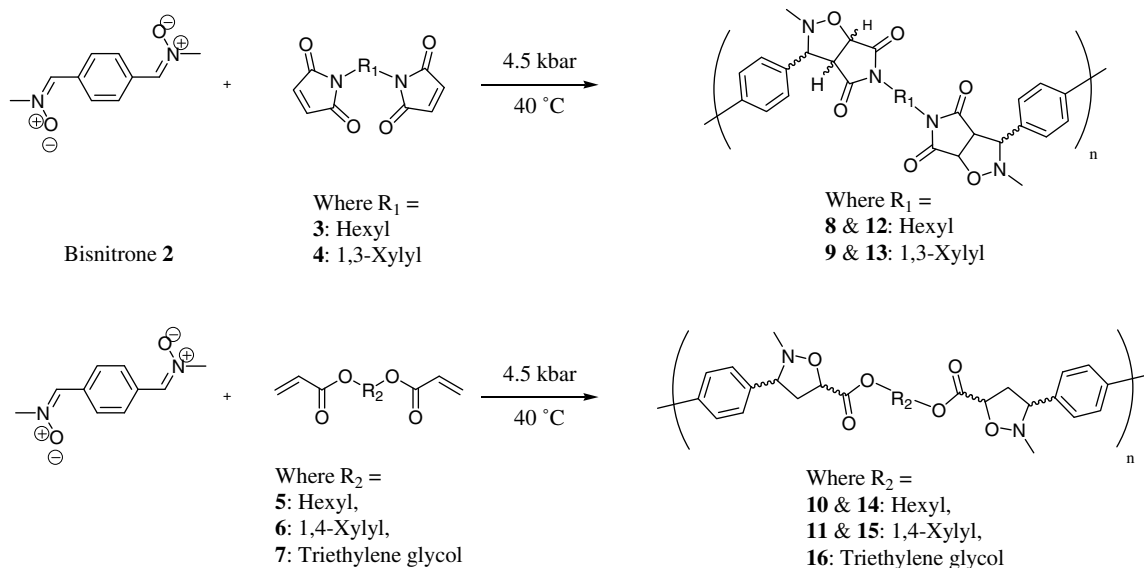
The $A_2$-type bisnitrone monomer **2** was copolymerised with $B_2$-type monomers featuring electron deficient maleimide and acrylic moieties (**3**–**7**) under high pressure reaction conditions (4.5 kbar, 40 °C,

DMF) over a period of 6 days to afford a range of poly(isoxazolidine) architectures (Scheme 2).

FT-IR spectroscopic analysis of all of the poly(isoxazolidine)s thus produced revealed an absorption band at $\sim 1170 \, cm^{-1}$ which indicated the presence of an N–O bond associated with the cyclic isoxazolidine repeat unit. The formation of isoxazolidine heterocycles within the polymers was also confirmed by similar resonances upon ^{1}H and ^{13}C NMR spectroscopic analysis to those found in model compounds.

In addition, ^{1}H NMR spectroscopic analysis was used to assess the polymer tacticity, utilising the resonances associated with the N-methyl protons of the isoxazolidine ring. The polymers 8 and 12 obtained from the reaction between bisnitrone 2 and alkyl bismaleimide 3 featured two resonances at 2.63 and 2.43 ppm, respectively, correlating to the protons of N-methyl groups from the endo and exo-isomers. Analysis of the integrations for these two key resonances confirmed that the poly(isoxazolidine) was comprised of isoxazolidine rings with a endo/exo ratio of 75:25, a ratio similar to that observed in the model reaction (vide supra) and, in addition, these polymers featured i-conformer exo-bicycles. Furthermore, in the case of polymers 9 and 13 obtained from the bisnitrone 2 and aromatic bismaleimide 4, resonances at 2.63 and 2.51 ppm, respectively, were observed in the ^{1}H NMR spectra that corresponded to the protons of the N-methyl moiety

in the endo and exo-forms of the isoxazolidine rings, respectively. In these cases, endo-selectivity was observed with the polymers comprising 87% endo and 13% exo-isoxazolidine rings. Furthermore, detailed analysis of the ^{1}H NMR spectra revealed that the exo-bicycles were also present in the boat-like i-conformation. Thus the original endo-selectivity observed in the model reactions under high pressure was preserved in the polymerization process under identical reaction conditions. Furthermore, the aryl-aryl orbital interaction (vide infra) within an endo-transition state, under a type-I regime could explain why polymer 13 featured an enhanced endo-selectivity when compared to polymer 12 by 12%. In contrast to our studies, Tanaka et al. have assessed [14] the reaction of styrene with N-methyl-C-(trifluoromethyl)nitrone under thermal conditions. In this study, it was discovered that the exo-isomer formed preferentially to the endo-isomer with relative ratios of 83:17, respectively. Each isomer was identified via ^{1}H NMR spectroscopic analysis with the resonance at 2.92 ppm being attributed to the protons of the N-methyl moiety for the exo-isoxazolidine and a resonance upfield at 2.80 ppm assigned to the endo-isoxazolidine isomeric form. It was postulated that using electronic considerations, this reaction should have proceeded in an endo-selective manner. However, it was observed that steric effects overrode any secondary orbital interactions or different cycloaddition



Scheme 2. The (3+2) cycloaddition polymerization employing bisnitrone monomer 2 with either bismaleimide (3–4) or bisacrylate (5–7) monomers.

HOMO–LUMO interaction 'type' effects in order to favour the *exo*-isomer.

^{1}H NMR spectroscopic analysis of polymers **10** and **14** featured resonances at 2.95 and 2.65 ppm, respectively, which were attributed to the *exo* and *endo* N-methyl protons. In the case of this polymer, the *endo*-isoxazolidine unit dominated the *exo*-isoxazolidines in a ratio of 80:20, respectively. In addition, polymers **11** and **15** also exhibited *endo*-selectivity of 87% and polymer **16** displayed *endo*-selectivity of 76%. Thus, when compared to thermal conditions, high pressure reaction conditions led to the opposite stereochemical selectivity. This stereoselectivity was proposed to occur as a consequence of the lower activation volume for the *endo*-isomer transition state when compared to the *exo*-isomer. In addition, the acrylate monomers feature carbonyl oxygen secondary orbitals which under a type-I regime would be proximal to aryl orbitals leading to a potential interaction in the *endo*-transition state, enhancing this selectivity. This effect could account for polymer **15** exhibiting greater *endo*-selectivity when compared to polymers **14** and **16** by 7 and 11%, respectively.

The poly(isoxazolidine)s obtained via this high pressure approach possessed molecular weights ($M_w$) up to 30.4 kDa as determined using GPC analysis. The polymer produced from bisnitrone **2** with either bismaleimide **3** or bisacrylate **7**, in dimethylformamide, exhibited the highest $M_n$ values of 13.0 and 10.5 kDa, and $M_w$ values of 27.9 and 18.9 kDa, respectively. Unfortunately, when the bisnitrone **2** was reacted with bismaleimide **4**, a low molecular weight material was generated ($M_w$ 6.9 kDa) (Table 1). These results were attributed to the solubility of the propagating polymer, since monomers **3** and **7** feature flexible, and thus more soluble, spacer groups. Thus, the resultant poly(isoxazolidine)s are solubilised and can con-
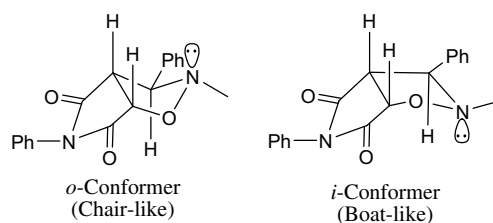


Fig. 3. Chair-like *o*-conformation and the boat-like *i*-conformations of the *exo*-bicycle [3c] model cycloadducts.

tinue to polymerize, whereas poly(isoxazolidine)s produced from monomers **4** and **6** featuring aromatic spacer-groups afforded ridged and less soluble polymer chains which precipitated out of solution at lower molecular weights (see Fig. 3).

The poly(isoxazolidine)s obtained possessed $T_m$ values from 195 to 224 °C and $T_d$ values from 172 to 255 °C and these thermal properties render these polymers potentially useful in hot melt applications. Discrete glass transitions were not observed for the majority of the cycloaddition polymers, and only one $T_g$ value could be determined (151 °C) for polymer **8** (see Fig. 4.). The results of our thermal analysis studies on the poly(isoxazolidine)s are consistent with the thermal data reported [7] by Ritter and Vretik. The polymers produced from those monomers featuring aromatic spacer groups (bismaleimide **4** and bisacrylate **6**) exhibited the highest $T_d$ values as a consequence of the greater rigidity and thermal stability that these moieties possess (see Table 2).

The polymers **9** and **13** possessed terminal maleimide end groups as confirmed by ^{1}H NMR spectroscopic analysis with key resonance observed at 6.80 ppm corresponding to the maleimide vinylic protons. This could account for the relatively low molecular weights observed as the nitrones reacted rapidly with the maleimide moieties resulting in low nitrone concentration in the polymerization and rapid chain termination.

Initial studies into the casting of films of these poly(isoxazoline)s and poly(isoxazolidine)s, in particular polymers **8** and **9**, have been carried out. For each polymer a 15% solution in N-methylpyrrolidone was prepared and then spread onto a glass substrate. The wet coating was dried in a vacuum oven at a constant temperature of 40 °C for a period of 16 h after which the temperature was increased slowly over a period of 4 h to 80 °C to remove residual solvent. The glass plate was then submerged into water for a period of 20 min in order to ease lifting

Table 1
Thermal and stereoselective data for cycloaddition polymers produced via high pressure reaction conditions

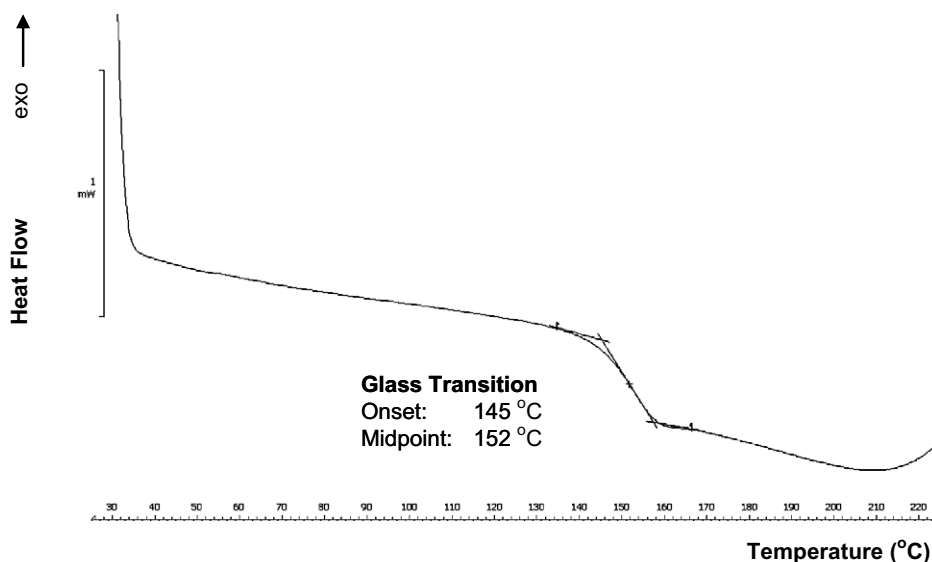| Polymer number | Monomers | $T_m$ (°C) | $T_d$ (°C) | Steroselectivity (%) | |
|---|---|---|---|---|---|
| | | | | *endo* | *exo* |
| **8 & 12** | **2 + 3** | 224 | 250 | 75 | 25 |
| **9 & 13** | **2 + 4** | 204 | 255 | 87 | 13 |
| **10 & 14** | **2 + 5** | [a] | 172 | 80 | 20 |
| **11 & 15** | **2 + 6** | 195 | 215 | 87 | 13 |
| **16** | **2 + 7** | 95 | 190 | 76 | 24 |

[a] Decomposed before melting.

Fig. 4. The DSC thermogram of polymer **8** which reveals a glass transition at 152 °C.

Table 2
Molecular weight data for cycloaddition polymers produced via high pressure reaction conditions

| Polymer number | Monomers | Solvent | GPC | | |
|---|---|---|---|---|---|
| | | | $M_n$ (kDa) | $M_w$ (kDa) | PDI |
| **8** | **2 + 3** | $CH_2CI_2$ | 15.1 | 30.4 | 2.0 |
| **9** | **2 + 4** | $CH_2CI_2$ | 6.2 | 13.5 | 2.2 |
| **10** | **2 + 5** | $CH_2CI_2$ | 6.9 | 14.4 | 2.1 |
| **11** | **2 + 6** | $CH_2CI_2$ | 6.0 | 13.8 | 2.3 |
| **12** | **2 + 3** | DMF | 13.0 | 27.9 | 2.1 |
| **13** | **2 + 4** | DMF | 4.1 | 8.5 | 2.1 |
| **14** | **2 + 5** | DMF | 3.1 | 6.9 | 2.2 |
| **15** | **2 + 6** | DMF | 3.3 | 7.5 | 2.3 |
| **16** | **2 + 7** | DMF | 9.7 | 18.9 | 2.0 |

The GPC was calibrated using polystyrene standards.

of the films from the glass. The resultant clear films possessed an average thickness of 10 μm and were moderately pliable, although polymer **8** was noticeably more brittle in nature than polymer **9**. Further studies are currently underway to assess the stability of these polymer films.

## 4. Conclusions

A diverse range of poly(isoxazolidine) architectures have been produced using high pressure reaction conditions. This study revealed that the polycycloadducts produced under these conditions possessed a significantly greater degree of *endo*-selectivity than structurally related polymers generated by thermal means. [4,8] These polymers possessed molecular weights in the range of 13–30 kDa and 7–28 kDa when the polymerizations were carried out in dichloromethane or dimethylformamide, respectively, they also exhibited interesting thermal properties and as a consequence could be potentially processed to produce coatings. Furthermore, the biological activity of these polymers has yet to be assessed and could lead to their application as anti-fungal or anti-bacterial coatings.

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