

## Supporting Information

# The Application of Blocked Isocyanate Chemistry in the Development of Tunable Thermoresponsive Crosslinkers

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## 1. Experimental Details

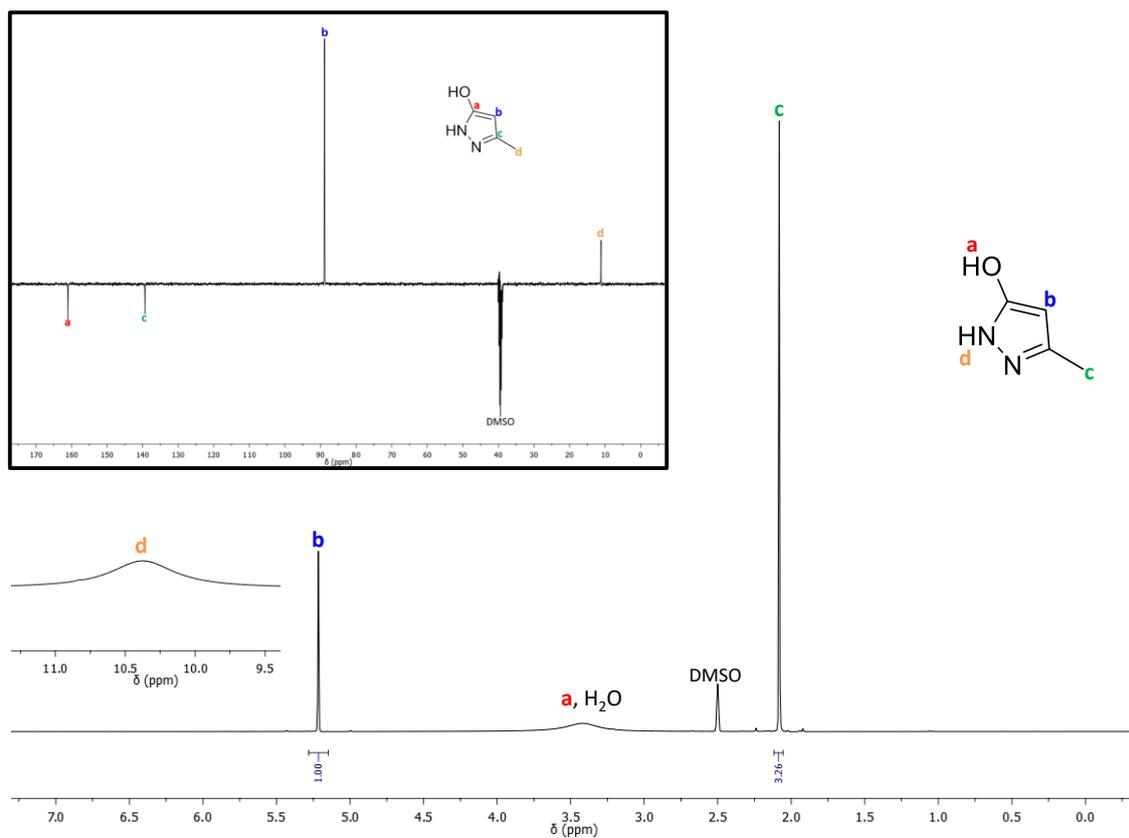
Variable temperature (VT)  $^1\text{H}$  NMR spectroscopic analysis was conducted as follows: polymer/crosslinker was dissolved in deuterated solvent (10 mg/mL) and placed in an NMR tube. The tube was inserted into the instrument. The temperature was automatically ramped to the preset start temperature, the sample was equilibrated in the instrument for 3 minutes and the spectrum acquired. The temperature was then automatically ramped to the next temperature, the sample equilibrated for 3 minutes and the spectrum acquired. The process continued until all the pre-set temperature range had been completed.

$^1\text{H}$  NMR spectrum on samples continually heated at a preset temperature were carried out by heating a solution of the polymer/crosslinker in a vial, dissolved in deuterated solvent, in an oil bath at a pre-set temperature. After heating for a set period, an aliquot was removed, quenched in liquid nitrogen, and analyzed using the NMR spectrometer.

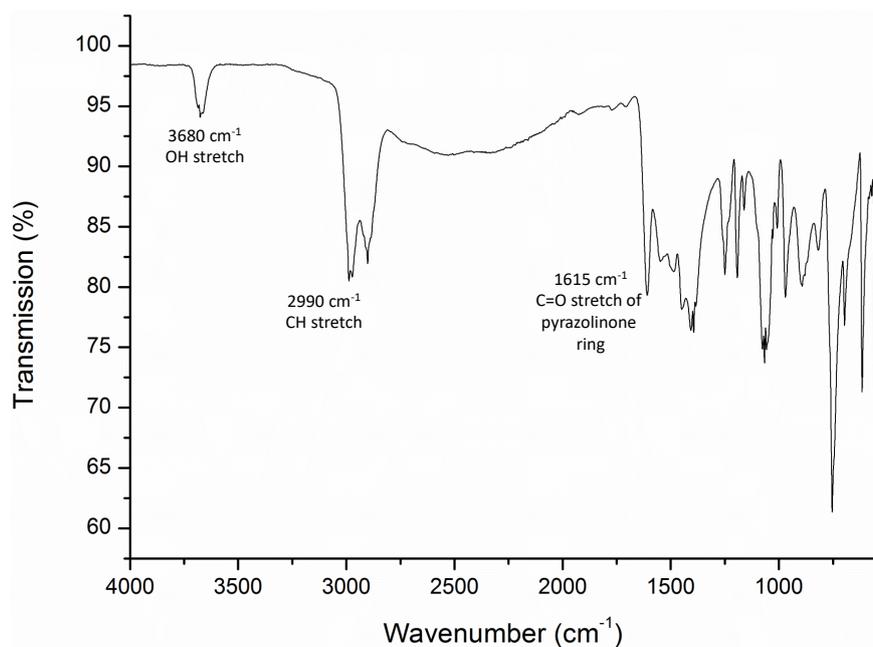
FTIR analysis of crosslinker was carried out by heating a sample of the crosslinker dissolved in solvent (10 mg/ml) in an oil bath at a preset temperature. After heating for 30 minutes, the sample was quenched in liquid nitrogen and analyzed on the FTIR spectrometer. Each sample was made by separately heating a vial containing the crosslinker solution at a set temperature.

Triple-detection analysis of the polymeric particles was carried out by heating a solution of the polymer dissolved in SEC eluent (DMF with 5 mM  $\text{NH}_4\text{BF}_4$ , PMMA standards, 10 mg/mL) in an oil bath at a preset temperature for 30 minutes. The solution was quenched in liquid nitrogen, filtered and analyzed.

## 2. Spectroscopic analysis of hydroxy pyrazole (1).



**Figure S1**  $^1\text{H}$  NMR spectrum of hydroxy pyrazole (1) (400 MHz,  $\text{DMSO-}d_6$ ), and  $^{13}\text{C}$  NMR spectrum (inset, 100 MHz,  $\text{DMSO-}d_6$ ).



**Figure S2** FTIR spectrum (neat) of hydroxy pyrazole (1), highlighting the C=O stretch of the pyrazolinone ring of the ketone tautomer at  $\nu = 1615 \text{ cm}^{-1}$ ,<sup>1</sup> and the broad hydrogen-bonding absorption band between  $\nu = 3300 - 1900 \text{ cm}^{-1}$ .<sup>2</sup>

### 3. Spectroscopic analysis of methacryloyl pyrazole (2).

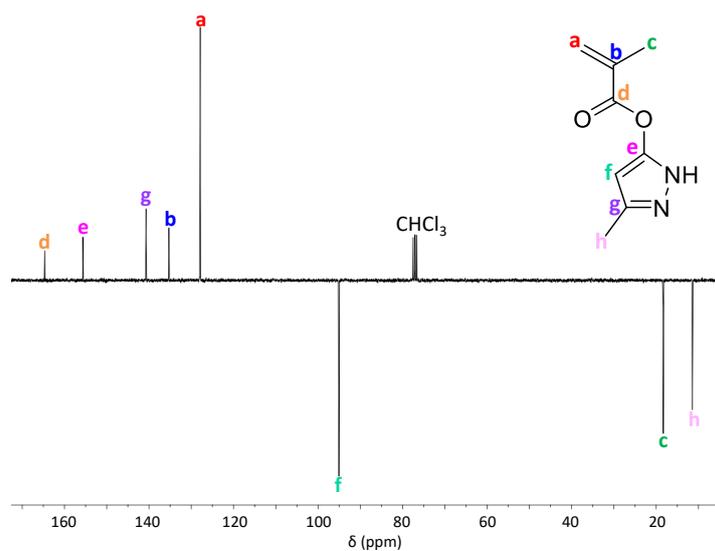


Figure S3 <sup>13</sup>C NMR spectrum of methacryloyl pyrazole (2) (100 MHz, CDCl<sub>3</sub>).

### 4. Spectroscopic determination for the deblocking temperature of methacryloyl pyrazole blocked TDI crosslinker (3).

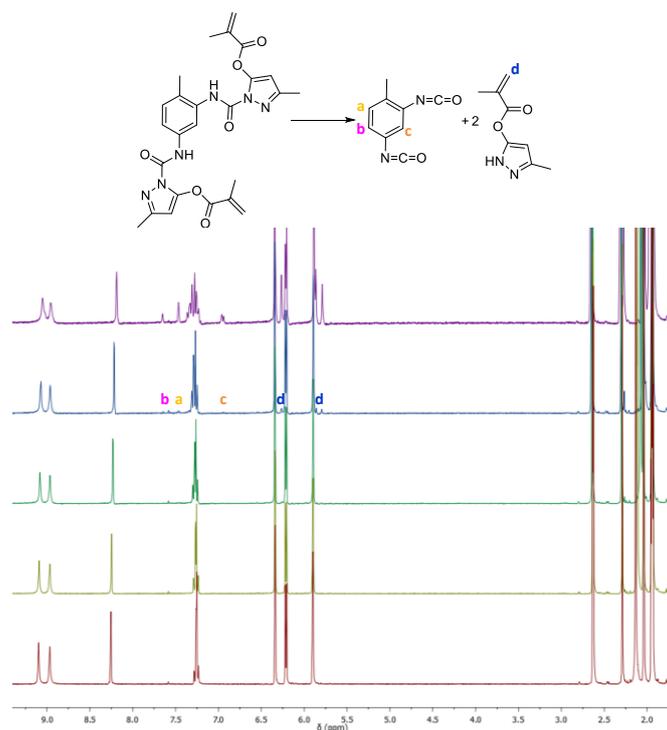
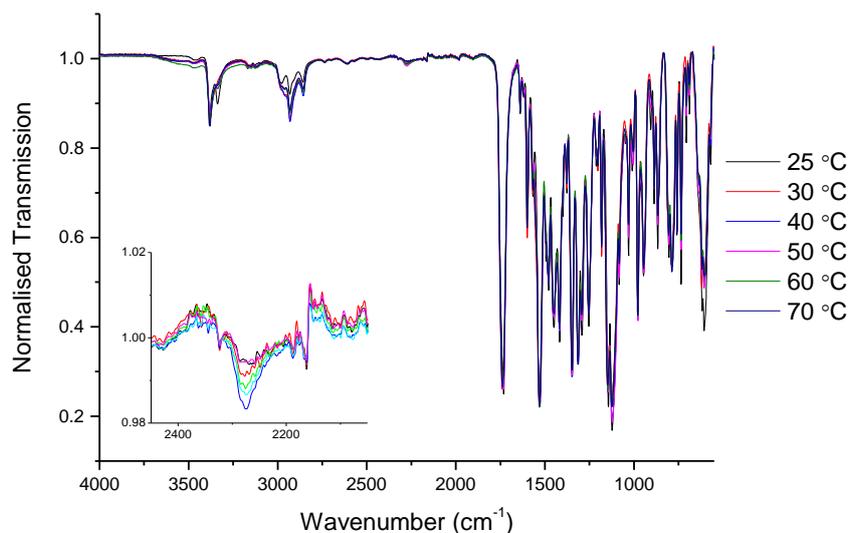
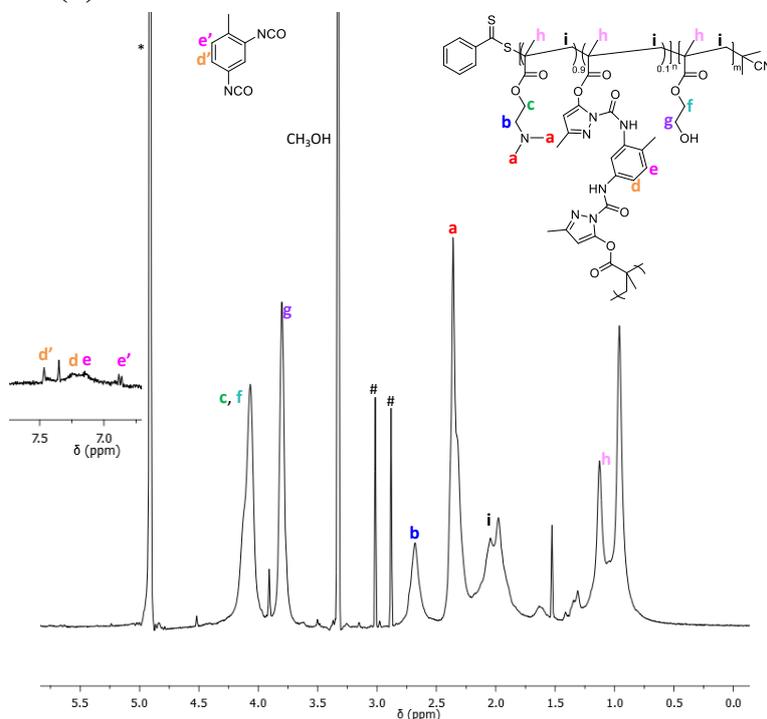


Figure S4a Determination of the deblocking temperature of methacryloyl pyrazole blocked TDI crosslinker (3) using variable temperature <sup>1</sup>H NMR spectroscopy at 25 °C (red), 30 °C (yellow), 40 °C (green), 50 °C (blue), and 60 °C (purple), showing the evolution of the free isocyanate (a, b and c) and the released methacryloyl pyrazole (d), normalized to the solvent peak the internal standard TMS at δ = 0 ppm (400 MHz, Acetonitrile-d<sub>6</sub>).

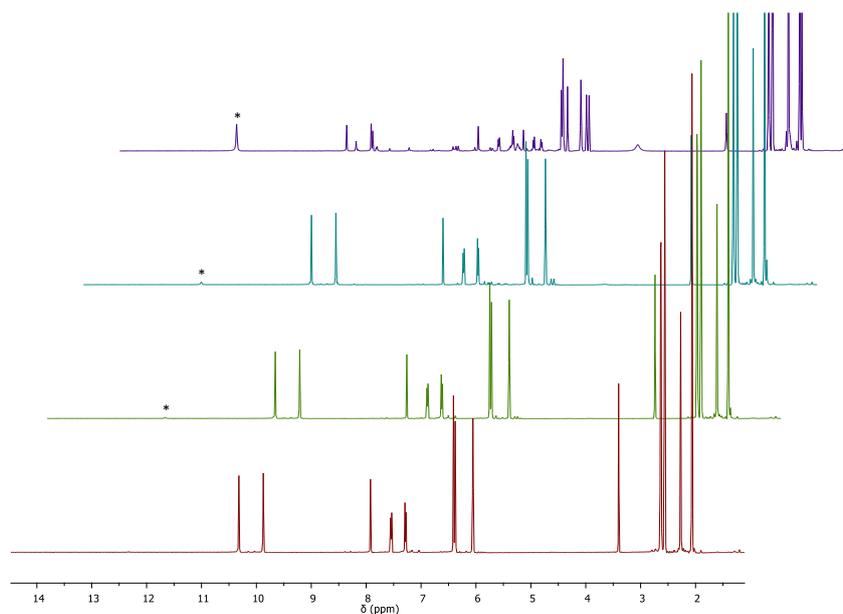


**Figure S4b** Determination of the deblocking temperature of the methacryloyl pyrazole blocked TDI crosslinker (**3**) using FTIR analysis of samples dissolved in acetonitrile and heated to a set temperature for 30 minutes prior to analysis (*inset*- zoomed-in region of the spectrum associated with free isocyanate stretch).

## 5. Spectroscopic analysis for the direct RAFT polymerization of the TDI crosslinker (**3**).

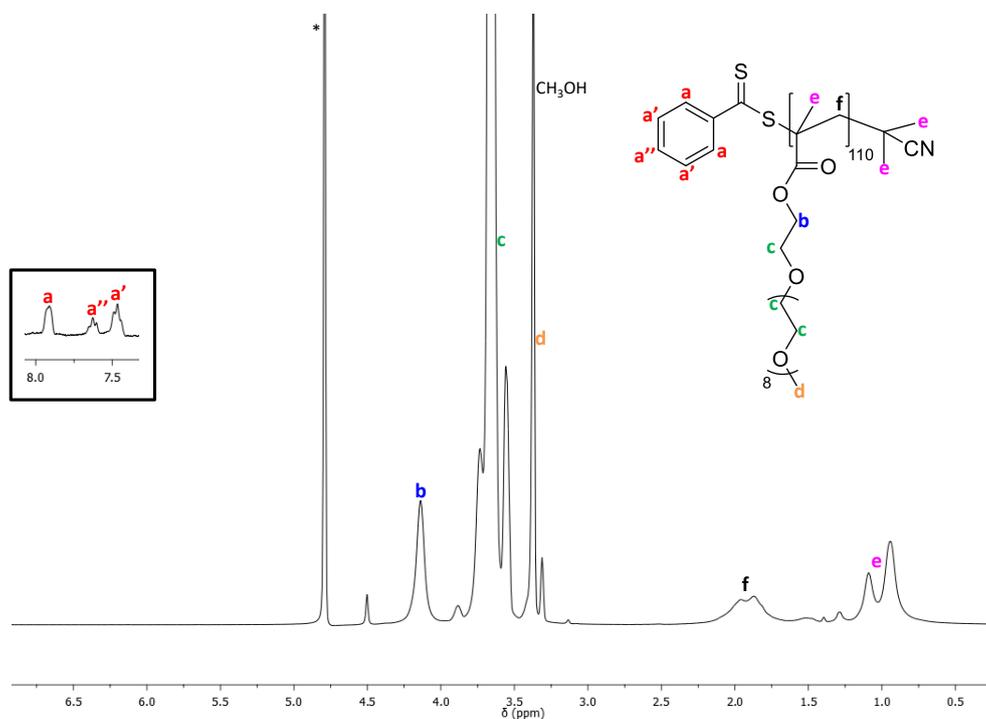


**Figure S5** <sup>1</sup>H NMR spectrum of PHEMA-*b*-P(DMAEMA-*co*-TDI crosslinker) indicating successful chain extension with DMAEMA and the crosslinker, yet also significant deblocking of the blocked TDI crosslinker (**3**) during polymerization. \* denotes H<sub>2</sub>O, # denotes DMF (400 MHz, CD<sub>3</sub>OD).

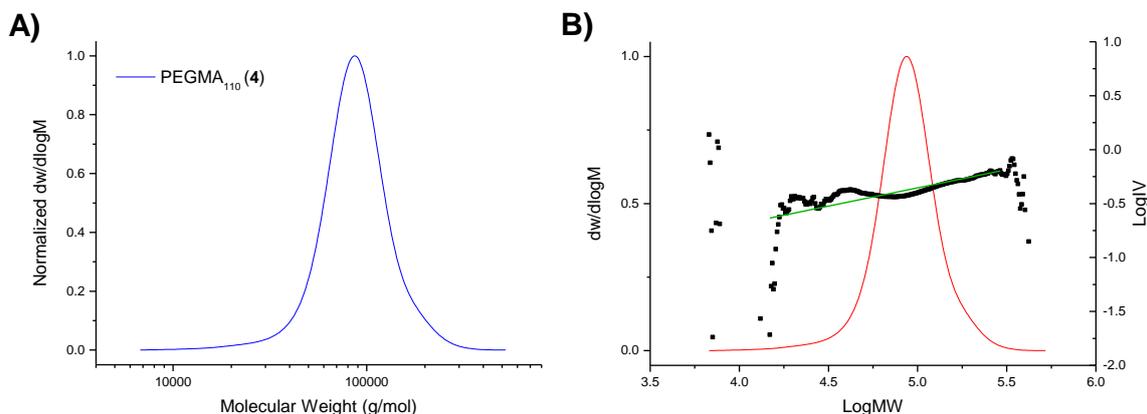


**Figure S6** Overlaid  $^1\text{H}$  NMR spectra of TDI crosslinker (**3**) in DMF (10 mg/mL) at different time points at 30 °C, at 0 min. (*red*), 60 min. (*green*), 180 min. (*turquoise*) and 5760 min. (*purple*), showing the evolution of the free NH of the pyrazole (\*), normalized to the internal standard TMS at  $\delta = 0$  ppm. (400 MHz, DMF- $d_7$ ).

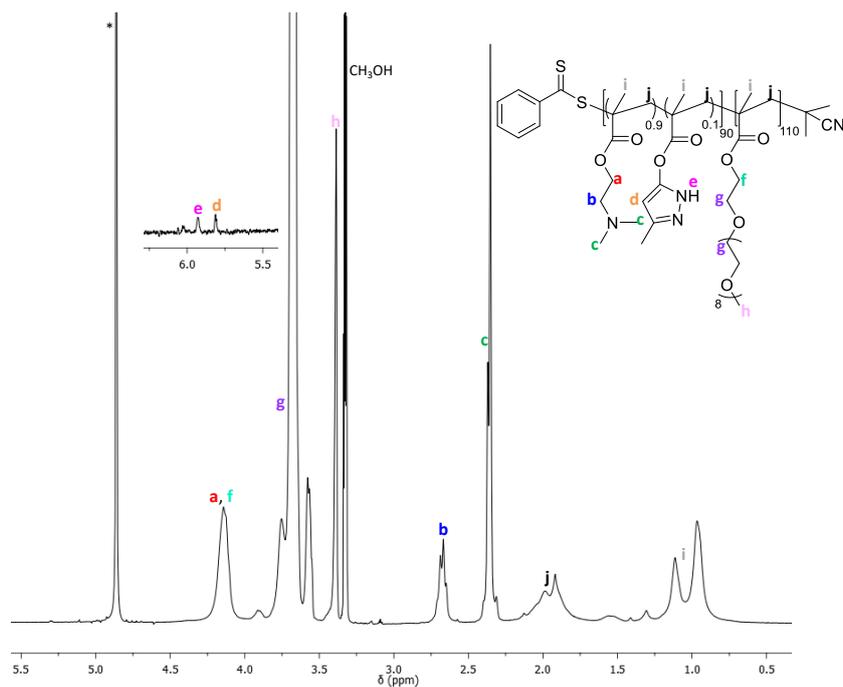
## 6. Spectroscopic analysis of PEGMA<sub>110</sub> macro-CTA (**4**) and linear precursor polymer PEGMA<sub>110</sub>-*b*-P(DMAEMA<sub>0.9</sub>-*co*-pyrazole<sub>0.1</sub>)<sub>90</sub> (**5**).



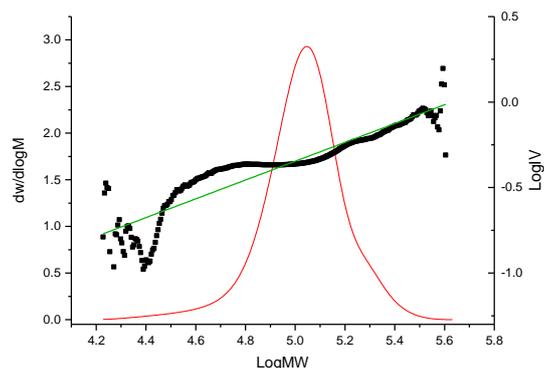
**Figure S7**  $^1\text{H}$  NMR spectrum of PEGMA<sub>110</sub> (**4**), with aromatic region inset. \* denotes H<sub>2</sub>O (400 MHz, CD<sub>3</sub>OD).



**Figure S8** Molecular weight distribution (A) for PEGMA<sub>110</sub> homopolymer (4), and (B) triple-detection SEC analysis of PEGMA<sub>110</sub> (4), with the Mark-Houwink curve overlaid on the molecular weight distribution (DMF with 5 mM NH<sub>4</sub>BF<sub>4</sub> eluent, with PMMA standards). Red line is the molecular weight distribution, black points are the Mark-Houwink plot and the green line is the linear fit of the Mark-Houwink plot.



**Figure S9** <sup>1</sup>H NMR spectrum of PEGMA<sub>110</sub>-*b*-P(DMAEMA<sub>0.9</sub>-*co*-pyrazole<sub>0.1</sub>)<sub>90</sub> (5), \* denotes H<sub>2</sub>O (400 MHz, CD<sub>3</sub>OD).

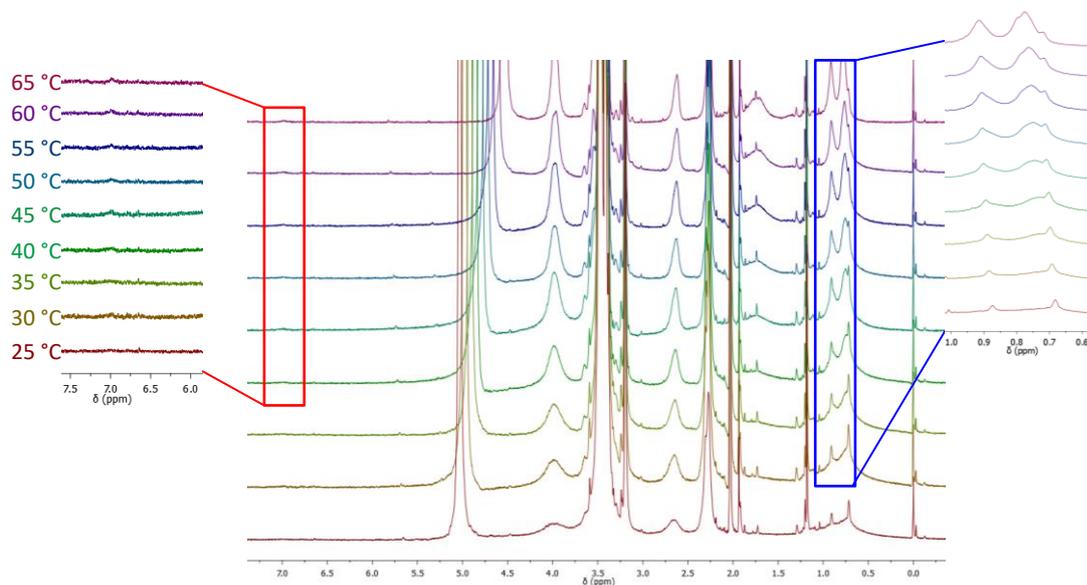


**Figure S10** Triple-detection SEC analysis of PEGMA<sub>110</sub>-*b*-P(DMAEMA<sub>0.9</sub>-*co*-pyrazole<sub>0.1</sub>)<sub>90</sub> (**5**), with the Mark-Houwink curve overlaid on the molecular weight distribution (DMF with 5 mM NH<sub>4</sub>BF<sub>4</sub> eluent, with PMMA standards). Red line is the molecular weight distribution, black points are the Mark-Houwink plot and the green line is the linear fit of the Mark-Houwink plot.

## 7. Degradation behavior of TDI crosslinked PEGMA<sub>110</sub>-*b*-P(DMAEMA<sub>0.9</sub>-*co*-pyrazole<sub>0.1</sub>)<sub>90</sub> particles (**6**).

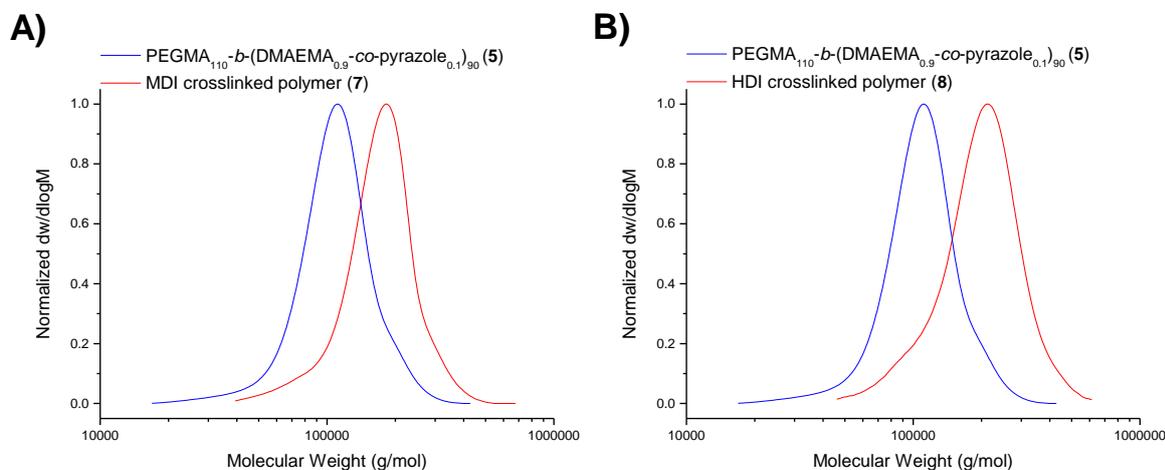
$$M_v = \left[ \frac{\sum M_i^{1+a} N_i}{\sum M_i N_i} \right]^{\frac{1}{a}}$$

**Equation S1** Viscosity-average molecular weight ( $M_v$ ) and its dependence on the Mark-Houwink characteristic constant  $a$ .

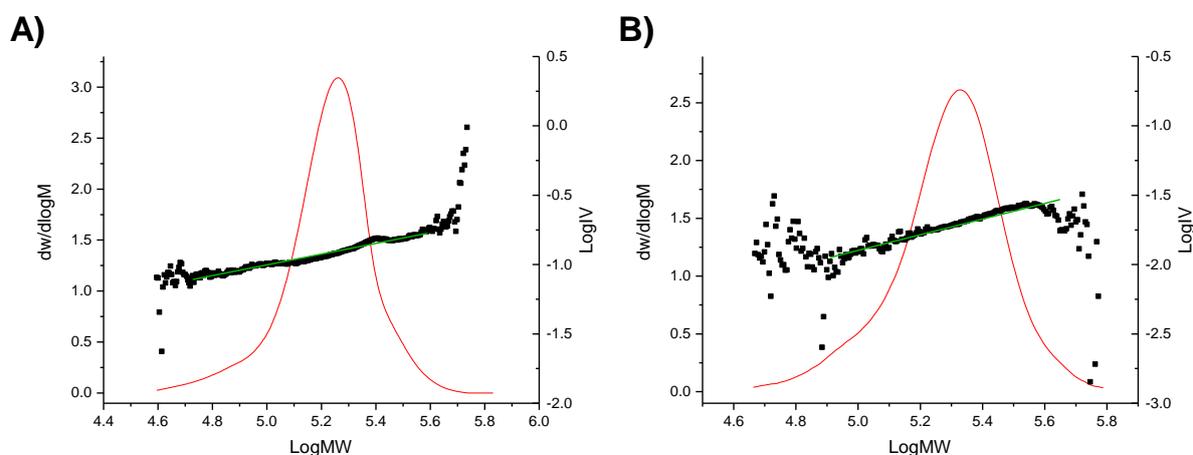


**Figure S11** Variable temperature <sup>1</sup>H NMR spectroscopic analysis of TDI crosslinked PEGMA<sub>110</sub>-*b*-P(DMAEMA<sub>0.9</sub>-*co*-pyrazole<sub>0.1</sub>)<sub>90</sub> particles (**6**) at 25 °C (red), 30 °C (yellow), 35 °C (light green), 40 °C (green), 45 °C (turquoise), 50 °C (light blue), 55 °C (blue), 60 °C (purple) and 65 °C (pink), showing the evolution of urethane resonance (highlighted in red) evolved as a consequence of the liberated isocyanate reacting with the ethylene glycol, and the changing polymer backbone (highlighted in blue) as a consequence of the deshielding of the polymer backbone as the polymeric particles degrade (400 MHz, ethylene glycol-*d*<sub>6</sub>).

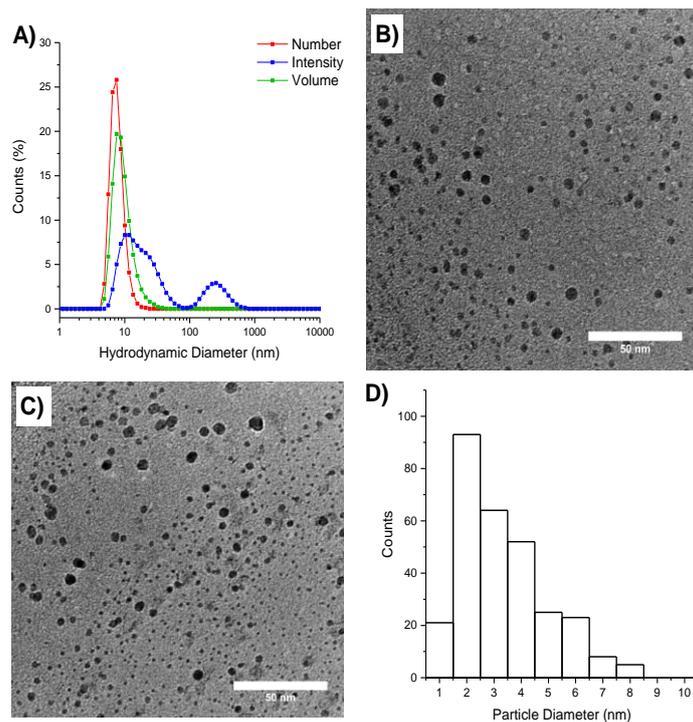
## 8. Characterization of MDI and HDI crosslinked PEGMA<sub>110</sub>-*b*-P(DMAEMA<sub>0.9</sub>-*co*-pyrazole<sub>0.1</sub>)<sub>90</sub> particles (7 and 8, respectively).



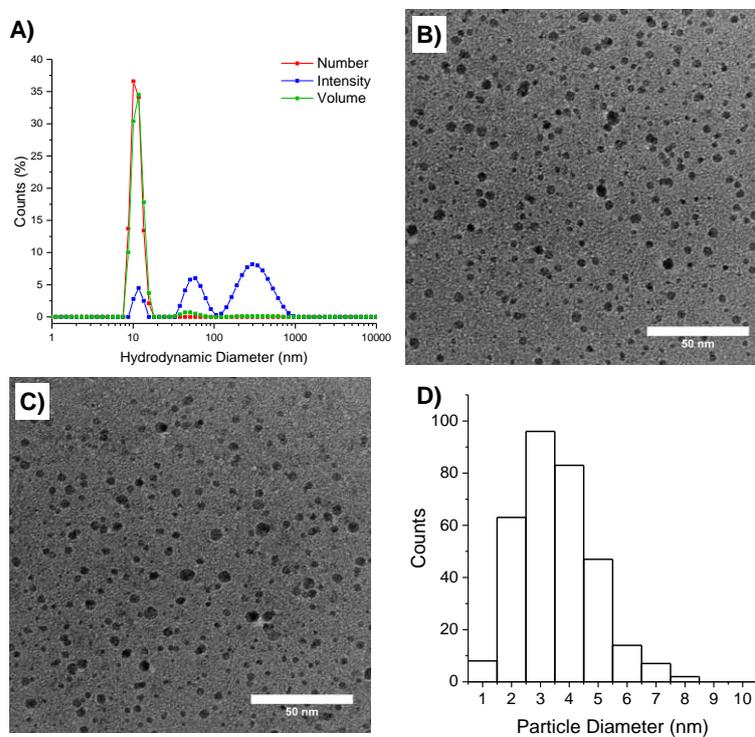
**Figure S12** Molecular weight distribution for MDI (A) and HDI (B) crosslinked PEGMA<sub>110</sub>-*b*-P(DMAEMA<sub>0.9</sub>-*co*-pyrazole<sub>0.1</sub>)<sub>90</sub> (7 and 8, respectively) (DMF with 5 mM NH<sub>4</sub>BF<sub>4</sub> eluent, with PMMA standards).



**Figure S13** Triple-detection SEC analysis of MDI (A) and HDI crosslinked (B) PEGMA<sub>110</sub>-*b*-P(DMAEMA<sub>0.9</sub>-*co*-pyrazole<sub>0.1</sub>)<sub>90</sub> (7 and 8, respectively), with the Mark-Houwink curve overlaid on the molecular weight distribution (DMF with 5 mM NH<sub>4</sub>BF<sub>4</sub> eluent, with PMMA standards). Red line is the molecular weight distribution, black points are the Mark-Houwink plot and the green line is the linear fit of the Mark-Houwink plot.



**Figure S14** Size distribution (A), as determined by DLS (3 mg/mL in methanol), and representative TEM images (B and C, methanol, 30 mg/ mL on GO supported TEM grids) of MDI crosslinked polymeric particles (7), with particle size histogram (D).



**Figure S15** Size distribution (A), as determined by DLS (3 mg/mL in methanol), and representative TEM images (B and C, methanol, 30 mg/ mL on GO supported TEM grids) of HDI crosslinked polymeric particles (8), with particle size histogram (D).

## 9. References

1. M. Amir, S. A. Javed and M. Zaheen Hassan, *Med. Chem. Res.*, 2012, 21, 1261-1270.
2. N. A. Evans, D. J. Whelan and R. B. Johns, *Tetrahedron*, 1965, 21, 3351-3361.