Supplementary Material (ESI) for Chemical Communications

Supporting Information

Reactive Thermoresponsive Copolymer Scaffolds

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General Experimental

Oligo(ethyleneglycol) methyl ether methacrylate ($OEGMA_{300}$, M_n ~ 300 g/mol, Aldrich) was dissolved in CH_2Cl_2, passed over a basic aluminium oxide column and dried under vacuum prior to use. All other chemicals, including *O*-(carboxymethyl)hydroxylamine (**2**), were purchased from Sigma-Aldrich or Alfa Aesar and were used as received without further purification. ^1H and ^{13}C NMR spectra were recorded on a Jeol ECS-400 spectrometer at 400 and 100 MHz, or a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively, with the residual solvent signal as an internal standard. Mass spectrometry was performed on a Waters LCT premier mass spectrometer (Waters Inc.). Gel permeation chromatography (GPC) was conducted on a Varian ProStar instrument (Varian Inc.) equipped with a pair of PL gel 5 μm Mixed D 300 × 7.5 mm columns with guard column (Polymer Laboratories Inc.), a Varian 325 UV-vis dual wavelength detector (254 nm), a Dawn Heleos II multi-angle laser light scattering detector (Wyatt Technology Corp.) and a Viscotek 3580 differential RI detector in series. Near monodisperse polystyrene standards (Polymer Laboratories) were used for calibration. Data collection was performed with Galaxie software (Varian Inc.) and chromatograms analyzed with the Cirrus software (Varian Inc.) and Astra software (Wyatt Technology Corp.). Melting points were determined on a Stuart Melting Point SMP11 apparatus.

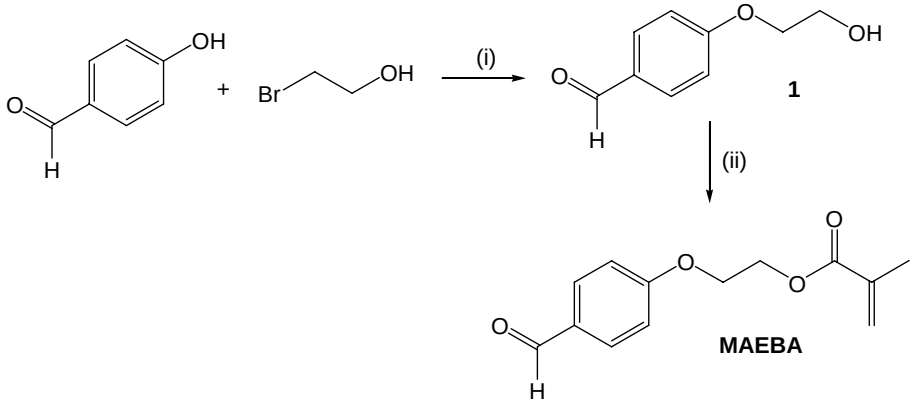
The cloud points of the polymer solutions (concentrations equal to 2 mg ml^{-1} of the parent polymer) in 0.1 M NaCl solution, at specified pH values, were measured on a Cary 100 Bio UV-Vis spectrophotometer (Varian Inc.) fitted with a peltier block. Transmittance of polymer solutions was monitored at 550 nm as a function of temperature (cell path length 10 mm). Heating /cooling cycles were conducted at a rate of 0.1°C min^{-1}.

Hydrodynamic diameters (D_h) for polymers and conjugates in aqueous 0.1 M NaCl solutions were determined by dynamic light scattering (DLS). The DLS instrumentation consisted of a MALVERN Instruments HPPS-ET 5002 operating at 25 °C with a 633-nm laser module. Measurements were made at a detection angle of 173° (back scattering), and Malvern DTS 4.20 software was utilized to analyze the data. All determinations were made in duplicate.

*p*H Measurements were recorded with a Hanna HI 98103 instrument that was calibrated daily with commercial buffer solutions (Sigma-Aldrich). The adjustment of pH was carried out using concentrated NaOH and concentrated HCl (or NaOD and DCl if required) solutions to avoid any significant increase in sample volume.

Synthetic Procedures

p-(2-Methacryloxyethoxy)benzaldehyde (**MAEBA**) was prepared according to the procedure reported[1] by Antonucci.



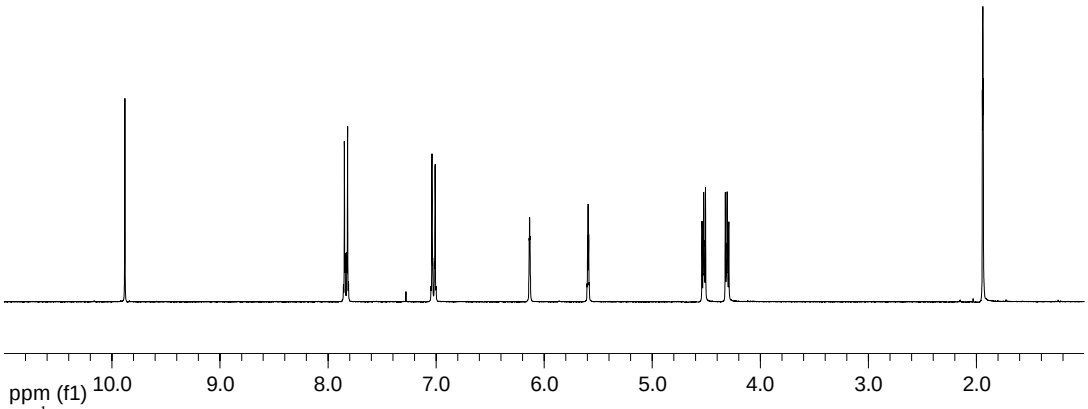
S1. Synthesis of *p*-(2-Methacryloxyethoxy)benzaldehyde (**MAEBA**): (i) K_2CO_3, DMF, Reflux, 24 h. (ii) Methacroyl chloride, Et_3N, CH_2Cl_2, 0 ˚C, 2 h.

***p*-(2-Hydroxyethoxy)benzaldehyde (1):**

Potassium carbonate (17.0 g, 0.123 mol) was suspended in a solution of 4-hydroxybenzaldhyde (5.0 g, 0.041 mol), 2-bromoethanol (5.1 g, 0.041 mol) and dimethylformamide (100 mL) under reflux conditions for 24 h. After filtration and evaporation to dryness crude material was transferred into a separating funnel in CH_2Cl_2 (100 mL). The organic layer was washed with $NaCl_{(aq)}$ (2 × 100 mL), dried over $MgSO_4$, filtered and evaporated to dryness to obtain a crude solid which was purified by column chromatography [SiO_2, Hexane-EtOAc (1:1)] to afford 4-(2-hydroxyethoxy)-benzaldehyde as a clear oil (4.2 g, 61.6 %). ^{1}H NMR ($CDCl_3$): δ 3.10 (br s, 1H), 3.95 (t, 2H, J = 4.8 Hz), 4.11 (t, 2H, J = 4.8 Hz), 6.95 (d, 2H, J = 8.7 Hz), 7.75 (d, 2H, J = 8.7 Hz), 9.79 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 61.4, 71.0, 115.2, 130.4, 132.4, 164.2, 191.5.

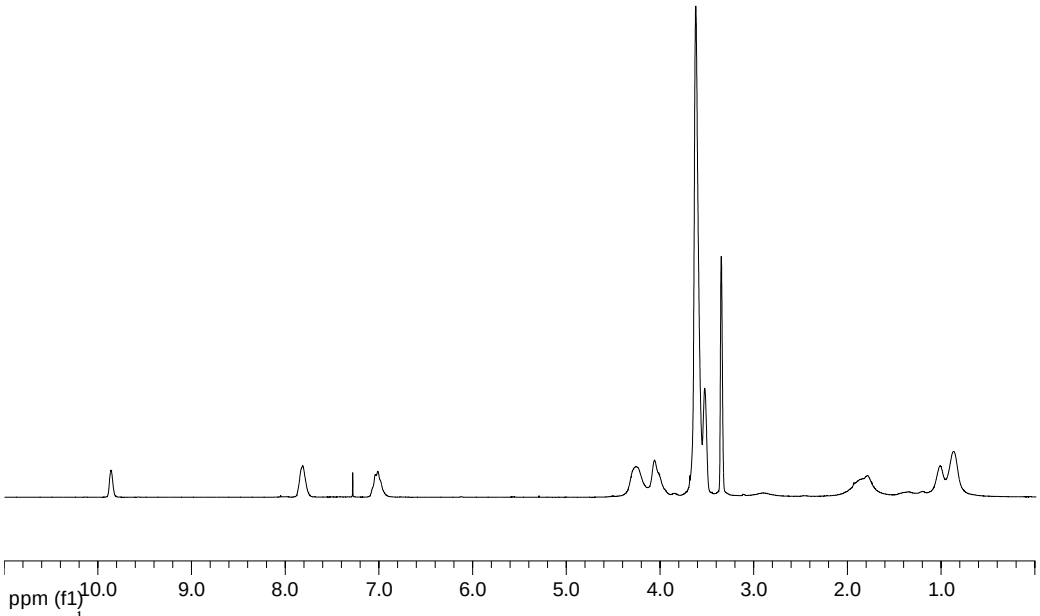
***p*-(2-Methacryloxyethoxy)benzaldehyde (MAEBA):**

p-(2-Hydroxyethoxy)benzaldehyde (3.8 g, 0.023 mol) and Et_3N (2.8 g, 0.027 mol) in CH_2Cl_2 (75 mL) were cooled to 0 ˚C. To this solution methacroyl chloride (2.7 g, 0.026 mol) in CH_2Cl_2 (25 mL) was added dropwise over 30 min while stirring under N_2. Reaction mixture was allowed to reach room temperature and was left to stir for 2 h before transferring to a separating funnel with H_2O (100 mL). Organic layer was washed with $NaCl_{(aq)}$ (2 × 100 mL), dried over $MgSO_4$, filtered and evaporated to dryness to obtain a crude oil which was purified by column chromatography [SiO_2, Hexane-EtOAc (4:1)] to afford 4-(2-Methacrylateethoxy)-benzaldehyde as a white solid (2.8 g, 52 %). ^{1}H NMR ($CDCl_3$): δ 1.92 (s, 3H), 4.29 (t, 2H, J = 5. 1 Hz), 4.51 (t, 2H, J = 5.1 Hz), 5.57 (s, 1H), 6.12 (s, 1H), 7.00 (d, 2H, J = 8.7 Hz), 7.81 (d, 2H, J = 8.7 Hz), 9.86 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 18.7, 63.0, 66.6, 115.3, 126.7, 130.7, 132.3, 136.2, 163.9, 167.5, 191.1.

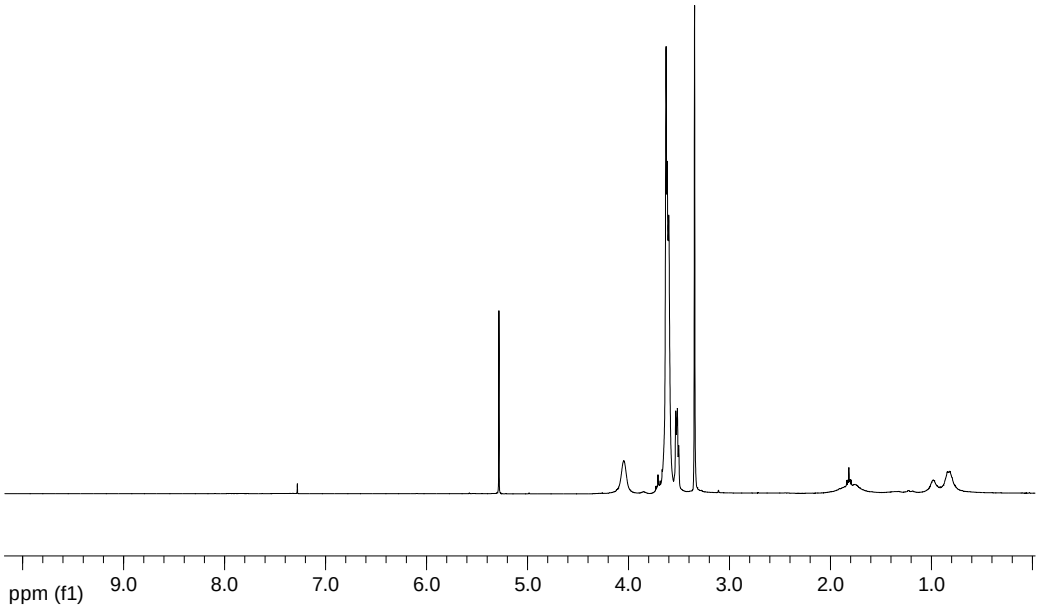


S2. ^{1}H NMR ($CDCl_3$) spectra of *p*-(2-Methacryloxyethoxy)benzaldehyde (**MAEBA**).

General RAFT copolymerization of $OEGMA_{300}$ and MAEBA: 4-(4-cyanopentanoic acid)dithiobenzoate (CPADB) (1 eq) and AIBN (0.2 eq) were added to a small schlenk tube. $OEGMA_{300}$ (66 eq) and MAEBA (33 eq) was then added followed by dioxane (100 eq). The reaction mixture was degassed five times via freeze-pump-thaw, and then the vessel was backfilled with N_2, purged with N_2, and allowed to warm to room temperature. The reaction mixture was then placed in an oil bath at 70 ˚C, and the polymerization was quenched after 23 h by rapid cooling and solvent was removed on the rotary evaporator. The resulting pink oil was dissolved in a minimal amount of THF and added dropwise to a large excess of ice-cold hexane, and the polymer isolated by filtration. Copolymers **P1** – **P6** were obtained as pink oils with yields typically between 50 and 70 %. A typical ^{1}H NMR spectrum of copolymer **P1** is shown in **S1**.



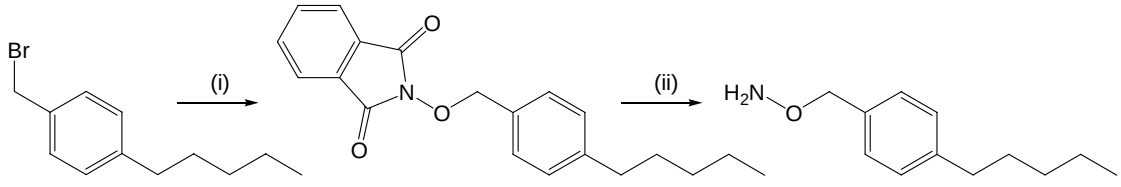
S1.(a) ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of poly($OEGMA_{300}$)-*c*-(MAEBA) (**P1**).



S1.(b) ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of poly($OEGMA_{300}$) (**P6**).

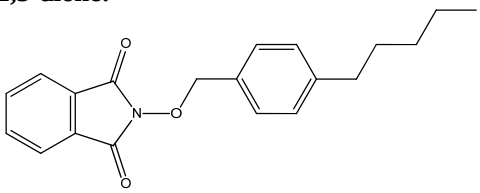
Compounds **1a**,[2] **1b**,[3] **4**,[4] **5**,[5] **6**,[6] and **8**[7] were prepared according to literature procedures to afford the corresponding compounds possessing satisfactory spectral and physical properties to those already reported. *O*-(4-pentylbenzyl)hydroxylamine **3** was prepared in two steps from 1-(bromomethyl)-4-pentylbenzene[8] as shown in **S2**. *O*-(pyren-1-ylmethyl)hydroxylamine **7** was prepared in two steps from 1-(bromomethyl)pyrene[9] as shown in **S3**. ^{1}H and ^{13}C NMR spectra for **3** and **7** and their precursors are shown in **S4**-**S7**.

S2. Synthesis of *O*-(4-pentylbenzyl)hydroxylamine: (i) *N*-hydroxyphthalimide, NEt_3, THF, reflux, 3 h. (ii) Hydrazine monohydrate, THF, reflux, 4 h.



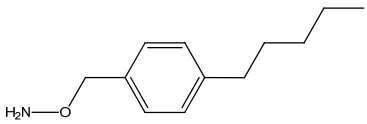
3

2-((4-Pentylbenzyl)oxy)isoindoline-1,3-dione:



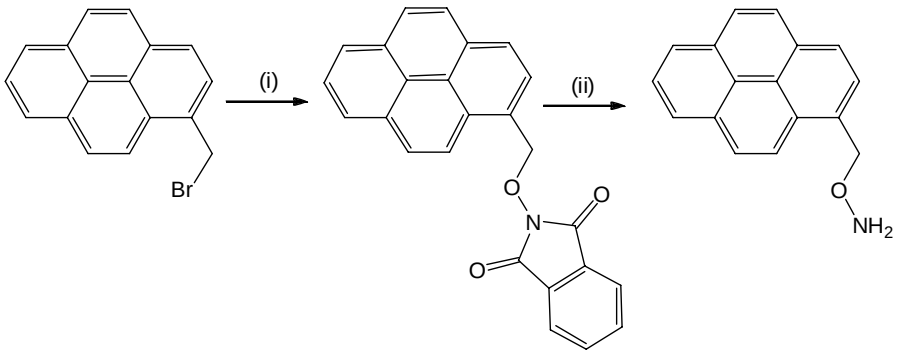
A solution of 1-(bromomethyl)-4-pentylbenzene (1.13 g, 4.69 mmol), *N*-hydroxyphthalimide (1.53 g, 9.38 mmol) and NEt_3 (1.31 mL, 9.4 mmol) in THF (50 mL) was heated at reflux for 3 h. The reaction mixture was left to cool, then H_2O (300 mL) was added to precipitate a solid that was collected by filtration then further washed with H_2O (30 mL). The solid was dried under reduced pressure then recrystallised from hot EtOH (50 mL) to yield the desired compound as a waxy white solid (0.75 g, 2.32 mmol, 49 %); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.83 – 7.71 (m, 4H, phthalimide), 7.44 (d, 2H, J = 8.0 Hz, Ar), 7.19 (d, 2H, J = 8.0 Hz, Ar), 5.18 (s, 2H, C*H*$_2$O), 2.60 (t, 2H, J = 8.0 Hz, pentyl), 1.57 (m, 2H, pentyl), 1.31 (m, 4H, pentyl), 0.88 (t, 3H, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.4 (C=O), 144.3 ($Ar_{(q)}$), 134.2 (Ar), 131.2 ($Ar_{(q)}$), 129.9 (Ar), 129.4 ($Ar_{(q)}$), 128.6 (Ar), 123.4 (Ar), 79.9 (*C*H_2O), 35.8, 31.5, 30.9, 22.5, 13.8 (pentyl); MS (ES^+) *m/z* 346.2 $[M + Na]^+$ 100 %; m.p. 99-101 °C.

***O*-(4-Pentylbenzyl)hydroxylamine:**

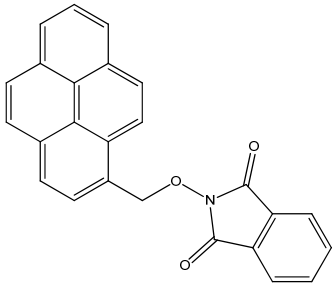


Hydrazine monohydrate (0.54 mL, 11.1 mmol) was added to a stirred solution of 2-((4-Pentylbenzyl)oxy)isoindoline-1,3-dione (0.74 g, 2.29 mmol) in THF (230 mL) at reflux to immediately yield a precipitate. The suspension was left at reflux for 4 h. at which point TLC analysis confirmed all starting material had been consumed. The suspension was allowed to cool then filtered, and the filtrate evaporated to dryness. The resultant crude yellow oil was purified by precipitation from hot MeOH to yield the desired product as a light yellow oil (0.42 g, 2.17 mmol, 95 %); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (d, 2H, J = 8.0 Hz, Ar), 7.18 (d, 2H, J = 8.0 Hz, Ar), 5.36 (br, 2H, ON*H*$_2$), 4.67 (s, 2H, C*H*$_2$ONH$_2$), 2.60 (t, 2H, J = 8.0 Hz, pentyl), 1.61 (m, 2H, pentyl), 1.33 (m, 4H, pentyl), 0.89 (t, 3H, J = 8.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.0 ($Ar_{(q)}$), 134.7 ($Ar_{(q)}$), 128.7, 128.6 (Ar), 78.1 (*C*H_2O), 35.8, 31.6, 31.3, 22.7, 14.2 (pentyl); MS (ES^+) *m/z* 194.2 $[M + H]^+$ 100 %.

S3. Synthesis of *O*-(pyren-1-ylmethyl)hydroxylamine: (i) *N*-hydroxyphthalimide, NEt_3, THF, reflux, 2 h (ii) Hydrazine monohydrate, THF, 2 h.

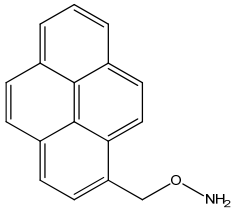


2-(Pyren-1-ylmethoxy)isoindoline-1,3-dione:



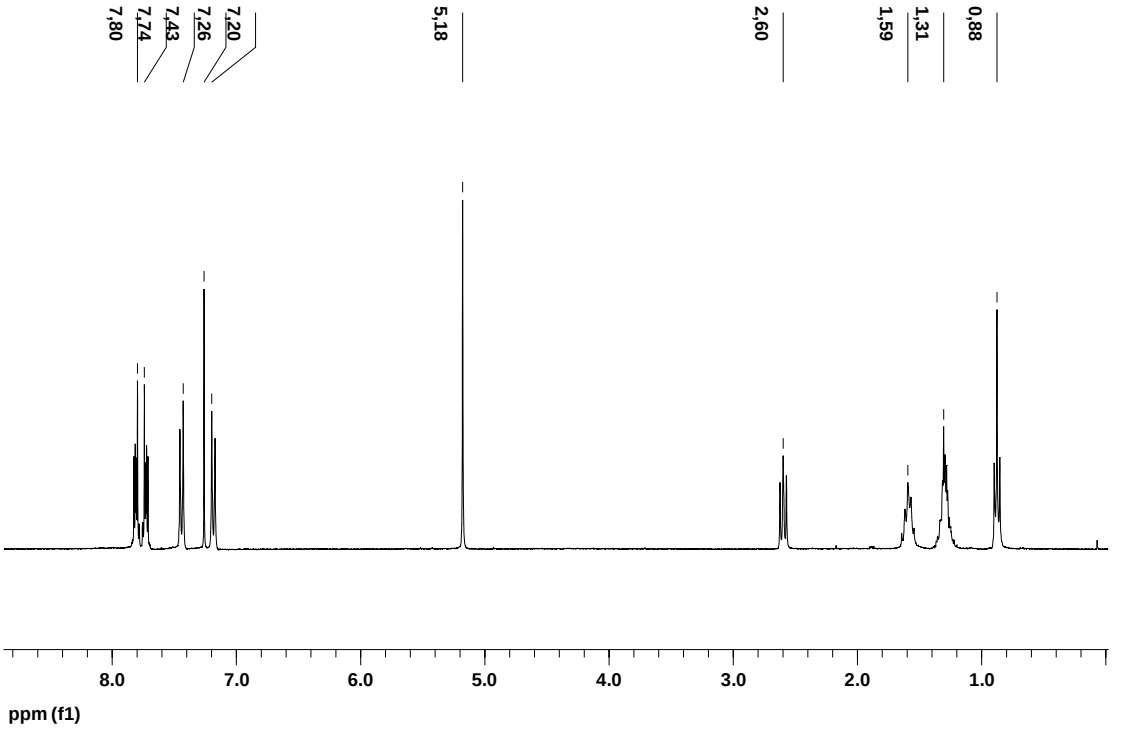
NEt_3 (1.9 mL, 13.6 mmol) was added to a refluxing solution of 1-(bromomethyl)pyrene (1.0 g, 3.4 mmol) and *N*-hydroxyphthalimide (1.1 g, 6.7 mmol) in THF to yield a deep red solution in which a precipitate rapidly formed (5 min). The suspension was left at reflux for 2 h., allowed to cool then filtered. The collected solid was washed with THF (5 mL), H_2O (10 mL) and ether (10 mL) to leave a straw coloured powder that was recrystallised from CH_2Cl_2-hexane to yield the desired compound as fibrous yellow crystals (0.90 g, 2.4 mmol, 71 %); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.84 (d, 1H, J = 8.0 Hz, pyrene), 8.29 – 8.03 (m, 8H, pyrene), 7.82 (m, 2H, phthalimide), 7.73 (m, 2H phthalimide), 5.91 (s, 2H, CH_2-O); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.8 (C=O), 134.6, 134.2, 132.7, 131.3, 131.1, 130.9, 129.4, 129.1, 128.8, 128.4, 127.7, 127.5, 126.6, 126.2, 125.9, 125.3, 124.6, 123.8, 123.7 (pyrene + phthalimide), 78.3 (CH_2O); MS (ES^+) *m/z* 378.2 $[M + H]^+$ 100 %; mp = 190-194 °C (dec).

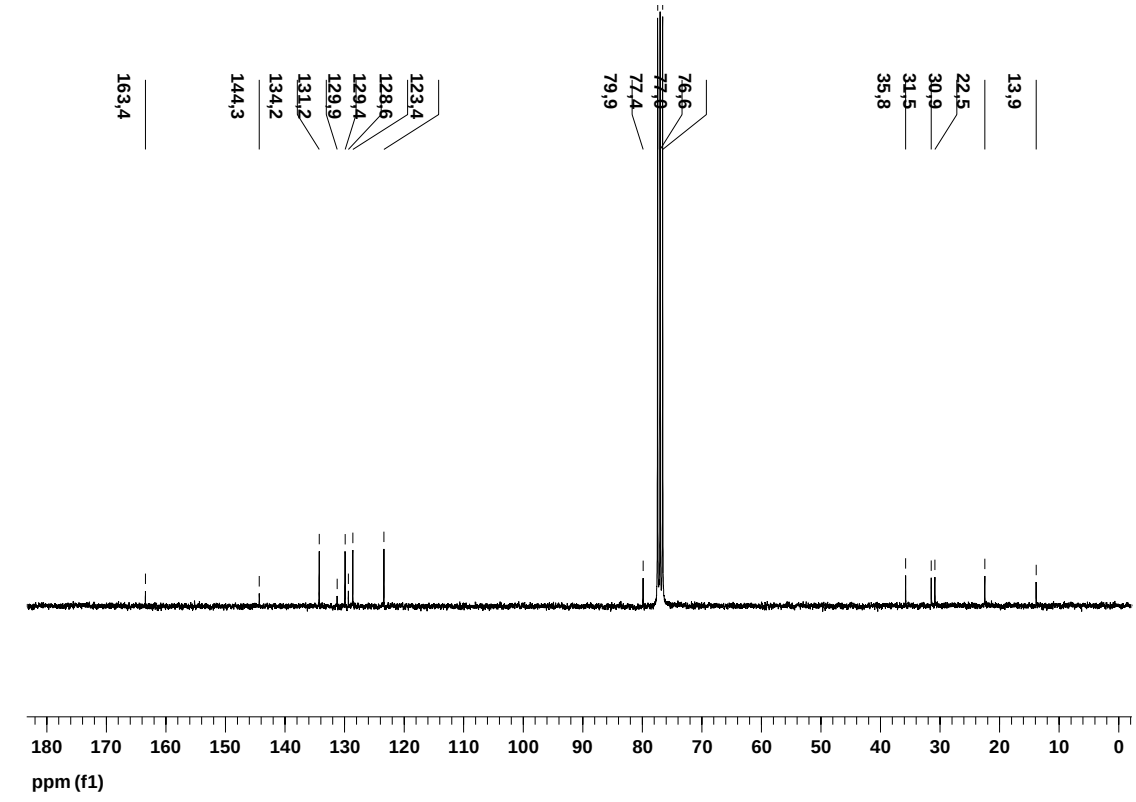
***O*-(Pyren-1-ylmethyl)hydroxylamine:**



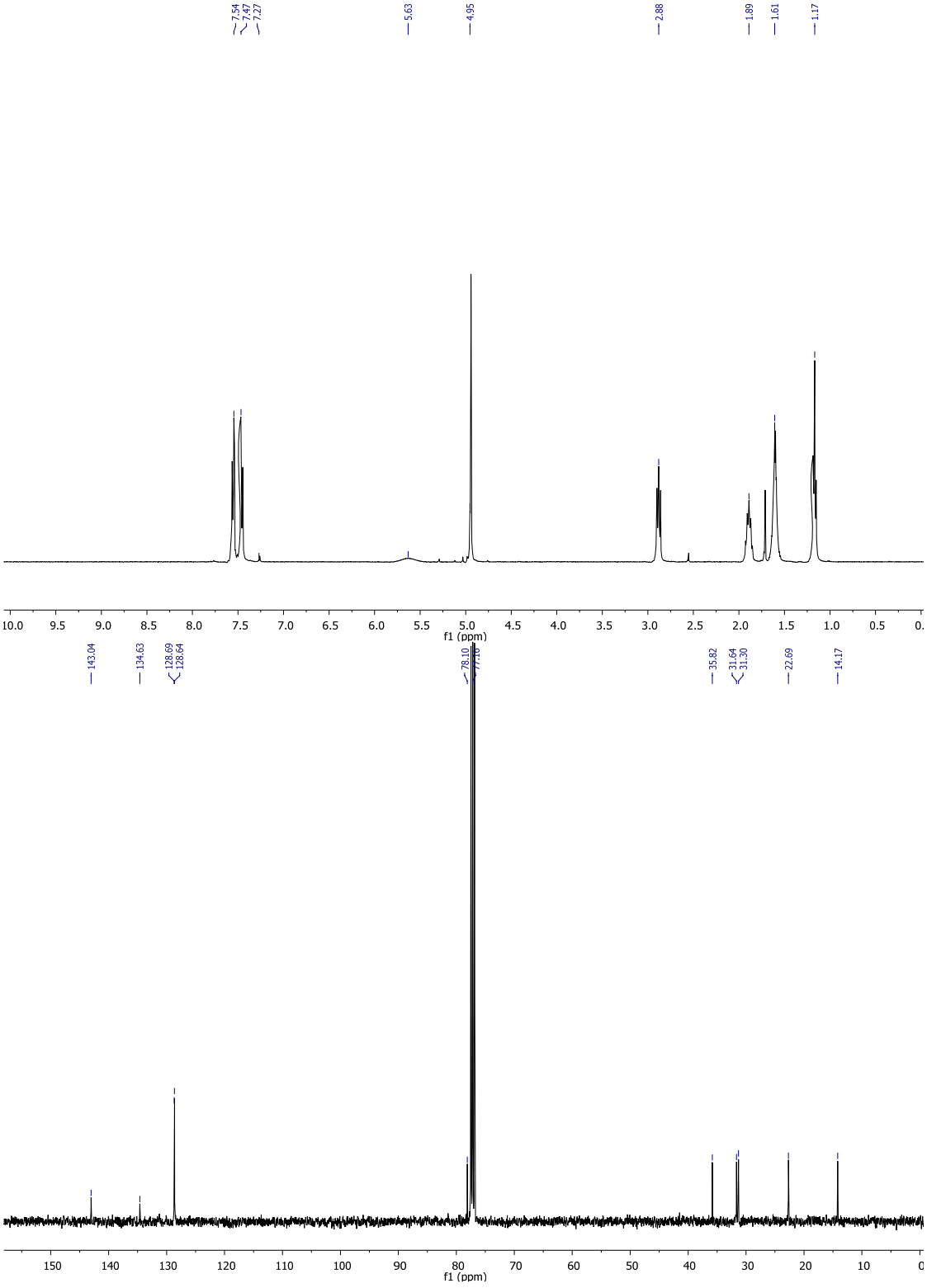
Hydrazine monohydrate (0.23 mL, 4.7 mmol) was added to a suspension of 2-(pyren-1-ylmethoxy)isoindoline-1,3-dione (0.90 g, 2.4 mmol) in THF (50 mL) at reflux to yield immediately a clear yellow solution followed by the precipitation of a white solid. The suspension was left at reflux for 2 h, allowed to cool to room temperature and then filtered. The filtrate was diluted by the addition of CH_2Cl_2 (50 mL) then washed with H_2O (2 x 50 mL). The organic fraction was dried over Na_2SO_4 then solvent was removed under reduced pressure to yield the desired compound as a yellow powder (0.4 g, 1.6 mmol, 67 %); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41 (d, 1H, J = 8.0 Hz, pyrene), 8.22 – 8.00 (m, 8H, pyrene), 5.48 (br, 2H, ONH_2), 5.42 (s, 2H, CH_2ONH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 131.7, 131.3, 130.9, 130.5, 129.9, 2 x 128.0, 127.7, 127.5, 126.1, 125.4, 125.1, 124.8, 124.6, 123.5 (pyrene), 76.5 (CH_2ONH_2); MS (ES^+) *m/z* 248.1 $[M + H]^+$ 100 %; mp = 73 75 °C.

S4. ^{1}H and ^{13}C NMR spectra (300/75 MHz, $CDCl_3$) of 2-((4-pentylbenzyl)oxy)isoindoline-1,3-dione:

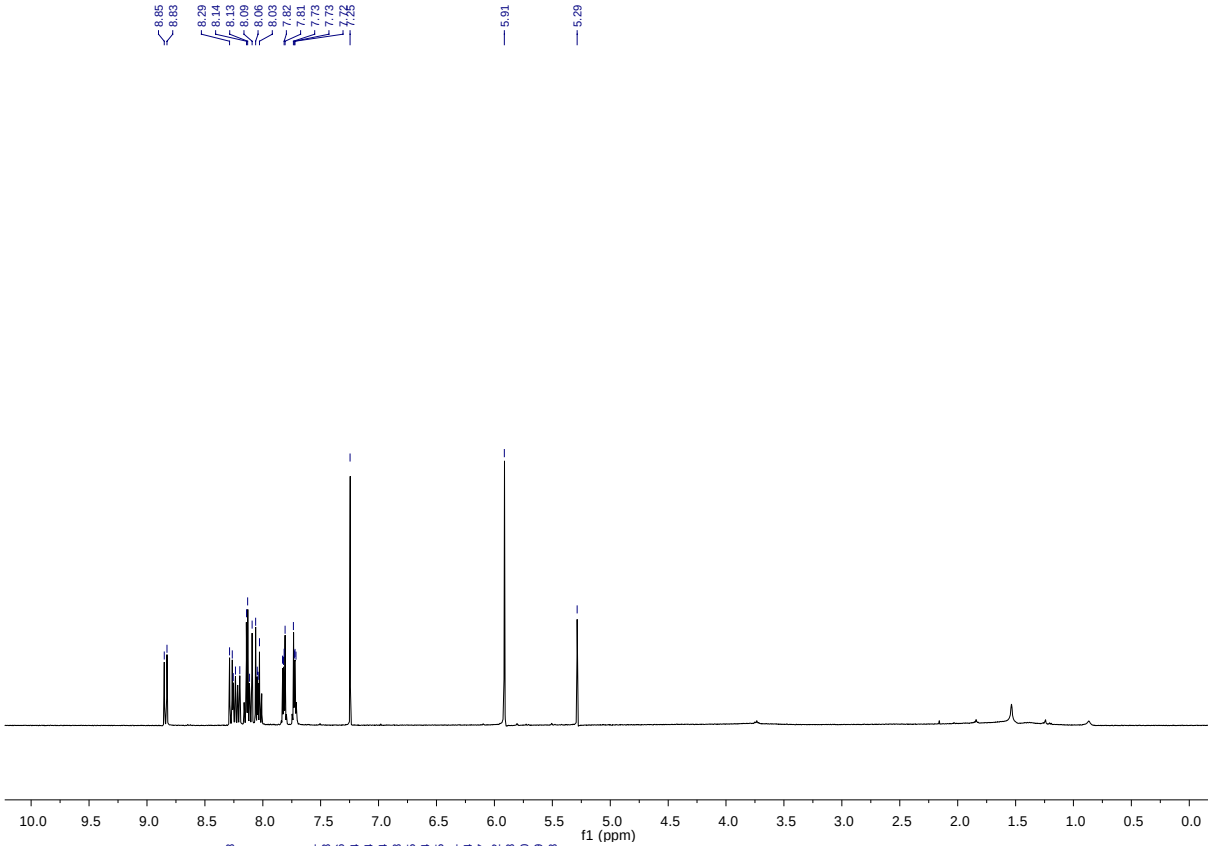


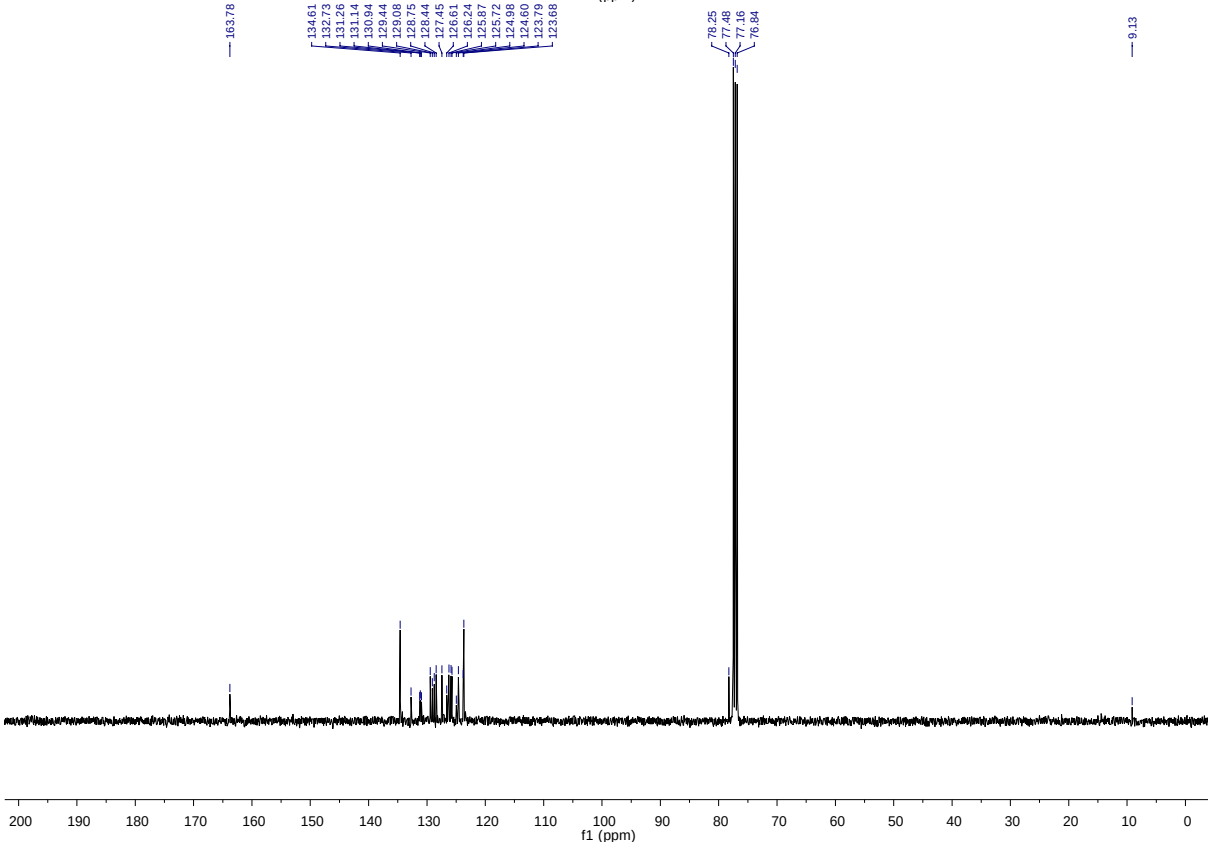


S5. ^{1}H and ^{13}C NMR spectra (400/100 MHz, $CDCl_3$) of *O*-(4-pentylbenzyl)hydroxylamine:

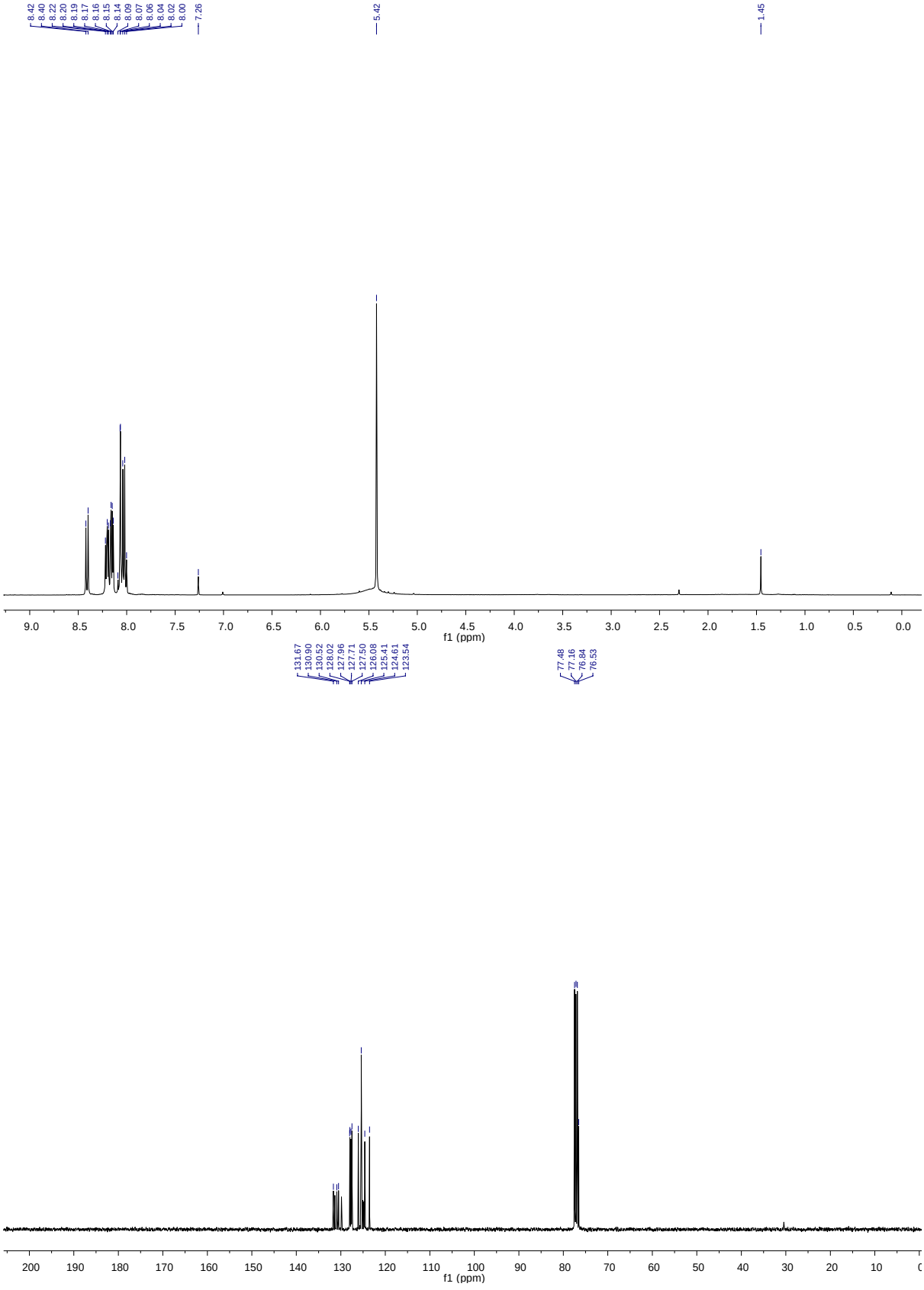


S6. ^{1}H and ^{13}C NMR spectra (400/100 MHz, $CDCl_3$) of 2-(pyren-1-ylmethoxy)isoindoline-1,3-dione:

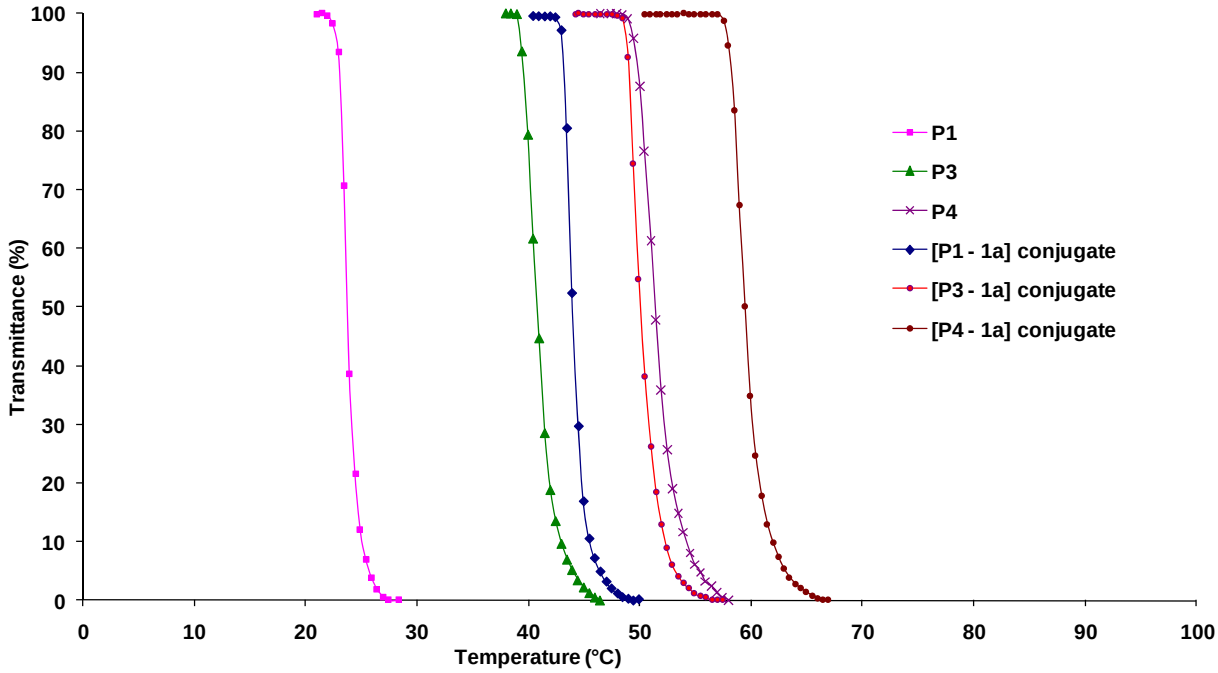




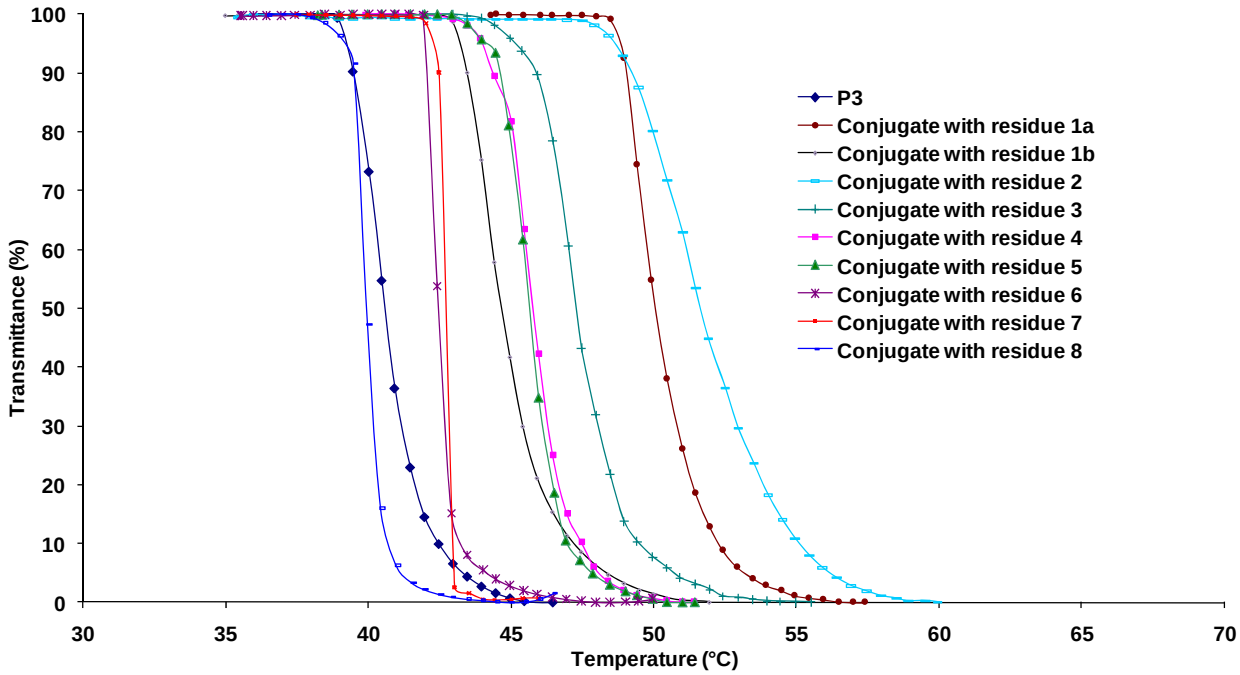
S7. ^{1}H and ^{13}C NMR spectra (400/100 MHz, $CDCl_3$) of *O*-(pyren-1-ylmethyl)hydroxylamine:



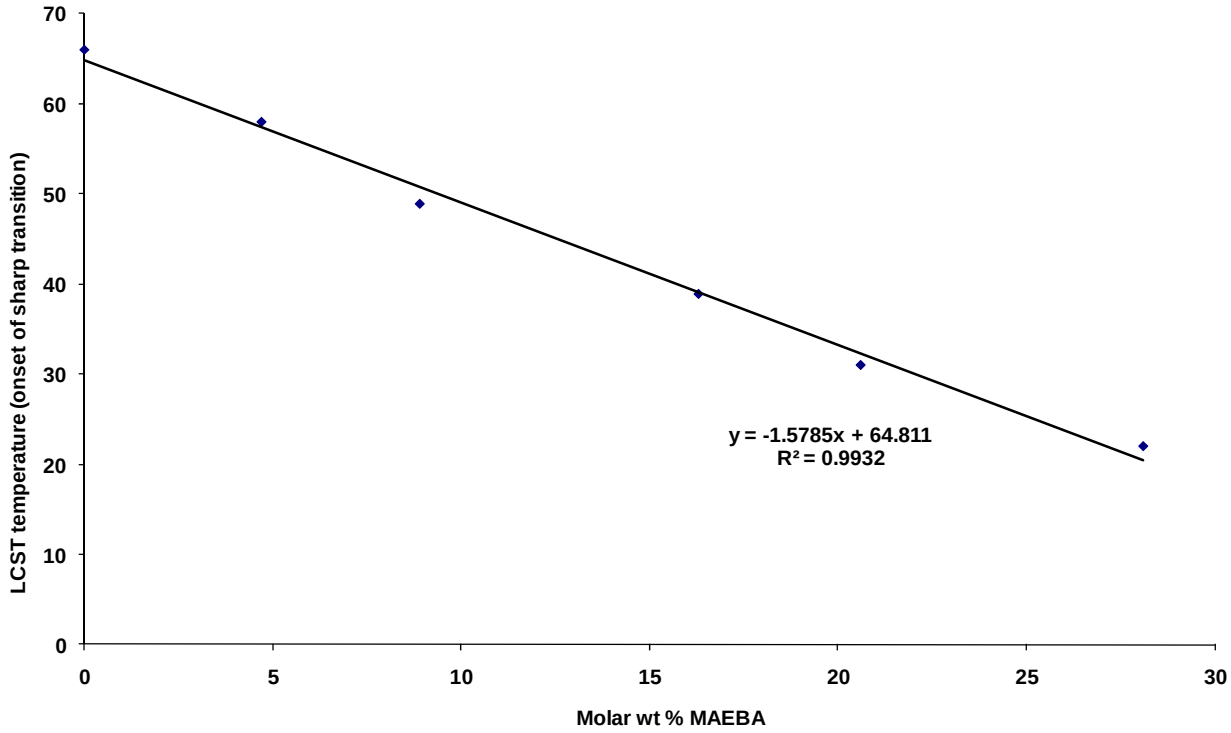
S8. Temperature-turbidity curves for copolymers **P1**, **P3** and **P4** and their conjugates with residue **1a**.



S9. Temperature-turbidity curves for copolymer **P3** and its conjugates with residues **1a-8**.



S10. Plot of LCST vs. Molar wt % MAEBA for polymers **P1**-**P6**.



Conjugation procedures

For water soluble hydrophilic and ionic residues, conjugation was performed directly in aqueous solution by addition of one equivalent of the residue to a solution of the parent copolymer (2 mg ml^{-1}) in 0.1 M NaCl solution followed by adjustment of pH to 7.4. The extent of conjugation could be followed by ^1H NMR spectroscopic analysis of dried aliquots of the reaction mixture or directly through repeating the analogous reaction in D_2O. The conjugation of hydrophobic residues was performed in $CDCl_3$ via the addition of one equivalent of alkoxyamine/hydrazide per polymer aldehyde to a solution of the polymer (10 mg mL^{-1}) in $CDCl_3$. The solutions were allowed to stand for 30 min before analysis by ^1H NMR spectroscopy to confirm complete conjugation of the polymer scaffold. These solutions were then evaporated to dryness and the residues dissolved in 0.1 M NaCl solution (yielding a copolymer solution whose concentration was equal to 2 mg mL^{-1} of the parent polymer scaffold) and the pH adjusted to 7.4.

Alternative Analyses of Heating Curves

In all of the work presented in this manuscript, we have defined LCST as the temperature at which the onset of sharp increase in UV absorption at 550 nm, as has previously reported by *e.g.* the group of Cameron Alexander (*JACS* **2008**, *130*, 10852-10853). Another common defintion of LCST is the temperature at 50% transmission, and another common way to define LCST is the temperature of the the inflection point of the heating curve. We have applied these three defintions to all of our heating curves and present the results below. The numbers in brackets are the difference in LCST relative to the copolymer scaffold **P3**.

Residue	LCST[a]	LCST[b]	LCST[c]
1a	48.5 ˚C (9.5 ˚C)	49.0 (9.0 ˚C)	50.0 (9.5 ˚C)
1b	42.5 ˚C (3.5 ˚C)	44.0 (4.0 ˚C)	44.5 (4.0 ˚C)
2	-	51.0 (pH 3.8) (11.0 ˚C)	51.5 (11.0 ˚C)
3	44.0 ˚C (5.0 ˚C)	47.0 (7.0 ˚C)	47.5 (7.0 ˚C)
4	43.0 ˚C (4.0 ˚C)	45.5 (5.5 ˚C)	46.0 (5.5 ˚C)
5	43.0 ˚C (4.0 ˚C)	45.5 (5.5 ˚C)	45.5 (5.0 ˚C)
6	42.0 ˚C (3.0 ˚C)	42.0 (2.0 ˚C)	42.5 (2.0 ˚C)
7	42.0 ˚C (3.0 C)	42.5 (2.5 ˚C)	43.0 (2.5 ˚C)
8	38.0 ˚C (-1.0 ˚C)	39.5 (-0.5 ˚C)	40.0 (-0.5 ˚C)
P3	39.0 ºC	40.0	40.5

[a]LCST defined as the onset of sharp change in transmission. [b]LCST defined as the temperature of the the inflection point of the heating curve. [c]LCST defined as the temperature temperature at 50% transmission.

From this table it is clear that irrespective of how LCST is defined, the LCST of all but one hydrophobic residue are higher than of the parent copolymer scaffold **P3**.

Discussion Concerning our Preliminary Hypothesis Concerning the Unexpected Increases in LCST When Hydrophobic Residues are Appended to Thermoresponsive Polymers

Ever since the work of Taylor and Cerankowski in 1975 (*J. Polym. Sci, Part A: Polym. Chem.* **1975**, *13*, 2551-2570), the LCST of a polymer has been considered by many to depend on the hydrophilic-hydrophobic balance of the polymer under consideration. When a hydrophilic monomer is *substituted* for a more hydrophobic monomer, the resulting polymer is more hydrophobic and sees a decreased LCST. Conversely, when a hydrophobic monomer is *substituted* for a more hydrophilic monomer, the resulting polymer is more hydrophilic and sees an increased LCST. What happens when a hydrophilic residue is *appended* upon the backbone of a polymer chain? The resulting polymer will have a higher degree of water solvation and its LCST will increase. But what happens when an hydrophobic residue is *appended* onto a polymer chain? As the results of this work show, the answer is less straightforward. It is our working hypothesis that when hydrophobic residues are *appended* onto a polymer chain, its degree of solvation is not necessarily reduced. We hypothesize that with the polymers understudy here, very few water molecules are displaced from the OEG grafts when a hydrophobe is appended. It is also important to note that hydrophobic molecules such as *n*-alkanes possess negative enthalpies of hydration (there are favourable Van der Waals interactions between *n*-alkanes and water), and thus the conjugation of a hydrophobic molecule onto a polymer chain may make some enthalpic contribution to the polymer-water interaction and consequently see an increase in LCST. How do appended hydrophobes affect the entropy of the polymer chain? This question is hard to answer, but some interesting insights may come from recent work investigating how hydrophobic ions such as NCS^- affect the LCST of polymers. Elegant work of by the groups of Bergbreiter and Cremer (*JACS* **2005**, *127*, 14505-14510) investigating ion effects on the solubility of poly(*N*-isopropylacrylamide) (PNIPAM) has shown that the LCST of this polymer actually increases when relatively hydrophobic ions such as SCN^- or ClO_4^- are added. As demonstrated by the group of Alexander (*JACS* **2008**, *130*, 10852-10853), even larger increases in LCST are observed (relative to PNIPAM) when hydrophobic ions are added to solutions of the polymer poly(ethylene glycol) methacrylate (POEGMA). This enhanced effect is presumably because the increased lengths of the oligoethylene glycol side chains impact solvation and local water structure more than for PNIPAM and thus changes to the solvation by the ions are greater. Similar enhancements in LCST have also been observed with the POEtOxMA comb polymers of Hoogenboom and Schubert (*Macromol. Rapid Commun.* **2010**, *31*, 724-728). Livney and coworkers have very recently demonstrated (*Macromolecules* **2010**, *43*, 480-487) that the binding to SCN^- onto PNIPAM is an endothermic entropy driven process, and when these hydrophobic ions bind to the polymer they disturb the hydrophobic hydration

waters on the nonpolar backbone and isopropyl groups, increasing the entropy of the polymer and raising its LCST. The possibility exists that organic hydrophobes appended onto the polymer may also disturb the hydration waters on our polymer chains with similar effects, contributing to the observed increase. It is likely that the appended hydrophobes in our system are not well solvated, an idea supported by the work of Hoogenboom and Schubert (*Angew. Chem. Int Ed.* **2009**, *48*, 5653-5656) who have prepared and investigated POEGMA polymers containing hydrophopic diazobenzene dyes, and strong evidence is presented to suggest that the hydrophobic dyes are not well solvated. This suggests that our hydrophobic appendages are unlikely to be solvated with ordered water molecules and thus any ethalpic contribution they make is probably small, and is more likely that the hydrophobic appendages raise the LCST through an entropic effect.

Why have observations similar to ours never been made before? We are, to the best of our knowledge, the first group to study the *appending* of residues onto PEGMA-type thermoresponsive polymers, polymer which possess a "comb" or "graft" architecture. There have been several investigations concerning the appending of residues onto PNIPAM-type polymers (*e.g.* Brooks, Kizhakkedathu *et al. Macromolecules* 2008, **41**, 5393-5405 and Schlaad *et al. Macromo. Biosci.* 2009, **9**, 157-161), polymers which possess a linear architecture. But these investigations have all found that when hydrophobic residues are conjugated the LCST drops, and when hydrophilic residues are conjugated, the LCST increases. There are, however, significant and crucial differences between the linear PNIPAM polymers and the comb POEGMA polymers which may explain the apparently conflicting findings. For a given length of polymer backbone, comb polymers are more soluble than their linear counterparts because the grafts solublize the polymer (hydrate it better) and also tend to 'mask' the polymer backbone. We hypothesize that when a hydrophobic residue is conjugated onto a linear PINPAM type polymer, the subsequent disruption of the interfacial waters has a more significant effect because there are fewer waters involved, and may result in enough water molecules being removed from the hydration sphere to make the polymer considerably more hydrophobic and thus lower its LCST. The situation with comb-type polymers is different. When a hydrophobic residue is conjugated onto a comb polymer, it is likely that relatively few waters will be displaced and the hydrophobe will disrupt all those which remain raising the entropy of the polymer and raising the LCST. In summary then, we hypothesize that appending hydrophobes onto our polymer chains probably disrupts the hydration of the polymer, raising its entropy and consequently raising its LCST.

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