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Thermally-induced hyperbranching of bromine-containing polyesters by insertion of *in situ* generated chain-end carbenes†

Panagiotis Bexis,[ab] Maria C. Arno,[bc] Craig A. Bell,[ade] Anthony W. Thomas[a] and Andrew P. Dove *[b]

Hyperbranched, biodegradable PCL-based polymers are obtained through a random but invasive migration of an *in situ* generated carbene end group which is unmasked *via* the thermolysis of its precursor diazirine moiety. These hyperbranched cores are used as macroinitiators for 'grafting-from' polymerisation using controlled radical polymerisation to achieve amphiphilic copolymers which can subsequently be self-assembled into spherical core–shell micelles.

Highly branched 3D macromolecular structures, including dendrimers and hyperbranched polymers (HBPs) have emerged as an important class of materials[1,2] on account of the large number of terminal functional groups, globular three-dimensional structures, and low intrinsic viscosities that they display compared to linear polymer species.[3,4] Of these species, HBPs exhibit the advantages of low (or no) chain entanglements, as observed in linear polymers, as well as low melt and solution viscosity, high solubility, and a wide variety of terminal functional groups which serve as handles for further modification.[5–7] Furthermore, in contrast to perfectly branched and monodisperse dendrimers consisting of only dendritic units and terminal units, HBPs are composed of dendritic units, linear units and terminal units, and display a randomly branched structure with a lower degree of branching (DB). More importantly, compared to the tedious and complicated synthetic procedures of dendrimers, the synthesis of HBPs is often based on simple one-pot reactions, requiring minimal or no further purification.[2,8–10]

Very recently, new progress in the self-assembly[11–13] of HBPs has been achieved. HBPs have proven to be excellent precursors in supramolecular self-assembly, allowing the generation of a diverse range of supramolecular structures and hybrids at all scales and dimensions. As such, assemblies obtained from HBPs have recently found applications in the biomedical field, owing to their ease of synthesis, their large number of end groups which provides a platform for the conjugation of functional moieties, their controlled responsive nature and their ability to incorporate a multiple array of guest molecules through covalent or noncovalent approaches.[5,9,14–16]

Diazirines[17] are a class of functional groups characterised by three-membered heterocycles featuring an azo group and an sp^3 hybridised carbon atom.[18,19] The defining property of diazirines is their ability to form highly reactive carbenes with concomitant release of molecular nitrogen upon suitable activation *via* exposure to light, high temperature[20] or ultrasonication. Carbenes are capable of reacting (*via* insertion) with saturated hydrocarbons and by addition with unsaturated hydrocarbons, including aromatic systems.[21] This ease of insertion makes diazirines the perfect tool for photoaffinity labelling,[22,23] crosslinking,[24] surface modification of polymers[25,26] and polymer branching when incorporated within functional monomers.[27,28]

Herein, we describe for the first time the use of a hydroxyl-functional aromatic diazirine as an initiator for the organocatalytic ring-opening polymerisation (ROP) of a bromine-functional caprolactone monomer, α-bromo-ε-caprolactone (BrCL) alongside copolymerisation with ε-caprolactone (CL). The diazirine moieties undergo thermolysis to generate a highly reactive carbene species which can directly attack the long macromolecular chains, forming branching points both inter- and intra-molecularly. The hyperbranched bromine-bearing hydrophobic polyesters are subsequently utilised as macroinitiators to graft hydrophilic PEG branches, yielding amphiphilic materials able to self-assemble into spherical core–shell micelles.[29]

[a] *Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, UK*
[b] *School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. E-mail: A.Dove@bham.ac.uk*
[c] *Institute of Cancer and Genomic Science, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK*
[d] *Centre for Advanced Imaging, The University of Queensland, Brisbane, QLD, 4072, Australia*
[e] *Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane, QLD, 4072, Australia*

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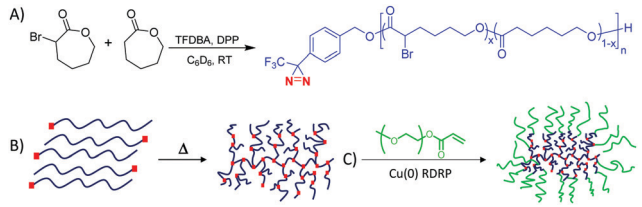

Fig. 1 (A) Copolymerisation of CL and BrCL catalysed by DPP and initiated by TFDBA leading to the gradient blocky α-diazirine copolymers; (B) thermal activation of the diazirine leading to the unmasking of the carbene and the subsequent hyperbranching of the linear precursor polymers; (C) application of Cu(0)-RDRP techniques enables 'grafting-from' the PCL-based materials, leading to amphiphilic polymers.

The BrCL monomer,[30,31] selected as the alkyl bromide, is a handle that enables copper-mediated radical polymerisations used in grafting techniques,[32–35] and is largely unreactive towards carbene insertion;[23,26–28,45,50] the polycaprolactone (PCL)-based polymer serves as the hydrophobic and biodegradable segment in the material.[30,36–39] Organocatalytic ROP[40] was selected for the initial polymerisation of the cyclic ester monomers. The ROP of CL and the subsequent copolymerisation of CL and BrCL was attempted using diphenyl phosphate (DPP) as the catalyst[41–43] and 4-[3-(trifluoromethyl)-3*H*-diazirin-3-yl] benzyl alcohol (TFDBA) as the initiator (Scheme S1, ESI† and Fig. 1A).

CL was first polymerised targeting degrees of polymerisation (DPs) of 5, 10 and 20 (Table S1, ESI†) to assess the viability of using an alcohol-functional diazirine as an initiator for ROP. The observed low dispersity and monomodal molar mass distribution of the polymers served as an indication of well-controlled polymerisations (Fig. S1, ESI†), and ^{1}H and ^{13}C NMR spectroscopy provided structural data as well as the experimental molar mass of the polymers. The ^{19}F NMR spectrum showed a single resonance at $\delta = -65$ ppm in all synthesised polymers, which proved the specific incorporation of the CF_3 group of the diazirine only in the desired α-position of the polymer chain (Fig. S2–S8, ESI†).

Hyperbranching of the TFDBA-initiated PCLs was initially investigated (Fig. 1B) by heating the polymers in bulk at 100 °C for 6 h. The conversion of the diazirine functionality was qualitatively monitored by ^{19}F NMR spectroscopy for the PCL_{10} (Fig. S9 and S10, ESI†) by monitoring the disappearance of the CF_3 group on the initiator. New peaks appeared between $\delta = -79$ and -66 ppm throughout the thermolysis, indicating that a change in fluorine environment was occurring – in line with carbenes being generated *in situ* and inserting into the polymer backbone causing the branching (Scheme S2, ESI†), further corroborated by ^{13}C NMR spectroscopic analysis (Fig. S6 and S11, ESI†).[44] At the reaction end-point (Fig. S10, ESI†), the parent fluorine peak had almost disappeared for all PCL polymers, indicating near quantitative loss of the starting diazirine functionality. As a consequence of the random character of this hyperbranching methodology,[27,28] and given the structural diversity of the linear and branched units within the polyester architecture, the ^{1}H and ^{13}C NMR spectra of the branched PCL homopolymers provided little structural information regarding the extent of branching (Fig. S11–S18, ESI†).[45,46] Clear trends of increasing molar mass (M_n, M_w) and dispersity ($Đ_M$)[47,48] were observed for all PCLs as the reaction proceeded, as evidenced by triple detection size exclusion chromatography (SEC-td) (Fig. S19, S20 and Table S2, ESI†). This is attributed to the formation of random branches within the polymer scaffold triggered by carbene-initiated C–H and C–O bond insertions.[27,28,49] SEC-td monitoring of the PCL_{10} polymer revealed a gradual molar mass and dispersity increase (Fig. S21 and Table S3, ESI†) in close agreement with the conversion of the diazirine functionality, as shown from the ^{19}F NMR spectra. Analysis of the Mark–Houwink[50] plot of the hyperbranched PCL materials revealed that despite an almost ten-fold increase in M_w compared to their linear precursors, the HB polymers retained similar values of η (intrinsic viscosity) (Fig. S22, ESI†). From these analyses, the alpha (α) values of these polymers were calculated to be between 0.38 and 0.48 (Tables S2 and S3, ESI†), which is a clear indication of branching.[51] Analysis of a linear PCL control that contained a benzyl α-end group (no diazirine) and an experimental M_w close to that of the HBPs (M_w = 11.4 kDa, $Đ_M$ = 1.03) revealed $\alpha = 0.78$ (Fig. S23A, ESI†). After heating this polymer in bulk at 100 °C for 6 h, SEC-td showed a significant reduction in the molar mass of the polymer. At the same time, the dispersity increased, but the Mark–Houwink alpha value retained its high value ($\alpha = 0.73$). Thus, without the diazirine end group, the polymer remains linear and undergoes extensive transesterification but no hyperbranching, which only occurs in the presence of the diazirine moiety (Fig. S23B, ESI†).

In order to create gradient copolymers of BrCL and CL suitable to create core–shell structures, ROP and hyperbranching was conducted in a similar manner. Targeting a total degree of polymerisation (DP) of 10, three different feed ratios of monomer (CL : BrCL) were used, 25 : 75, 50 : 50, 75 : 25 (Table S4, ESI†). An increased catalyst loading ($[TFDBA]_0 : [DPP]_0 = 1 : 2$) was used in order to accelerate the reactions due to the lower propagation rate of BrCL.[30] After 4 h, the conversion of CL was near quantitative in all three polymerisations, whereas the conversion of BrCL was *ca.* 60% in all three experiments. After quenching the polymerisations and purification of the polymers, ^{1}H, ^{13}C and ^{19}F NMR spectroscopy was used to show retention of diazirine functionality on the α-chain end of the copolymers as well as to characterise the copolymers (Fig. S24–S32, ESI†). Analysis by SEC-td revealed the experimental M_n of the copolymers to be in close accordance with the calculated values (between 1.8–2.9 kDa depending on the desired composition), with dispersities slightly higher than expected ($Đ_M$ = 1.37–1.59), possibly as a consequence of the extended reaction times causing unavoidable transesterification side-reactions and a gradient-block copolymer microstructure (Fig. S33, ESI†).[30]

The hyperbranching of the P(CL-*co*-BrCL) copolymers followed by ^{19}F NMR spectroscopy showing the unmasking of the carbene and its gradual insertion into the saturated polyester backbone until almost full completion (Fig. 2 and Fig. S36, S41, ESI†). The ^{1}H and ^{13}C NMR spectra of the resulting

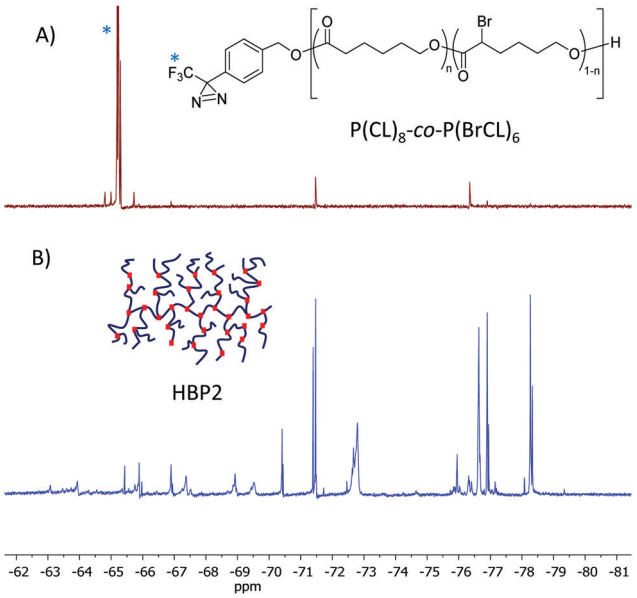

Fig. 2 Stacked ^{19}F NMR spectra of the linear P(CL)$_8$-*co*-P(BrCL)$_6$ (top) and the branched structure HBP2 (bottom, after 6 h of branching – end point data). The diazirine has decomposed, thereby unmasking the carbene, which has then inserted in various C–H and C–O bonds of the polymer, thus creating a random hyperbranched structure ($CDCl_3$).

hyperbranched polymers (Fig. S34, S35, S37–S40, ESI†) do not elucidate the degree of branching but do confirm the retention of the C–Br resonance at δ = 45.9 ppm. Significant increases in molar masses and dispersities compared to their linear precursors (SEC-td) further confirms the formation and subsequent reaction of the carbene to form branched structures. (Fig. S42–S44 and Table S5, ESI†). Mark–Houwink analysis showed that the intrinsic viscosity of the HBPs was maintained at similar values compared to their linear copolymer precursors, while their larger molar mass and the obtained low α values (< 0.5) confirmed their hyperbranched nature (Fig. S46 and Table S6, ESI†). Further analysis of the available SEC and ^{1}H NMR spectroscopy data enabled the elucidation of the average number of arms (N_{arms})[52–54] of each of the HBPs (Table S6, ESI†).[47] Based on the absolute molar masses (obtained *via* SEC-td), dispersity ($Đ_{M,RI}$ obtained by refractive index detection[55]) of the HBPs, and the M_n of the linear precursor polymers (obtained by NMR spectroscopic analysis), N_{arms} was found to decrease from 12 to 7, as the content of BrCL decreased for each polymer. This phenomenon can be ascribed to the bromine's steric hindrance, which prevents the approach of carbenes to free C–C or C–H bonds, thus limiting the branching events.

The HB polymers bearing pendent Br (Fig. S45, ESI†) can subsequently serve as suitable macroinitiators for the application of Cu(0)-mediated RDRP,[56–61] thus enabling 'grafting-from' the PCL-based polymers.[30] Judicious choice of the synthetic method, grafting density, composition and length of the polymer backbone and side-arms, allows graft copolymers with unique structural characteristics and a range of functionalities to be prepared.[62–65] HBP2 was selected as the macroinitiator, and methyl acrylate (MA) was first polymerised in a grafting-from approach, targeting 20 MA grafted units per initiating site (Br unit) for each arm. After 24 h the monomer conversion was $>$99%, and upon purification the polymer appeared as a waxy transparent solid. ^{1}H NMR spectroscopy confirmed the synthesis of PMA (Fig. S47, ESI†), and successful grafting was proved by SEC-td as the molecular weight distribution of the starting polymer completely shifted to higher molecular weight, while its dispersity decreased significantly ($Đ_{M,SEC\text{-}td}$ = 1.5, Fig. S51A, ESI†).

Following the successful grafting of MA, poly(ethylene glycol) methyl ether acrylate (PEGMEA) was polymerised targeting 10, 20 and 50 units per initiating site for each arm. All reactions reached quantitative conversion after 24 h. ^{1}H NMR spectroscopy and SEC-td of the purified materials again proved the successful grafting of the acrylate had occurred (Fig. S51B–D, S48–S50 and Table S7, ESI†). The alpha (α) values of all PEGMEA-grafted polymers were maintained below 0.5, thus confirming the retention of their branched structure. The multimodality of the SEC chromatograms is possibly an effect of the random spatial nature of hyperbranching causing the irregular placement of initiating sites for the grafting of brushes, which in turn might cause intense radical coupling, termination events or extremely high grafting density.

Self-assembly was performed on the HBP2-*g*-PEGMEA$_{50}$ amphiphilic polymer using a traditional solvent switch method by dissolving the polymer in THF and slowly adding water to induce micelle formation (Fig. 3A). Micelles of $\sim$50 nm in diameter were observed by dynamic light scattering (DLS) analysis, with spherical morphology confirmed by transmission electron microscopy (TEM) (Fig. 3B, C and Fig. S52, ESI†).

In conclusion, this work reports a new thermally induced methodology for preparing hyperbranched PCL-based materials. These bromine-bearing structures are shown to serve as ideal

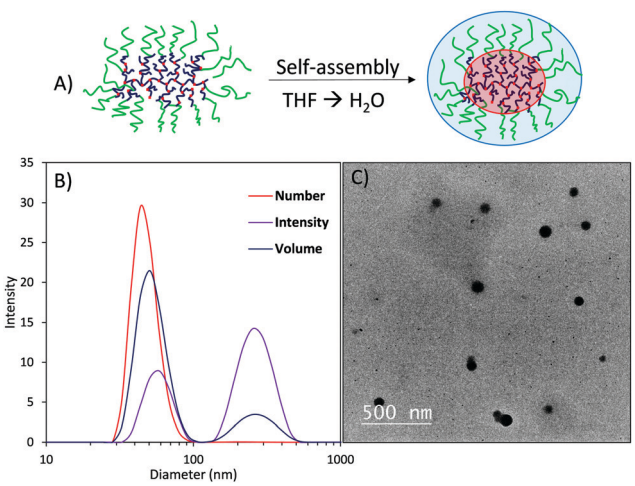

Fig. 3 (A) Self-assembly of HBP2 using a solvent switch method (slow addition of H_2O into THF/polymer solution) leading to the formation of spherical core–shell particles; (B) DLS analysis of HBP2-*g*-PEGMEA$_{50}$ micelles (1 mg mL^{-1}), and (C) TEM micrograph of HBP2-*g*-PEGMEA$_{50}$ micelles.

macroinitiators for the application of Cu(0)-RDRP techniques, which lead to further grafted polymers. These amphiphilic polymers of extremely high molar mass can be self-assembled into spherical core–shell particles, thus making them attractive candidates for further downstream bio-applications.

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Conflicts of interest

There are no conflicts to declare.

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