Supplementary Information

Degradable Polyisoprene by Radical Ring-Opening Polymerization and Application to Polymer Prodrug Nanoparticles

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Table S1. Values of $f_{DOT,0\ th}$, F_{DOT}, DOT and isoprene conversion used to determine reactivity ratios.

$f_{DOT,0\ th}$	F_{DOT}	Conv. DOT	Conv. I
0.1	0.29	14	4
0.2	0.51	23	20
0.3	0.65	23	12
0.4	0.83	5	13
0.5	0.86	12	14
0.6	0.88	11	34
0.7	0.9	17	17
0.9	0.94	3	3

Figure S1. 95% joint confidence region (blue trace) for reactivity ratios (red dot) of DOT (r_1) and isoprene (r_2) determined by the CONTOUR software.
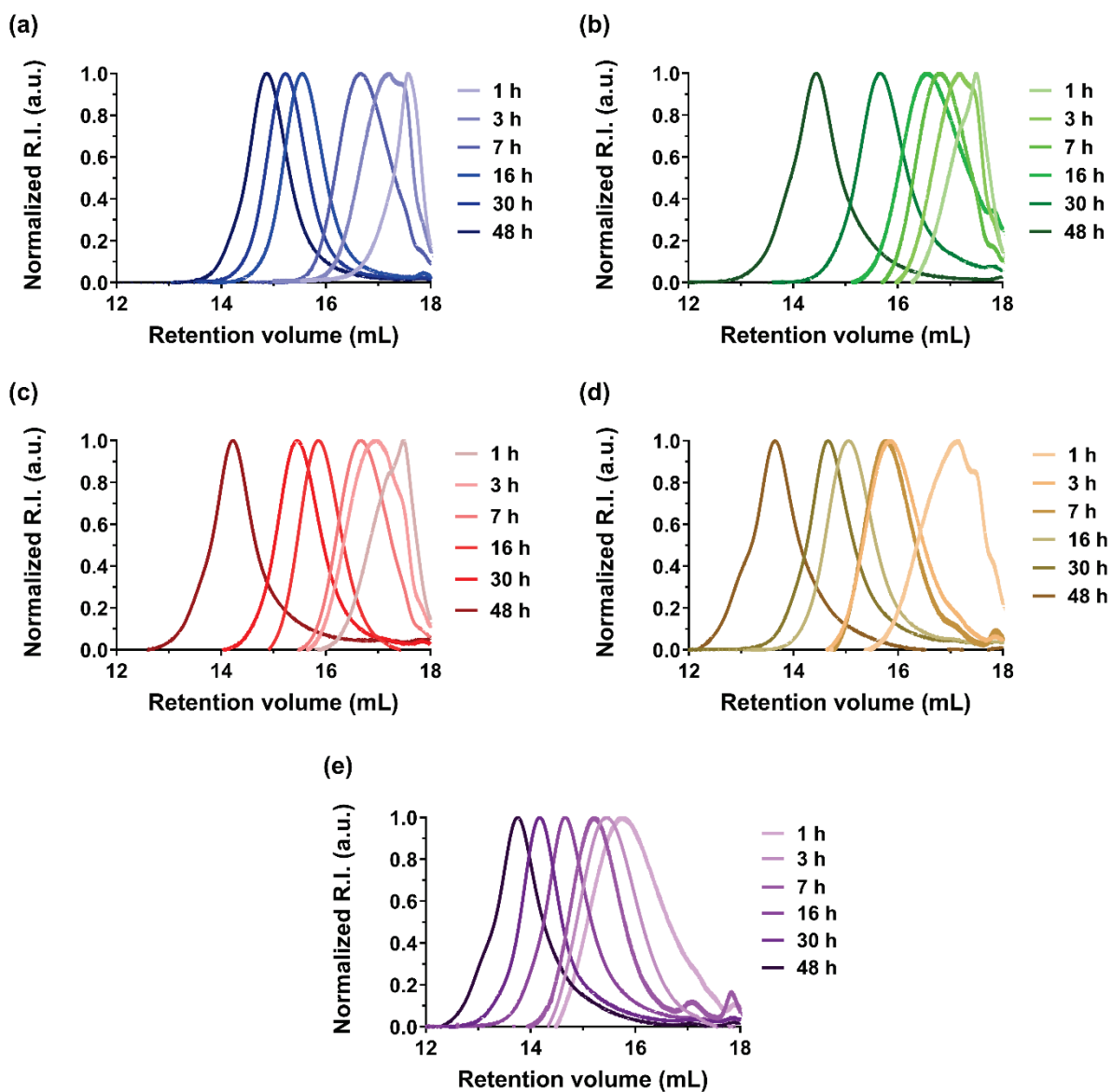
Figure S2. Evolution of the SEC chromatograms vs time during the synthesis of P(I-*co*-DOT) copolymers by nitroxide-mediated polymerization: (a) **N0** experiment ($f_{DOT,0}$ = 0 mol.% $DP_{n,th}$ = 100); (b) **N1** ($f_{DOT,0}$ = 1 mol.% $DP_{n,th}$ = 100); (c) **N2** ($f_{DOT,0}$ = 2 mol.% $DP_{n,th}$ = 100); (d) **N3** ($f_{DOT,0}$ = 2 mol.% $DP_{n,th}$ = 215) and (e) **N4** ($f_{DOT,0}$ = 2 mol.% $DP_{n,th}$ = 435) (see Table 1).
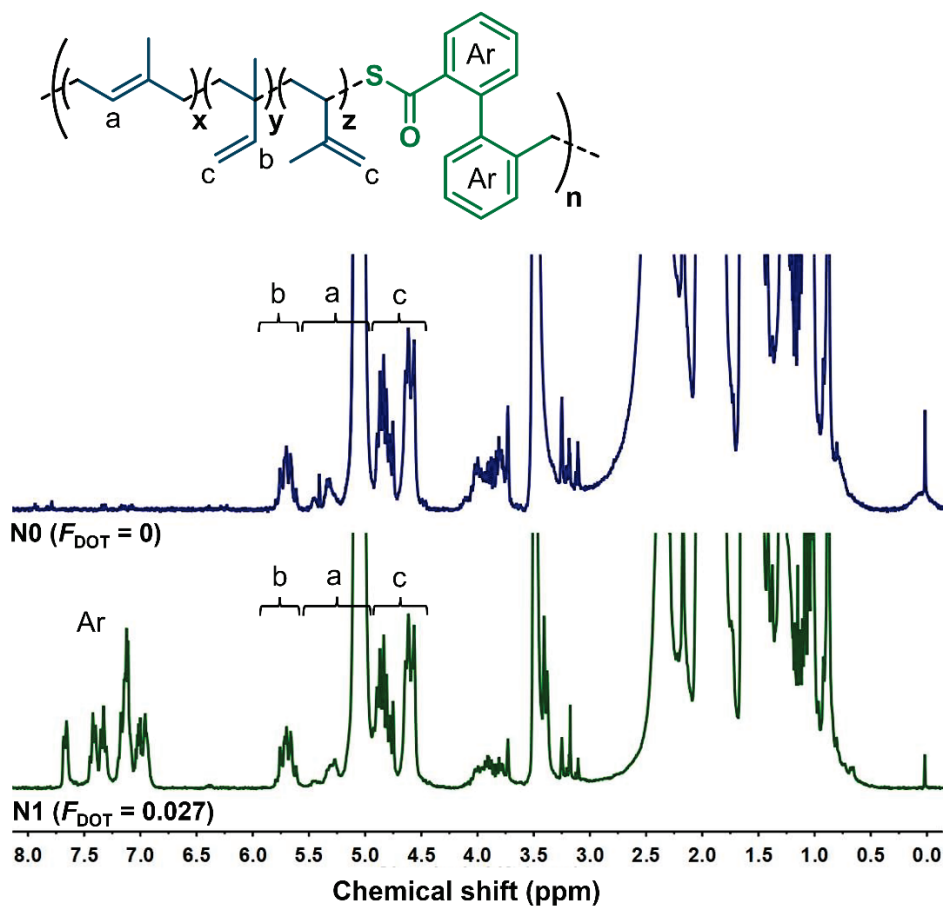
Figure S3. ^{1}H NMR spectrum (300 MHz, d$_8$-THF) in the 0–8 ppm region of P(I-*co*-DOT) copolymers **N0** and **N1** (see Table 1).
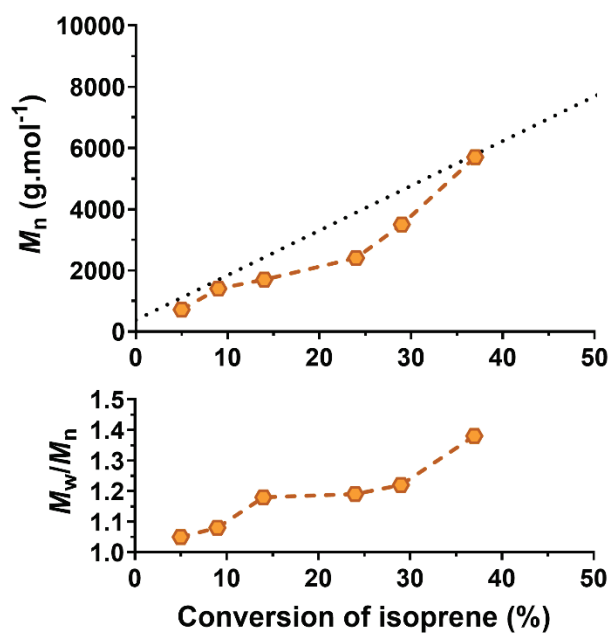

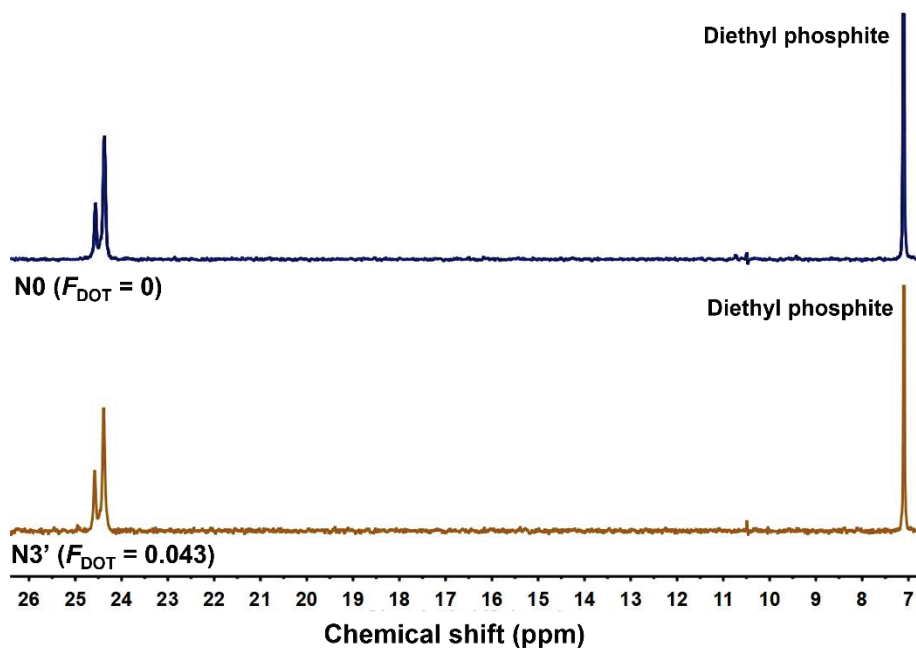**Figure S4.** Evolution of M_n and Đ vs. I conversion for **N3'**.

Figure S5. ^{31}P NMR spectrum (400 MHz, CDCl$_3$) in the 7–26 ppm region of purified PI and P(I-*co*-DOT) copolymers **N0** and **N3'**, respectively (see Table 1), in the presence of diethyl phosphite.
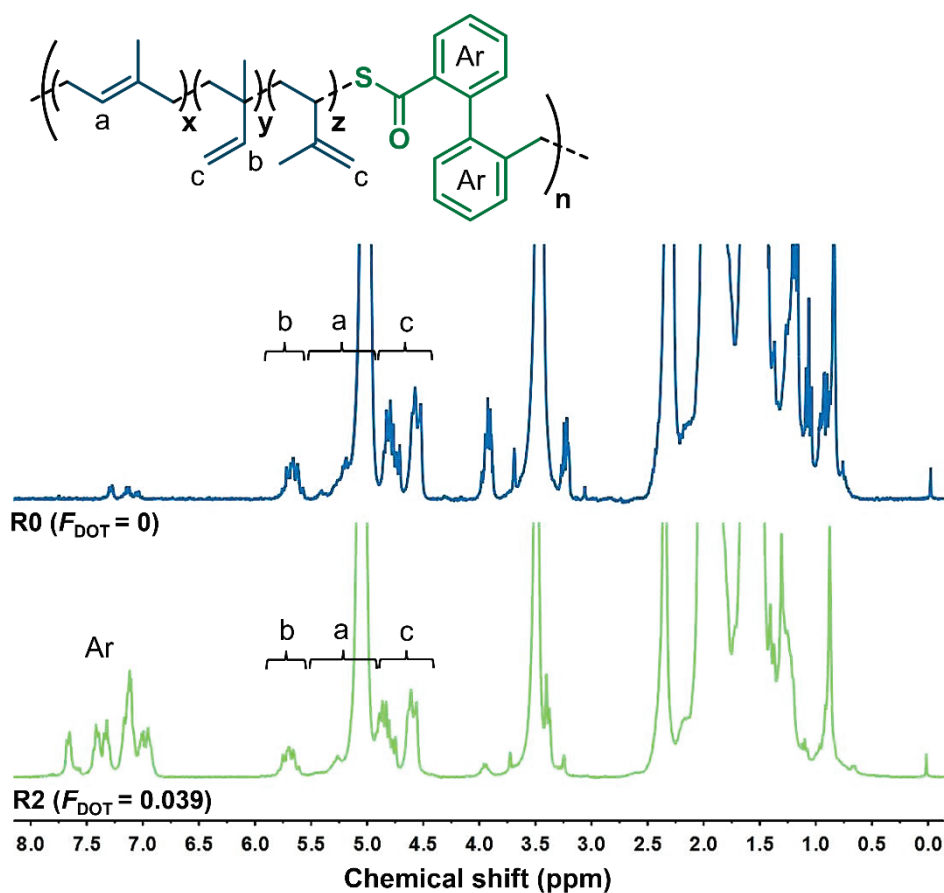

Figure S6. ^{1}H NMR spectrum (300 MHz, d$_8$-THF) in the 0–8 ppm region of P(I-*co*-DOT) copolymers **R0** and **R2** (see Table 1).
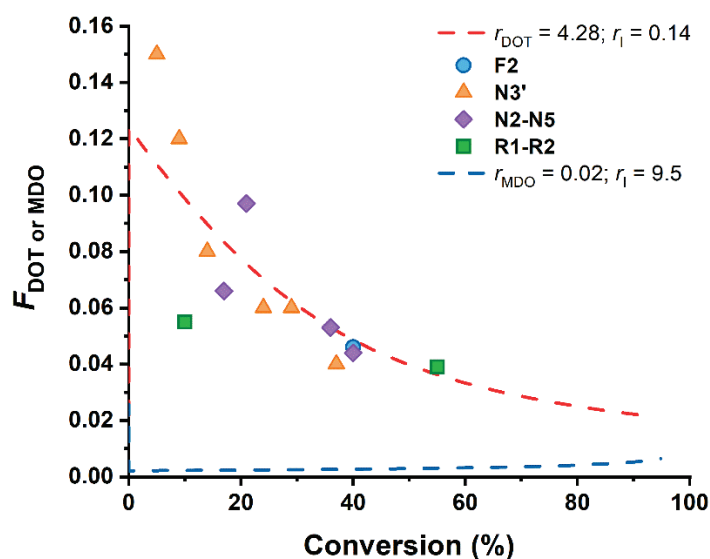
Figure S7. Evolution of F_{DOT} vs. conversion (dashed red line) and F_{MDO} vs. conversion (dashed blue line) plotted using the estimated reactivity ratios (r_{DOT} = 4.29 and r_I = 0.14; r_{MDO} = 0.02 and r_I = 9.5)[1] and a PREDICI numerical simulation for predicting the compositional drift occurring during the copolymerization between vinyl and cyclic monomers.[2] The experimental points are the values of F_{DOT} vs. conversion of **F2**, **N2**–**N5**, **N3'** and **R1**–**R2** (Table 1).

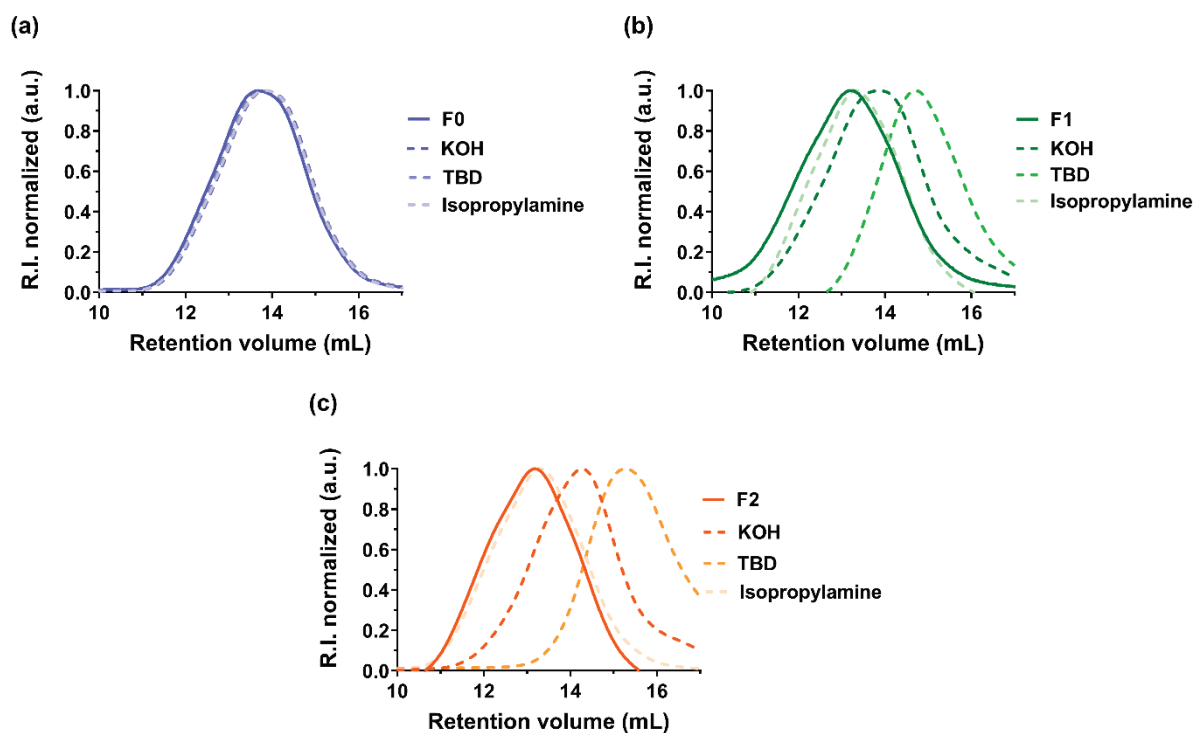**Figure S8.** Evolution of SEC chromatograms of P(I-*co*-DOT) copolymers: (a) **F0** ($f_{DOT,0}$ = 0 mol.%), (b) **F1** ($f_{DOT,0}$ = 1 mol.%), (c) **F2** ($f_{DOT,0}$ = 2 mol.%) after degradation under basic or aminolytic conditions.

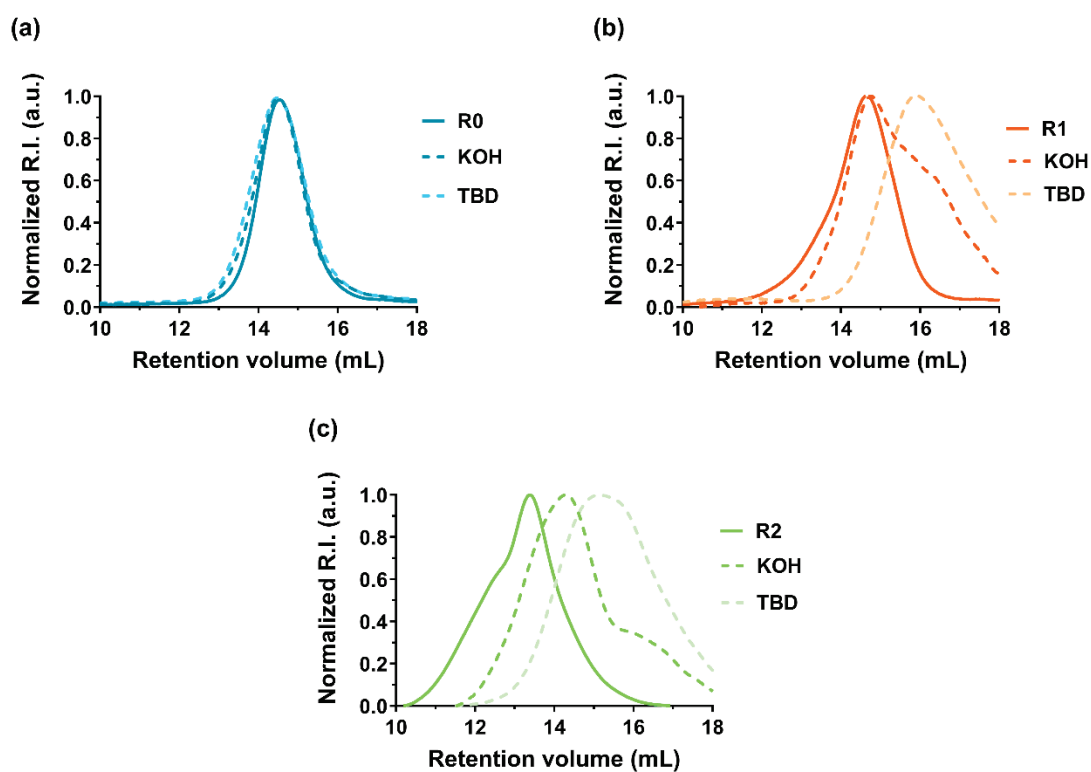**Figure S9.** Evolution of the SEC chromatograms of P(I-*co*-DOT) copolymers: (a) **R0** ($f_{DOT,0}$ = 0 mol.%, $DP_{n,th}$ = 500, 24 h); (b) **R1** ($f_{DOT,0}$ = 2 mol.%, $DP_{n,th}$ = 500, 24 h) and (c) **R2** ($f_{DOT,0}$ = 2 mol.%, $DP_{n,th}$ = 600, 72 h) after degradation under basic or aminolytic conditions.
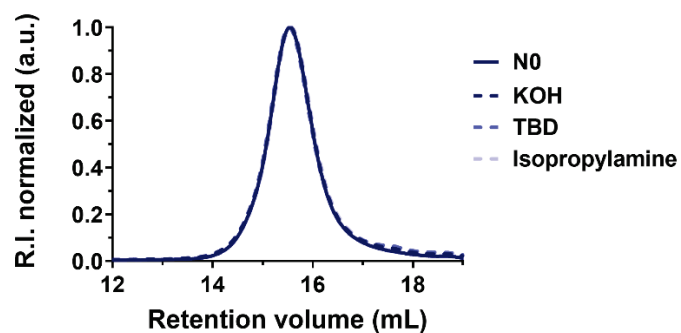

Figure S10. Evolution of the SEC chromatograms of PI (**N0**, see Table 1) after degradation under basic or aminolytic conditions.

Figure S11. Picture of PI and P(I-*co*-DOT) nanoparticles obtained by nanoprecipitation from **N0** and **N2**, respectively (see Table 2).
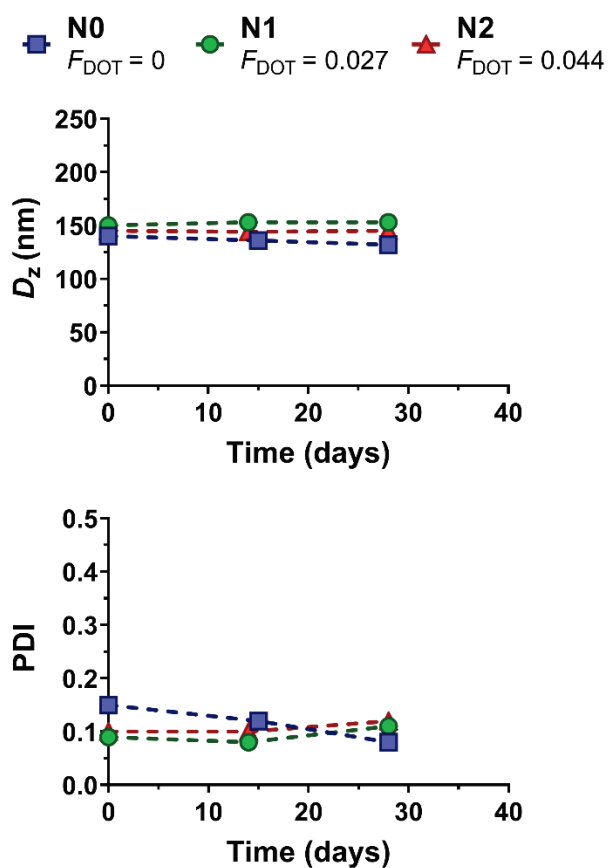

Figure S12. Evolution of the intensity-average diameter (D_z) and polydispersity index (PDI) with time measured by DLS of PI and P(I-*co*-DOT) nanoparticles (**N0**, **N1** and **N2**, see Table 3) as function of F_{DOT}.
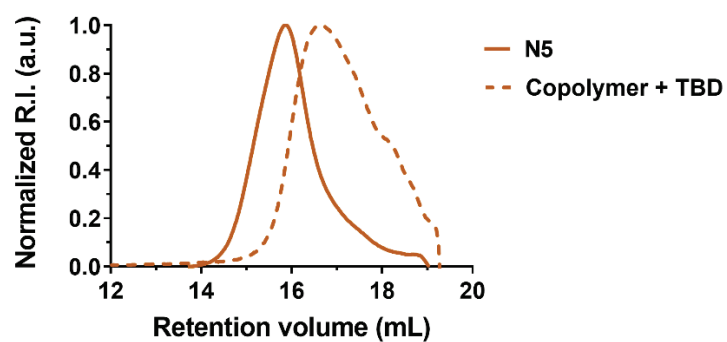
Figure S13. Evolution of the SEC chromatograms of Gem-P(I-*co*-DOT) polymer prodrug (**N5,** see Table 2) after degradation with TBD.

References

1. A. Tardy, N. Gil, C. M. Plummer, C. Zhu, S. Harrisson, D. Siri, J. Nicolas, D. Gigmes, Y. Guillaneuf and C. Lefay, *Polym. Chem.*, 2020, **11**, 7159-7169.
2. D. Gigmes, P. H. M. Van Steenberge, D. Siri, D. R. D'hooge, Y. Guillaneuf and C. Lefay, *Macromol. Rapid Commun.*, 2018, **39**, 1800193.