Supporting Information

Novel Monomers in Radical Ring-Opening Polymerisation for Biodegradable and pH Responsive Nanoparticles

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1. Materials and Methods

a. Materials

Unless stated otherwise, all chemicals were used as received. Bis(2-hydroxypropyl)amine, K_2CO_3, 2-iodopropane, *bis*(2-hydroxyethyl)amine, methyl-capped poly(ethylene glycole) (MW = 550 g/mol), 2-bromopropane, ethyl chloroformate, titanocene dichloride, trimethylamine, 3 M methyl magnesium chloride (MeMgCl) in THF, dry tetrahydrofurane (THF), were purchased from Sigma-Aldrich and used without further purification. Dimethylformide (DMF), petrol ether (PE), methanol, toluene, ethyl acetate, were purchased from Biosolve (Biosolve Chimie SARL, France). MeCN, NaCl, $MgSO_4$, NH_4Cl (technical grade) were purchased from ThermoFisher scientific.

b. Methods including Instruments

Lyophilisation: Substances were freeze-dried on a Christ Alpha 2-4 LD Plus lyophiliser.
Dialysis: Purification by dialysis was performed with CE dialysis membranes from Spectra/Por® with a MWCO ranging from 100 to 500 Daltons. Each batch was dialyzed five times against ethanol for at least 3 h at room temperature.
Dynamic Light Scattering: DLS measurements were performed on a light scattering spectrometer from LS Instruments conducted in a two-dimensional pseudocross mode with a Helium-Neon (HeNe) laser (633 nm) at three different scattering angles (45 °, 90 ° and 135 °) for 20 s each. Each angle was measured three times. The count rate was averaged over three measurements. For pH-responsiveness analyses, the laser intensity was set to 1.95 mW at a scattering angle of 90 °. The pH-responsiveness was tested after every titration point by monitoring the according count rates. The laser intensity for biodegradation monitoring was set to 1.70 mW at a scattering angle of 90 °. The degradation process was assayed after different time points.
Flash Column Chromatography: Column chromatography was carried out with high purity grade silica gel with a pore size of 6 nm and a pore volume of 0.75 cm^3/g and 70-230 mesh particle size.
Gel Permeation Chromatography: GPC analyses were run on a SECcurity2 System PSS 1260 Infinity chromatogram from Agilent Technologies with three linear S columns at 35 °C in THF or $CHCl_3$ with a running time of 1 mL/min.
Liquid Chromatography-Mass Spectroscopy: LC-MS spectra were recorded on a Shimadzu LabSolutions mass detector using a ZB-5HT column (30 mm x 0.25 mm x 0.25 mm) at a He-flow rate of 1 mL/min.
Nuclear Magnetic Resonance Spectroscopy: All NMR experiments were performed at 25 °C on a Bruker Avance 500 spectrometer with a frequency of 500 MHz for ^{1}H-NMR and 2D [^{1}H^{1}H]-COSY and with a frequency of 125 MHz for ^{13}C-NMR, respectively. Chemical shifts (δ) are declared in ppm in relation to the internal standard trimethylsilane (TMS), or residual solvent peaks. The H-H coupling constants *J* are reported in Hz. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad.
pH-Titration: Acid-base titrations for the determination of the corresponding pH values were performed on a pH meter from Mettler Toledo™ SG2 SevenGo. pKa values were determined by visual evaluation based on changes in the compound's titration curve pattern with respect to the titrated volume of base.
Photochemistry: Photoinitiated experiments were carried out with BME as photoinitiator and a xenon-mercury lamp by an UV light source from HamamatsuPhotonics UV-Spot LC4 with an output of 140 mW/cm^2 at 365 nm.
Thin-Layer Chromatography: For TLC, silica gel 60 F254/alumina plates were used. The spots were monitored with a UV-lamp at 253/366 nm or with a $KMnO_4$ stain solution

2. Synthetic Procedures

a. *N-iso*-propyl-*bis*(2-hydroxypropyl)amine **3a**

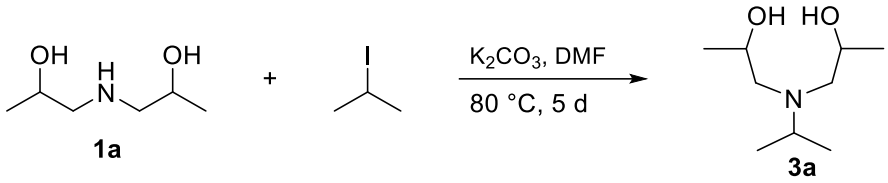


*Figure S 1: Reaction towards the N-functionalised diol **3a***

Bis(2-hydroxypropyl)amine (**1a**, 6.00 g, 45.0 mmol, 1.0 eq.) and K_2CO_3 (4.36 g, 31.5 mmol, 0.70 eq.) were dissolved in DMF (25 mL). 2-iodopropane (4.50 mL, 45.0 mmol, 1.0 eq.) was added and the reaction mixture was refluxed at 80 °C for 5 days. The reaction was diluted with H_2O (50 mL) and the mixture extracted with ethyl acetate (3x 50 mL). The organic phases were washed with sat. aq NaCl (2x 50 mL), dried over $MgSO_4$. The solvent was removed under reduced pressure to yield *N-iso*-propyl-*bis*(2-hydroxypropyl)amine (**3a**, 6.72 g, 38.3 mmol, 85%) as a pale-yellow oily liquid. The product was a mixture of two diastereomers (2:1) ((*R,S*)/(*S,R*) and (*R,R*)/(*S,S*)) and was used without further purification.

^{1}H-NMR (500 MHz, $CDCl_3$, δ = ppm): 3.78-3.70 (m, 2H, OC*H*), 3.25 (br, 2H, O*H*), 2.92 (hept, *J* = 6.7 Hz, 1H, NC*H*), 2.47-2.20 (m, 4H, NCH_2), 1.11 (d, *J* = 6.2 Hz, 6H, O(CH)-CH_3), 1.07-0.93 (m, 6H, N(CH)CH_3)
^{13}C-NMR (125 MHz, $CDCl_3$, δ = ppm): (*R,S*)/(*S,R*): 66.0 (2C, O*C*H), 59.5 (2C, N*C*H$_2$), 52.8 (1C, N*C*H), 20.5 (2C, O*C*H$_3$), 18.4 (2C, N*C*H$_3$) / (*R,R*)/(*S,S*): 64.2 (2C, O*C*H), 58.0 (2C, N*C*H$_2$), 50.8 (1C, N*C*H), 20.3 (2C, O*C*H$_3$), 15.4 (s, 2C, N*C*H$_3$).
Mass spectroscopy: LC-MS (EI$^+$) calculated for $C_9H_{21}NO_2$ 175.16, found 175.15 $[M]^+$

b. *N-iso*-propyl-4,8-dimethyl-1,3,6-dioxazocan-2-one 4a

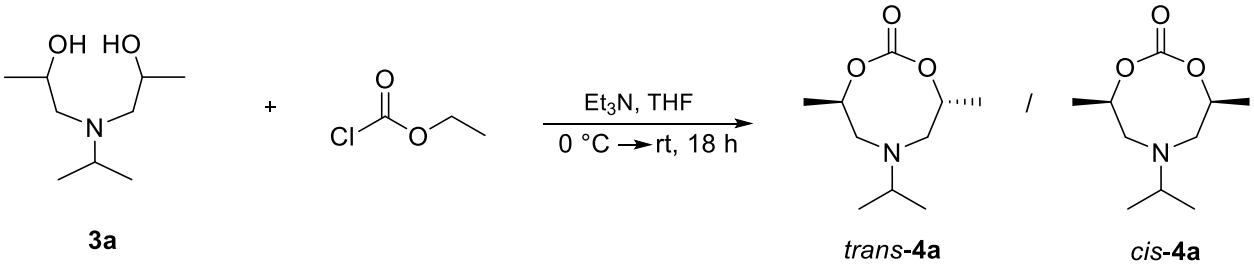


*Figure S 2: Reaction towards the N-functionalised cyclic carbonate **4a***

Bis(2-hydroxy- propyl) isopropylamine (**3a**, 2.00 g, 11.4 mmol, 1.0 eq.) and ethyl chloroformate (4.40 mL, 45.6 mmol, 4.0 eq.) were dissolved in THF (20 mL) and chilled to 0 °C in an ice bath for 30 min. Et_3N (6.40 mL,45.6 mmol, 4.0 eq.) was placed in the addition funnel and added drop-wise over 10 min. The reaction mixture was stirred for 2 h at 0 °C and 18 h at room temperature. The resulting precipitate was filtered off and the filtrate concentrated under reduced pressure to give the crude product that was purified by flash column chromatography (PE/EtOAc, 7:3) to give (in order of elution from the column) the pure diastereomers *cis*-**4a** (1.20 g, 5.96 mmol, 52%) and *trans*-**4a** (669 mg, 3.32 mmol, 29%) as viscous yellow liquids.

cis-isomer of **4a**:
^{1}H-NMR (500 MHz, $CDCl_3$, δ = ppm): 4.53-4.47 (m, 2H, O-C*H*), 2.93 (hept, *J* = 6.6 Hz, 1H, N-C*H*), 2.66-2.55 (m, 4H, N-CH_2), 1.39 (d, *J* = 6.7 Hz, 6H,O(CH)-CH_3), 1.04 (d, *J* = 6.7 Hz, 6H, N(CH)-CH_3).

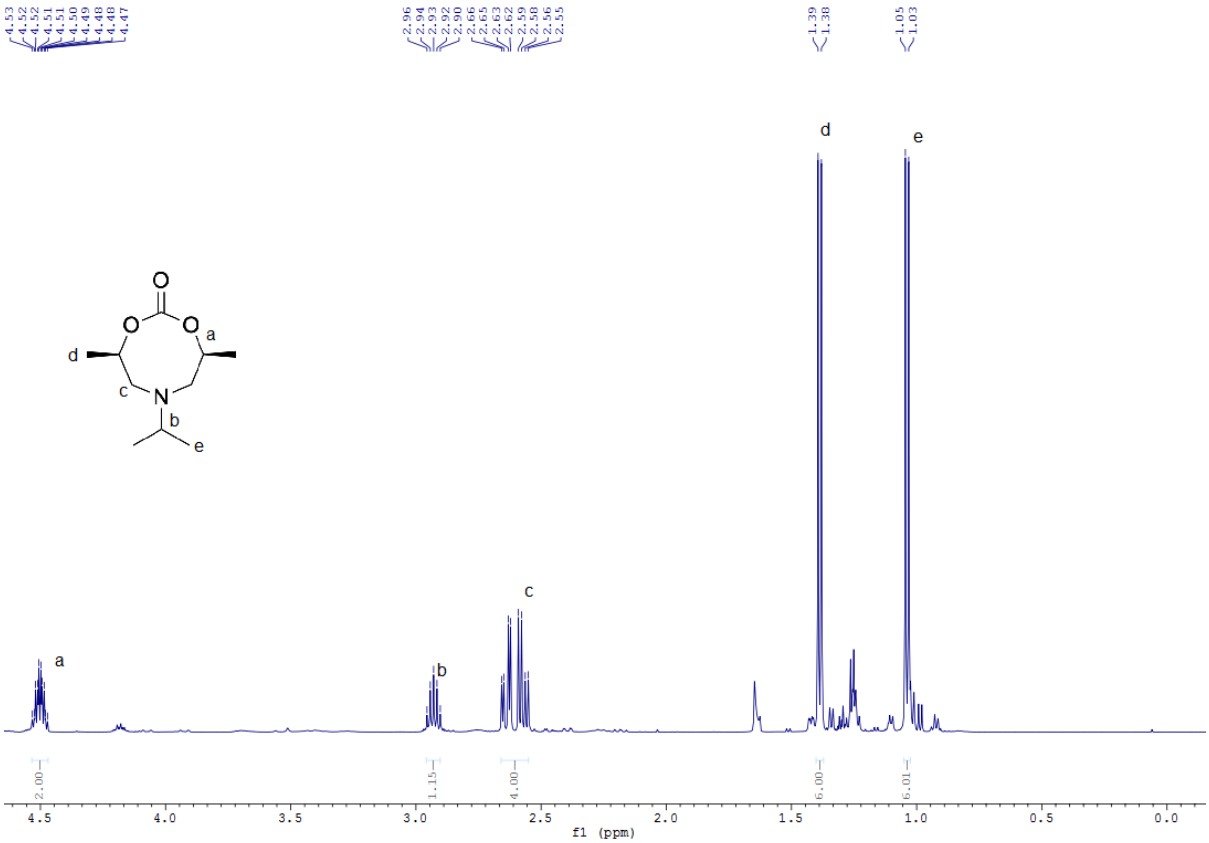


Figure S 3: [1]H-NMR of N-iso-propyl-4,8-dimethyl-1,3,6-dioxazocan-2-one 4a

^{13}C-NMR (125 MHz, $CDCl_3$, δ = ppm): 156.0 (1C, *C*O), 56.5 (1C, N-*C*H), 56.4 (2C, N-*C*H_2), 19.6 (2C, O(CH)-*C*H_3), 18.2 (2C, N(CH)-*C*H_3).

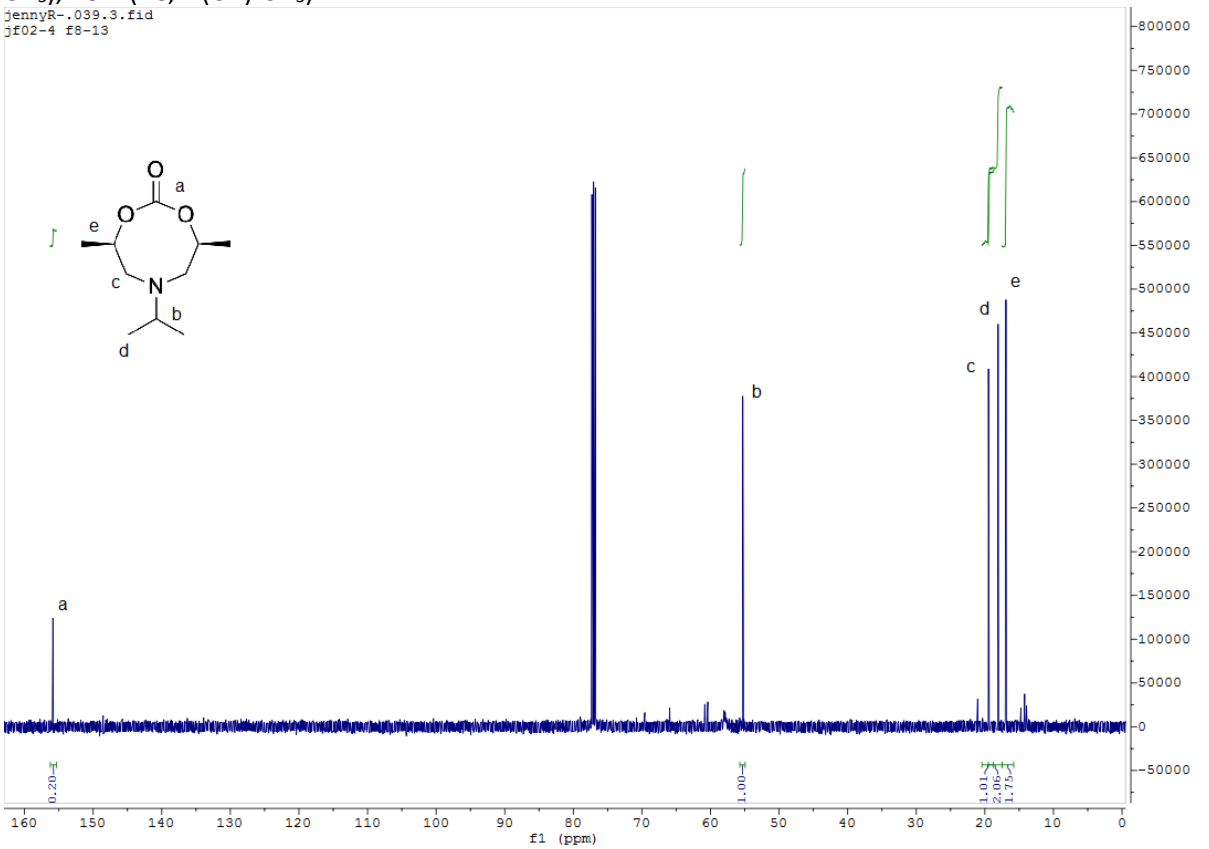


Figure S 4: [13]C-NMR of N-iso-propyl-4,8-dimethyl-1,3,6-dioxazocan-2-one 4a

Mass spectroscopy: HRMS (ESI+) calculated for $C_{10}H_{20}NO_3$-H^+: 202.1438, found 202.1439 $[M+H]^+$.

trans- isomer of **4a**:
^{1}H-NMR (500 MHz, $CDCl_3$, δ = ppm): 4.56-4.51 (m, 2H, O-C*H*), 2.93 (d, *J* = 6.6 Hz, 1H, N-C*H*), 2.75-2.27 (br, 4H, N-CH_2), 1.25 (d, *J* = 6.4 Hz, O(CH)-CH_3), 1.01 (d, *J* = 6.7 Hz, 3H, N(CH)-CH_3), 0.98 (d, *J* = 6.6 Hz, 3H, N(CH)-CH_3). (graphically similar to above)
^{13}C-NMR (125 MHz, $CDCl_3$, δ = ppm): 156.0 (1C, *C*O), 55.4 (1C, N-*C*H), 19.6 (2C, N-*C*H_2), 18.8 (2C, O(CH)-*C*H_3), 17.1 (2C, N(CH)-*C*H_3). (graphically similar to above)
Mass spectroscopy: HRMS (ESI-H+) calculated for $C_{10}H_{20}NO_3$-H^+: 202.1438, found 202.1432 $[M+H]^+$.

c. Petasis reagent (dimethyltitanocene) 5

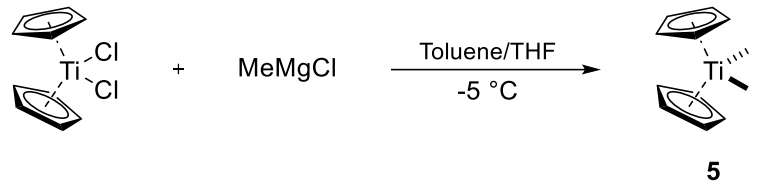


*Figure S 5: Reaction towards the Petasis reagent **5***

We adopted a method from Petasis et al.[2] Titanocene dichloride (8.00 g, 32.1 mmol, 1.0 eq.) was suspended in toluene (80 mL) and cooled to −5°C in an NH_4Cl/ice bath while stirring for 30 min. A solution of 3 M MeMgCl (25.0 mL, 74.9 mmol, 2.3 eq.) in tetrahydrofuran (THF) was placed in the addition funnel and added dropwise over 10 min. The reaction mixture was kept at −5 °C, stirred for 1 h until the insoluble titanocene dichloride was no longer observed. The reaction was carefully quenched via a cannula into an ice-chilled and well-stirred 6% aq. NH_4Cl solution (1.40 g in 22 mL H_2O) over a period of 1 h. THF (10 mL) was used to rinse the reaction flask. The biphasic mixture was placed in a separatory funnel with another rinse of THF (5 mL). The organic phase was washed with cold H_2O (3x 20 mL) and cold brine (1x 20 mL). The organic extract was dried over Na_2SO_4 while cooling in ice and filtered. An ^{1}H-NMR assay revealed that the orange-red filtrate contained 6 to 7.5 wt-% dimethyltitanocene in toluene/THF (**5**, 5.38 g, 25.9 mmol, 80%). The solution was stored under argon at −20 °C.

^{1}H-NMR (500 MHz, $CDCl_3$, δ = ppm): 6.07 (s, 10H, Cp-*H*), -0.11 (s, 6H, Ti-CH_3)
^{13}C-NMR (125 MHz, $CDCl_3$, δ = ppm): 13.2 (10C, Cp_2), 45.77 (s, 2C, *C*H_3)

d. *N-iso*-propyl-4,8-dimethyl-2-methylene-1,3,6-dioxazocane 2a

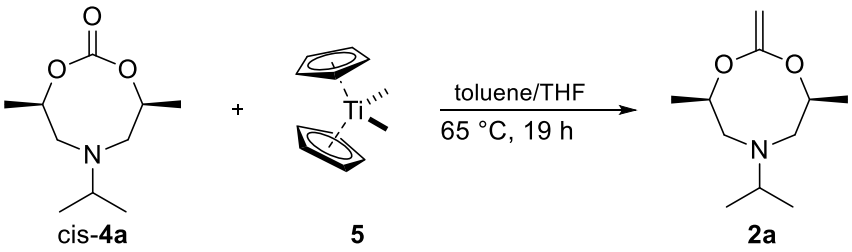


*Figure S 6: Reaction towards the pH sensitive CKA **2a***

Cis-CKA **2a** (1.00 g, 4.97 mmol, 1.0 eq.) was dissolved in toluene (7 mL). The reaction flask was covered with tinfoil to protect the photosensitive CKA. Dimethyltitanocene (**5**, 7.5 wt%, in toluene/THF, 2.07 g, 33.0 mL, 2.0 eq.) was added and the reaction mixture was heated to 65 °C for 19 h. The reaction was diluted with n-hexane (50 mL) and the precipitated orange titanium salts were filtered off over filtration paper. The filtrate was concentrated under reduced pressure and the crude product was

purified by vacuum distillation (75 °C at 20 mbar) to yield *cis*-**4a** (4, 233 mg, 1.17 µmol, 24%) as a pale yellow oil.
The same procedure was attempted for *trans*-**4a**, but yielded no defined product.

^{1}H-NMR (500 MHz, $CDCl_3$, δ = ppm): 4.21-4.14 (m, 2H, OC*H*), 3.63 (s, 2H, CCH_2), 2.91 (hept, *J* = 6.5 Hz, 1H, NC*H*), 2.64-2.44 (m, 4H, NCH_2),1.16 (d, *J* = 6.6 Hz, 6H, O(CH)CH_3), 0.97 (d, *J* = 6.6 Hz, 6H, N(CH)CH_3).

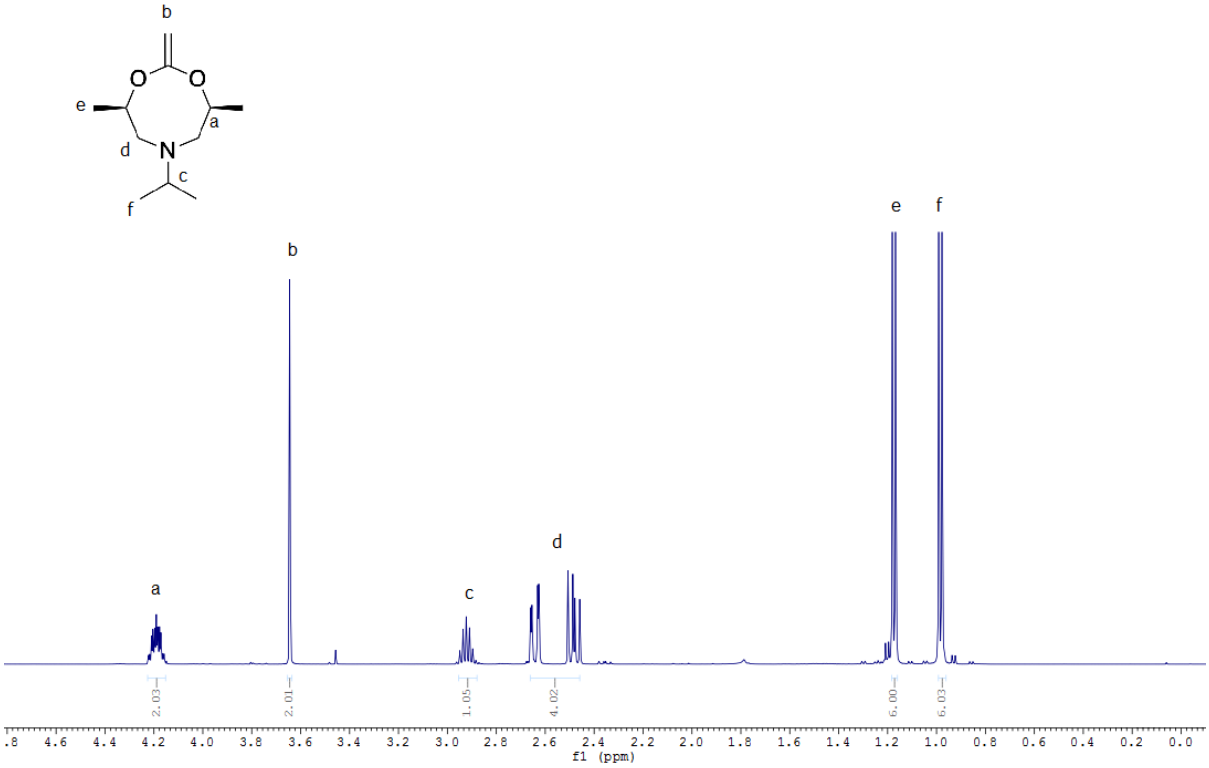


Figure S 7: ^{1}H-NMR of N-iso-propyl-4,8-dimethyl-2-methylene-1,3,6-dioxazocane 2a

^{13}C-NMR (125 MHz, $CDCl_3$, δ = ppm): 58.8 (s, 1C, CCH_2), 76.8 (s, 2C, O*C*H), 75.8 (s, 1C, CCH_2), 57.6 (s, 2C, NCH_2), 56.0 (s, 1C, N*C*H), 18.7 (s, 2C, O(CH)*C*H_3), 18.1 (s, 2C, N(CH)-*C*H_3).

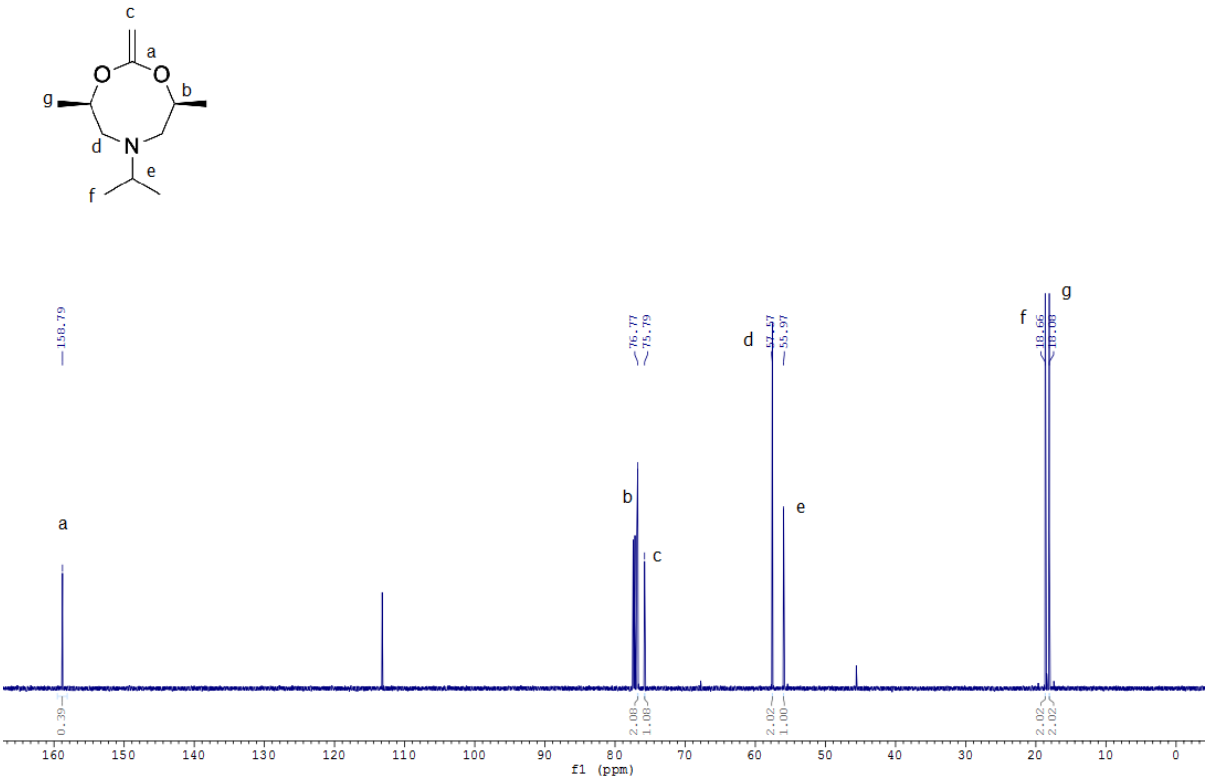


Figure S 8: ^{13}C-NMR of N-iso-propyl-4,8-dimethyl-2-methylene-1,3,6-dioxazocane 2a

Mass spectroscopy: HRMS (ESI+) calculated for $C_{11}H_{22}NO_2$-H^+ 200.1645, found 200.1641. $[M+H]^+$

e. *N-iso*-propyl-diethanolamine **3b**[3]

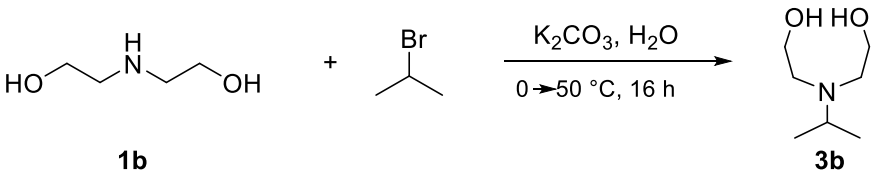


*Figure S 9: Reaction towards the N-functionalised diol **3b***

Bis(2-hydroxyethyl)amine (**1b**, 2.10 g, 20.0 mmol, 1.0 eq.) and K_2CO_3 (1.10 g, 8.00 mmol, 0.4 eq.) were dissolved in H_2O (2 mL) and stirred while cooling to 0 °C in an ice bath. To the mixture, 2-bromopropane (1.20 mL, 12.0 mmol, 0.6 eq.) was added dropwise with continuous stirring. The reaction mixture was stirred for 1 h at room temperature and then heated at stirred at 50 °C for 18 h. H_2O was then removed under reduced pressure. The residue was diluted with MeOH (5 mL), the precipitated KBr was filtered off and MeOH was removed under reduced pressure. The crude oil was dissolved in H_2O (2 mL), extracted gently (avoid strong shaking!) with toluene (2x 1 mL) and then extracted DCM (3x 10 mL). The combined DCM phases were dried over $MgSO_4$ and the filtrate was evaporated under reduced pressure to give *N-iso*-propyl-diethanolamine[3] (**3b**, 1.87 g, 12.7 mmol, 64%) as a light brown oil.

^{1}H-NMR (500 MHz, $CDCl_3$, δ = ppm): 3.57 (t, *J* = 5.4 Hz, 4H, OC*H*$_2$), 3.02-2.91 (m, 1H, NC*H*; 2H, OH br), 2.61 (t, *J* = 5.4 Hz, NC*H*$_2$), 1.02 (d, *J* = 6.6 Hz, NC*H*$_3$).
^{13}C-NMR (125 MHz, $CDCl_3$, δ = ppm): 58.8 (1C, C*C*H$_2$), 76.8 (2C, O*C*H), 75.8 (1C, C*C*H$_2$), 57.6 (2C, NCH$_2$), 56.0 (1C, N*C*H), 18.7 (2C, O(CH)*C*H$_3$), 18.1 (2C, N(CH)-*C*H$_3$).

f. *N-iso*-propyl-1,3,6-dioxazocan-2-one **4b**

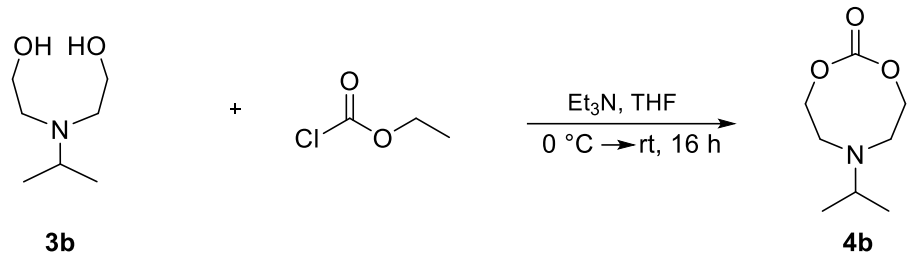


*Figure S 10: Reaction towards N-functionalised cyclic carbonate **4b***

N-iso-propyl-diethanolamine (**3b**, 1.00 g, 6.80 mmol, 1.0 eq.) and ethyl chloroformate (2.60 mL, 27.2 mmol, 4.0 eq.) were dissolved in THF (16 mL) and chilled to 0 °C in an ice bath for 30 min. Et_3N (3.80 mL, 27.2 mmol, 4.0 eq.) was placed in the addition funnel and added dropwise over a period of 20 min. The reaction mixture was stirred for 2 h at 0 °C and for another 16 h at room temperature. The resultant precipitate was filtered off and the filtrate concentrated under reduced pressure to give the crude product that was purified by flash column chromatography (PE/EtOAc 2:1) to give the cyclic carbonate, (**2b**, 802 mg, 4.63 mmol, 68%) as a dark yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$, δ = ppm): 4.16 (t, *J* = 5.4 Hz, 4H, OC*H*), 2.93(hept, *J* = 6.6 Hz, 1H, NC*H*), 2.73 (t, *J* = 5.4 Hz, 4H, NCH_2), 1.0 (d, *J* = 6.6 Hz, 6H, N(CH)-CH_3).

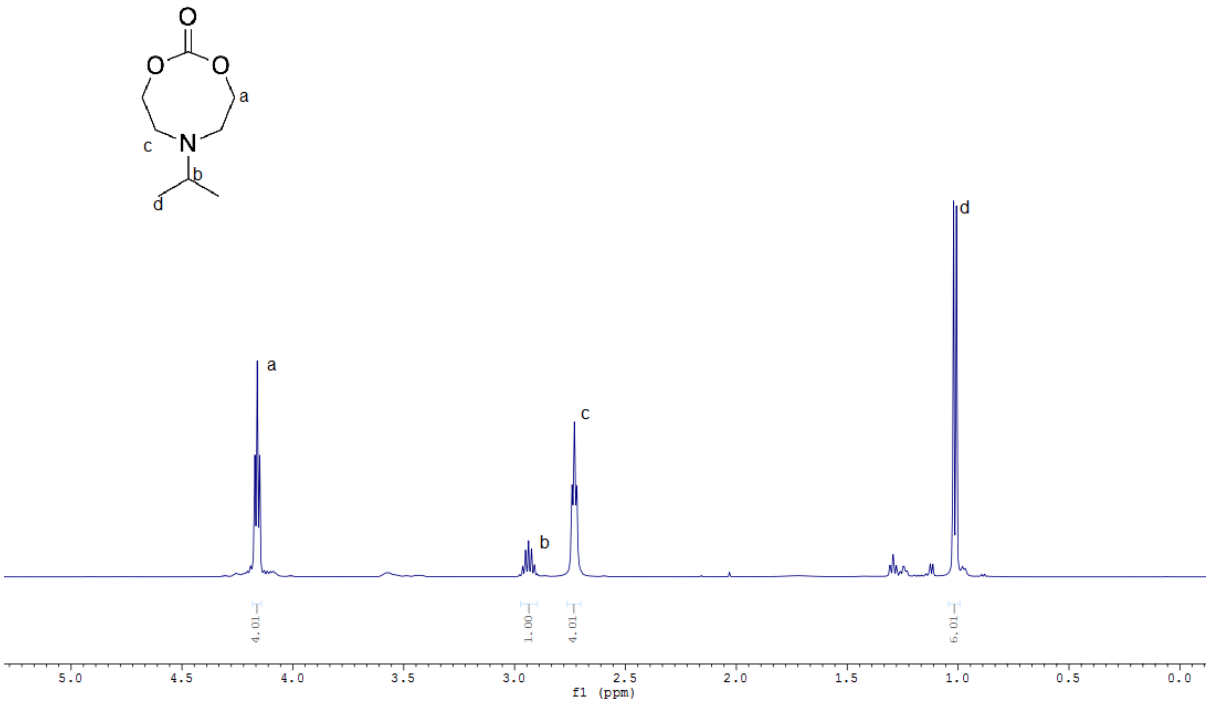


Figure S 11: ^{1}H-NMR of N-iso-propyl-1,3,6-dioxazocane 4b

^{13}C-NMR (125 MHz, $CDCl_3$, δ = ppm): 56.5 (1C, CCH_2), 69.4 (2C, OCH_2), 55.3 (1C, N*C*H), 50.7 (2C, NCH_2, 18.9 (2C, N(CH)-CH_3).

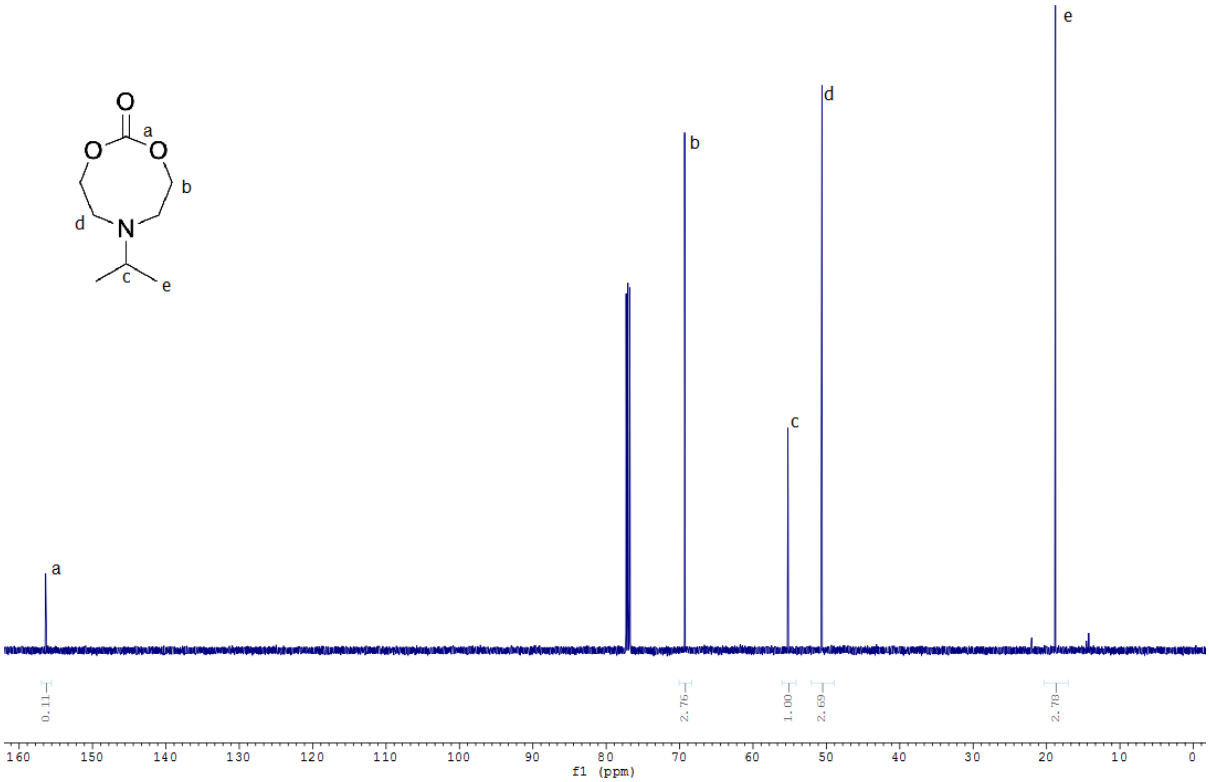
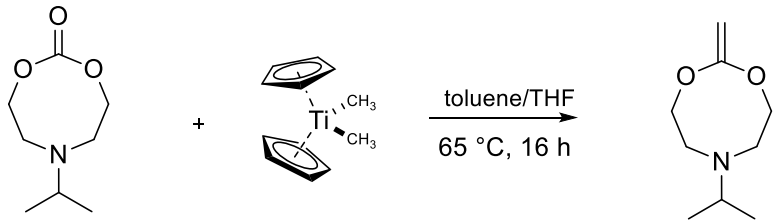


Figure S 12: ^{13}C-NMR of N-iso-propyl-1,3,6-dioxazocane 4b

Mass spectroscopy: HRMS (ESI+) calculated for $C_8H_{15}NO_3$-H^+ 174.1125, found 174.1127. $[M+H]^+$

g. 6-isopropyl-2-methylene-1,3,6-dioxazocane **2b**



4b **5** **2b**

*Figure S 13: Reaction towards the pH sensitive CKA **2b***

The carbonate-precusor to i-MAC, *N-iso*-propyl-1,3,6-dioxazocan-2-one (**4b**, 1.50 g, 5.77 mmol, 1.0 eq.), was dissolved in THF (15 mL) and dimethyltitanocene (**5**, 5 wt% in toluene/THF, 3.60 g, 80.4 mL, 2.0 eq.) was added. The reaction flask was covered with tinfoil to protect the photosensitive CKA formation. The reaction mixture heated to 65 °C for 16 h. The reaction was diluted with n-hexane (80 mL) and the precipitated orange titanium salts were filtered off using filtration paper. The filtrate was concentrated under reduced pressure and the crude product was purified by vacuum distillation (63 °C at 10 mbar) to yield *i*-MAC (**2b**, 167 mg, 975 µmol, 11%) as a dark yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$, δ = ppm): 3.99-3.96 (m, 4H, OCH_2), 3.56 (s, 2H, CCH_2), 2.93 (hept, *J* = 6.6 Hz, 1H, NC*H*), 2.74-2.68 (m, 4H, NCH_2), 0.99 (d, *J* = 6.6 Hz, 6H, N(CH)CH_3).

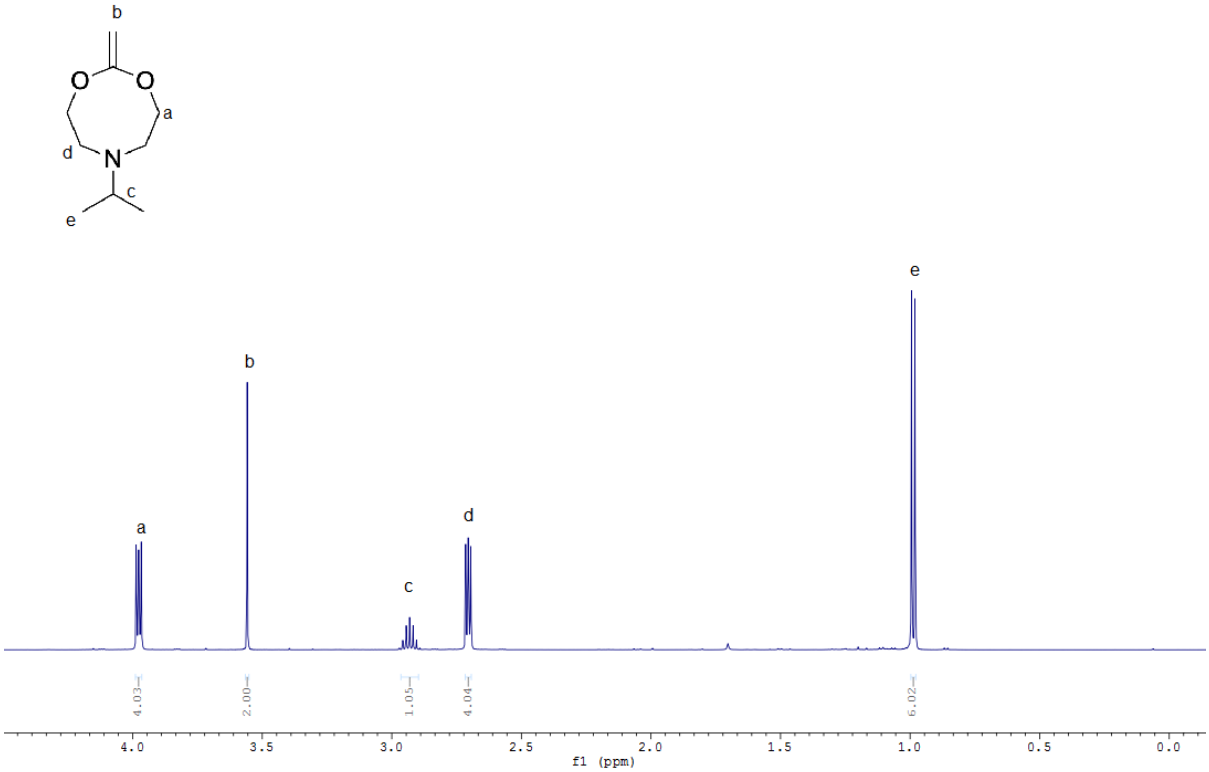


Figure S 14: [1]H-NMR of N-iso-propyl-2-methylene-1,3,6-dioxazocane 2a

^{13}C-NMR (125 MHz, $CDCl_3$, δ = ppm): 64.7 (1C, H_2CC), 71.2 (2C, OCH_2), 69.5 (1C, CCH_2), 55.3 (1C, NCH), 51.4 (2C, NCH_2), 18.7 (2C, N(CH)CH_3).

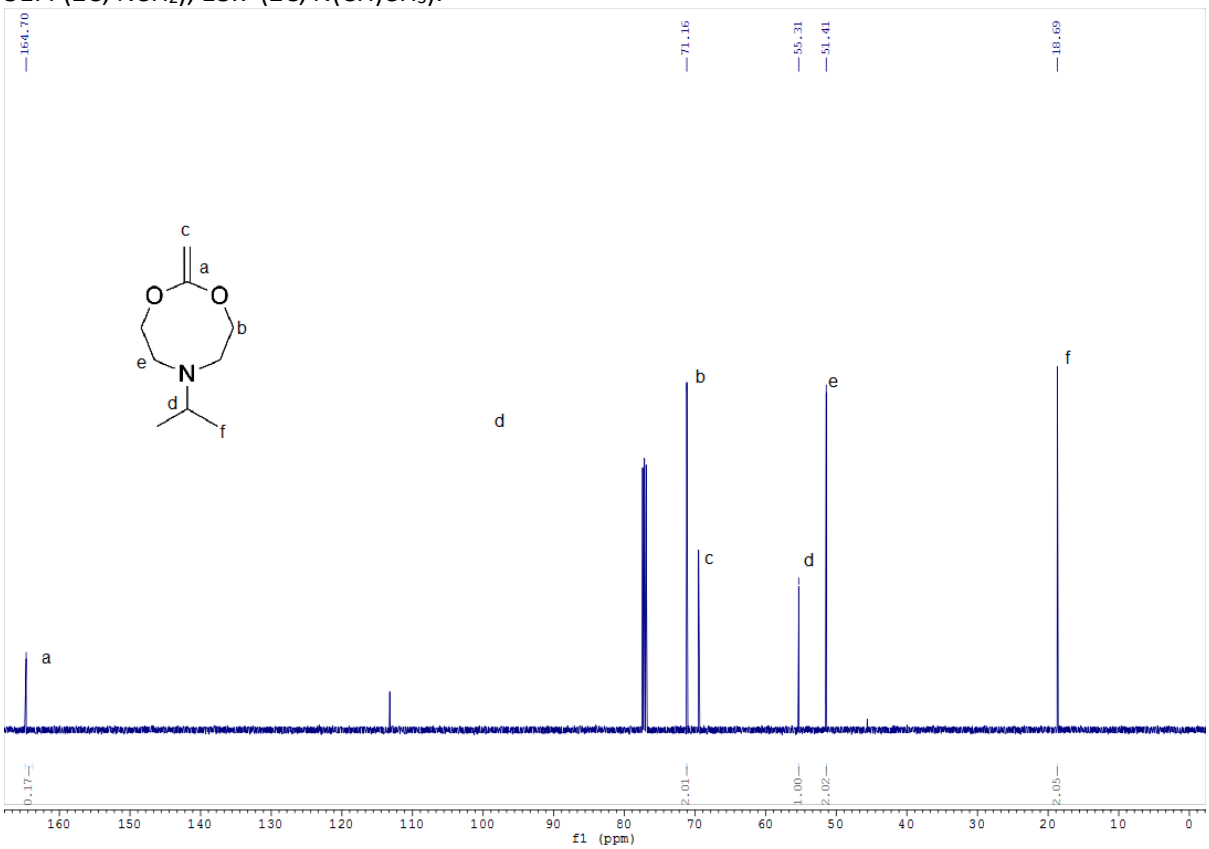


Figure S 15: Figure S 16: [13]C-NMR of N-iso-propyl-2-methylene-1,3,6-dioxazocane 2a

Mass spectroscopy: HRMS (ESI+) calculated for $C_9H_{17}NO_2$-H^+ 172.1332, found 172.1332. $[M+H]^+$

h. 4,7-dimethyl-2-methylene-1,3-dioxepane (DMMDO) **8**

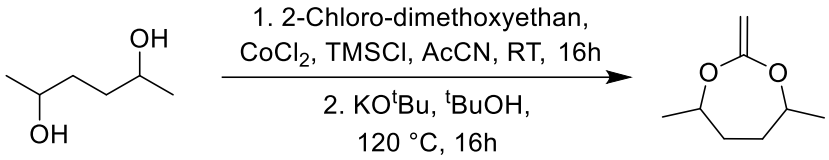


Figure S 17: Synthesis of the CKA DMMDO in two steps as published previously

DMMDO was synthesised using a previously published procedure.[2] 2,5-Hexanediol (10.0 g, 84.7 mmol, 1.0 eq.) was dissolved in anhydrous MeCN (840 mL). To this solution, $CoCl_2$ (3.62 g, 27.9 mmol, 0.33 eq.), TMSCl (9.30 g, 85.4 mmol, 1.01 eq.) and 2-chloro-1,1-dimethoxyethane (10.64 g, 85.4 mmol, 1.01 eq.) were added sequentially. The mixture was stirred under argon overnight at room temperature. The mixture was then poured into H_2O (in two batches, 450 mL each), each extracted with EtOAc (3x 400 mL) and the combined organic phases from both batches washed with sat. aq $NaHCO_3$ (500 mL). The solution was then dried (Na_2SO_4), filtered and the solvent evaporated at reduced pressure. Distillation gave DMMDO (**8**): 8.63 g, b.p. 73 °C (6 mBar). Yield: 61%
The acetal **8** (4.10 g 23.0 mmol, 1.0 equiv.) was then dissolved in ^{t}BuOH (5 mL) and KO^{t}Bu (3.10 g, 27.6 mmol, 1.2 equiv.) to give a thick slurry. The mixture was stirred for 16 h in a sealed tube at 120 °C. During the reaction, the solution became much less viscous. The reaction was cooled to room temperature and the addition of Et_2O (50 mL) lead to the formation of a precipitate. The solution was centrifuged (2000 rpm, 5 min) and the supernatant decanted and evaporated. The residue was distilled to give DMMDO **8:** 1.24 g, b.p. 51 °C (12 mbar). Yield: 32%

^{1}H-NMR (500 MHz, $CDCl_3$, δ = ppm): 1.05-1.13 (m, 6H, CH_3 (contains distinct d *J* = 6.7 Hz), 1.31 - 1.75 (m, 4H, C*H*$_2$), 3.17/3.18/3.22 (3 x d, *J* = 5.2 Hz / 5.0 Hz / 5.5 Hz, 2H, C*H*$_2$), 3.60 - 3.97 (m, 2H, C*H*), 4.61/4.76/4.87 (3 x t, *J* = 5.2 Hz / 5.3 / 5.3 , 1H, C*H*).
^{13}C-NMR (125 MHz, $CDCl_3$, δ = ppm): 22.2 / 22.3 (*C*H$_3$), 32.5 / 33.1 (*C*H$_2$) 35.7 / 36.0 (*C*H$_2$), 75.9 / 76.0 (*C*H), 98.3 / 100.9 (*C*H)

i. Homopolymerisation with AIBN

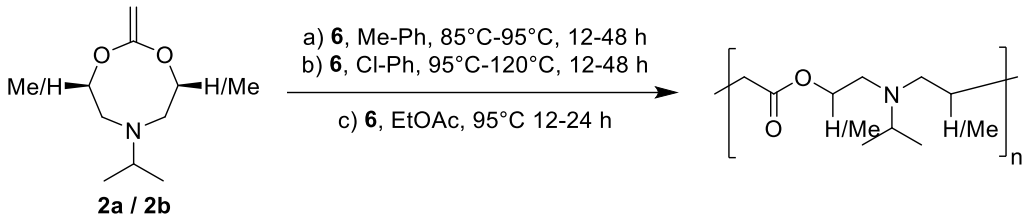


*Figure S 18: Homopolymerisation of pH sensitive CKAs **2a** and **2b** with thermal activation (**6** = AIBN)*

The following experimental procedure was adopted from a previous report.[3] In a vial, i-MAC (**2b**, 106 mg, 621 µmol, 1.0 eq.) and AIBN (4.10 mg, 24.8 µmol, 0.04 eq.) were dissolved in three drops of toluene. The solution was purged with argon gas for 20 min and then heated to 85 °C for 24 h. The reaction mixture was allowed to cool to room temperature and dialyzed against EtOH (solvent was exchanged three times (100 mL each), leaving each batch at least 4h). The solvent was removed under reduced pressure to give the polymer P(i-MAC) (21.4 mg). Dispersity from GPC: 1.6. Molecular weight: 1700 g/mol

P(i-DMMAC) could not be achieved in any of the conditions mentioned, as the ^{1}H NMR data shows:

toluene	85 °C	48 h
ethyl acetate	75 °C	24 h
toluene	95 °C	24 h
chlorobenzene	95 °C	12 h
toluene	85 °C	12 h
ethyl acetate	75 °C	12 h

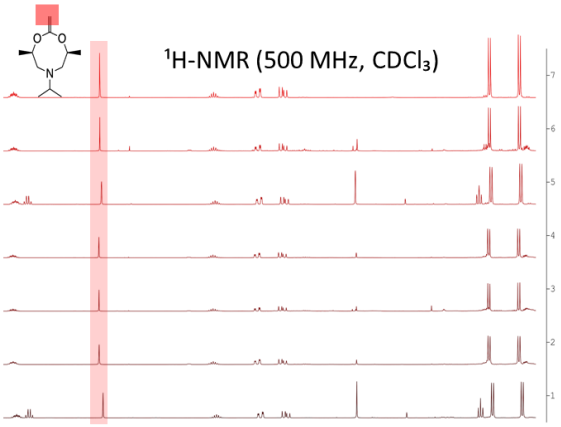


Figure S 19: Homopolymerisation-Attempts of i-DMMAC only gave versions of degraded monomer, the characteristic of the methylene group within the CKA was always present after the polymerisations

j. Homopolymerisation with BME

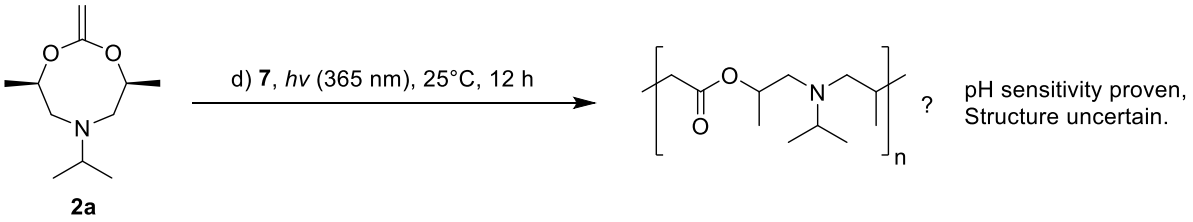


*Figure S 20: Homopolymerisation of pH sensitive CKA **2b** with UV-light activation (**7** = BME)*

In a vial, i-DMMAC (**2a**, 200 mg, 1.00 mmol, 1.0 eq.) and BME (**7**, 4.54 mg, 20.1 µmol, 0.02 eq.) were stirred under irradiation from a UV-lamp (365nm) source at 50 °C for 16 h. The crude product was dialysed against EtOH (MWCO 1 kDa, SpectraPor 6), exchanging the solvent three times, leaving each batch for at least 3 h. The solvent was removed under reduced pressure to give the polymer P(DMNPA) (12.2 mg). Dispersity from GPC: 1.8. Molecular weight: 1500 g/mol

k. PEG-based macroinitiator

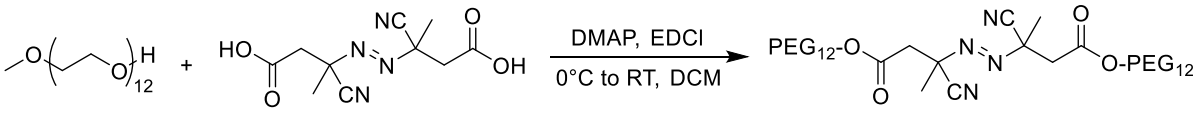


Figure S 21: Steglich-Esterification of PEG to get the macroinitiator for free radical polymerisation

The macroinitiator was synthesised using a previously published procedure[2] without any changes to the Steglich esterification.
Polyethylene glycol monomethyl ether (M_n 550 g/mol, 1.10 g, 2.00 mmol, 5.0 eq., PEG) and DMAP (6, 24.4 mg, 200 µmol, 0.50 eq.) were dried by adding toluene (5.00 mL) and evaporating the solvent under reduced pressure. EDCI (169 mg, 880 mol, 2.2 eq.) was dissolved in DCM (4 mL). In a second round bottom flask, PEG, DMAP 6 and 4,4'-(diazene- 1,2-diyl)bis(4-cyanopentanoic acid) (112 mg, 400 µmol, 1.0 eq.) were dissolved in DCM (4 mL). Both solutions were stored in the freezer at −20 °C for 1 h. The EDCI7 solution was added to the second solution dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 48 h in an argon atmosphere. Then the reaction mixture was added to Et_2O (100 mL) to precipitate unreacted acid and longer polymers. The supernatant was skimmed and the solvent evaporated. The residue was redissolved in DCM (2 mL) and added to hexane (100 mL) to precipitate the polymer. The precipitation in hexane was repeated twice.

l. Block-copolymer PEG-P(i-MAC)

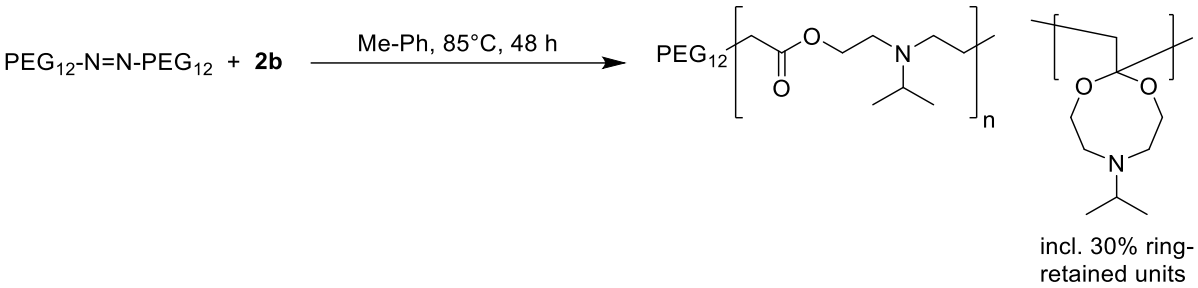


Figure S 22: Formation of the PEG-P(i-MAC) block-copolymer, including the structure of the ring-retained units.

In a vial, PEG-macroinitiator (11.7 mg) and the CKA i-MAC (**2b**, 101 mg) were dissolved in three drops of toluene and heated to 85 °C for 48 h. The reaction mixture was cooled to room temperature and dialysed against EtOH (solvent was exchanged three times (100 mL each), leaving each batch at least 4h). The solvent was removed under reduced pressure to give the amphiphilic block-copolymer (6.00 mg). Dispersity from GPC: 1.4. Molecular weight: 2000 g/mol
A detailed description of the ring-retention mechanism and determination of the resulted ratio thereof can be found in section 3b of the supporting information.

m. Block-Copolymer PEG-P(DMMDO-*stat*-i-MAC)

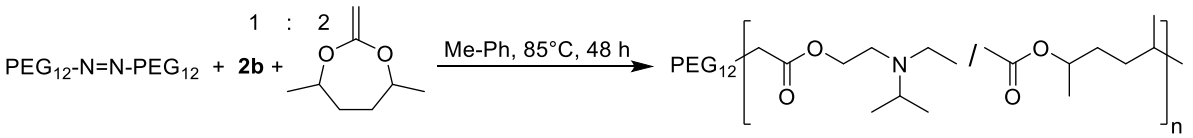


Figure S 23: Formation of the PEG-P(DMMDO-stat-i-MAC) block-copolymer

In a vial, the PEG-macroinitiator (14.2 mg) was added to a mixture of the CKAs i-MAC (**2b**, 33.5 mg) and DMMDO (**8**, 65.1 mg). The reaction mixture was dissolved in three drops of toluene and heated to 85 °C for 48 h. The reaction mixture was cooled to room temperature and dialysed against EtOH (solvent was exchanged three times (100 mL each), leaving each batch at least 4h). The solvent was removed under reduced pressure to give the amphiphilic block-copolymer (10.8 mg). Dispersity from GPC: 1.3. Molecular weight: 2700 g/mol

3. Polymer characterisation

a. GPC traces

Photoinitiated polymerisation of BME gave a solidified oligomer with a GPC trace as shown below.

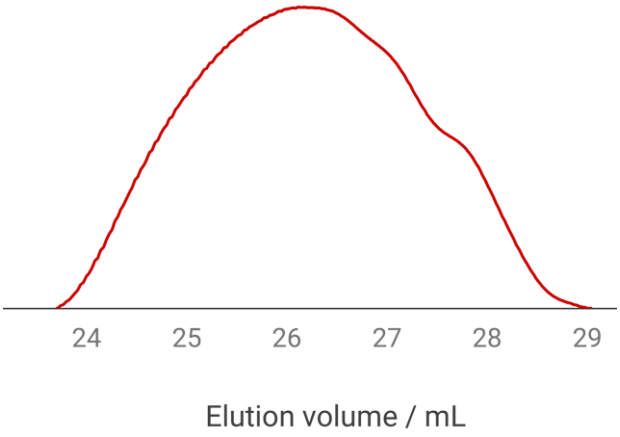


Figure S 24.GPC trace of P(i-DMMAC), as obtained by photoinitiated polymerisation with BME

Thermal polymerisation of the PEG macroinitiator (GPC trace published earlier) with i-MAC gave a block-copolymer with the following GPC trace:

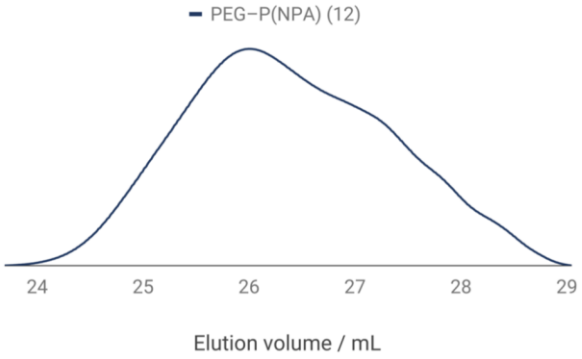


Figure S 25: GPC trace of PEG-P(i-MAC) obtained after thermal polymerisation

b. Amount of ring-opening

In RROP the reaction can progress in 2 possible ways, as shown here for i-MAC:

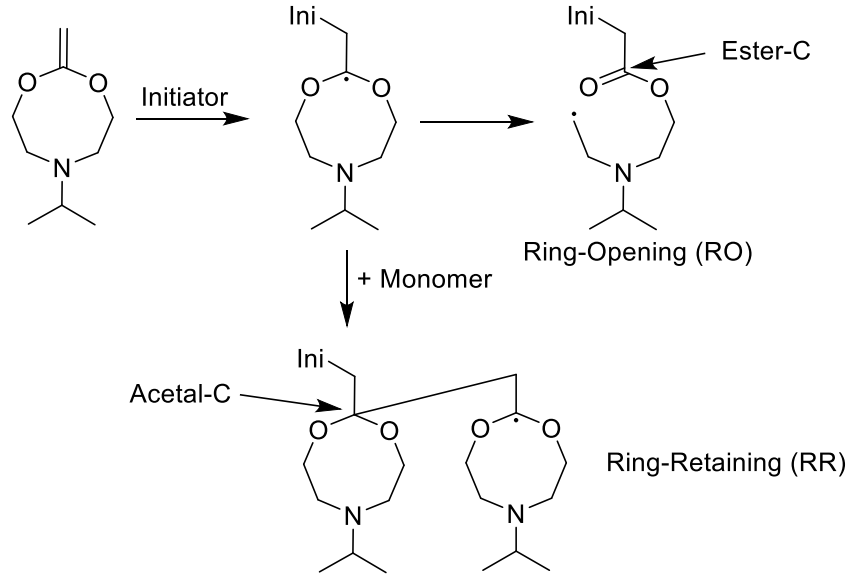


Figure S 26: Mechanism of RROP including the possible side reaction towards the propagating acetal

The amount of ring-opened polymer was determined using ^{13}C-NMR spectroscopy by comparing the acetal-peak at around 120 ppm (Acetal-C in Figure above) with the peak of the ester-carbonyl at around 170 ppm (Ester-C in Figure above). A sample spectrum can be seen below. The peaks of interest are at 170.4 ppm (carbonyl from ester) and at 120.4 ppm for the acetal from the non-opened ring.

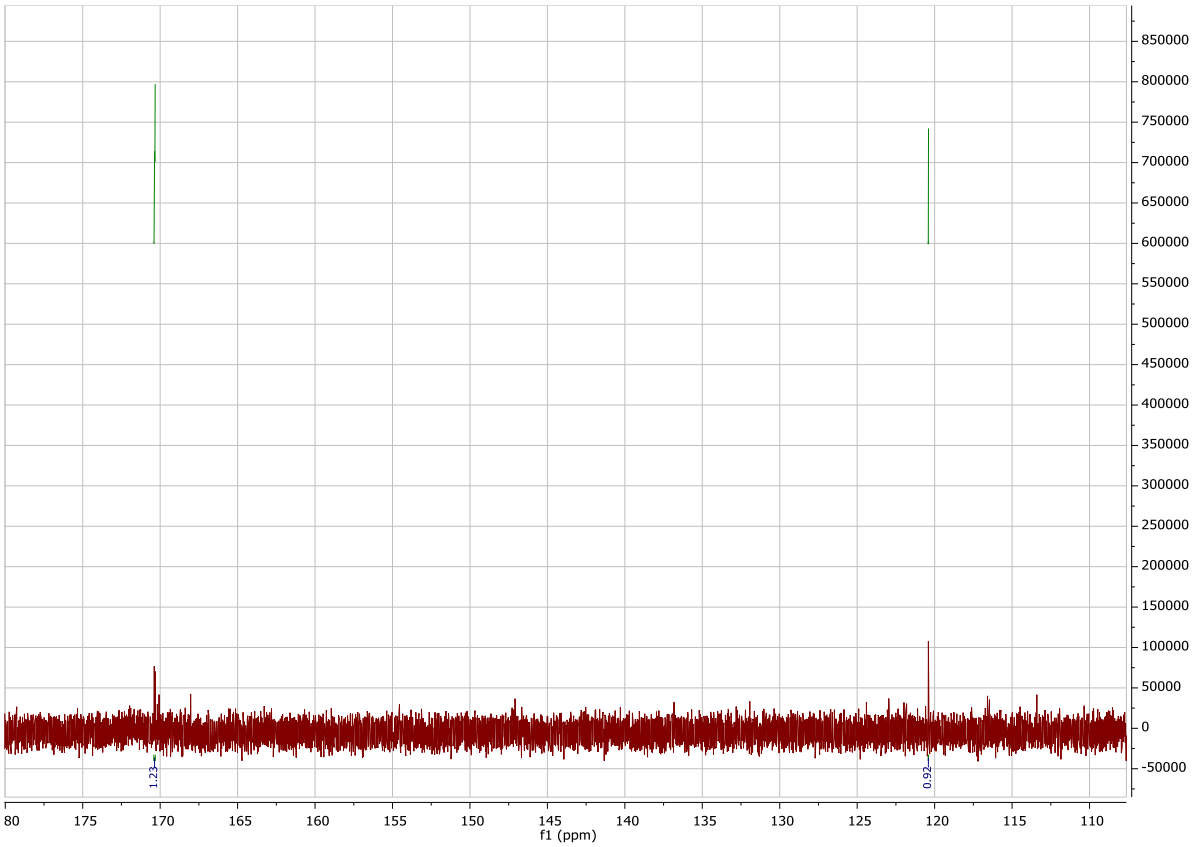


Figure S 27: ^{13}C-NMR spectrum of PEG-P(iMAC) showing the Ester-C and Acetal-C, including their integrals. A detailed spectrum for the integrals is given below in Figure S28.

Both peaks were integrated in the areas, which can be seen below:

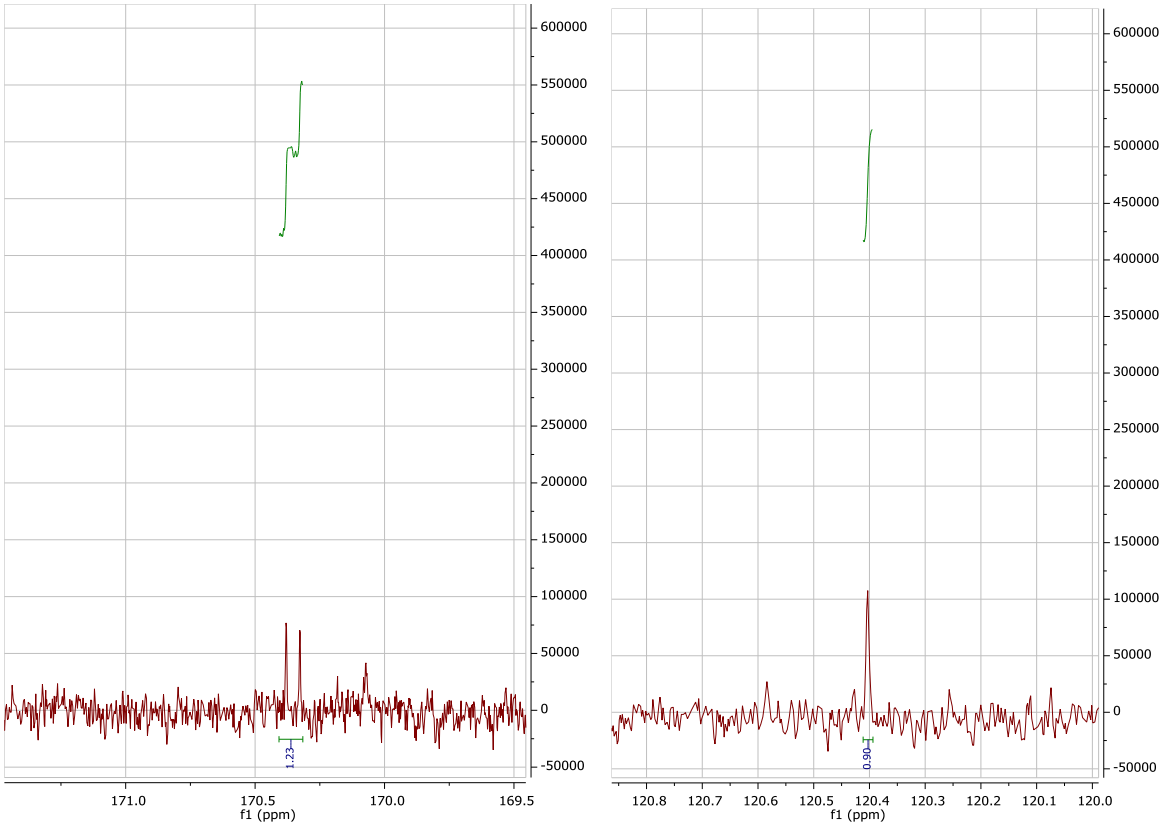


Figure S 28: ^{13}C-NMR spectrum of PEG-P(iMAC) showing the region of interest for the Ester-C and Acetal-C, including their integrals. The upper spectrum is the full spectrum for information.

The ring-opening content is now the amount of ring-opened integral vs. the closed one. Since both carbons are fully substituted, their integrals are comparable, although these numbers have to be treated with caution. Our method will only give a close approximation:

$$\%RO = \frac{I(RO)}{I(RO)+I(RR)} = \frac{1{,}24}{1{,}24+0{,}90} = 0{,}579 = 57.9\%$$

Due the measurement errors, the value is rounded up to 60%.

A similar calculation was done for P(i-MAC) homopolymer. Here the numbers are as follows:

$$\%RO = \frac{I(RO)}{I(RO)+I(RC)} = \frac{1{,}45+1{,}07}{2{,}52} = 0{,}575 = 57.5\%$$

This value is again rounded up to 60%

As for PEG-P(DMMDO-*stat*-i-MAC), no peak around 120 ppm was found:

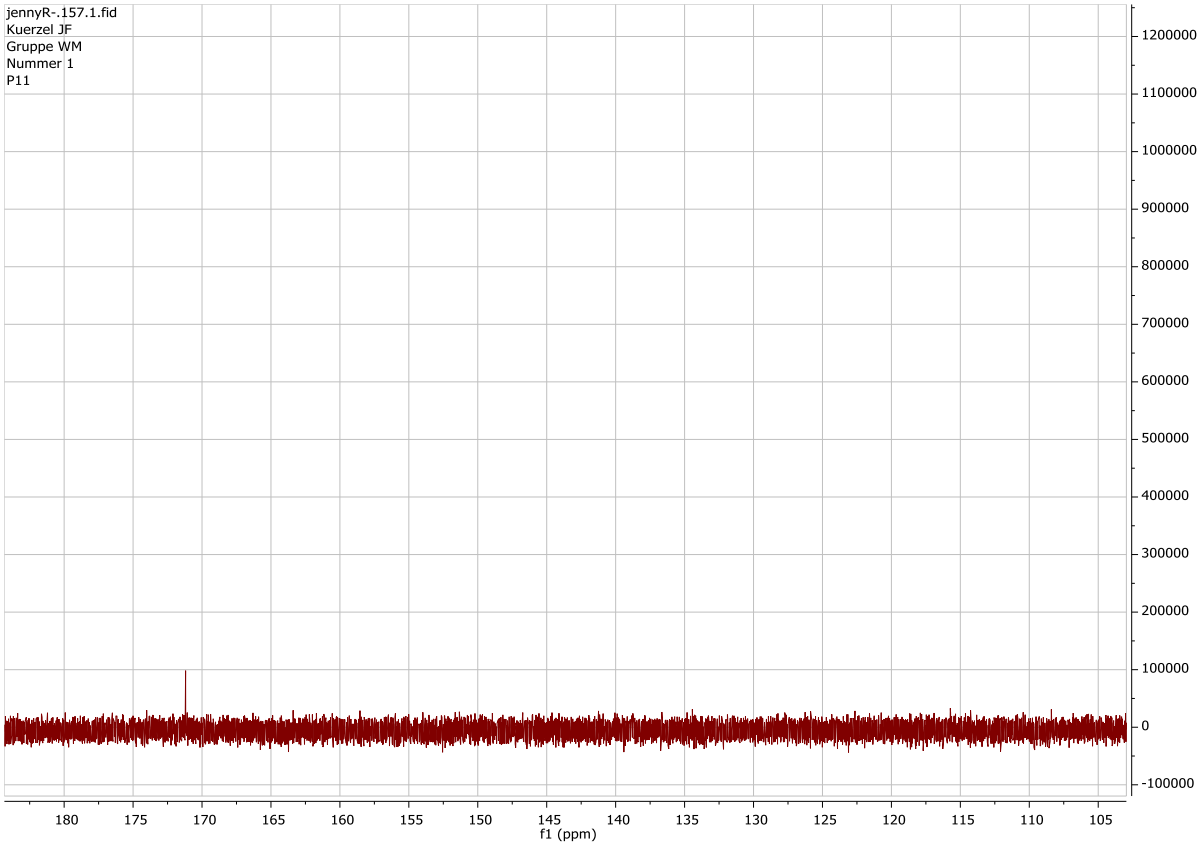


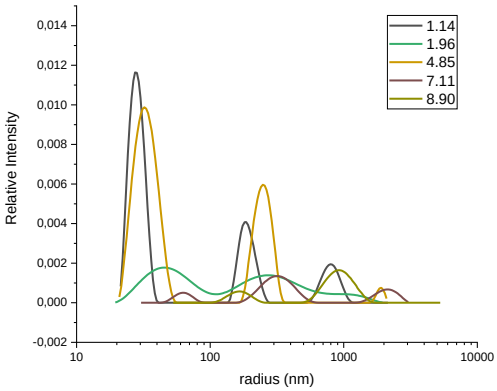
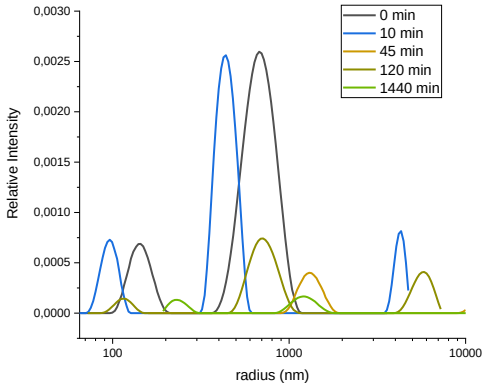
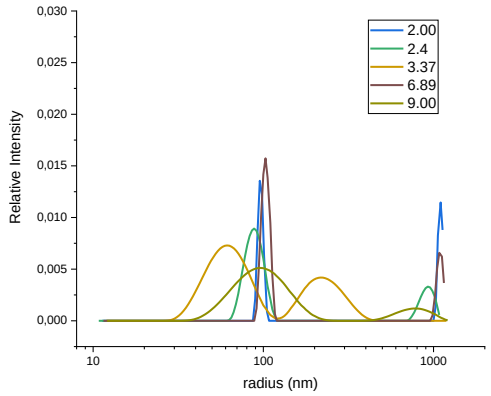
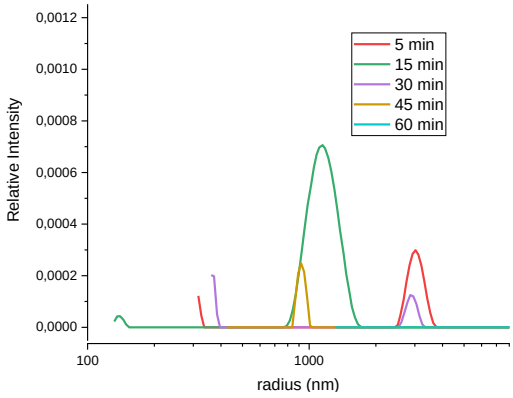
Figure S 29: ^{13}C-NMR spectrum of PEG-P(DMMDO-stat-i-MAC). This shows that no acetal peak is recorded.

4. Responsive behaviour of NPs

a. DLS for NPs

All nanoparticles disassemble upon either esterase or acidification. Besides the change in count rate (Figure 4 of the main paper and Figures S21 and S22). The following figure comprises the development of the DLS pages during the disassembly or digestions. The DLS settings are mentioned in the methods section. It should be noted that degradation can be seen in two ways. Either the relative intensity decreases as less material decreases (all except pH switch of PEG-P(i-MAC)) , or (if detected) the maxima move to smaller sizes (pH switch of PEG-P(i-MAC)).

*Table S1: Development of DLS traces (intensity plot) over the course of the degradations. Top: P(i-MAC) pH switch is left and esterase degradation on the right. Bottom: PEG-P(DMMDO-*stat*-i-MAC) pH switch is left a nd esterase degradation on the right.*

	pH switch	Esterase degradation
PEG-P(i-MAC)		
PEG-P(DMMDO-*stat*-i-MAC)		

b. pH responsive behaviour of the homopolymers

For the homopolymers, 3 mg of the polymer were dissolved in 2 mL of DI water, which was acidified with 1 M HCl to give a pH of 2. A stepwise addition of 10 µL of 0.01 M NaOH yielded the pH response, which was recorded after each addition.

For P(i-MAC), the results are included in Figure 4 of the main paper.

For P(i-DMMAC), they are displayed in the following figure:

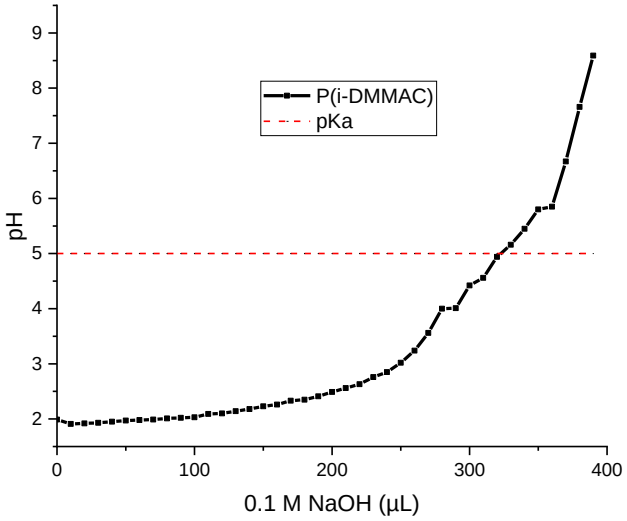


Figure S 30: Responsive behaviour of P(i-DMMAC), recorded by classic pH titration.

c. pH responsive behaviour of the homopolymers

As for the pH responsive behaviour of the nanoparticles, the following procedure was conducted:

In a vial, the amphiphilic block-copolymer PEG-P(i-MAC) or PEG-P(DMMDO-*stat*-i-MAC), 3.00 mg) was dissolved in chloroform (2 mL). The solvent was evaporated in a vacuum oven at 45 °C under a pressure of 300 mbar overnight. Afterwards, the pressure was reduced to 0 mbar for 1 h. The formed polymer film was rehydrated with H_2O (2 mL), which was filtered prior to use through a hydrophilic polytetrafluoroethylene (PTFE) syringe filter of 0.45 µm pore size. The suspension was stirred at 800 rpm at room temperature for at least 24 h. The count rates of the formed nanoparticles were assayed by DLS (see methods section for details).

The pH-responsiveness assay was applied on the self-assembled nanoparticles from both amphiphilic block-copolymers PEG-P(i-MAC) and PEG-P(DMMDO-*stat*-i-MAC). The aqueous nanoparticles suspension (1.5 mg/mL) was gradually acidified with a 0.1 M solution of HCl in 5 µL portions and the pH determined manually. A DLS measurement (see details in Methods) was conducted immediately after every titration point.

For PEG-P(DMMDO-*stat*-i-MAC), the results are included in Figure 4 of the main paper.

For nanoparticles from PEG-P(i-MAC), the data is displayed in the following Figure:

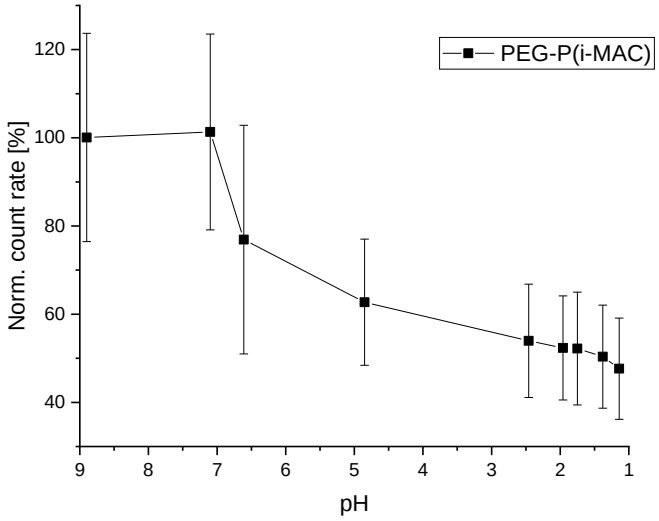


Figure S 31: pH responsive behaviour recorded for nanoparticles from PEG-P(i-MAC)

d. Esterase responsive behaviour

Formation of the nanoparticles: In a vial, the amphiphilic block-copolymer (PEG-P(i-MAC) or PEG-P(DMMDO-*stat*-i-MAC), 1.50 mg) was dissolved in chloroform (1 mL). The solvent was evaporated in a vacuum oven at 45 °C under a pressure of 300 mbar overnight. Afterwards, the pressure was reduced to 0 mbar for 1 h. The formed polymer film was rehydrated with PBS (1 mL), which was filtered prior to use through a hydrophilic polytetrafluoroethylene (PTFE) syringe filter of 0.45 µm pore size. The suspension was stirred at 800 rpm at room temperature for at least 24 h. The count rates of the formed nanoparticles were assayed by DLS (see methods section for details).

The following enzymatic degradation, i.e., biodegradation strategy was adopted from a previous work[2] and applied for the earlier self-assembled nanoparticles (see above) from both amphiphilic block copolymers PEG-P(i-MAC) and PEG-P(DMMDO-*stat*-i-MAC). Porcine liver esterase (PLE) (10 µL, 3.00 mg/mL in PBS, 2 wt% of the amphiphilic block copolymer) was added to the PBS solution of the earlier self-assembled nanoparticles. The mixture was heated to 35 °C with continuous stirring. The degradation progress of the nanoparticles was monitored by DLS (see methods section for details) over a period of 1.5 h for nanoparticles from PEG-P(i-MAC) and 24 h for nanoparticles from PEG-P(DMMDO-*stat*-i-MAC), respectively.

For PEG-P(DMMDO-*stat*-i-MAC), the results are included in Figure 4 of the main paper.

For nanoparticles from PEG-P(i-MAC), the data is displayed in the following Figure:

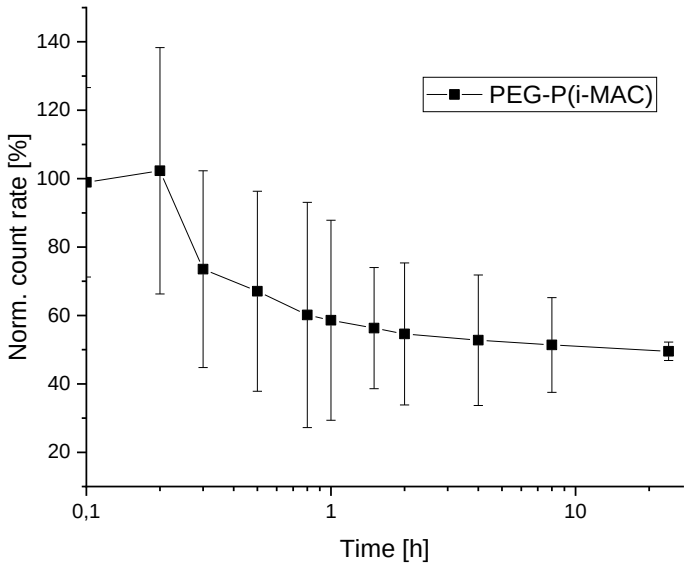


Figure S 32: Biodegradation of pH responsive nanoparticles from PEG-P(i-MAC)

5. References

[1] Petasis, N. A.; Lu, S. P., Methylenations of Heteroatom-Substituted Carbonyls with Dimethyl Titanocene, *Tetrahedron Lett.* **1995,** *36* (14), 2393-2396.

[2] Gaitzsch, J.; Welsch, P. C.; Folini, J.; Schoenenberger, C.-A.; Anderson, J. C.; Meier, W. P., Revisiting Monomer Synthesis and Radical Ring Opening Polymerization of Dimethylated MDO Towards Biodegradable Nanoparticles for Enzymes, *Eur. Polym. J.* **2018,** *101*, 113-119.

[3] Mistry, J. S.; Abraham, D. J.; Hanin, I., Neurochemistry of Aging .1. Toxins for an Animal-Model of Alzheimers-Disease, *J Med Chem* **1986,** *29* (3), 376-380.