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# Double hydrophilic poly(ethylene glycol)-*block*-poly(dehydroalanine)

## four-arm star block copolymers: synthesis and solution behavior

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**Figure S1:** Exemplary <sup>1</sup>H-NMR spectrum of *t*BAMA (CDCl<sub>3</sub>).



Figure S2: Exemplary <sup>13</sup>C-NMR spectrum of [PEG<sub>27</sub>-amide-Br]<sub>4</sub> (CDCl<sub>3</sub>).



**Figure S3:** Exemplary <sup>13</sup>C-NMR spectrum of [PEG<sub>27</sub>-*b*-P*t*BAMA]<sub>4</sub> (CDCl<sub>3</sub>).



**Figure S4:** Exemplary <sup>1</sup>H-NMR spectrum of [PEG<sub>56</sub>-amide-br]<sub>4</sub> (CDCl<sub>3</sub>).



Figure S5: Exemplary overlay of FTIR measurements of [PEG<sub>56</sub>-amide-Br]<sub>4</sub> and [PEG<sub>56</sub>-NH<sub>2</sub>]<sub>4</sub>.

## Dispersity optimization by added deactivator species

To overcome the loss of reaction control which results in higher D, the addition of different amounts of CuCl<sub>2</sub> as deactivator species was investigated. Figure S2A shows the corresponding SEC traces of the block copolymers obtained after 4 h of reaction time while Table S1 (entry 1-5) summarizes the conditions used up.

**Table S1** Reaction conditions used to synthesize  $[PEG_{27}-b-PtBAMA_y]_4$  via ATRP, showing the influence of amount deactivator and copper species used. Corresponding polymer properties are characterized by SEC and <sup>1</sup>H-NMR spectroscopy.

Entry	[I]	[Cu(I)X]	[Cu(II)X]	[tBAMA]	[L]	T [°C]	DPn, NMR /arm <sup>b</sup>	M <sub>n</sub> [g/mol] <sup>a</sup>	$[D]^{\mathrm{a}}$
		X= Cl	X=Cl		[TPMA]				
1	1	4	<u>0</u>	400	8	60	13	22,800	1.46
2	1	4	<u>0.6</u>	400	8	60	13	28,000	1.53
3	1	4	<u>1.2</u>	400	8	60	11	22,400	1.27
4	1	4	<u>2</u>	400	8	60	12	19,500	1.18
5	1	4	<u>2.4</u>	400	8	60	12	17,000	1.40
6	1	4	<u>2</u>	400	8	60	20	15,600	1.50
		X= Cl	<u>X= Br</u>						
7	1	4	2	400	8	60	9	16,000	1,25
		X= Br	X=Cl						
8	1	4	2	400	8	60	14	16,000	1.29
		X= Br	X=Br						
9	1	<u>4</u>	<u>2</u>	400	8	60	12	14,100	1.34

<sup>a</sup> Determined by SEC (eluent: DMAc/LiCl [99.79/0.21], PMMA calibration) and by <sup>b</sup> <sup>1</sup>H-NMR spectroscopy. All reactions use a monomer concentration= 0.63 mmol/mL (ratio: dioxane/*iso*-propanol=1:8).



**Figure S6** Comparison of experiments using different amounts of  $CuCl_2$  as deactivator species (A); Comparison of experiments showing the influence of different Cu(I) and Cu(II)-species (B).

## Influence of variation of Cu Species

In contrast to the CuCl/CuCl<sub>2</sub>-system introduced before we were interested in the influence of the copper species used on the reaction control and the resulting conversion. Several experiments were compared using all possible combinations of CuCl, CuBr, CuCl<sub>2</sub>, and CuBr<sub>2</sub>. All experiments were carried out for 21 h. The new reaction conditions are summed up in **Table S1 (entry 6-9)** and the corresponding SEC traces are shown in **Figure S2B**.

#### **Influence of Temperature**

Next to the alkyl halide<sup>1</sup>, temperature,<sup>2,3</sup> pressure<sup>4,5</sup>, and the solvent, especially the polarity of the media<sup>6</sup> has the most pronounced influence on the conduction of ATRP reactions. Several temperatures were used to investigate the influence on the CuCl/CuCl<sub>2</sub>-System (**Table S2** entry 1). Starting from room temperature (23 °C) the temperature was varied to 40, 50, 60 (used before), 70, or 80 °C (**Table S2** and **Figure S3A**).

Entry	[I]	[Cu(I)Cl]	[Cu(II)Cl]	[tBAMA]	[L]	T [°C]	DPn,NMR /arm <sup>b</sup>	M <sub>n</sub> [g∕mol]ª	$[D]^{\mathrm{a}}$
1	1	4	2	400	8	60	20	15,600	1.50
2	1	4	2	400	8	23	20	24,800	1.65
3	1	4	2	400	8	40	17	18,400	1.18
4	1	4	2	400	8	50	15	22,000	1.24
5	1	4	2	400	8	70	12	15,400	1.16
6	1	4	2	400	8	80	20	12,200	1.7

**Table S2** Reaction conditions used to synthesize  $[PEG_{27}-b-PtBAMA_y]_4$  via ATRP, showing the influence of temperature on the system. Corresponding polymer properties are characterized by SEC and <sup>1</sup>H-NMR spectroscopy.

<sup>a</sup> Determined by SEC (eluent: DMAc/LiCl [99.79/0.21], PMMA calibration) and by <sup>b</sup> <sup>1</sup>H-NMR spectroscopy. All reactions use a monomer concentration= 0.63 mmol/mL (ratio: dioxane/*iso*-propanol=1:8).



**Figure S7** SEC elution traces (eluent: DMAc/LiCl [99.79/0.21]) corresponding to temperature variation experiments of Table 2 (A); SEC elution traces (eluent: DMAc/LiCl [99.79/0.21]) corresponding to monomer concentration variation experiments (B, Table 3).

#### Influence of monomer concentration

To investigate the influence of initiator and monomer concentration on conversion and star-star coupling side reactions the monomer concentration was varied and the resulting polymers are compared *via* SEC and <sup>1</sup>H-NMR spectroscopy. **Table S3** summarizes the corresponding reactions performed. Starting with a monomer to initiator ratio of 1:400 the ratio was varied to either 1:200 or 1:100 keeping the initiator concentration constant. In contrast to that entry 4 of Table 3 describes a constant initiator to monomer ratio of 400:1 while the initiator concentration itself is halved. Figure 3 shows the corresponding SEC traces.

**Table S3** Reaction conditions used to synthesize  $[PEG_{27}-b-PtBAMA_y]_4$  via ATRP, showing the influence of monomer concentration on the system. Corresponding polymer properties are characterized by SEC and <sup>1</sup>H-NMR spectroscopy.

Entry	[I]	[Cu(I)Cl]	[Cu(II)Cl]	[tBAMA]	[L]	T [°C]	DPn,NMR /arm <sup>b</sup>	M <sub>n</sub> [g/mol]ª	$[D]^{\mathrm{a}}$
1	1	4	<u>2</u>	400	8	60	20	15,600	1.50
2	1	4	2	200	8	60	19	13,200	1,15
3	1	4	2	100	8	60	8	13,000	1,09
4	1	4	2	400	8	60	28	20,800	1.8

<sup>a</sup> Determined by SEC (eluent: DMAc/LiCl [99.79/0.21], PMMA calibration) and by <sup>b</sup> <sup>1</sup>H-NMR spectroscopy. All reactions use a solvent ratio of dioxane/*iso*-propanol=1:8 and a initiator concentration of 1.55 μmol/mL (expect entry 4 which is using a initiator concentration of 0.77 μmol/mL).

#### The right solvent: Key between long and short chains

Besides the temperature, the type of solvent used plays an important role in terms of reaction kinetics.<sup>6</sup> Therefore, different ratios of dioxane and *iso*-propanol as well as the use of pure alcohols with different polarities as reaction solvent were compared. Hence, we decided to use ethanol as a more polar solvent and 1-octanol as a rather unpolar solvent when compared to *iso*-propanol. **Figure S4A** shows the corresponding SEC-traces for the ratio variation at dioxane/*iso*-propanol systems while **Figure S4B** shows the SEC-traces of reaction variation using either pure ethanol, *iso*-propanol or 1-octanol as a reaction solvent. All reactions were performed under the same ratios of *t*BAMA:TPMA:CuCl: initiator = 400:8:4:1 with a monomer concentration of 0.63 mmol/mL for 4 h at 60 °C, except for the solvent variation discussed. In addition, the reaction in pure *iso*-propanol, used room temperature instead of 60 °C, which is why it can only serve as a limited comparison reaction considering that in our case lower

temperatures are associated with higher D but comparable conversions to the one at 60 °C (see influence of temperature).

**Table S4** Reaction conditions used to synthesize  $[PEG_{27}-b-PtBAMA_y]_4$  via ATRP, showing the influence of solvent media used on the system. Corresponding polymer properties are characterized by SEC and <sup>1</sup>H-NMR spectroscopy.

Entry	Solvent [mL]	Cosolvent [mL]	Initatorconcentratio n [µmol/mL]	T [°C]	DPn,NMR/arm	$M_{ m n}[ m g/mol]^{ m a}$	$[D]^{a}$
1	Dioxane 0.5	Iso-propanole 4	1.55	60	20	15,600	1.50
2	Dioxane 2.25	Iso-propanole 2.25	1.55	60	32	16,300	2,72
3	Dioxane 4	Iso-propanole 0.5	1.55	60	16	13,100	2,02
4	Iso-propanol 4.5	-	1.55	23	20	23,900	1,76
5	Octanole 4.5	-	1.55	60	41	37,000	1.87
6	Ethanol 4.5	-	1.55	60	3	11,700	1.17

<sup>a</sup> Determined by SEC (eluent: DMAc/LiCl [99.79/0.21], PMMA calibration) and by <sup>b</sup> <sup>1</sup>H-NMR spectroscopy. All reactions use a monomer concentration= 0.63 mmol/mL (ratio: dioxane/*iso*-propanol=1:8).



**Figure S8** SEC elution traces (eluent: DMAc/LiCl [99.79/0.21]) showing the influence of ratio variation between the amounts of dioxan and iso-propanol used (A); SEC elution traces (eluent: DMAc/LiCl [99.79/0.21]) of reaction variation using either pure ethanol, iso-propanol, or octanol as a reaction solvent (B).

#### **Towards increasing conversion**

As shown before, the use of different solvents at 60 °C reaction temperature and a CuCl/CuCl<sub>2</sub> system reveal that the conversion can be drastically increased if pure alcohol with longer alkyl chains serves as solvent (ethanol < iso-propanol < 1-octanol). Additionally, with the higher conversion, the reaction lacks control due to the appearance of more star-star coupling side reactions which can be observed *via* SEC. As already mentioned before, alcohols as solvents are well known to promote the disproportionation of Cu(I)X into Cu(0) and Cu(II)X which is a crucial step in SET-LRP.<sup>7</sup> Additionally, more recent work of avoiding star-star coupling reactions show that Cu(0) mediated controlled radical polymerization techniques combine high-end group fidelity with fewer star-star coupling reactions observed.<sup>8-11</sup> To overcome the problem of star-star-coupling observed in **Figure S4A** the reaction type was changed from ATRP to SET-LRP, comparing *iso*-propanol and 1-octanol as solvent. **Table S5** sums up the reaction conditions used and **Figure S5** shows the corresponding SEC traces.



**Figure S9** SEC-traces (eluent: DMAc/LiCl [99.79/0.21]) comparing different solvents used for block extension of [PEG<sub>27</sub>-amide-Br]<sub>4</sub> with tBAMA via SET-LRP reactions.

**Table S5** Reaction conditions used to synthesize [PEG<sub>27</sub>-*b*-P*t*BAMA<sub>y</sub>]<sub>4</sub> *via* SET-LRP, showing the influence of solvent used. The corresponding block copolymer characteristics were determined by SEC and <sup>1</sup>H-NMR spectroscopy.

Entry	[I]	[Cu(0)]	[Cu(II)Cl ]	[tBAMA]	[L]	T [°C]	DPn,NMR /arm	$M_{\rm n}$ [g/mol]	[D]	Reaction time
1	1	4	0.8	400	8	RT	41	27,800	1.37	48 h
2	1	4	0.4	400	8	RT	70	69,400	2.49	24 h

<sup>a</sup> Determined by SEC (eluent: DMAc/LiCl [99.79/0.21], PMMA calibration) and by <sup>b</sup> <sup>1</sup>H-NMR spectroscopy. All reactions use a monomer concentration= 0.63 mmol/mL and either *iso*-propanol (entry 1) or 1-octanol (entry 2) as solvent.



**Figure S10** Example <sup>1</sup>H-NMR of [PEG<sub>56</sub>-amide-Br] before (A) treatment with TFA at 50 °C for 10 and after (**B**) using CDCl<sub>3</sub>.



**Figure S11** Potentiometric titration of  $[PEG_{27}-b-PDha_{41}]_4$  dissolved in 0.1 M NaOH at a concentration of 0.2 mg/mL and titrated with 0.1 M HCl; **B**: Zoom of Figure S9A in the range of 8-16 mL; **C**:  $\zeta$ -Potential of  $[PEG_{27}-b-PDha_{41}]_4$  at different pH values determined by titration.

## **Dynamic Light Scattering**

The amplitude correlation functions  $g^{(1)}(q,t)$  received from the DLS were fitted with a biexponential function

$$g^{(1)}(q,\tau) = A_1 \cdot exp\left(-\frac{\tau}{\tau_{R,1}}\right) + A_2 \cdot exp\left(-\frac{\tau}{\tau_{R,2}}\right),$$

,where  $A_i$  is the amplitude and  $\tau_{R,i}$  with i =1,2 is the characteristic relaxation time of the corresponding process. The diffusion coefficient is extracted from the relaxation time using the scattering vectors q of the respective scattering angle.

$$D = \left(\frac{1}{\tau_{R,i} \cdot q^2}\right)$$

The hydrodynamic radii are calculated using the Stokes-Einstein equation

$$R_H = \frac{k_B T}{6\pi\eta_s D}$$

with the Boltzmann constant  $k_B$ , the absolute temperature T, and the viscosity of the solvent  $\eta_s$ . The results of this analysis are summarized in **Table S6**.

Polymer	A <sub>1</sub>	R <sub>H,1</sub> (nm)	A <sub>2</sub>	R <sub>H,2</sub> (nm)	рН
[PEG <sub>27</sub> -b-PDha <sub>6</sub> ] <sub>4</sub>	0,21	29	0,79	92	13,0
[PEG <sub>27</sub> -b-PDha <sub>20</sub> ] <sub>4</sub>	0,28	27	0,72	72	13,0
$[PEG_{27}-b-PDha_{41}]_4$	0,26	26	0,74	73	13,1
[PEG <sub>55</sub> -b-PDha <sub>6</sub> ] <sub>4</sub>	0,21	22	0,78	76	13,1
[PEG <sub>112</sub> -b-PDha <sub>7</sub> ] <sub>4</sub>	0,27	21	0,73	69	13,1
[PEG <sub>27</sub> -b-PDha <sub>6</sub> ] <sub>4</sub>	0,70	88	0,30	242	5,1
[PEG <sub>27</sub> -b-PDha <sub>20</sub> ] <sub>4</sub>	0,39	21	0,61	163	5,0
$[PEG_{27}-b-PDha_{41}]_4$	0,43	23	0,56	102	4,9
[PEG55-b-PDha6]4	0,35	66	0,65	200	4,9
[PEG <sub>112</sub> -b-PDha <sub>7</sub> ] <sub>4</sub>	0,29	30	0,71	163	5,0
[PEG <sub>27</sub> -b-PDha <sub>6</sub> ] <sub>4</sub>	0,60	115	0,40	721	3,0
[PEG <sub>27</sub> -b-PDha <sub>20</sub> ] <sub>4</sub>	0,76	44	0,24	533	3,0
$[PEG_{27}-b-PDha_{41}]_4$	0,10	305	0,90	3550	3,0
[PEG <sub>55</sub> -b-PDha <sub>6</sub> ] <sub>4</sub>	0,60	64	0,40	383	2,9
[PEG <sub>112</sub> -b-PDha <sub>7</sub> ] <sub>4</sub>	0,41	50	0,59	235	2,9

**Table S6** Amplitudes  $(A_1, A_2)$  of the biexponential fits and extracted hydrodynamic radii at a scattering angle of 90° and c= 0.2 mg/mL corresponding to figure 4A. The correlation functions were normalized to unity.



**Figure S12** AFM height image showing the size distributions of  $[PEG_{27}-b-PDha_6]_4$  aggregates at pH=13 at a concentration of 1.0 mg/mL (A). Zoomed in AFM height image for the region marked by the green box in A (B); AFM height image showing the size distributions of  $[PEG_{27}-b-PDha_{41}]_4$  aggregates at pH=3 at a concentration of 1.0 mg/mL (C).



**Figure S13A** and **C** AFM height images showing the size distributions of  $[PEG_{27}-b-PDha_{41}]_4$  aggregates at pH= 3 (Figure S10B) and pH=13 (Figure S10A) at a concentration of 0.2 mg/mL respectively. **B**: Zoomed in AFM height image for the region marked by the green box in A. **D**: Zoomed in AFM height image for the region marked by the green box in C.

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