Core-shell inversion by pH modulation in dynamic covalent micelles

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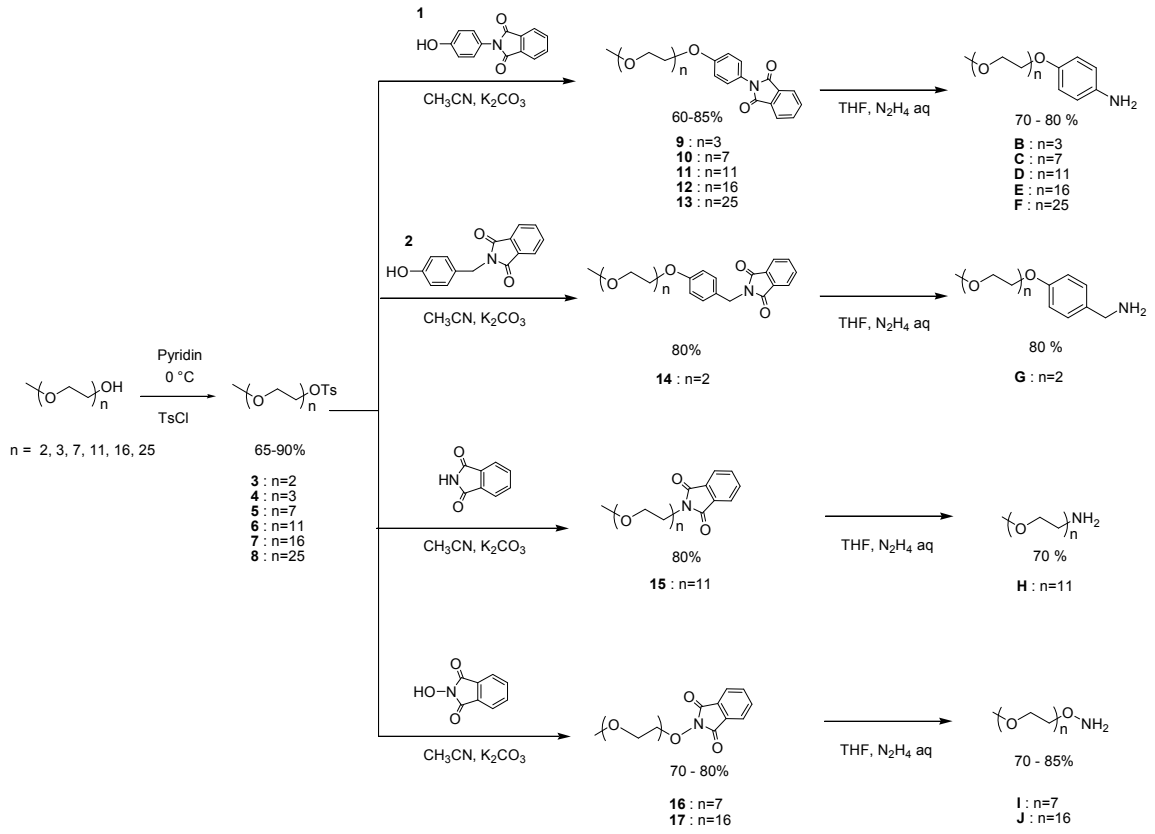
Synthesis

General aspects.

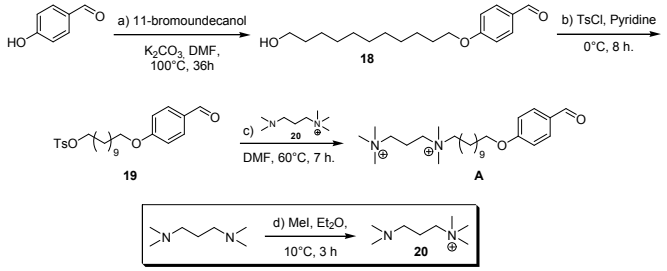
All *reagents and solvents* were purchased at the highest commercial quality and used without further purification unless otherwise noted. Dry solvents were obtained using a double column SolvTech purification system. Yields refer to purified spectroscopically (^{1}H NMR) homogeneous materials. *Thin Layer Chromatographies* were performed with TLC silica plastic sheets (Polygram SIL G/UV$_{254}$, Macherey-Nagel). In most cases, irradiation using a *Bioblock VL-4C* UV-Lamp (6 W, 254 nm and/or 365 nm) as well as Ce-molybdate stainings were used for visualization. *Preparative Adsorption Flash Column Chromatographies* were performed using silica gel (Geduran, silica gel 60 (230 – 400 mesh, 40 – 63 µm, Merck)). *Ultra Performance Liquid Chromatographies coupled to Mass Spectroscopy* (UPLC-MS) were carried out on a *Waters Acquity UPLC-SQD* apparatus equipped with a PDA detector (190-500 nm, 80Hz), using a reverse phase column (Waters, BEH C18 1.7 µm, 2.1mm x 50 mm), and the MassLynx 4.1 – XP software. *^{1}H NMR spectra* were recorded on a *Bruker Avance 400* spectrometer at 400 MHz and ^{13}C spectra at 100 MHz in $CDCl_3$ (or MeOD) at 25°C. The spectra were internally referenced to the residual proton solvent signal. For ^{1}H NMR assignments, the chemical shifts are given in ppm. Coupling constants *J* are listed in Hz. The following notation is used for the ^{1}H NMR spectral splitting patterns: singlet (s), doublet (d), triplet (t), multiplet (m), large (l). *Microanalyses* were performed by the Service de Microanalyse, Institut Charles Sadron, CNRS.

Synthetic Pathways.

The general synthetic pathway of hydrophilic blocks (Scheme 1) starts from the tosylation of the hydroxy group of the monomethylether PEG in order to get an efficient leaving group for the subsequent nucleophilic substitution (3 - 8). The resulting tosylate is then substituted by a phtalimide derivative (amine protected group) in the presence of a base and in acetonitrile at reflux. Depending on the nature of the amine that we would like to enter on the PEG, four different phtalimide groups were used. At this stage, the conditions of this substitution reaction could differ depending on the size of the PEG (**9 - 17**). After a deprotection reaction in THF using aqueous hydrazine (N_2H_4 aq), the corresponding amino-PEGs (**B – J**) were obtained with suitable overall yields. The charged hydrophobic aldehyde A was synthesized using a dissymmetric bifunctionalyzed aliphatic chain, namely 11-bromoundecanol. Nucleophilic substitution was first performed between this compound and 4-hydroxybenzaldehyde (Scheme 13) and dissymmetric compound **18** containing a benzaldehyde group was obtained. Alcohol 18 was then tosylated into compound **19**, which was substituted by a charged diammonium group to obtain the charged hydrophobic aldehyde A as a salt with tosylate counter anions. This diammonium group (**20**) was obtained from the di-tertiary amine N,N,N',N'-tetramethylpropane-1,3-diamine (TMPDA) by methylation with iodomethane in ether (scheme 2).



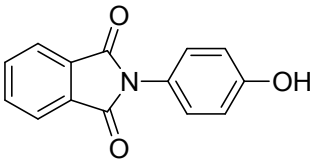
Scheme 1: General scheme for the functionalization of PEG with amine groups. Only simple reactions are involved and products are obtained a gram scale quantities without any heavy purification step.



Scheme 2: Synthesis of charged hydrophobic aldehyde A

Characterization of organic molecules.

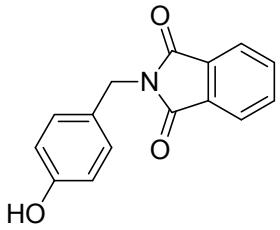
Compound 1 : 2-(4-hydroxyphenyl)isoindoline-1,3-dione



A mixture of 4-aminophenol (14.6 g, 133 mmol) and phthalic anhydride (20 g, 135 mmol) in DMF (100 mL) was vigorously stirred for 6 h at 90°C. Distilled water (400 mL) was added and the reaction mixture was filtered. The residue was dissolved and heated in methanol (100 mL) at 30°C for 1 hour. After cooling to room temperature, the precipitate was filtered and pure compound **1** (28.6 g, 90%) was obtained as a white solid. A second treatment with methanol may be needed to obtain a clear white product.

^{1}H NMR in $CDCl_3$: 7.94 (m, 2H), 7.78 (m, 2H), 7.30 (d, ^{3}J = 8.8 Hz, 2H), 6.95 (d, ^{3}J = 8.8 Hz, 2H); ^{1}H NMR in DMSO: 9.77 (s, 1H), 7.93 (m, 2H), 7.88 (m, 2H), 7.21 (d, ^{3}J = 8.7, 2H), 6.88 (d, ^{3}J = 8.7, 2H); ^{13}C NMR in DMSO: 167.43, 157.32, 134.64, 131.61, 128.84, 123.31, 122.85, 115.42; Anal. calcd. for $C_{14}H_9NO_3$: C 70.29, H 3.79, N 5.86; found C 67.70, H 4.06, N 5.80.

Compound 2 : 2-(4-hydroxybenzyl)isoindoline-1,3-dione



A mixture of 4-hydroxybenzylamine (46 mmol; 5.66 g) and phtalic anhydride (46 mmol; 6.8 g) in DMF (20 mL) was stirred overnight under reflux. Distilled water (100 mL) was added to the reaction mixture and pure compound **9** (11.3 g, 97%) precipitated as a white solid (m.p. = 204-206°C).

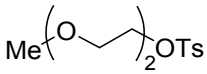
^{1}H NMR in $CDCl_3$: 7.83 (m, 2H), 7.69 (m, 2H), 7.33 (d, ^{3}J = 8.5 Hz, 2H), 6.76 (d, ^{3}J = 8.5 Hz, 2H), 4.77 (s, 2H), 4.74 (s, 1H); ^{13}C NMR in $CDCl_3$: 168.10, 155.20, 133.94, 132.15, 130.37, 128.82, 123.30, 115.42, 41.02; Anal. calcd. for $C_{15}H_{11}NO_3$: C 71.14, H 4.38, N 5.53; found C 70.71, H 4.45, N 5.68; HRMS (ESI-TOF): calcd for $C_{15}H_{11}NO_3$ 260.089 $[M+Li]^+$; found 260.090.

General procedure for the tosylation of monomethylether polyethylenglycol compounds (n=2 to 11)

Monomethylether polyethylene glycol (1 eq.) was dissolved in pyridine (1 mL for 1 g of PEG approx.) at 0°C. A solution of tosyl chloride (1.2 eq.) in pyridine (0.3 mL for 1 mmol of tosyl chloride) was then added slowly at 0ºC. The mixture was stirred for 4 to 8 h at 0ºC, and treated by adding ice with a 6N HCl solution (5 mL for 1 mL of the total volume of pyridine). The mixture was extracted three times with dichloromethane and the organic layer was washed with a 2N HCl solution. The organic layer was dried with magnesium sulfate and evaporated to provide pure tosylated compounds as clear yellow oil (92% - 97%).

General procedure for the tosylation of monomethylether polyethylenglycol compounds (n=16 to 25)

Monomethylether polyethylene glycol (1 eq.) was dissolved in pyridine (1 mL for 1 g of PEG approx.) with a small amount of dichloromethane at 0°C. A solution of tosyl chloride (2 eq.) in pyridine (0.3 mL for 1 mmol of tosyl chloride) was then added in two portions at 0ºC (30 min between each addition). The mixture was stirred for 6 to 8 h at 0ºC, and treated by adding ice with a 6N HCl solution (5 mL for 1 mL of the total volume of pyridine). The mixture was extracted three times with dichloromethane and the organic layer was washed with a 2N HCl solution. The organic layer was dried with magnesium sulfate and evaporated to provide pure tosylated compounds as clear yellow oil (91% - 94%).



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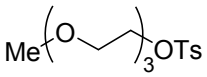
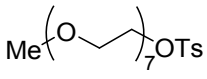
^{1}H NMR in $CDCl_3$: 7.75 (d, ^3J = 8.4 Hz, 2H), 7.30 (d, ^3J = 8 Hz, 2H), 4.12 (t, ^3J = 4.8 Hz, 2H), 3.64 (t, ^3J = 4.8 Hz, 2H), 3.54 (m, 2H), 3.44 (m, 2H), 3.30 (s, 3H), 2.41 (s, 3H); ^{13}C NMR in $CDCl_3$: 144.82, 132.96, 129.96, 127.96, 71.78, 70.63, 69.25, 68.67, 58.99, 21.60; ESI-MS: calcd for $C_{12}H_{18}O_5S$ 275.09 $[M+H]^+$; found 275.23.



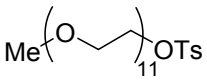
4

^{1}H NMR in $CDCl_3$: 7.77 (d, ^3J = 8.4 Hz, 2H), 7.32 (d, ^3J = 8.2 Hz, 2H), 4.14 (t, ^3J = 4.8 Hz, 2H), 3.67 (t, ^3J = 4.8 Hz, 2H), 3.59 (m, 6H), 3.51 (m, 2H), 3.35 (s, 3H), 2.43 (s, 3H); ^{13}C NMR in $CDCl_3$: 144.81, 133.02, 129.76, 128.01, 71.90, 70.74, 70.55, 69.24, 68.67, 59.02, 21.63; ESI-MS: calcd for $C_{14}H_{22}O_6S$ 319.11 $[M+H]^+$; found 319.28.



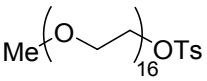
5

^{1}H NMR in $CDCl_3$: 7.76 (d, ^3J = 8.4 Hz, 2H), 7.31 (d, ^3J = 8.3 Hz, 2H), 4.12 (t, ^3J = 4.8 Hz, 2H), 3.66 (t, ^3J = 5.0 Hz, 2H), 3.58 (brm, 26H), 3.34 (s, 3H), 2.41 (s, 3H); ^{13}C NMR in $CDCl_3$: 144.66, 132.90, 129.70, 127.84, 71.80, 70.60, 70.47, 70.43, 70.37, 69.13, 68.54, 58.88, 21.50. Anal. calcd. for $C_{22}H_{38}O_{10}S$: C 53.42, H 7.74, S 6.48; found C 52.65, H 7.82, S 5.93; ESI-MS: calcd for $C_{22}H_{38}O_{10}S$ 495.22 $[M+H]^+$; found 495,45.



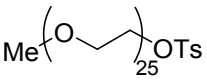
6

^{1}H NMR in $CDCl_3$: 7.76 (d, ^3J = 8.4 Hz, 2H), 7.30 (d, ^3J = 8.3 Hz, 2H), 4.12 (t, ^3J = 4.8 Hz, 2H), 3.64 (t, ^3J = 5 Hz, 2H), 3.62 (m, 6H), 3.60 (m, 24H), 3.57 (m, 4H), 3.54 (m, 4H), 3.51 (m, 2H), 3.34 (s, 3H), 2.41 (s, 3H); ^{13}C NMR in $CDCl_3$: 144.77, 133.02, 129.82, 127.96, 71.92, 70.72, 70.55, 70.49, 69.25, 68.67, 59.01, 21.63; ESI-MS: calcd for $C_{30}H_{54}SO_{14}$ 688.34 $[M+H_2O]^+$; found 688.58.



7

^{1}H NMR in $CDCl_3$: 7.79 (d, ^3J = 8.4 Hz, 2H), 7.33 (d, ^3J = 8.3 Hz, 2H), 4.14 (t, ^3J = 4.8 Hz, 2H), 3.67 (t, ^3J = 4.8 Hz, 2H), 3.64 (m, 6H), 3.62 (m, 44H), 3.60 (m, 4H), 3.56 (m, 4H), 3.53 (m, 2H), 3.37 (s, 3H), 2.44 (s, 3H); ^{13}C NMR in $CDCl_3$: 144.78, 133.05, 129.83, 127.99, 71.94, 70.75, 70.57, 70.51, 69.25, 68.69, 59.04, 21.66; ESI-MS: calcd for $C_{40}H_{74}SO_{19}$ 908.47 $[M+H_2O]^+$; found 908.90.



8

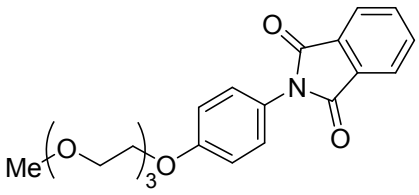
^{1}H NMR in $CDCl_3$: 7.76 (d, ^3J = 8.4 Hz, 2H), 7.31 (d, ^3J = 8.3 Hz, 2H), 4.12 (t, ^3J = 4.8 Hz, 2H), 3.62 (m, 92H), 3.54 (m, 4H), 3.50 (m, 2H), 3.34 (s, 3H), 2.41 (s, 3H); ^{13}C NMR in $CDCl_3$: 144.79, 132.99, 129.82, 127.96, 71.89, 70.70, 70.50, 69.25, 68.67, 59.03, 21.63; ESI-MS: calcd for $C_{58}H_{110}SO_{28}$ 1304.70 $[M+H_2O]^+$; found 1305.14.

General procedure for the substitution of the tosylate with aromatic phthalimide 1 (n = 3 to 7).

Compound **1** (1.2 eq.) was dissolved in acetonitrile (35 mL for 1 g of **1**) and the solution was heated up to reflux. Potassium carbonate (1.2 eq.) was then added followed by the tosylated polyethylene glycol (1 eq.). The mixture was stirred for 12 h at reflux. The solvent was then evaporated and water was added. The aqueous mixture was extracted three times with dichloromethane. The resulting organic phase was then washed with a pH 12 aqueous solution, dried with magnesium sulfate and further evaporation under reduced pressure afforded pure compound (75% - 90%).

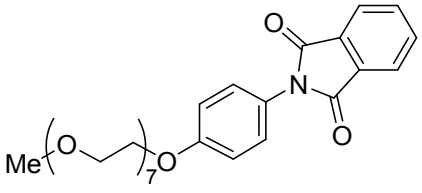
General procedure for the substitution of the tosylate with aromatic phthalimide 1 (n = 11 to 25).

Compound **1** (2.5 eq.) was dissolved in acetonitrile (25 mL for 1 g of **1**) and the solution was heated up to reflux. Potassium carbonate (3.5 eq.) was then added followed by the tosylated polyethylene glycol (1 eq.). The mixture was stirred for 6 to 10 h at reflux. The solvent was then evaporated and water was added. The aqueous mixture was extracted three times with dichloromethane. The resulting organic phase was then washed with a pH 12 aqueous solution, dried with magnesium sulfate and further evaporation under reduced pressure afforded pure compound (65% - 80%).



9

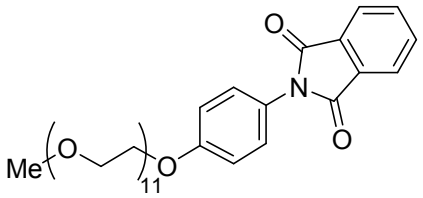
^{1}H NMR in $CDCl_3$: 7.94 (m, 2H), 7.78 (m, 2H), 7.32 (d, ^{3}J = 9.2 Hz, 2H), 7.04 (d, ^{3}J = 9,2 Hz, 2H), 4.17 (t, ^{3}J = 5.2 Hz, 2H), 3.88 (t, ^{3}J = 5.2 Hz, 2H), 3.75 (m, 2H), 3.67 (m, 4H), 3.56 (m, 2H), 3.33 (s, 3H); ^{13}C NMR in $CDCl_3$: 167.52, 158.46, 134.33, 131.84, 127.91, 124.57, 123.68, 115.13, 71.97, 70.90, 70.70, 70.62, 69.64, 67.69, 59.09; ESI-MS: calcd $C_{21}H_{23}NO_6$ 386.15 $[M+H]^+$; found 386.37.



10

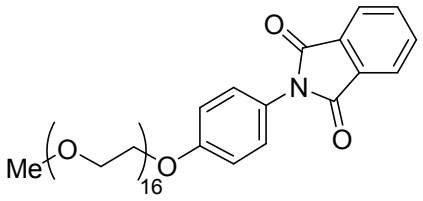
^{1}H NMR in $CDCl_3$: 7.94 (m, 2H), 7.78 (m, 2H), 7.32 (d, ^{3}J = 9.2 Hz, 2H), 7.03 (d, ^{3}J = 9.2 Hz, 2H), 4.17 (t, ^{3}J = 5.2 Hz, 2H), 3.87 (t, ^{3}J = 5.2 Hz, 2H), 3.73 (m, 2H), 3.64 (m, 20H), 3.54 (m, 2H), 3.37 (s, 3H); ^{13}C NMR in

$CDCl_3$: 167.54, 158.42, 134.31, 131.82, 127.90, 124.56, 123.68, 115.17, 71.95, 70.92, 70.67, 70.59, 69.65, 67.72, 59.07; ESI-MS: calcd $C_{29}H_{39}NO_{10}$ 579.27 $[M+H_2O]^+$; found 579.60.



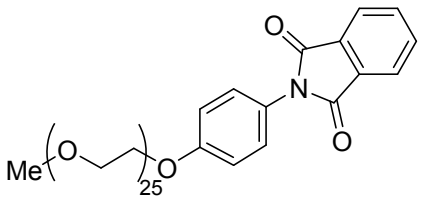
11

^{1}H NMR in $CDCl_3$: 7.94 (m, 2H), 7.78 (m, 2H), 7.32 (d, ^3J = 9.2 Hz, 2H), 7.03 (d, ^3J = 9.2 Hz, 2H), 4.17 (t, ^3J = 5.2 Hz, 2H), 3.87 (t, ^3J = 5.2 Hz, 2H), 3.73 (m, 2H), 3.64 (m, 36H), 3.54 (m, 2H), 3.37 (s, 3H); ^{13}C NMR in $CDCl_3$: 167.54, 158.47, 134.31, 131.84, 127.91, 124.57, 123.68, 115.18, 71.94, 70.88, 70.65, 70.57, 69.65, 67.74, 59.05; ESI-MS: calcd $C_{37}H_{55}NO_{14}$ 755.38 $[M+H_2O]^+$; found 755.75.



12

^{1}H NMR in $CDCl_3$: 7.94 (m, 2H), 7.78 (m, 2H), 7.33 (d, ^3J = 9.0 Hz, 2H), 7.02 (d, ^3J = 9.0 Hz, 2H), 4.18 (t, ^3J = 5.2 Hz, 2H), 3.87 (t, ^3J = 5.0 Hz, 2H), 3.73 (m, 2H), 3.68 (m, 56H), 3.54 (m, 2H), 3.37 (s, 3H); ^{13}C NMR in $CDCl_3$: 167.54, 158.46, 134.33, 131.83, 127.90, 124.56, 123.68, 115.15, 71.96, 70.87, 70.57, 69.65, 67.73, 59.07.

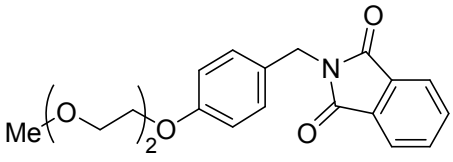


13

^{1}H NMR in $CDCl_3$: 7.94 (m, 2H), 7.78 (m, 2H), 7.32 (d, ^3J = 9.2 Hz, 2H), 7.03 (d, ^3J = 9.2 Hz, 2H), 4.18 (t, ^3J = 5.0 Hz, 2H), 3.88 (t, ^3J = 5.0 Hz, 2H), 3.75 (m, 2H), 3.64 (m, 92H), 3.54 (m, 2H), 3.38 (s, 3H).

General procedure for the substitution of the tosylate with benzylic phthalimide 2 (n = 2).

Compound **2** (1.2 eq.) was dissolved in acetonitrile (35 mL for 1 g of **3**) and the solution was heated up to reflux. Potassium carbonate (1.2 eq.) was then added followed by the tosylated polyethylene glycol (1 eq.). The mixture was stirred for 10 h at reflux. The solvent was then evaporated and water was added. The aqueous mixture was extracted three times with dichloromethane. The resulting organic phase was then washed with a pH 12 aqueous solution, dried with magnesium sulfate and further evaporation under reduced pressure afforded pure compound (72% - 78%).

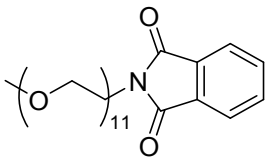


14

^{1}H NMR in $CDCl_3$: 7.83 (m, 2H), 7.69 (m, 2H), 7.36 (d, ^{3}J = 8.8 Hz, 2H), 6.85 (d, ^{3}J = 8.8 Hz, 2H), 4.77 (s, 2H), 4.10 (t, ^{3}J = 4.0 Hz, 2H), 3.83 (t, ^{3}J = 4.8 Hz, 2H), 3.69 (m, 2H), 3.55 (m, 2H), 3.37 (s, 3H); ^{13}C NMR in $CDCl_3$: 168.09, 158.41, 133.94, 132.18, 130.1, 128.70, 123.30, 114.73, 71.95, 70.75, 69.71, 67.43, 59.09, 41.07; ESI-MS: calcd $C_{20}H_{21}NO_5$ 356.15 $[M+H]^+$; found 356.28.

General procedure for the substitution of the tosylate with phthalimide (n = 11)

Phhtalimide (2.0 eq.) was dissolved in acetonitrile (30 mL for 1 g of phthalimid) and the solution was heated up to reflux. Potassium carbonate (3.0 eq.) was then added followed by the tosylated polyethylene glycol (1.0 eq.). The mixture was stirred for 6 to 10 h at reflux. The solvent was then evaporated and water was added. The aqueous mixture was extracted three times with dichloromethane. The resulting organic phase was then washed with a pH 12 aqueous solution, dried with magnesium sulfate and further evaporation under reduced pressure afforded pure compound

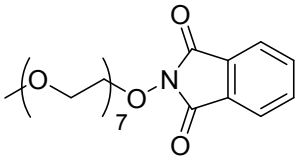


15

^{1}H NMR in $CDCl_3$: 7.83 (m, 2H), 7.70 (m, 2H), 3.88 (t, ^{3}J = 5.8 Hz, 2H), 3.73 (t, ^{3}J = 5.8 Hz, 2H), 3.63 (m, 40H), 3.37 (s, 3H); ^{13}C NMR in $CDCl_3$: 168.24, 133.92, 132.14, 123.24, 71.94, 70.57, 70.09, 67.92, 59.05, 37.28; ESI-MS: calcd $C_{31}H_{51}NO_{13}$ 663.34 $[M+H_2O]^+$; found 663.68.

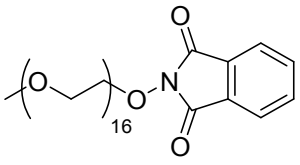
General procedure for the substitution of the tosylate with *N*-hydroxyphthalimide

N-hydroxyphthalimide (1.2 eq.) was dissolved in acetonitrile (20 mL for 1 g of *N*-hydroxyphthalimide) and the solution was heated up to reflux. Triethylamine (1.2 eq.) was then added followed by the tosylated polyethylene glycol (1.0 eq.). The mixture was stirred for 10 h at reflux. The solvent was then evaporated and water was added. The aqueous mixture was extracted three times with dichloromethane. The resulting organic phase was then washed with a pH 12 aqueous solution, dried with magnesium sulfate and further evaporation under reduced pressure afforded pure compound (70% - 80%).



16

^{1}H NMR in $CDCl_3$: 7.84 (m, 2H), 7.74 (m, 2H), 4.37 (t, ^{3}J = 4.4 Hz, 2H), 3.86 (t, ^{3}J = 4.4 Hz, 2H), 3.63 (m, 24H), 3.37 (s, 3H); ^{13}C NMR in $CDCl_3$: 163.42, 134.40, 129.00, 123.48, 77.21, 71.93, 70.78, 70.56, 70.51, 69.27, 59.02.



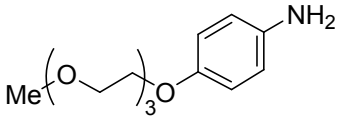
17

^{1}H NMR in $CDCl_3$: 7.83 (m, 2H), 7.74 (m, 2H), 4.37 (t, ^{3}J = 4.6 Hz, 2H), 3.86 (t, ^{3}J = 4.6 Hz, 2H), 3.62 (m, 60H), 3.37 (s, 3H); ^{13}C NMR in $CDCl_3$: 163.48, 134.48, 129.05, 123.53, 77.27, 71.99, 70.82, 70.61, 69.35, 59.08; ESI-MS: calcd $C_{41}H_{71}NO_{19}$ 899.47 $[M+H_2O]^+$; found 899.88.

General procedure for the deprotection of the phthalimide

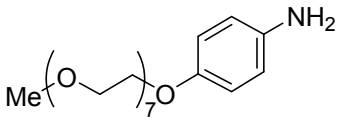
The phthalimid protected polyethylene glycol (1 eq.) was dissolved in THF (30 mL for 1 g of phthalimid protected PEG) and aqueous hydrazine (40 eq.) was added slowly. The mixture was stirred for 4 h at room temperature. The solvent was evaporated and water was added. The aqueous phase was extracted three times with chloroform and the combined organic layer was dried with magnesium sulphate. Further evaporation under reduced pressure afforded pure hydrophilic amines as yellow-brown oils (70% - 85%).

Compound B



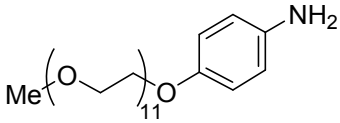
^{1}H NMR in $CDCl_3$: 7.20 (d, ^3J = 8.8 Hz, 2H), 6.93 (d, ^3J = 8.8 Hz, 2H), 4.12 (t, ^3J = 4.8 Hz, 2H), 3.81 (t, ^3J = 4.8 Hz, 2H), 3.73 (m, 2H), 3.66 (m, 4H), 3.55 (m, 2H), 3.33 (s, 3H); ^{13}C NMR in $CDCl_3$: 160.86, 157.83, 129.12, 114.67, 71.95, 70.89, 70.84, 70.65, 70.56, 59.09, 30.95. ESI-MS: calcd $C_{13}H_{21}NO_4$ 256.15 $[M+H]^+$; found 256.49.

Compound C



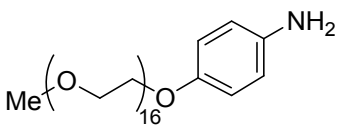
^{1}H NMR in $CDCl_3$: 6.75 (d, ^3J = .0 Hz, 2H), 6.62 (d, ^3J = 8.0 Hz, 2H), 4.04 (t, ^3J = 4.8 Hz, 2H), 3.80 (t, ^3J = 4.6 Hz, 2H), 3.64 (m, 22H), 3.54 (m, 2H), 3.37 (s, 3H); ESI-MS: calcd $C_{21}H_{37}NO_8$ 432.26 $[M+H]^+$; found 432.51.

Compound D



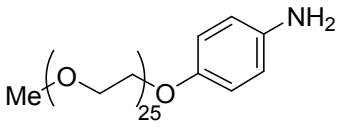
^{1}H NMR in $CDCl_3$: 6.73 (d, ^3J = 8.0 Hz, 2H), 6.62 (d, ^3J = 8.0 Hz, 2H), 4.05 (t, ^3J = 4.8 Hz, 2H), 3.80 (t, ^3J = 4.8 Hz, 2H), 3.65 (m, 40H), 3.37 (s, 3H). ESI-MS: calcd for $C_{29}H_{53}NO_{12}$ 608.36 $[M+H]^+$, found: 608.47.

Compound E



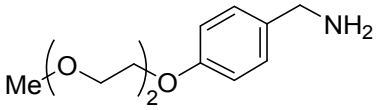
^{1}H NMR in $CDCl_3$: 6.74 (d, ^3J = 8.0 Hz, 2H), 6.64 (d, ^3J = 8.0 Hz, 2H), 4.05 (t, ^3J = 4.4 Hz, 2H), 3.81 (t, ^3J = 4.4 Hz, 2H), 3.65 (m, 60H), 3.37 (s, 3H).

Compound F



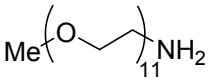
^{1}H NMR in $CDCl_3$: 6.73 (d, ^3J = 8.0 Hz, 2H), 6.61 (d, ^3J = 8.0 Hz, 2H), 4.03 (t, ^3J = 4.8 Hz, 2H), 3.79 (t, ^3J = 4.8 Hz, 2H), 3.62 (m, 96H), 3.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25°C): δ = 151.8, 140.2, 116.3, 115.8, 71.9, 70.7, 70.52, 70.45, 69.9, 68.2, 58.9; ESI-MS: calcd for $C_{57}H_{109}NO_{26}$ 1222.72 $[M-H]^-$, found: 1222.20.

Compound G



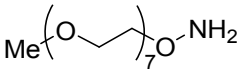
^{1}H NMR in $CDCl_3$: 7.21 (d, ^3J = 8.4 Hz, 2H), 6.88 (d, ^3J = 8.4 Hz, 2H), 4.13 (t, ^3J = 4.8 Hz, 2H), 3.85 (t, ^3J = 4.8 Hz, 2H), 3.79 (s, 2H), 3.72 (m, 2H), 3.58 (m, 2H), 3.39 (s, 3H).

Compound H



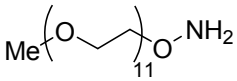
^{1}H NMR in $CDCl_3$: 3.64 (m, 40H), 3.52 (m, 2H), 3.37 (s, 3H); 2.89 (t, ^3J 4.8 Hz, 2H); ESI-MS: calcd $C_{23}H_{49}NO_{11}$ 516.34 $[M+H]^+$; found 516.66.

Compound I

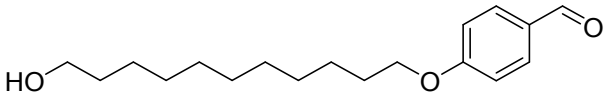


^{1}H NMR in $CDCl_3$: 3.86 (m, 2H), 3.66 (m, 24H), 3.55 (m, 2H), 3.38 (s, 3H); ESI-MS: calcd $C_{15}H_{33}NO_8$ 356.23 $[M+H]^+$; found 356.41.

Compound J



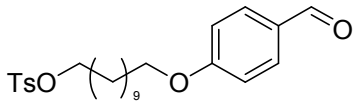
^{1}H NMR in $CDCl_3$: 3.83 (t, ^3J = 5.0 Hz, 2H), 3.66 (m, 40H), 3.54 (m, 2H), 3.37 (s, 3H).



18

4-hydroxybenzaldehyde (1.32 g, 5 mmol) and potassium carbonate (10 g, 72 mmol) were dissolved in DMF (80 mL) and the resulting solution was heated up to 100°C for 40 min. 11-bromoundecan-1-ol (1.26 g, 5 mmol) was then added and the mixture was stirred for 36 h at reflux. Potassium carbonate was then filtered and the filtrate was evaporated. Dichloromethane (15 mL) was added and the organic solution was washed with water (20 mL). The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried with magnesium sulfate. Evaporation under reduced pressure afforded compound **18** as a clear brown solid (1.34 g, 92%).

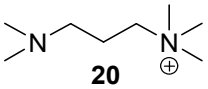
^{1}H NMR in $CDCl_3$: 9.87 (s, 1H), 7.82 (d, ^{3}J = 8.4 Hz, 2H), 6.99 (d, ^{3}J = 8.4 Hz, 2H), 4.04 (t, ^{3}J = 5.8 Hz, 2H), 3.63 (t, ^{3}J = 5.8 Hz, 2H), 1.81 (m, 2H), 1.56 (m, 2H), 1.45 (m, 2H), 1.3 (m, 12H); ^{13}C NMR in $CDCl_3$: 190.54, 160.1, 152.27, 132.06, 114.62 70.57, 68.44, 63.05, 61.76, , 32.82, 30.93, 29.59, 29.54, 29.43, 25.99, 25.77. ESI-MS: calcd for $C_{18}H_{28}O_3$ 293.20 $[M+H]^+$, found: 293.45.



19

Compound **69** (1.34 g, 4.6 mmol) wa dissolved in pyridine (2 mL) at 0 °C and a solution of (1.0 g, 5.5 mmol) of tosyl chloride in pyridine (2 mL) was added dropwise. The mixture was stirred for 8 h at 0°C and treated by adding ice with a 6N HCl solution (40 mL). The product was extracted with dichloromethane and the organic layer was washed with a 2N HCl solution. The organic layer was dried with magnesium sulfate and further evaporation under reduced pressure afforded compound **19** as a white solid (1.65 g, 81%).

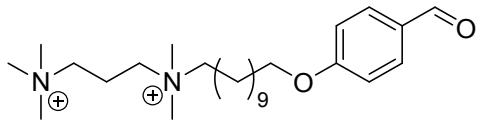
^{1}H NMR in $CDCl_3$: 9.87 (s, 1H), 7.82 (d, ^{3}J = 8.0 Hz, 2H), 7.79 (d, ^{3}J = 8.4 Hz, 2H), 7.34 (d, ^{3}J = 8.4 Hz, 2H), 6.99 (d, ^{3}J = 8.0 Hz, 2H), 4.03 (m, 4H), 2.41 (s, 3H), 1.81 (m, 2H), 1.63 (m, 2H), 1.45 (m, 2H), 1.30 (m, 12H).



20

Tetramethylpropylendiamine (TMPDA, 5.02 mL, 30 mmol) was dissolved in diethylether (40 mL). The solution was cooled at 10°C and a solution of iodomethane (1.86 mL, 30 mmol) in diethylether (10 mL) is added dropwise. After 30 min, a white precipitate was formed, filtered, washed with ether and dried under vacuum to afford compound **20** (4.0 g, 91%).

^{1}H NMR in $CDCl_3$: 3.65 (m, 2H), 3.46 (s, 9H), 2.41 (t, ^{3}J = 6.0 Hz, 2H), 2.20 (s, 6H), 1.94 (m, 2H); ^{13}C NMR in $CDCl_3$: 66.03, 55.46, 54.07, 45.45, 21.45. ^{13}C NMR ($CDCl_3$, 100 MHz, 25°C): δ = 66.0, 55.5, 54.1, 45.5, 21.5; ESI-MS: calcd for $C_8H_{21}N_2I$ 145.17 [M-I^-]+, found: 145.36.



A

Compound **19** (317 mg, 1.38 mmol) and compound **20** (210 mg, 0.77 mmol) were dissolved in DMF (5 mL). The mixture was stirred at 60°C for 7 h and then cooled at room temperature. Diethylether (25 mL) was then added. The yellow precipitate was filtrated, washed with ether and dried under vacuum to afford compound **A** as the bis-tosylate salt and as a clear yellow solid (457 mg, 78%).

^{1}H NMR in $CDCl_3$: 9.86 (s, 1H), 7.81 (d, ^{3}J = 8.4 Hz, 2H), 7.67 (d, ^{3}J = 8.4 Hz, 4H), 7.15 (d, ^{3}J = 8.4 Hz, 4H), 6.97 (d, ^{3}J = 8.4 Hz, 2H), 4.02 (t, ^{3}J = 6.2 Hz, 2H), 3.66 (m, 2H), 3.54 (m, 2H), 3.27 (s, 9H), 3.19 (m, 2H), 3.11 (s, 6H), 2.56 (s, 2H), 2.30 (s, 6H), 1.79 (m, 2H), 1.54 (m, 2H), 1.44 (m, 2H), 1.30 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25°C): δ = 190.9, 164.3, 143.5, 139.8, 132.0, 129.8, 129.0, 125.7, 114.8, 68.4, 66.0, 62.7, 60.8, 53.7, 50.6, 29.52, 29.47, 29.44, 29.33, 29.22, 29.07, 26.3, 26.0, 22.7, 21.3,18.4; ESI-MS: calcd for $C_{26}H_{48}N_2O_{22}^{2+}$ 210.18 [M-2OTs]$^{2+}$, found: 210.49.

General protocol for the synthesis of the charged dynablocks in water

Compound **A** (19.1 mg, 0.025mmol, 1 eq.) was dissolved in deuterated water (500 µL, C = 50 mM) and amine PEG (1-3 eq.) was added. After 12 h, an equilibrated mixture was obtained, composed of the corresponding imine forming vesicular and micellar structures, the non-condensed aldehyde **A** and the non-condensed amine PEG. The reversible nature of the imine bonds obeys to thermodynamic. Thus, it is hard to obtain an accurate molecular analysis of one dynablock and, in the project, they will always be studied as a mixture of imine with non-condensed aldehyde and amine. In 1H NMR, the chemical shifts are 9.4 – 10 for the aldehyde proton and 7.8 – 8.5 for the imine proton. It is thus possible to quantify each compound by integrating each signal.

General protocol for competition between charged dynablocks in water

Sample formation:

Amine PEG **a** (Xa eq.) and amine PEG **b** (Xb eq.) were dissolved in deuterated water (500 μ L, C = 50 mM) and compound **A** (19.1 mg, 0.025mmol, 1 eq.) was added. After 12 h, an equilibrated mixture was obtained, composed by the corresponding imine forming micellar and vesicular structures, the non-condensed compound **A** and the non-condensed amine PEGs.

A solution of deuterated trifluoroacetic acid (1.3 M) or triethylamine were used to control the pH of the samples and for each pH, 1H NMR and pH (measured with a pHmeter) measurements were performed. SANS, SAXS, and/or DLS measurements were performed for each solution.

Stockes Einstein Equation (DOSY NMR)

In DOSY NMR measurements, the hydrodynamic radius is related to the diffusion coefficient through the Stockes Einstein relation:

$r_h = (kT) / (6 D \pi \eta)$

where k is the boltzman constant, T is the absolute temperature, and η is the viscosity.

Analytical fits of SAXS and SANS data

Core/shell form factor

The complete fitting procedure has been detailed elsewhere[1] using SASfit program (http:\\kur.web.psi.ch/).

Brieftly, the total SAS intensity I(q) of centrosymetrical colloidal objects can be expressed by the following equation:

$$I(q) = \Phi \Delta\rho^2 V P(q) S(q)$$

where Φ is the volume fraction, $\Delta\rho^2=(\rho-\rho_{solvent})^2$ the contrast term, V the volume of scattered objects (related to the molecular weigth M_w of the oblects), P(q) the form factor and S(q) is the structure factor. In first approximation we will consider that inter-objects interactions are negligible (diluted regime i.e. S(q) is tending to 1 for large q) and that cross terms and virial effects are neglected in our fitting procedure (analysis realized in a q-range where I(q)≈P(q)). The polydispersity in size can then be described by a log-normal distribution $l(r,R_0,\sigma)$ where r is the radius, R_0 the mean radius and σ the variance:

$$l(r,R_0,\sigma) = \frac{1}{\sqrt{2\pi} r\sigma} \exp\left(-\frac{1}{2\sigma^2} \ln^2\left(\frac{r}{R_0}\right)\right)$$

Thus, the global scattering intensity is defined by the following relation:

$$I(q) = \Phi \Delta\rho^2 V \int_0^\infty P(q,r) l(r,R_0,\sigma) dr$$

For spherical core-shell model, whose parameters are the radius of the core R_c and the shell thickness e, the form factor can be written as follow:

$$P_{core/shell}(q,R_c,e) = \left[\begin{array}{l} \frac{4\pi}{3} R_c^{\,3} (\rho_c - \rho_s) F_c(q,R_c) \\ + \frac{4\pi}{3} (R_c+e)^3 (\rho_s - \rho_o) F_s(q,(R_c+e)) \end{array} \right]^2$$

with

$$F_c(q,R_c) = \frac{3\left[\sin(qR_c) - qR_c\cos(qR_c)\right]}{(qR_c)^3}$$

and

$$F_s(q,R_c+e) = \frac{3\left[\sin(q(R_c+e)) - q(R_c+e)\cos(q(R_c+e))\right]}{(q(R_c+e))^3}$$

where ρ_c, ρ_s, and ρ_o are respectively the scattering length densities per unit volume (SLDs) of the core, the shell and the solvent.

Branched (star-like) model analysis

Figure 1 presents the graphical analysis for Dynablock **AF**. Using this procedure we determine the functionality f as $f^{3/2}=I_1/I_2$, and the radius $R=\xi f^{1/2}$.

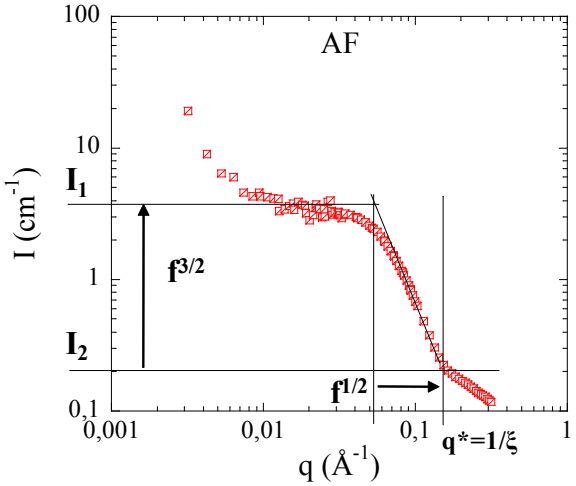


Figure 1: Graphical analysis of SANS data for Dynablock **AF**.

If the number of arms, f, is larger than 6, it is usual to consider the model developed by Daoud and Cotton, which takes into account repulsive interactions between arms. In this model, each arm is represented by a series of blobs of size ξ(r,f) that increases with the distance to the star centre, r, and decreases with the functionality f (at a distance r, we have f blobs of size ξ(r,f) and the stretching of the arms becomes more marked with an increase of f). The compact stacking condition of these blobs leads to $\xi(r,f)=r f^{-1/2}$. The model depends on three characteristic lengths: the radius of the star-like micelle, R, the size of the larger blob ξ(R,f) that is the outer blob of the corona, and the statistical unit b. These lengths define the three q-domains observed in Fig. 1: the Guinier regime $q<R^{-1}$; $R^{-1}<q<\xi(R)^{-1}$; and $\xi(R)^{-1}<q<b^{-1}$. In the intermediate regime two successive power laws with exponents -2/ν and -1/ν (Gaussian arms, ν=0.5; arms with excluded volume, ν=0.588) with a crossover value at $q^*=1/\xi(R)$ are predicted for $1<qR<f^{1/2}$ and $f^{1/2}<qR$, respectively. We can estimate the average functionality by using the intensities ratio at $qR<<1$ and $q^*R=f^{1/2}$ as $I_1(q=0)/I_2(q^*)$ gives $f^{3/2}$. Also in first approximation we can consider that $R=R_g$ if f~10, where R_g is the radius of gyration determined at low-q.

[1] N. Jouault, R. Nguyen, M. Rawiso, N. Giuseppone, E. Buhler, *Soft Matter* **2011**, *7*, 4787-4800.