Micellization of sequence-controlled polyurethane ionomers in mixed aqueous solvents

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1. ESI Methods of PUI synthesis

Materials

All reagents, chemicals, materials and solvents were obtained from commercial sources, and were used as received: Cambridge Isotope Laboratories for (deuterated) solvents, Aldrich, Acros, ABCR, Merck and Fluka for chemicals, materials and reagents. All solvents were of AR quality. Moisture or oxygen-sensitive reactions were performed under an atmosphere of dry argon. Analytical thin layer chromatography was performed on Kieselgel F-254 precoated silica plates. Column chromatography was carried out on Screening Devices B.V. flashsilica gel (40-63 μm mesh) or normal silica gel (60-200 μm mesh). In the polymer extension reactions, and for scavenging the excess of BB building block, an amine terminated resin was employed (Silicycle Si-Amine catnr. R5203B loading 1.89 mmol/g). For hydrogenations 10% Pd/C Degussa type E101 NE/W (Sigma-Aldrich) was used. Biobeads SX-1 material was used for preparative column separation (here, separation is based on hydrodynamic volume differences, so on molecular mass differences).

Molecular characterization

NMR spectra were recorded on a 400 MHz Varian Mercury spectrometer at 298 K. Chemical shifts are reported in ppm downfield from TMS at r.t. using deuterated chloroform (CDCl₃) as a solvent and internal standard unless otherwise indicated. Abbreviations used for splitting patterns are s = singlet, t = triplet, q = quartet, m = multiplet (or multiple signals), dd = double doublet, and b or br = broad. IR spectra were recorded on a Perkin Elmer 1600 FT-IR (UATR). Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) was performed on a PerSeptive Biosystems Voyager-DE PRO spectrometer. As indicated, the measurements were done by using a α-cyano-4-hydroxycinnamic acid (CHCA) matrix (or otherwise a trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]-malononitrile, DCTB-matrix), KAc was optionally added to the matrix to primarily generate K⁺-adducts, and a linear positive mode or reflector positive mode was employed. Size-exclusion chromatography (SEC) was measured on a Shimadzu LC-10AD VP system with a RID-10A detector and a SPD-M20A diode array detector using a PL gel 5μm mixed-C and a mixed-D column in sequence and using THF (or chloroform, as indicated) as the eluent (flow rate 1 mL min⁻¹). The SEC molecular weight and distribution data were recorded relative to polystyrene (PS) standards using RI-detection. HPLC-PDA/MS was performed using a Shimadzu LC-10 AD VP series HPLC coupled to a diode array detector (Finnigan Surveyor PDA Plus detector, Thermo Electron Corporation) and an Ion-Trap (LCQ Fleet, Thermo Scientific). Analyses were performed using a Alltech Alltima HP C18 3μ column using an injection volume of 1-4 μL, a flow rate of 0.2 mL min⁻¹ and typically a gradient (5% to 100% in 10 min, held at 100% for a further 3 min) of CH₃CN in H₂O (both containing 0.1% formic acid) at 298 K.

Abbreviations

Tetramethylsilane (TMS), room temperature (r.t.), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), ethyl acetate (EtOAc), dichloromethane (DCM), diisopropylethylamine (DIPEA), trifluoroacetic
acid (TFA), benzyl (Bn), total ion current (TIC), size-exclusion chromatography (SEC), nuclear magnetic resonance (NMR), matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS), high performance liquid chromatography-photo diode array/mass spectrometry (HPLC-PDA/MS).

The synthesis of sequence-controlled PUI materials

The syntheses of the symmetrical PUI-S2 and the asymmetrical PUI-A2 and their intermediates are shown in Schemes S1 and in the Schemes S2, S3 and S4 further below.

Sequence controlled precision versus purity versus mono-dispersity

Note that all prepared PU products are in fact composed of a complex mixture of regio- and stereo-isomers. This is due to the employed IPDA reactant that is a mixture of stereo- and diastereo-isomers. Moreover, IPDA can react at both amine groups with Boc-anhydride, so amine 1 becomes a mixture of two regioomers (see Scheme S1). Of course, all molecules 1 have only one amine and only one Boc-protected amine group, so in this sense amine 1 is ‘pure’. Similarly, building block BB is ‘pure’ as it has only one active carbonate group, only one benzyl-ester group and only one Boc-protected amine group. Note, however, that the produced PUs are not chemically pure, where this is not only due to the used IPDA component (introducing isomeric diversity), but also because of the employed poly-THF component (introducing a distribution in molecular weight). Accordingly, the produced materials are also not monodisperse, as all macromolecules would then have to be of the same molecular weight.

Importantly, and in conclusion, the designed organic synthetic approach allows for the build-up of PUs with a strictly controlled order of components, i.e. macromolecules with a sequence-controlled or a sequence-defined microstructure. In the PUI-S2 and PUI-A2 precision polymers, the number of IPDA, DMPA and pTHF groups is precisely controlled, as well as the positioning of these groups within the macromolecular structure.
Scheme S1: Synthesis route to the building block BB, that is used for preparing a series of sequence-controlled PUs. (i) Boc-anhydride, DCM; (ii) BnBr, KOH, DMF, 100°C; (iii) 4-nitrophenyl chloroformate, pyridine, DCM; (iv) amine 1, pyridine, dioxane, reflux.

Isophorone diamine (IPDA) was reacted with Boc-anhydride to give, after purification, the mono-Boc-protected mono-amine 1 (Scheme S1). Di-methylol-propionic acid (DMPA) was protected with a benzyl-(Bn)-ester group and then activated using 4-nitrophenyl chloroformate to prepare the di-activated di-carbonate 3. Molecule 3 was reacted with mono-amine 1 to produce the extension building block BB (a stable white solid).

The iterative syntheses of both the PUIs in this paper rely on the use of building block BB. It contains (i) a 4-nitrophenyl-carbonate group that is stable at room temperature and that reliable reacts with amines to produce urethane linked products, (ii) a stable benzyl-ester group that can conveniently be deprotected by mild Pd/C-H2 reduction to give the ionomeric COOH-group, and (iii) a Boc-group that is stable and that allows mild deprotection with TFA to produce a mono-amine reactive group that is suited and ready for the next iterative extension reaction with BB.

Mono-Boc isophorone diamine (Boc-IPDA-NH2): isomeric mixture of tert-butyl [3-(aminomethyl)-3,5,5-trimethylcyclohexyl]carbamate and tert-butyl [(5-amino-1,3,3-trimethylcyclohexyl)methyl]carbamate (molecule 1)

A solution of isophorone diamine (IPDA; 3 g, 17.6 mmol, 2 molar equivalents) in DCM (20 mL) was stirred at -78°C. Boc-anhydride (1.92 g, 8.8 mmol) in DCM (80 mL) was added drop wise. After addition the
mixture was allowed to heat up to room temperature, upon which it became hazy. HPLC-MS analysis showed that about 75% of mono-Boc product and 23% of di-Boc product had formed. The reaction mixture was evaporated, a solution of 0.1M formic acid (pH=3) was added, and this solution was washed two times with DCM (2 x 20 mL) to remove di-Boc product. The water layer was then brought to pH=9 with a 0.1M NaOH solution, and the product was extracted using two portions of DCM (20 mL). The combined organic layers were repeatedly washed with a solution of borax buffer (pH 9.3; 9 mL 0.1M NaOH and 91 mL 0.05M sodium tetraborate), until non-functionalized IPDA had disappeared from the organic layer. The presence of IPDA was checked by HPLC-MS analysis on a small sample after reaction with phenyl isocyanate. The organic layer was dried with Na2SO4 and concentrated to obtain the product as a waxy solid. Yield 3.6 grams (76%).

1H NMR (400 MHz, chloroform-d) δ 4.60 (NH, m, 1H), 3.19 – 2.61 (CHN and CH2N, m, 3H), 1.82 – 1.57 (CCH2C, m, 2H), 1.55 – 1.40 ((CH3)3, s, 9H), 1.40 – 0.59 (NH2, CCH2C and CH2C, m, 15H). HPLC-MS: 4.80 minutes, single peak, (M+H+) = 271.08 m/z. Calculated: C15H36N2O2 (exact 270.23; molecular weight 270.42).

**DMPA(Bn)-diol: benzyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate (molecule 2)**

Molecule 2 has previously been reported in ““On-Off” Multivalent Recognition: Degradable Dendrons for Temporary High-Affinity DNA Binding”, Daniel J. Welsh, Simon P. Jones and David K. Smith. Angew. Chem. Int. Ed. 2009, 48, 4047–4051.

Di-methylol-propionic acid (DMPA, 100 g, 746 mmol) and KOH (48.2 g, 732 mmol) were stirred in DMF (500 mL) for one hour at 100°C. Benzyl bromide (153.4 g, 890 mmol, 1.2 molar equivalents) was added dropwise to the hot mixture that was thereafter stirred overnight at 100°C under argon. A KBr-suspension formed. The mixture was concentrated to dryness by evaporation of the volatiles. The crude product was dissolved in a 1/1 mixture of ethyl acetate and hexane (1L), and this solution was washed with several portions of water (2L total volume). The organic layer was dried with Na2SO4, filtered and the filtrate was concentrated. The residue was recrystallized from toluene (300 mL) to yield a first crop of 96.6 g (58%) of product. The filtrate was concentrated and once more recrystallized to give a second crop (6.3 grams).

1H NMR (400 MHz, chloroform-d) δ 7.34 (Ar-H, m, 5H), 5.18 (CH2:Bn, s, 2H), 3.90 – 3.70 (CH2:O, dd, 4H), 3.3 (OH, b, 2H), 1.09 (CH3, s, 3H). HPLC-MS: 4.55 minutes, single peak, (M+H+) = 225.00 m/z. Calculated: C12H14O4 (exact 224.10; molecular weight 224.26).

**DMPA(Bn) di-(4-nitrophenyl carbonate): benzyl 2-methyl-3-(((4-nitrophenoxy)carbonyl)oxy)-2-(((4-nitrophenoxy)carbonyl)oxy)methylpropanoate (molecule 3)**

Molecule 3 has previously been reported in ““On-Off” Multivalent Recognition: Degradable Dendrons for Temporary High-Affinity DNA Binding”, Daniel J. Welsh, Simon P. Jones and David K. Smith. Angew. Chem. Int. Ed. 2009, 48, 4047–4051.

Diol 2 (3 g, 13.3 mmol) and 4-nitrophenyl chloroformate (5.92 g, 29.3 mmol, 2.2 molar equivalents) and pyridine (2.1 mL, 26.6 mmol, 2 molar equivalents) were dissolved in dichloromethane (80 mL). The reaction mixture was stirred at room temperature for 1 hour; completion of the reaction was monitored by
HPLC-MS and $^1$H-NMR analysis. The mixture was washed with two portions of NaHSO$_4$ solution and thereafter with a NaHCO$_3$ (or a 0.1M NaOH) solution to remove 4-nitrophenol. Finally, the organic layer was dried with Na$_2$SO$_4$ and concentrated. The crude product was purified with column silica chromatography, first eluting with chloroform to remove traces of 4-nitrophenol and then eluting with 7v/v% ethyl acetate in chloroform to collect the product. Yield 4.17 g (56%).

$^1$H NMR (400 MHz, chloroform-d) δ 8.26 (Ar-H, m, 4H), 7.41 – 7.29 (Ar-H, m, 9H), 5.24 (CH$_2$-Bn, s, 2H), 4.68 – 4.42 (CH$_2$O, m, 4H), 1.41 (CH$_3$, s, 3H).

Nitrophenyl carbonate DMPA(Bn)-IPDA-Boc (molecule 4, building block BB)

Di-carbonate 3 (4.17 g, 7.54 mmol, 2 molar equivalents), Boc-IPDA-NH$_2$ (amine 1, 1.02 g, 3.77 mmol) and pyridine (357 mg, 4.52 mmol, 1.2 molar equivalents) were dissolved in dioxane (30 mL). The reaction mixture was refluxed for 16 hours at an oil bath temperature of 115°C. The dioxane was removed by evaporation, the residue was dissolved in DCM and the organic solution was washed with a 10w/w% NaHSO$_4$ solution to remove the pyridine. The 4-nitrophenol was removed by washing the organic layer with a 0.1M NaOH solution (until the yellow color had disappeared). Finally, the organic layer was washed with saturated NaCl (aq) and then dried with Na$_2$SO$_4$. Filtration and concentration of the filtrate gave an oil that was purified with silica column chromatography. Elution started with 5 v/v% EtOAc in chloroform to remove a minor amount of di-activated DMPA(Bn) 3. Switching to 15 v/v% EtOAc in chloroform gave product compound BB as a white solid. Yield: 1.86 g (72%).

$^1$H NMR (400 MHz, chloroform-d) δ 8.27 (Ar-H, dd, 2H), 7.45 – 7.30 (Ar-H, m, 7H), 5.20 (CH$_2$-Ph, s, 2H), 4.76 – 4.29 (NH + CH$_2$OCOO, m, 6H), 3.98 – 3.51 (CHN, m, 1H), 3.39 – 2.55 (CH$_2$N, m, 2H), 1.80 – 1.54 (CCH$_2$C, m, 2H), 1.55 – 1.41 ((CH$_3$)$_3$, m, 9H), 1.41 – 0.61 (CCH$_2$C and CH$_3$, m, 16H). HPLC-MS: 8.06 minutes, single peak, (M+Na$^+$) = 708.42 m/z, (M+Boc+H$^+$) = 586.4 m/z, (M-tBu+H$^+$) = 630.1 m/z. Calculated: C$_{35}$H$_{47}$N$_3$O$_{11}$ (exact 685.32; molecular weight 685.77).
The symmetrical PU-S0 (a solid) and PUI-S2 (a waxy solid) were prepared in 2 and 5 steps, respectively, from commercially available hydroxy terminated telechelic poly-THF2000 5 (Scheme S2). The alcohol end groups of poly-THF2000 were converted with phenyl chloroformate to produce 6. Reaction of 6 with Boc-IPDA-NH2 (mono-amine 1) gave PU-S0 that was Boc-deprotected by reaction with TFA in DCM to afford 7. Diamine 7 was converted in 2 steps to PUI-S2 by employing extension building block BB. In the coupling reaction, BB was used in molar excess. After complete conversion of the coupling reaction, an amine functional scavenger resin was added to the reaction mixture to remove BB, and thus separate it from the desired PUI product 8. Finally, debenzylation yielded PUI-S2.

**Poly-THF2000 diphenyl carbonate (polymer 6)**

Hydroxy terminated telechelic poly-tetrahydrofuran 2000 5 (pTHF2000, 100 g, 50 mmol) was dried for 2 hours at 110°C under vacuum. Thereafter the polymer was dissolved in DCM (300 mL) and pyridine (16 mL, 200 mmol, 4 molar equivalents). Phenyl chloroformate (17.22 g, 110 mmol, 2.2 molar equivalents)
dissolved in DCM (100 mL) was added dropwise to the poly-THF2000 solution that was cooled at about 0°C using an ice bath. The reaction mixture was stirred overnight. After checking completion of reaction by 1H-NMR, DCM (600 mL) was added, and the organic mixture was washed two times with a 1M H₂SO₄-solution, and then two times with saturated Na₂CO₃ (aq). The organic layer was dried with MgSO₄ and concentrated to yield 100.5 gram (97%) of di-activated poly-THF2000 product.

1H NMR (400 MHz, chloroform-d) δ 7.43 – 7.35 (Ar-H, m, 4H), 7.26 – 7.21 (Ar-H, m, 2H), 7.21 – 7.11 (Ar-H, m, 4H), 4.28 (CH₂OCON, t, J = 6.6 Hz, 4H), 3.66 – 3.15 (CH₂O, m, ca. 105H), 1.83 (CH₂CH₂OCON, dq, J = 8.9 Hz, 6.5 Hz, 4H), 1.62 (CH₂CH₂O, m, ca. 105H).

SEC (THF-RI): Mn= 3.7 kD, Mw = 6.8 kD, PD = 1.84.

**Boc-IPDA-pTHF2000-IPDA-Boc (“PU-S0”)**

Poly-THF2000 diphenyl carbonate (6, 46.7 g, 20.8 mmol) was dissolved in dioxane (800 mL) and Boc-IPDA-NH₂ (amine 1, 16.9 g, 62.3 mmol, 1.5 molar equivalents) was added. The reaction mixture was stirred at an oil bath temperature of 100°C, and was checked with 1H-NMR for completion of the reaction. The mixture was concentrated, the residue was dissolved in diethyl ether (500 mL). Washing with 1M formic acid to remove the excess of amine 1, 1M NaOH and saturated NaCl (aq), was followed by drying of the organic layer with MgSO₄. Evaporation of the filtrate gave the polyurethane product PU-S0. Yield 52 g (98%).

1H NMR (400 MHz, chloroform-d) δ 4.57 (NH, d, 4H), 4.05 (CH₂OCON, t, J = 6.2 Hz, 4H), 3.75 (CHN, m, 2H), 3.65 – 3.20 (CH₂O, m, ca. 100H), 2.86 (CH₂N, d, J = 6.7 Hz, 4H), 1.95 – 1.53 (CCH₂C and CH₂CH₂O, m, ca. 105H), 1.44 ((CH₃)₃, s, 18H), 1.36 – 0.72 (CCH₂C and CH₃C, m, 26H).

SEC (THF-RI): Mn= 5.5 kD, Mw = 8.6 kD, PD = 1.57.

Found MALDI-TOF-MS array (CHCA matrix with added KAc, positive linear mode): (M + Na⁺) = ... 1569.7, 1642.1, 1714.0, 1786.0 ... (p = 12-15) for 682.94 + [72.11]p + 22.99 and minor array (M + K⁺) = ... 1586.4, 1658.9, 1730.6, 1802.8 ... (p = 12-15) for 682.94 + [72.11]p + 39.09. Calculated molecular weight of end group (C₃₅H₇₆NaO₆; n=0): 682.49.

**H₂N-IPDA-THF2000-IPDA-NH₂ (polymer 7)**

Boc-IPDA-pTHF2000-IPDA-Boc (PU-S0, 3.52 g) was dissolved in DCM (20 mL) and TFA (12 mL). The mixture was stirred for 3 hours and checked with 1H-NMR for conversion. After evaporation of the solvents, the residue was dissolved in diethyl ether. The ether layer was washed twice with saturated Na₂CO₃(aq) and once with saturated NaCl (aq). Drying with Na₂SO₄, evaporation of the ether and stripping with toluene gave 3.3 grams of product 7.

1H NMR (400 MHz, chloroform-d) δ 4.48 (NH, s, 2H), 4.05 (CH₂OCON, t, J = 6.1 Hz, 4H), 3.82 (CHN, m, 2H), 3.66 – 3.19 (CH₂O, m, ca. 115H), 2.35 (CH₂NH₂, s, 4H), 1.84 – 1.45 (CCH₂C and CH₂CH₂O, m, ca. 120H), 1.35 – 0.63 (NH₂, CCH₂C and CH₃C, m, 30H).
SEC (THF-RI): $M_n = 0.94$ kD, $M_w = 2.2$ kD, PD = 2.39. The polymer clearly shows adsorbance onto the stationary phase due to interaction of amine end groups. Accordingly, a lower than expected molecular weight and a higher than expected polydispersity is observed.

Found MALDI-TOF-MS array (CHCA matrix, positive reflector mode): $(M + Na^+) = \ldots 1369.8, 1441.9, 1513.9, 1586.0 \ldots (p = 12-15)$ for 482.71 + [72.11]p + 22.99. Calculated molecular weight of end group $(C_{26}H_{50}N_4O_4; n=0)$: 482.71.

**Boc-IPDA-DMPA(Bn)-IPDA-pTHF2000-IPDA-DMPA(Bn)-IPDA-Boc (polymer 8)**

Building block molecule BB (1.27 g, 1.85 mmol, 3 molar equivalents) and amine terminated polymer 7 (1.44 g, 0.615 mmol) were dissolved in a minimal amount of dioxane (2 mL) and pyridine (0.11 mL). The mixture was stirred overnight at 70°C under an argon atmosphere, was cooled down and then diluted with chloroform. The organic layer was washed once with NaHSO$_4$ and then with 0.1M NaOH until the yellow color of p-nitrophenol had disappeared. In the final washing step saturated NaCl (aq) was used. The chloroform layer was dried with Na$_2$SO$_4$ and concentrated. The oily residue was dissolved in dioxane (2 mL) and pyridine (0.11 mL) and amine terminated resin (2.1 grams; Silicycle Si-Amine catnr. R5203B loading 1.89 mmol/g) was added to remove the still present excess of building block molecule BB. The mixture was stirred for 1 hour at 110°C under argon, and was monitored with $^1$H-NMR for the disappearance of starting compound. The mixture was filtrated, the residue washed with dioxane and the filtrate was concentrated and then taken up in chloroform. The organic solution was washed again in the same way as described above (with a NaHSO$_4$ solution, then with 0.1M NaOH until the yellow color of p-nitrophenol had disappeared and finally with a saturated NaCl-solution). Yield: 2.1 gram (100%) of a sticky oil.

$^1$H-NMR (400 MHz, chloroform-d) δ 7.42 – 7.32 (Ar-H, m, 10H), 5.16 (CH$_3$Bn, s, 4H), 4.91 – 4.35 (NH, m, 8H), 4.22 (CH$_2$OCON, s, 8H), 4.05 (CH$_2$OCON, s, 4H), 3.75 (CHNH, 4H), 3.41 (CH$_3$O, m, ca. 110H), 2.87 (CH$_2$NH, 8H), 2.00 – 1.53 (CHCH$_2$ and CH$_2$CH$_2$O, m, ca. 125H), 1.44 ((CH$_3$)$_3$, s, 18H), 1.30 – 0.7 (CH$_2$C and CH$_3$, m, 58H).

SEC (THF-RI): $M_n = 6.0$ kD, $M_w = 8.8$ kD, PD = 1.46.

Found MALDI-TOF-MS array (CHCA matrix, positive linear mode): $(M + Na^+) = \ldots 1959.1, 2031.2, 2103.1, 2175.3 \ldots (p = 5-8)$ for 1576.03 + [72.11]p + 22.99 and minor array $(M + K^+) = \ldots 1975, 2047, 2119, 2191 \ldots (p = 5-8)$ for 1576.03 + [72.11]p + 39.09. Calculated molecular weight of end group $(C_{84}H_{134}N_8O_{20}; n=0)$: 1576.03.

**Boc-IPDA-DMPA-IPDA-pTHF2000-IPDA-DMPA-IPDA-Boc (“PUI-S2”)**

The benzyl protected precursor polymer 8 (3 g) was dissolved in dioxane (25 mL) and Pd/C catalyst (600 mg; Aldrich 10% loading Degussa type E101 NE/W) was added. The mixture was stirred under an atmosphere of hydrogen using a hydrogen filled balloon. Monitoring of the reaction with $^1$H-NMR showed completion of deprotection in 1 to 3 days. The mixture was filtrated over zeolite to remove the catalyst, and the filtrate was concentrated to acquire the waxy product in a quantitative yield.
$^1$H NMR (400 MHz, chloroform-\textit{d}) $\delta$ 5.15 – 4.50 (COOH and NH, br, 10H), 4.3 – 4.1 (CH$_2$OCON, m, 8H), 4.1 – 4.0 (CH$_2$OCON, m, 4H), 3.85 – 3.60 (CHN, 4H), 3.41 (CH$_2$O, m, ca. 105H), 2.9 – 2.7 (CH$_2$N, m, 8H), 1.75 – 1.50 (CCH$_2$C and CH$_2$CH$_2$O, m, ca. 115H), 1.45 ((CH)$_3$, s, 18H), 1.3 – 0.75 (CCH$_2$C and CH$_3$, m, 58H).

SEC (THF-RI): M$_n$ = 6.4 kD, M$_w$ = 8.8 kD, PD = 1.37.

Found MALDI-TOF-MS array (CHCA matrix with added KAc, positive linear mode): (M + K$^+$) = ... 1795.1, 1867.6, 1939.4, 2011.6 ... (p = 5-8) for 1395.78 + [72.11]p + 39.09. Calculated molecular weight of end group (C$_{70}$H$_{122}$N$_8$O$_{20}$; n=0): 1395.78.

![Scheme S3](image)

Scheme S3: Synthesis route to the monofunctional polyether building block MeO-polyTHF2000-IPDA-NH$_2$ (12). (i) 2,6-di-tert-butyl-pyridine (DTBP), 0$^\circ$C; (ii) phenyl chloroformate, pyridine, DCM; (iii) amine 1, pyridine, dioxane, reflux; (iv) TFA, DCM.

Starting point for the synthesis of the asymmetrical PUI-A2 is the mono-hydroxy poly-THF2000 material 9 that was prepared by cationic polymerization of THF employing trifluoromethanesulfonate as initiator (Scheme S3). The alcohol end group of 9 was activated by reaction with phenyl chloroformate to produce 10. Reaction of carbonate 10 with Boc-IPDA-NH$_2$ (mono-amine 1) gave polymer 11 that was consecutively Boc-deprotected by reaction with TFA in DCM. Accordingly, key intermediate MeO-pTHF2000-IPDA-NH$_2$ (12) was acquired. This material was purified by silica column chromatography, removing any by-
products (minor amounts of 10, cyclic material and other by-products originating from the cationic polymerization step).

**MeO-polyTHF2000-OH (polymer 9)**

THF was dried over molsieves for two days and was then distilled. The THF was collected in and stored on molsieves and was kept under an argon atmosphere. The applied glassware was previously dried. The thus dried and distilled THF (100 mL, 1.23 mol) was mixed with di-tert-butyl pyridine (DTBP, 2.91 g, 3.4 mL, 15.2 mmol), and the solution was cooled to 0°C and was kept under an argon atmosphere. The initiator methyl trifluoromethanesulfonate (5 g, 34 mmol) was added in one go. The polymerization reaction was allowed to proceed for 45 minutes at 0°C, followed by quenching of the reaction by addition of water. The mixture was then extracted with chloroform, and the collected chloroform layers were washed three times with 1M HCl and once with a saturated NaCl solution. The chloroform solution was dried with Na2SO4 and concentrated to dryness yielding a yellowish oil (60 grams). The oil was dissolved in methanol (50 mL) and precipitated into water. The supernatant was decanted and the solid residue was washed with cold water. Finally, the residue was dried in a vacuum oven at 80°C under vacuum to afford a waxy white solid (50.4 grams) with an average molecular weight $M_n$ of about 2.0 kDa, as according to $^1$H-NMR.

$^1$H NMR (400 MHz, chloroform-d) $\delta$ 3.63 (CH$_2$OH, q, $J = 5.7$ Hz, 2H), 3.61 – 3.34 (CH$_2$O, m, ca. 130H), 3.33 (CH$_3$O, s, 3H), 2.58 (OH, t, $J = 5.8$ Hz, 1H), 1.82 (CH$_2$CH$_2$O, m, 2H), 1.81 – 1.41 (CH$_2$CH$_2$O, m, ca. 130H).

SEC (chloroform-RI): $M_n= 4.4$ kD, $M_w = 6.6$ kD, PD = 1.52.

Found MALDI-TOF-MS array (CHCA matrix, positive reflector mode): (M + Na$^+$) = ... 2001.5, 2073.6, 2145.6, 2217.7 ... (p = 26-29) for 104.15 + [72.11]p + 22.99. Calculated molecular weight of end group (C$_3$H$_{12}$O$_2$; n=0): 104.15.

**MeO-polyTHF2000 phenyl carbonate (polymer 10)**

MeO-poly-THF2000-OH (9, 20 g, 10 mmol) was dissolved in dioxane (100 mL) and pyridine (2 mL) was added. Finally, phenyl chloroformate (1.88 g, 1.5 mL, 12 mmol, 1.2 molar equivalents) was added and the reaction mixture was left to stir overnight under argon at r.t. The reaction mixture was filtrated, chloroform was added to the filtrate and the solution was subsequently washed with saturated NaHCO$_3$ (aq) solution, a 0.5M citric acid solution, again with saturated NaHCO$_3$ (aq) and finally with saturated NaCl (aq). The organic layer was dried with Na$_2$SO$_4$ and concentrated to yield an oily product (20.4 grams).

$^1$H-NMR (400 MHz, chloroform-d) $\delta$ 7.48 – 7.14 (Ar-H, m, 5H), 4.28 (CH$_2$OCOO, t, $J = 6.6$ Hz, 2H), 3.52 – 3.34 (CH$_2$O, m, ca. 110H), 3.33 (CH$_3$O, s, 3H), 1.72 – 1.42 (CH$_2$CH$_2$O, m, ca. 110H).

SEC (THF-RI): $M_n= 6.0$ kD, $M_w = 8.1$ kD, PD = 1.36.

Found MALDI-TOF-MS array (CHCA matrix, positive reflector mode): (M + Na$^+$) = ... 2193.6, 2265.7, 2337.7, 2409.8 ... (p = 27-30) for 224.26 + [72.11]p + 22.99 and minor array (M + K$^+$ + Na$^+$) radical cation = ... 2159.7, 2230.0, 2303.8, ... (p = 26-28) for 224.26 + [72.11]p + 62.08. Calculated molecular weight of end group (C$_{12}$H$_{10}$O$_4$; n=0): 224.26.
MeO-polyTHF2000-IPDA-Boc (polymer 11)

MeO-poly-THF2000 phenyl carbonate (10, 19.6 g, 6.39 mmol) and Boc-IPDA-NH₂ (amine 1, 5.18 g, 19 mmol, 3 molar equivalents) and pyridine (0.92 grams) were dissolved in dioxane (dried on molsieves; 100 mL). The reaction mixture was stirred for 4 days at 100°C, with monitoring of the conversion using ¹H-NMR. The mixture was concentrated and the residue was dissolved in chloroform. The chloroform solution was then washed with a 0.5M citric acid solution, 0.1M NaOH solution and finally with a saturated NaCl solution. The organic layer was dried with Na₂SO₄. The obtained product was dissolved in MeOH and precipitated in cold water. The supernatant was decanted, the product was washed with cold water and was dried. A minor amount of starting MeO-poly-THF2000 phenyl carbonate was still present in the product that was used as isolated in the next step. Yield: 19 grams.

¹H-NMR (400 MHz, chloroform-d) δ 4.61 (NH, s, 2H), 4.06 (CH₂OCON, s, 2H), 3.75 (CHN, m, 1H), 3.55 – 3.33 (CH₂O, m, ca. 125H), 3.33 (CH₃O, s, 3H), 3.20 – 2.73 (CH₂N, m, 2H), 1.83 – 1.48 (CCH₂C and CH₂CH₂O, m, ca. 130H), 1.44 ((CH₃)₂, s, 9H), 1.28 – 0.72 (CH₃ and CCH₂C, m, 13H).

SEC (chloroform-RI): Mₙ= 5.6 kD, Mₘ = 7.6 kD, PD = 1.32.

Found MALDI-TOF-MS array (CHCA matrix, positive linear mode, broad peaks): (M + Na⁺) = ... 2298.4, 2370.8, 2442.9, 2515.2 ... (p = 26-29) for 400.56 + [72.11]p + 22.99 and minor array (M + K⁺) = ... 2317.1, 2389.5, 2461.3, 2533.2 ... (p = 26-29) for 400.56 + [72.11]p + 39.09. Calculated molecular weight of end group (C₂₁H₄₀N₂O₅; n=0): 400.56.

MeO-polyTHF2000-IPDA-NH₂ (polymer 12)

MeO-polyTHF2000-IPDA-Boc (11, 19 grams) was dissolved in DCM (100 mL) and TFA (60 mL). A nitrogen flow was bubbled through the solution, and the progress of the reaction was monitored by ¹H-NMR. Upon completion of the deprotection, the mixture was coevaporated two times with toluene followed by dissolution of the residue in chloroform. The organic layer was washed with a 0.5M NaOH solution (two times) and with a saturated NaCl solution (once), and then dried with Na₂SO₄. Filtration and concentration of the filtrate gave a yellowish oil. The crude product was purified by silica column chromatography starting the elution with 2 v/v% MeOH/CHCl₃ to remove impurities, then switching to 10 v/v% MeOH/CHCl₃ to collect the product. Yield: 10.3 grams. The polymer was a waxy solid.

¹H NMR (400 MHz, chloroform-d) δ 4.69 – 4.33 (NH, m, 1H), 4.06 (CH₂OCONH, d, 2H), 3.83 (CHN, s, 1H), 3.41 (CH₂O, m, ca. 130H), 3.33 (CH₃O, s, 3H), 2.49 (CH₂NH₂, s, 2H), 1.62 (CCH₂C and CH₂CH₂O, m, ca. 135H), 1.34 – 0.72 (NH₂₂, CH₃ and CCH₂C, m, 15H).

Found MALDI-TOF-MS array (CHCA matrix, positive reflector mode): (M + Na⁺) = ... 1765.4, 1837.5, 1909.5, 1981.6 ... (p = 20-23) for 300.44 + [72.11]p + 22.99. Calculated molecular weight of end group (C₁₀H₂₂N₂O₅; n=0): 300.44.

SEC (THF-RI): Mₙ= 5.0 kD, Mₘ = 6.8 kD, PD = 1.35. A lower than expected molecular weight and a higher than expected polydispersity is observed, presumably due to the amine terminated polymer adsorbing slightly onto the stationary phase.
Scheme S4: Synthesis route to the asymmetric polyether-urethane ionomer PUI-A2. (i) BB, pyridine, dioxane, reflux; (ii) Pd/C, H₂, dioxane; (iii) TFA, DCM.

In an iterative synthesis, and employing extension building block BB, poly-ether amine 12 was converted in 4 steps to PUI-A2 (Scheme S4). In the coupling reactions, BB was typically used in molar excess. After complete conversion of the coupling reaction, an amine functional scavenger resin was added to the reaction mixture to remove BB, and thus separate it from the desired PUI product. Debenzylation was required to arrive at the PUI-A2 end product.

MeO-polyTHF2000-IPDA-DMPA(Bn)-IPDA-Boc (polymer 13)

Building block molecule BB (0.31 g, 0.45 mmol, 2 molar equivalents) was dissolved in dioxane (3 mL) together with MeO-polyTHF2000-IPDA-NH₂ (polymer 12, 0.7 g, 0.23 mmol) and pyridine (72 µL, 4 equivalents). The mixture was heated to reflux for 16 hours and was kept under an atmosphere of argon. When the reaction was complete (¹H-NMR monitoring) a silica gel functionalized with amine groups (Silicycle Si-Amine catnr. R5203B loading 1.89 mmol/g) was added to react with the excess of building block BB. The mixture was stirred for 4 hours at the elevated temperature. After filtration of the reaction mixture to remove the resin, the filtrate was concentrated by evaporation of the solvent to yield a yellowish oil (780 mg).

¹H NMR (400 MHz, chloroform-d) δ 7.34 (Ar-H, m, 5H), 5.17 (CH₂Bn, s, 2H), 4.87 – 4.30 (NH, m, 4H), 4.22 (CH₂OCON, d, J = 8.0 Hz, 4H), 4.06 (CH₂CH₂OCON, dd, J = 11.9, 6.1 Hz, 2H), 3.77 (CHN, m, 2H), 3.62 – 3.35 (CH₂O, m, ca. 130H), 3.33 (CH₂O, s, 3H), 3.10 – 2.87 (CH₂N, m, 4H), 1.62 (CCH₂C and CH₂CH₂O, m, ca. 140H), 1.44 ((CH₃)₃, s, 9H), 1.40 – 0.70 (CCH₂C and CH₃C, m, 29H).

SEC (THF-RI): Mₙ = 6.9 kD, Mₘ = 8.3 kD, PD = 1.21.
Found MALDI-TOF-MS array (CHCA matrix, positive linear mode, broad peaks): (M + Na\(^+\)) = 2312.1, 2384.3, 2456.5 ... (p = 20-22) for 847.10 + [72.11]p + 22.99 and minor array (M + K\(^+\)) = 2330.0, 2401.9, 2473.4 ... (p = 20-22) for 847.10 + [72.11]p + 39.09. Calculated molecular weight of end group (C\(_{46}\)H\(_{74}\)N\(_{4}\)O\(_{11}\); n=1): 847.10.

MeO-polyTHF2000-IPDA-DMPA(Bn)-IPDA-NH\(_2\) (polymer 14)

MeO-pTHF2000-IPDA-DMPA(Bn)-IPDA-Boc (polymer 13, 3.4 g) was mixed with DCM (8 mL) and TFA (8 mL) and was stirred at r.t. overnight. The reaction mixture was concentrated and coevaporated two times with chloroform to remove the TFA. The product was dissolved in chloroform, and the solution was washed with a 0.1 M NaOH solution and then a NaCl saturated solution. The organic layer was dried with Na\(_2\)SO\(_4\), and concentrated to yield a yellowish oil (3.0 g; 95%).

\(^1\)H NMR (400 MHz, chloroform-d) \(\delta\) 7.40 – 7.28 (Ar-H, m, 5H), 5.15 (CH\(_2\)Bn, s, 2H), 4.65 (NH, m, 3H), 4.20 (CH\(_2\)OCON, br, 4H), 4.1 – 3.9 (CH\(_2\)CH\(_2\)OCON, br, 2H), 3.75 (CHN, m, 2H), 3.47 – 3.33 (CH\(_2\)O, m, ca. 140H), 3.32 (CH\(_3\)O, s, 3H), 2.90 – 2.7 (CH\(_2\)N, m, 2H), 2.35 (CH\(_2\)NH\(_2\), s, 2H), 1.95 – 1.51 (CCH\(_2\)C and CH\(_2\)CH\(_2\)O, m, ca. 150H), 1.32 – 0.60 (NH\(_2\), CCH\(_2\)C and CH\(_3\)C, m, 29H).

SEC (THF-RI): \(M_n=\) 5.8 kD, \(M_w=\) 7.4 kD, PD = 1.28. A lower than expected molecular weight and a higher than expected polydispersity is observed, presumably due to the amine terminated polymer adsorbing slightly onto the stationary phase.

Found MALDI-TOF-MS array (CHCA matrix, positive reflector mode): (M + Na\(^+\)) = 2067.5, 2139.7, 2211.6, 2283.7 ... (p = 18-21) for 746.99 + [72.11]p + 22.99. Calculated molecular weight of end group (C\(_{46}\)H\(_{74}\)N\(_{4}\)O\(_{11}\); n=1): 746.99.

MeO-polyTHF2000-IPDA-DMPA(Bn)-IPDA-DMPA(Bn)-IPDA-Boc (polymer 15)

MeO-pTHF2000-IPDA-DMPA(benz)-IPDA-NH\(_2\) (polymer 14, 695 mg; 0.21 mmol) was mixed with molecule BB (213 mg; 0.31 mmol, 1.5 molar equivalents) and pyridine (41 mg; 0.52 mmol, 2.5 molar equivalents) in dioxane (5 mL). The mixture was stirred under argon at an oil bath temperature of 115\(^\circ\)C for 16 hours. When the reaction was completed, as checked with \(^1\)H-NMR, a silica gel functionalized with amine groups (Silicycle Si-Amine catnr. R5203B loading 1.89 mmol/g) was added to react with the excess of BB. Accordingly, the reaction was stirred for another 2 hours, and was then filtrated. The filtrate was concentrated, taken up in chloroform and washed: two times with a 0.1 M NaOH solution and once with a saturated NaCl solution. The chloroform layer was dried with Na\(_2\)SO\(_4\) and concentrated to yield a yellowish oil (858 mg) that turned solid on cooling to 0\(^\circ\)C.

\(^1\)H NMR (400 MHz, chloroform-d) \(\delta\) 7.33 (Ar-H, m, 10H), 5.16 (CH\(_2\)Bn, s, 4H), 4.91 – 4.39 (NH, m, 6H), 4.22 (CH\(_2\)OCON, m, 8H), 4.06 (CH\(_2\)CH\(_2\)OCON, m, 2H), 3.96 – 3.72 (CHN, m, 3H), 3.62 – 3.35 (CH\(_2\)O, m, ca. 135H), 3.33 (CH\(_3\)O, s, 3H), 2.87 (CH\(_2\)N, m, 6H), 1.89 – 1.51 (CCH\(_2\)C and CH\(_2\)CH\(_2\)O, m, ca. 145H), 1.44 ((CH\(_3\))\(_3\), s, 9H), 1.35 – 0.71 (CCH\(_2\)C and CH\(_3\)C, m, 45H).

SEC (THF-RI): \(M_n=\) 7.1 kD, \(M_w=\) 8.7 kD, PD = 1.23.
Found MALDI-TOF-MS array (DCTB matrix, positive linear mode, broad): (M + Na\(^+\)) = ... 3263.1, 3335.4, 3407.4, 3479.8 ... (p = 27-30) for 1293.65 + [72.11]p + 22.99 and minor array (M + K\(^+\)) = ... 3281.8, 3355.3, 3427.0, 3497.9 ... (p = 27-30) for 1293.65 + [72.11]p + 39.09. Calculated molecular weight of end group (C\(_{66}\)H\(_{108}\)N\(_6\)O\(_{17}\); n=1): 1293.65.

MeO-polyTHF2000-IPDA-DMPA-IPDA-DMPA-IPDA-Boc (“PUI-A2”)

MeO-pTHF2000-IPDA-DMPA(Bn)-IPDA-DMPA(Bn)-IPDA-Boc (polymer 15; 828 mg) was mixed with Pd/C Degussa type catalyst (100 mg) in dioxane (4 mL). The reaction mixture was stirred for 3 days at r.t. under a hydrogen atmosphere. The suspension was filtrated over a plug of zeolite and the filtrate was concentrated to yield the product, a slightly yellowish oil (789 mg) that turned solid on cooling to 0\(^\circ\)C.

\(^1\)H NMR (400 MHz, chloroform-d) \(\delta\) 5.4 – 4.4 (COOH and NH, m, 8H), 4.22 (CH\(_2\)OCON, m, 8H), 4.06 (CH\(_3\)CH\(_2\)OCON, m, 2H), 3.75 (CHN, m, 3H), 3.60 – 3.35 (CH\(_2\)O, m, ca. 130H), 3.33 (CH\(_3\)O, s, 3H), 3.10 – 2.85 (CH\(_2\)N, m, 6H), 1.95 – 1.50 (CCH\(_3\)C and CCH\(_3\)CH\(_2\)O, m, ca. 140H), 1.44 ((CH\(_3\))\(_3\), s, 9H), 1.35 – 0.70 (CCH\(_2\)C and CH\(_3\)C, m, 45H).

SEC (THF-RI): \(M_n\) = 7.2 kD, \(M_w\) = 8.5 kD, PD = 1.19.

Found MALDI-TOF-MS array (CHCA matrix with added KAc, positive linear mode): (M + K\(^+\)) = ... 2017.2, 2090.5, 2161.5, 2234.5 ... (p = 12-15) for 1113.40 + [72.11]p + 39.09. Calculated molecular weight of end group (C\(_{55}\)H\(_{96}\)N\(_6\)O\(_{17}\); n=1): 1113.40.
2. ESI Figures and Tables of PUI synthesis

Figure S1: HPLC-MS/PDA chromatograms and spectrum of BB. Top: HPLC-MS (TIC). Middle: HPLC-PDA. Bottom: MS-spectrum, also showing fragments with lost Boc or t-Bu groups.
Figure S2: MALDI-TOF-MS of intermediate “MeO-polyTHF2000-IPDA-NH₂”, polymer 12. The inset is a zoom-in of the MS-spectrum: $(M + Na^+) = ... 1765.4, 1837.5, 1909.5, 1981.6 ... (p = 20-23)$ for $300.44 + [72.11]p + 22.99$. Matrix: CHCA. Mode: positive reflector.

Figure S3 MALDI-TOF-MS of PUI-S2 (A) and PUI-A2 (B). Matrix: CHCA with added KAc. Mode: positive linear. A) The inset is a zoom-in of the MS-spectrum: $(M + K^+) = ... 1795.1, 1867.6, 1939.4, 2011.6 ... (p = 5-8)$ for $1395.78 + [72.11]p + 39.09$. B) The inset is a zoom-in of the MS-spectrum: $(M + K^+) = ... 2017.2, 2090.5, 2161.5, 2234.5 ... (p = 12-15)$ for $1113.40 + [72.11]p + 39.09$. 
Table S1: Compilation of SEC data for PU-S0, PUI-S2 and PUI-A2. The molecular weight and distribution data are relative to polystyrene (PS) standards. Eluent: THF. Detection: RI.

| PU(I)-material | \( M_n \) (kDalton) | \( M_w \) (kDalton) | PD or \( M_w/M_n \) |
|----------------|----------------------|---------------------|---------------------|
| PU-S0          | 5.46                 | 8.57                | 1.57                |
| PUI-S2         | 6.40                 | 8.76                | 1.37                |
| PUI-A2         | 7.16                 | 8.53                | 1.19                |

Table S1 shows that the asymmetric PUI-A2 is more narrowly distributed than the symmetric PUI-S2. Apparently, the commercially available dihydroxy telechelic poly-tetrahydrofuran (MW = 2000), used as the starting point to prepare the symmetric PUI-S2, has a broader distribution that the cationically polymerized mono-hydroxy poly-tetrahydrofuran (MW = 2000) that was prepared as precursor to the asymmetric PUI-A2.
3. ESI Figures and Tables of LS study

**Figure S4** Dynamic viscosity as a function of $\varphi_{\text{solv}}$, THF (square), IPA (circle) and EtOH (triangle).

**Table S2** Refractive indices of water:THF, water:IPA and water:EtOH mixtures.

| $\varphi_{\text{solv}}$ | $n_{\text{THF}}$ | $n_{\text{IPA}}$ | $n_{\text{EtOH}}$ |
|-------------------------|------------------|------------------|------------------|
| 0.1                     | 1.34             | 1.34             | 1.34             |
| 0.2                     | 1.35             | 1.35             | 1.34             |
| 0.3                     | 1.36             | 1.36             | 1.35             |
| 0.4                     | 1.37             | 1.36             | 1.36             |
| 0.5                     | 1.38             | 1.37             | 1.36             |
Figure S5 Representative size distributions from DLS at $\phi_{\text{solv}} = 0.1$ (square), $\phi_{\text{solv}} = 0.2$ (circle) and $\phi_{\text{solv}} = 0.3$ (triangle) for PUI-S2 (A-C) and PUI-A2 (D-F) in water:EtOH (A, D), water:IPA (B, E) and water:THF (C, F) mixtures.

Figure S6 Static light scattering on PUI-S2 assemblies for water:THF (square), water:IPA (circle) and water:EtOH (triangle) mixtures at $\phi_{\text{solv}} = 0.1$ (solid symbols) and $\phi_{\text{solv}} = 0.3$ (open symbols). Dashed lines represent linear fits.