SUPPORTING INFORMATION

Synthesis of a new hydrophilic poly(ethylene glycol)-ionic liquid and its application in peptide synthesis.

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Experimental (Instrumentation, Analysis and Starting Materials).

All reagents were commercially available and used without any further purification, with the exception of pyrene and pyrene-1-carboxaldehyde (Aldrich), recrystallized from ethanol. Solvents utilized were of spectroscopic grade. Steady-state fluorescence spectra were acquired in a Spex Fluorolog 3-11 equipped with a 450 W xenon lamp. The data were acquired using the front-face configuration. The spectra were processed with the appropriate correction files. ^{1}H and ^{13}C NMR analyses were performed with Bruker Avance DPX 200 MHz, Bruker Avance AM 300 MHz or Bruker AC-400 MHz and are reported in *ppm* and calibrated using residual undeuterated solvents as an internal reference. Data are reported as: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in *Hz*, integration. The molecular weight of the poly(ethylene glycol)s was determined by MALDI mass spectrometry and the identification of modified PEG's by Mass Spectrometry was achieved by the computer program CALCPEG[1,2] (download free of charge at http://www.ibmm.univ-montp1.fr/CALCPEG), using data generated by Mass Spectrometry (MALDI or ESI). CALCPEG has been developed by the Department of Aminoacids, Peptides and Proteins of the Institut of Biomolecules Max Mousseron (IBMM, Montpellier - France). MALDI-TOF MS mass spectra were acquired on Ultraflex III (Bruker) in positif mode. The irradiation source was a solid-state laser. The α-cyano-4-hydroxycinnamic acid (CHCA) was used as matrix. A solution of CHCA (10mg/mL) and a product solution were mixed in a ratio of 10:1 v/v. A 1 µL aliquot of the matrix/product mixture was deposited and air dried. External mass calibrations were performed with a standard peptide mixture. For MeO-PEG_{350}-Br (**2**) a solution of sodium iodide (10mg/mL) is also added (CHCA: product solution: NaI in a ratio 10:1:1 v/v/v). The analyses were recorded in reflector mode. Mass spectra were analyzed with FlexAnalysis software. Mass spectra (electrospray ionization mode, ESIMS) were recorded on a Micromass (Manchester, UK) Q-TOF quadrupole mass spectrometer fitted with an electrospray interface. The mass spectrometer was calibrated in the positive- and negative-ion ESI mode. The samples were dissolved in a mixture H_2O/CH_3CN (50/50 v/v). Microwave-assisted reactions were performed in sealed vessels with a Biotage Initiator 60 EXP® instrument. The temperature was measured with an IR sensor on the outer surface of the reaction vial. Analytical high performance liquid chromatography (HPLC) was performed on a Waters Millenium 717 equipped with an Autosampler, with a variable wavelength diode detector using a CHROMOLITH RP18 column (50 x 4,6 mm), flow 5 mL/min, linear gradient CH_3CN in water 0-100% (+ 0.1% TFA) in 4.5 min or on a Beckman System Gold 126 instrument with a variable detector and the following conditions :

column Chiracel OD, 5, (250 × 10 mm), flow: 1 mL/min, hexane/2-propanol: 95:5 v/v. Spectral data of dipeptides **6**,[3] **7**,[4] **8**,[5, 6] **9**[7] and **12**[8] are identical to those previously described.

MeO-PEG$_{350}$-Br (2). To a previously dried and degassed round bottomed flask, equipped with a rubber septum, commercial MeO-PEG$_{350}$-OH **(1)** (8.04 g, 19.5 mmol) was added and held under dynamic vacuum at 60°C for 6 hours. Then, at room temperature and under a nitrogen atmosphere, anhydrous 1,4-dioxane (30 ml) was added to the degassed reaction vessel and the round bottom flask, under static vacuum, was then frozen in a liquid nitrogen bath. Whilst keeping the vessel under static vacuum, the frozen solution was left to warm up to room temperature until all the solid had liquified. The vacuum freezing/defreezing step was repeated twice. Nitrogen was then flushed into the flask, and the solution was cooled to 0°C and kept at this temperature for 1 h. PBr_3 (3.17 g, 11.8 mmol) was added dropwise to the rapidly stirred solution over a period of 15-30 minutes. The solution was then heated to 50ºC and stirred at this temperature for 20 h. The 1,4-dioxane was eliminated by evaporation *in vacuo* and the crude oil obtained was diluted with water (50 mL) and then treated with aqueous Na_2CO_3 solution (10%) until a neutral solution was obtained. The aqueous phase was washed with $CHCl_3$ (3 x 50 mL), dried over $MgSO_4$, and the organic phase was filtered. The chloroform was eliminated by evaporation *in vacuo* affording pure MeO-PEG$_{350}$-Br (**2**) (8.42 g, 97% yield) as a pale yellow liquid.
^{1}H NMR (300 M*Hz*, $CDCl_3$) δ (ppm): 3.78 (t, J = 6.35 *Hz*, 2H, OCH_2CH$_2$Br), 3.68-3.60 (m, 32H, -[OCH_2CH_2O]$_n$-), 3.45 (t, J = 6.35 *Hz*, 2H, OCH$_2$CH_2Br), 3.35 (s, 3H, OCH_3).^{13}C NMR (300 M*Hz*, $CDCl_3$) δ (ppm): 71.93 (CH_3OCH_2), 71.21 ($CH_3OCH_2CH_2$), 70.66 (-[OCH$_2$CH_2O]$_n$-), 70.58 (CH$_2$OCH$_2$CH$_2$Br), 70.53 (OCH$_2$CH$_2$Br), 59.04 (CH_2Br), 30.32 (CH_3O). MALDI TOF (+) *m/z*: 468.459/470.461 $[M+Na]^+$.

[MeO-PEG$_{350}$-N(Me)$_2$-PEG$_{350}$-OMe] [Br] (3). MeO-PEG$_{350}$-Br **(2)** (6.31 g, 15.30 mmol) was heated to 50°C and was then kept under vacuum for 30 minutes. The solution was then allowed to cool to room temperature under a nitrogen atmosphere, and absolute ethanol (4 mL) was added. The round bottom–flask was then degassed under vacuum and then finally kept under nitrogen at -15°C, before adding gaseous *N*,*N*-dimethylamine (0.345 g, 7.65 mmol). The reaction mixture was brought to room temperature and stirred for 72 h. At the end of the reaction the solvent was eliminated by evaporation *in vacuo*, the crude product was recovered with $CHCl_3$ (30 mL) and the organic phase washed with a saturated solution of

Na_2CO_3 (2 x 20 mL) and water (20 ml). The organic phase was dried over Na_2SO_4, filtered and evaporated to afford [MeO-PEG_{350}-$N(Me)_2$-PEG_{350}-OMe] [Br] (**3**) (15.77 g, 97 % yield) as a viscous deep orange liquid.

^{1}H NMR (300 M*Hz*, $CDCl_3$) δ (ppm): 3.95 (s_{braod}, 8H, OCH_2CH_2N), 3.68-3.54 (m, 64H, -$[OCH_2CH_2O]_n$-), 3.45-3.32 (m, 8H, OCH_2CH_2N), 3.34 (s, 6H, OCH_3), 2.73 (s_{braod}, 6H, $N(CH_3)_2$).^{13}C NMR (300 M*Hz*, $CDCl_3$) δ (ppm): 71.63 (CH_3OCH_2), 70.24 ($CH_3OCH_2CH_2$), 70.21 (-$[OCH_2CH_2O]_n$-), 70.02 ($CH_2CH_2OCH_2CH_2N$), 69.92 ($CH_2CH_2OCH_2CH_2N$), 64.36 (NCH_2CH_2), 58.74 (OCH_3), 52.64 (CH_3NCH_3). MALDI TOF (+) *m/z*: 690.500 $[M+H]^+$.

[MeO-PEG_{350}-$N(Me)_2$-CH_2CH_2- $N(Me)_2$-PEG_{350}-OMe] [2Br] (14). The synthesis has been carried out in the same experimental conditions as for [MeO-PEG_{350}-$N(Me)_2$-PEG_{350}-OMe] [2Br] (**3**). The alkylation reaction of MeO-PEG_{350}-Br (**2**) (2.0 equiv) has been realized in the presence of *N,N,N'N'*-tetramethylethylenediamine (1.0 equiv.) at room temperature (72 h), affording [MeO-PEG_{350}-$N(Me)_2$-CH_2CH_2- $N(Me)_2$-PEG_{350}-OMe] [2Br] (**14**) (14.54 g, 95 % yield) as a viscous clear liquid. ^{1}H NMR (300 M*Hz*, $CDCl_3$) δ (ppm): 4.68-4.55 (m, 4H, NCH_2CH_2N), 3.95 (s_{braod}, 8H, OCH_2CH_2N), 3.80-3.45 (m, 64H, -$[OCH_2CH_2O]_n$-), 3.45-3.32 (m, 8H, OCH_2CH_2N), 3.34 (s, 6H, OCH_3), 2.73 (s_{braod}, 12H, $N(CH_3)_2$).

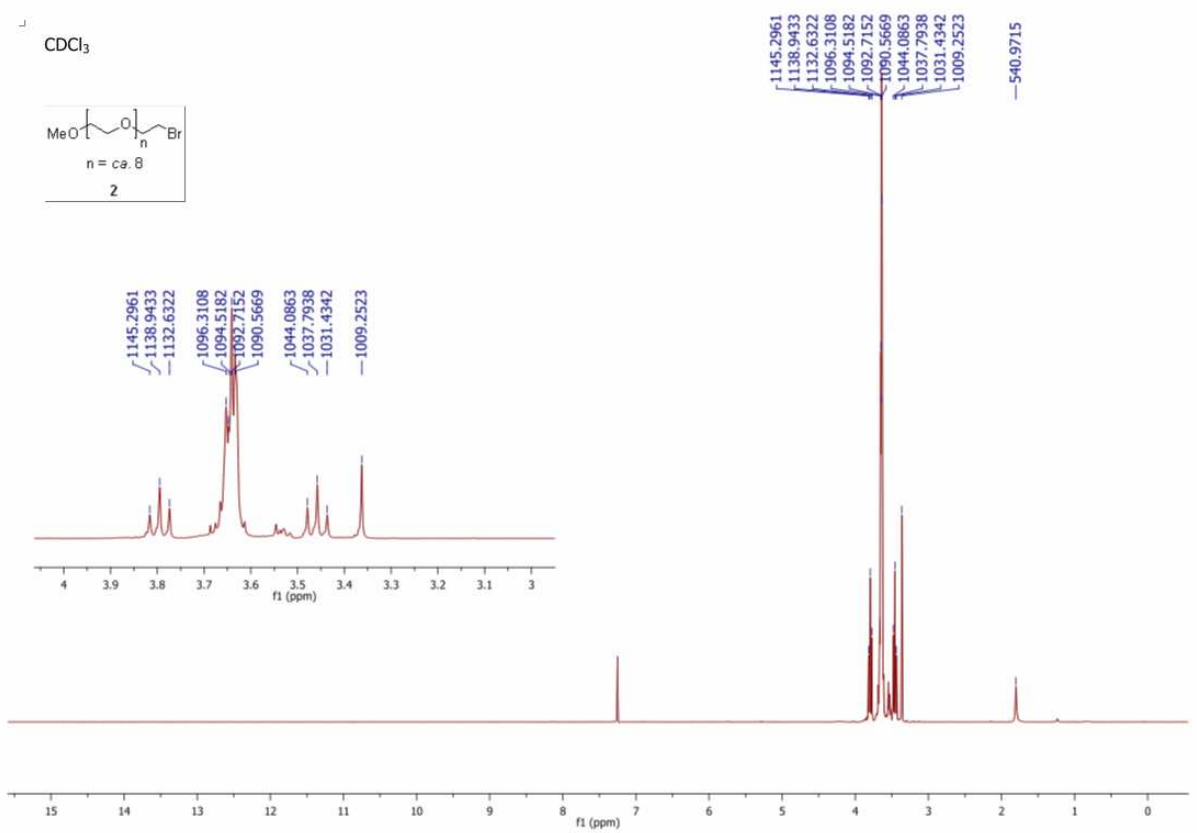

Figure 1. ^{1}H NMR spectra of **MeO-PEG$_{350}$-Br (2).**

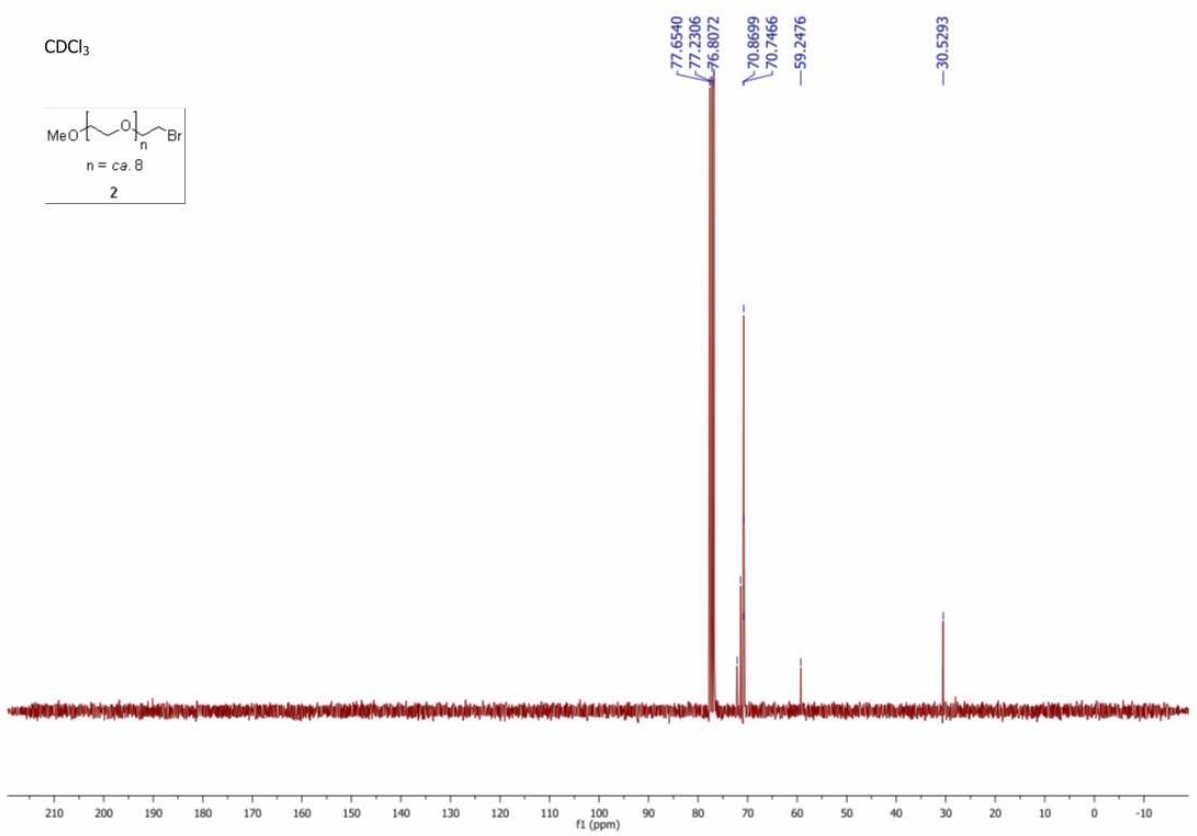

Figure 2. ^{13}C NMR spectra of **MeO-PEG$_{350}$-Br (2).**

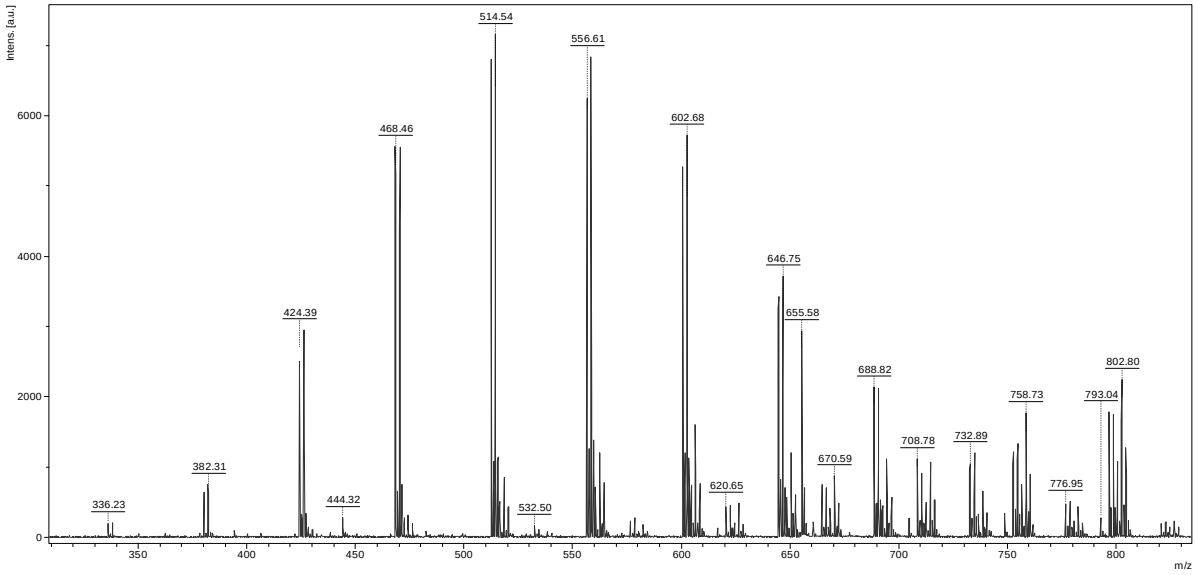

Figure 3. MALDI mass spectra of **MeO-PEG$_{350}$-Br (2).**

Table 1. MALDI mass spectra analysis of **MeO-PEG$_{350}$-Br (2)**, by CALCPEG program[1, 2] for R = ^{79}Br isotope.

MeOPEG-R			Average Mol. Weight		
R (Dalton)	79.00		**Precision Criteria**		0.05
Pics	**Charge**	***n*-mers**	**Ions**	**Precision**	**Theoretical Value**
336.23	1	5	1 Na^+	0.02	337.29
380.30	1	6	1 Na^+	0.02	381.34
424.39	1	7	1 Na^+	0.02	425.39
468.46	1	8	1 Na^+	0.02	469.45
512.53	1	9	1 Na^+	0.02	513.50
556.61	1	10	1 Na^+	0.02	557.55
600.68	1	11	1 Na^+	0.02	601.60
644.75	1	12	1 Na^+	0.02	645.66
690.83	1	13	1 Na^+	0.03	689.71

Table 2. MALDI mass spectra analysis of **MeO-PEG$_{350}$-Br (2)**, by CALCPEG program[1, 2] for R = ^{81}Br isotope.

MeOPEG-R			Average Mol. Weight		
R (Dalton)	81.00		**Precision Criteria**		0.05
Pics	**Charge**	***n*-mers**	**Ions**	**Precision**	**Theoretical Value**
338.22	1	5	1 Na^+	0.02	339.29
382.31	1	6	1 Na^+	0.02	383.34
426.38	1	7	1 Na^+	0.02	427.39
470.46	1	8	1 Na^+	0.02	471.45
514.54	1	9	1 Na^+	0.02	515.50
558.61	1	10	1 Na^+	0.02	559.55
602.68	1	11	1 Na^+	0.02	603.60
646.75	1	12	1 Na^+	0.02	647.66
690.83	1	13	1 Na^+	0.02	691.71

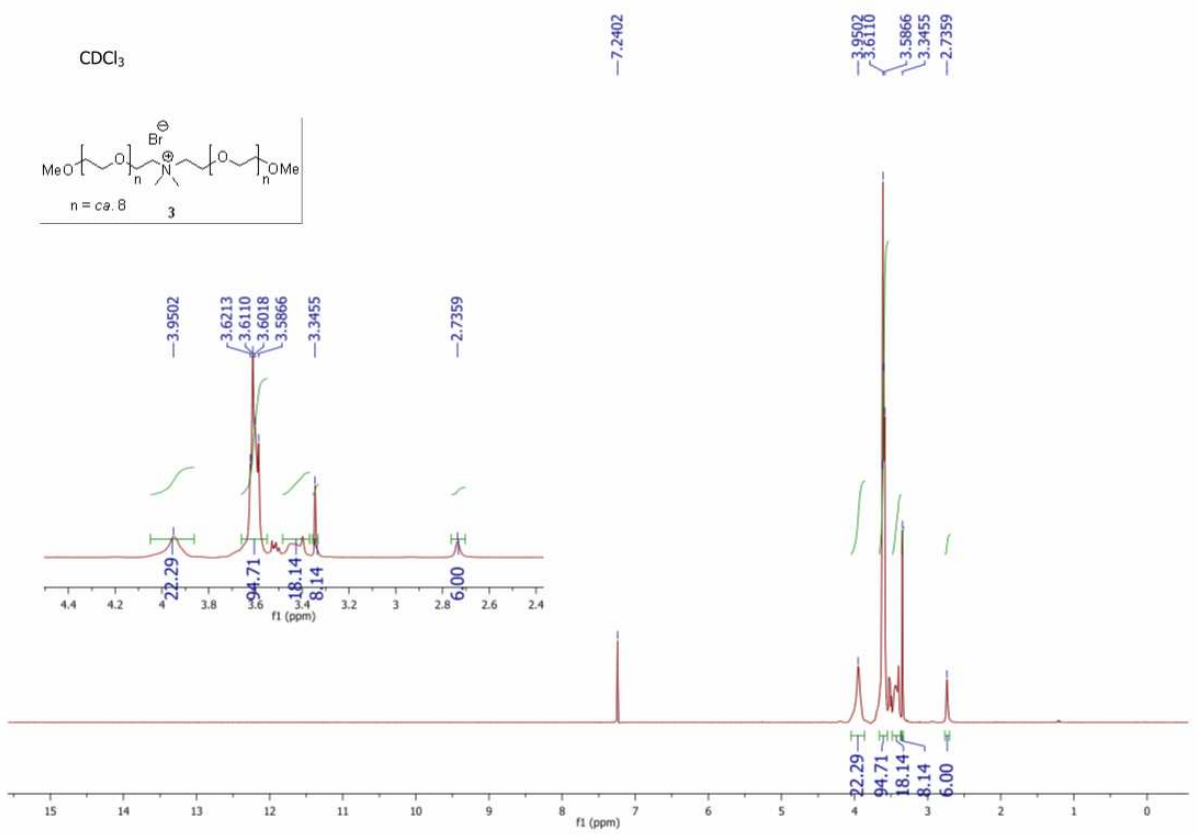

Figure 4. [1] H NMR spectra of **[MeO-PEG$_{350}$-N(Me)$_2$-PEG$_{350}$-OMe][Br] (3)**.

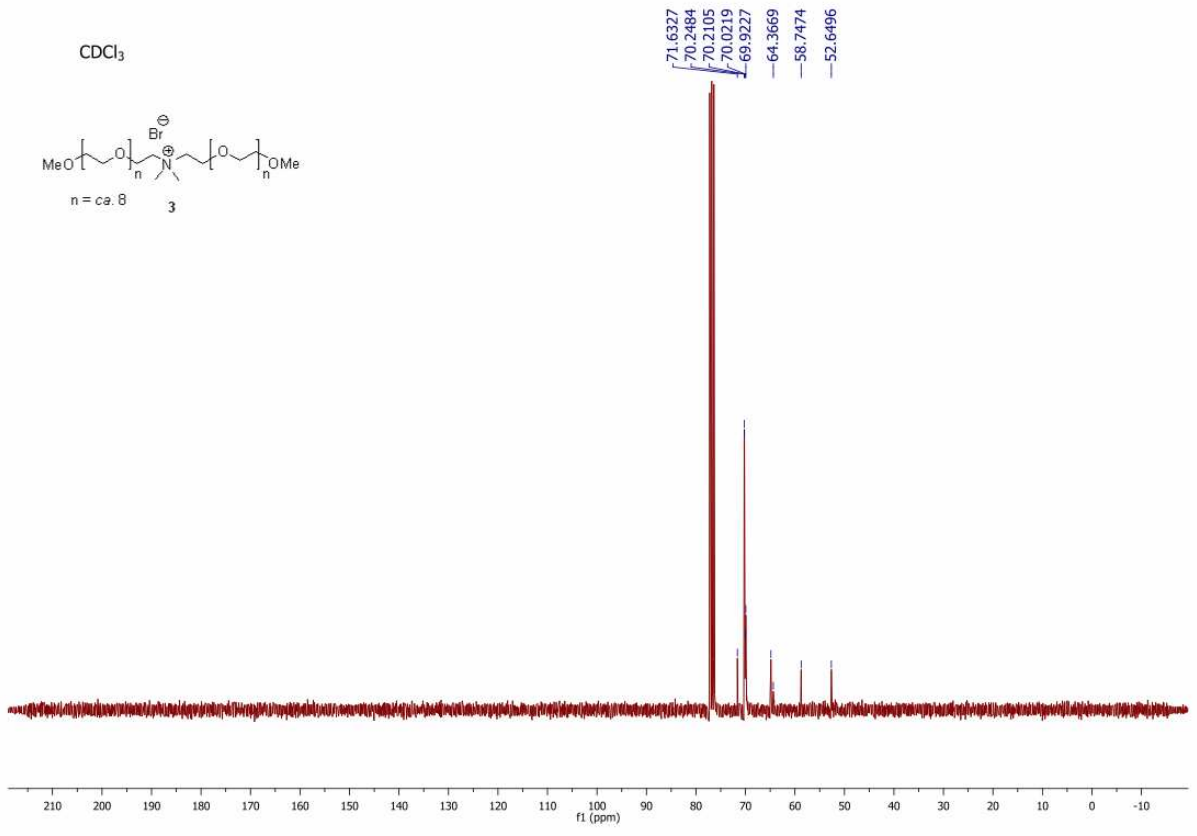

Figure 5. [13] C NMR spectra of **MeO-PEG$_{350}$-N(Me)$_2$-PEG$_{350}$-OMe][Br] (3)**.

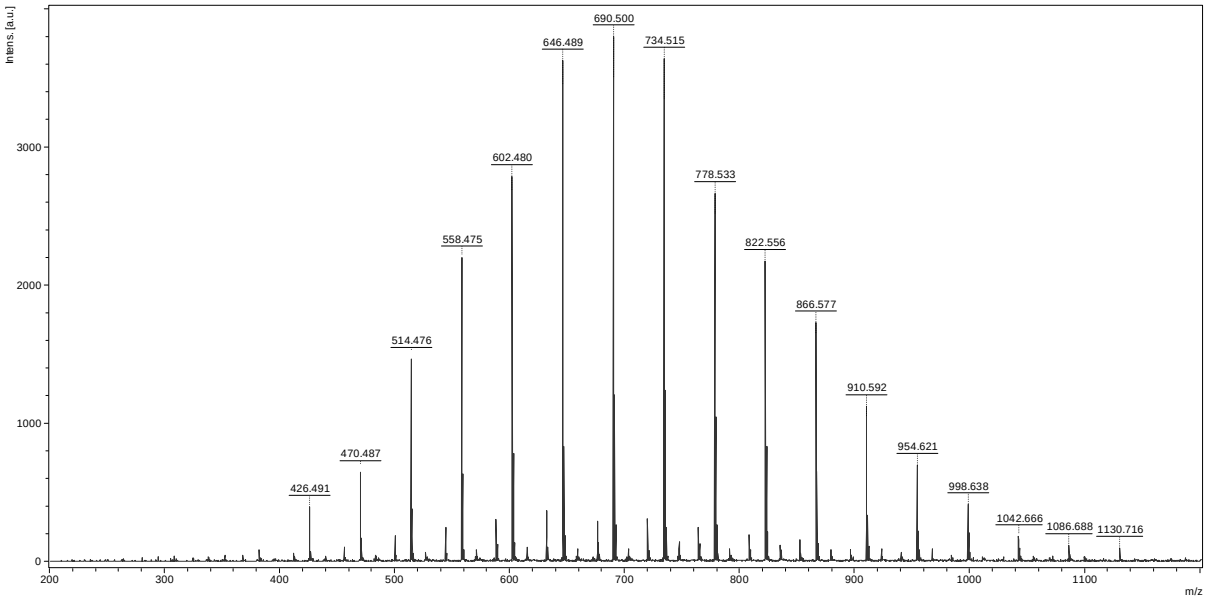

Figure 6. MALDI mass spectra of **[MeO-PEG$_{350}$-N(Me)$_2$-PEG$_{350}$-OMe][Br] (3)**.

Table 3. MALDI mass spectra analysis of **[MeO-PEG$_{350}$-N(Me)$_2$-PEG$_{350}$-OMe][Br] (3)**, by CALCPEG program,[1, 2] with R = -N(Me)$_2$-[CH$_2$CH$_2$O]$_8$-Me.

MeOPEG-R		Average Mol. Weight			
R (Dalton)	411.00		**Precision Criteria**		0.05
Pics	**Charge**	***n*-mers**	**Ions**	**Precision**	**Theoretical Value**
470.49	1	1	1 H^+	0.01	471.10
514.48	1	2	1 H^+	0.02	515.15
558.48	1	3	1 H^+	0.02	559.20
602.48	1	4	1 H^+	0.02	603.25
646.49	1	5	1 H^+	0.02	647.31
690.50	1	6	1 H^+	0.02	691.36
734.52	1	7	1 H^+	0.02	735.41
778.53	1	8	1 H^+	0.02	779.46
822.56	1	9	1 H^+	0.02	823.52
866.58	1	10	1 H^+	0.02	867.57
910.59	1	11	1 H^+	0.02	911.62
954.62	1	12	1 H^+	0.02	955.67

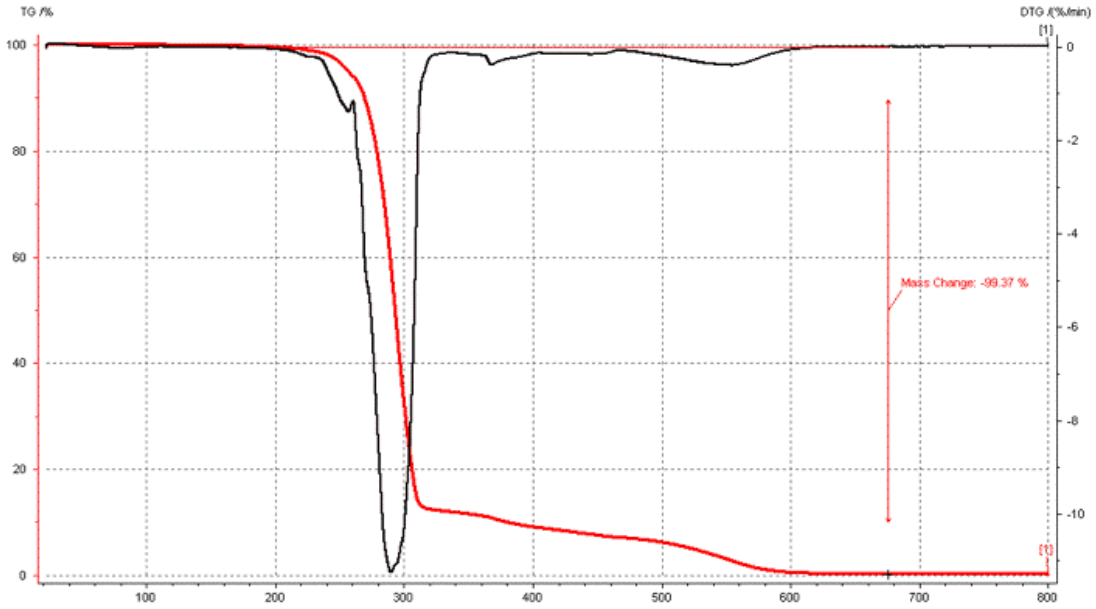

Figure 7. TGA curve of **[MeO-PEG$_{350}$-N(Me)$_2$-PEG$_{350}$-OMe][Br] (3)**

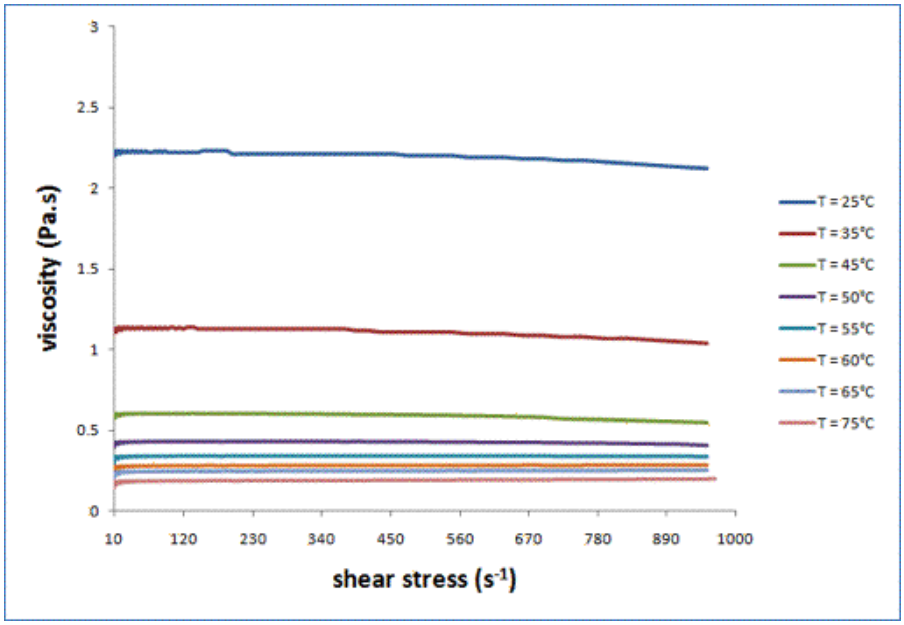

Figure 8. Temperature dependent viscosity curve of **[MeO-PEG$_{350}$-N(Me)$_2$-PEG$_{350}$-OMe][Br] (3).**

Table 4. Temperature dependent viscosity of **[MeO-PEG$_{350}$-N(Me)$_2$-PEG$_{350}$-OMe][Br] (3)**.

T (°C)	**Viscosity** (Pa.s)
25	2.230
35	2.190
45	0.605
50	0.434
55	0.338
60	0.287
65	0.251

Fluorescence measurements for [MeO-PEG$_{350}$-N(Me)$_2$-PEG$_{350}$-OMe][Br] (3) (referred to as PEG$_{700}$-IL).

To estimate the polarity of PEG$_{700}$-IL **3**, a series of spectroscopic measurements were made, with pyrene and pyrene-1-carboxaldehyde as fluorescent probes. In many cases, the fluorescence emission of pyrene-1-carboxaldehyde has been reported to strongly depend on the dielectric constant of the medium.[9, 10] In non-polar solvents like cyclohexane or *n*-hexane the fluorescence arises from a n-π^* level, the spectrum is composed of several vibronic bands appearing around 390-410 nm. In the case of polar solvents, the π-π^* level is stabilized becoming lower in energy than the n-π^* level. As a consequence, the emission occurs from the lower energy π-π^* level (higher wavelengths) and the shape of the spectrum is characteristically broad. It is estimated that the equilibration of energies of the n-π^* and π-π^* levels takes place in solvents with $\varepsilon > 10$.

A sample of pyrene-1-carboxaldehyde (*ca.* 5 x 10^{-6} M) was dissolved in PEG$_{700}$-IL **3** and excited with light at $\lambda = 345$ nm. The recorded spectrum is a very broad band around 410-450 nm with no defined maximum (Figure 1). This emission is clearly different from the fluorescence presented by the same probe in *n*-hexane (Figure 9) and more similar to other polar solvents like methanol or acetonitrile, suggesting a dielectric constant above 10. However, the large width of the fluorescence band in PEG$_{700}$-IL **3** impedes a more precise estimation of its polarity. It has been reported that the fluorescence maximum for the emission of the same probe in [BMIM][PF_6] and in [EtMeIm][Tf_2N] are respectively at 428 nm[11] and 431 nm,[12] thus indicating a moderate polarity of the medium. The fluorescence results for PEG$_{700}$-IL **3** show similar polarities. A possible explanation for the anomalous shape of the recorded spectrum could be that the high viscosity of PEG$_{700}$-IL **3** might favour aggregation

of the polymer around the probe. The possibility of excimer formation[13] (a complex between two probe molecules, one in the excited state and the other one in the ground state) is ruled out, since the excimer of pyrene-1-carboxaldehyde is described to appear at 530 nm in non-polar solvents[10] and at 560 nm in polar solvents.[10]

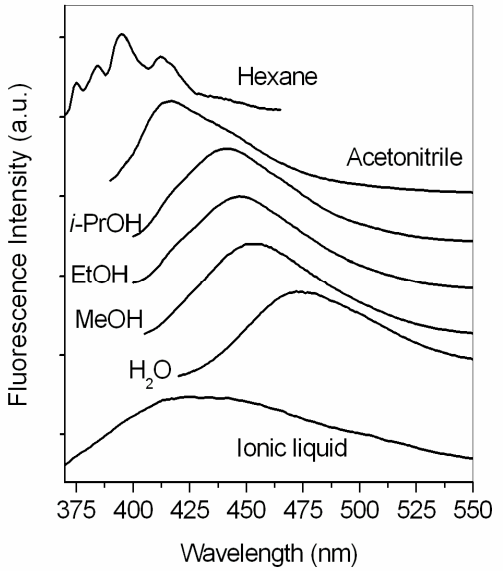

Figure 9. Normalized fluorescence spectra of pyrene-1-carboxaldehyde in different solvents. PEG_{700}-IL **3** is referred to as ionic liquid. Excitation at λ = 345 nm. Probe concentration: *ca.* 5 x 10^{-6} M.

In order to get a deeper insight into the physical characterization of PEG_{700}-IL **3**, pyrene was used as second fluorescent probe. The emission of pyrene is very structured, and the relative intensities of bands I and III are dependent on the polarity of the probe's environment. In fact, the third band (band III at *ca*. 384 nm) is solvent-insensitive, but the 0-0 band (or band I at *ca*. 373 nm) gains considerable intensity in polar solvents.[14] This feature allowed the construction of an empirical polarity scale based on the I/III ratio (or *py* scale).[15,16] It should be noted that the scale is empirical, and allows only estimations of similarities between solvents. Besides, it is best to measure the *py* value in the series of solvents being compared using exactly the same experimental conditions. Using this method, the fluorescence of pyrene (*ca*. 5 x 10^{-6} M) was measured in solvent PEG_{700}-IL **3** as well as in *n*-hexane, methanol and acetonitrile (Figure 10).

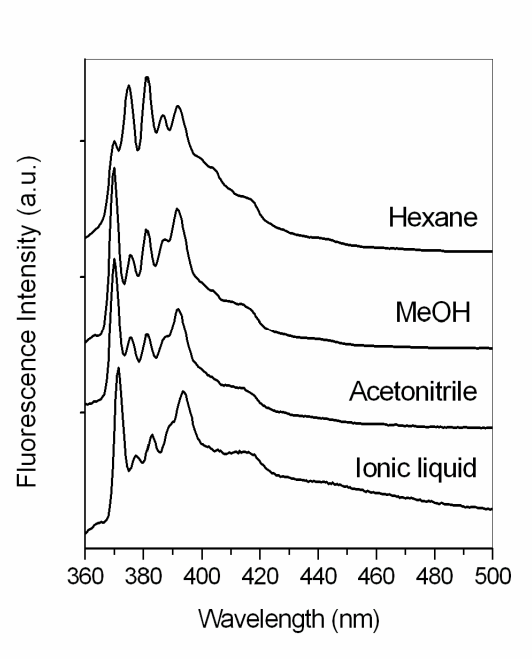

Figure 10. Normalized fluorescence spectra of pyrene in several solvents. Excitation at λ = 338 nm. Probe concentration: *ca*. 5 x 10^{-6} M.

The I/III ratios were calculated and after correction of the fluorescence spectra, which took into account the instrumental response, yielded: 0.63 (*n*-hexane), 1.50 (methanol), 1.68 (PEG_{700}-IL **3**) and 1.83 (acetonitrile). The values obtained for the non-ionic liquids are in concordance with values found in literature.[11] The I/III ratio displayed by pyrene in PEG_{700}-IL **3** suggests that the polarity experienced by the probe is in between that of methanol and acetonitrile. A *py* value of 1.84 has been reported for pyrene in [BMIM][PF_6][11] which could indicate that PEG_{700}-IL **3** has a lower *apparent* polarity than that of the widely utilized imidazolium-type ionic liquid.

General procedure for peptide synthesis.

The [MeO-PEG_{350}-$N(Me)_2$-PEG_{350}-OMe][Br] (**3**) (0.5 mL) was introduced in a 0.5-2.0 mL microwave reactor. Then, the *N*-protected amino acid (0.283 mmol), the amino ester hydrochloride (0.311 mmol), the coupling reagent (HATU or EDC/HOBT, refer to Table 2 for respective quantities) and *N*,*N*-diisopropyl-*N*-ethylamine (3.3 equiv. with respect to the coupling agent) were introduced into the reactor and the mixture was stirred with gentle heating at 30°C, until the medium homogenized. The mixture was successively heated under microwave irradiation at 65°C for 2 hours. The crude was diluted with water (0.5 mL), and the dipeptide was extracted from the ionic phase after washing with Et_2O (20 mL x 3). The

organic phase was dried on $MgSO_4$, filtered and evaporated to afford the dipeptide as a pure compound.

Boc-Phe-Lys-(Z)-O*t*Bu (10): ^{1}H NMR ($CDCl_3$, 300 M*Hz*), δ (ppm): 7.45–7.10 (m, 10 H, ArH), 6.70 (s_{broad}, 1H, NH_{Phe}), 5.45 (s_{broad}, 1H, NHCOO$_{Lys}$), 5.22 (s_{broad}, 1H, NH_{Lys}), 5.12 (s, 2H, PhCH_2-O), 3.28-2.90 (m, 4H, CH_2Ph and CH_2NHCO), 4.45-4.30 (m, 2H, CH_{Phe} and CH_{Lys}), 1.40 [s, 9H, NHCO$_2$C(CH_3)$_3$], 1.30 [s, 9H, CO$_2$C(CH_3)$_3$], 1.85–1.12 [m, 6H, (CH_2)$_3$]. ESI (+) *m/z* : 606 $[M + Na]^+$; 584 $[M + H]^+$; 528 $[(M - t\text{Bu}) + H]^+$; 484 $[(M - CO_2t\text{Bu}) + H]^+$; 428 $[(M - 2t\text{Bu}) + H]^+$.

Boc-Phe-Glu-(OBzl)-O*t*Bu (11): ^{1}H NMR ($CDCl_3$, 300 M*Hz*), δ (ppm): 7.35–7.10 (m, 10 H, ArH), 6.60 (d, 1H, *J* = 7.55 *Hz*, NH_{Phe}), 5.12 (s_{broad}, 3H, PhCH_2O and NH_{Glu}), 4.45-4.25 (m, 2H, CH_{Phe} and CH_{Glu}), 2.95 (d, 1H, *J* = 6.41 *Hz*, CHCH_2Ph), 2.32-2.12 (m, 4H, CH_2CH_2), 1.40 [s, 9H, CHCO$_2$C(CH_3)$_3$], 1.30 [s, 9H, NHCO$_2$C(CH_3)$_3$]. ESI (+) *m/z* : 563 $[M + Na]^+$; 541 $[M + H]^+$; 485 $[(M - t\text{Bu}) + H]^+$; 441 $[(M - CO_2t\text{Bu}) + H]^+$; 429 $[(M - 2t\text{Bu}) + H]^+$.

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Abbreviation list

Ala	*L*-Alanine
[BMIM][PF6]	Butylmethyl imidazolium hexafluorophosphate ionic liquid
Boc	*t*-Butyl carbamate (protection for the amino group)
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride (coupling agent)
DCC	Dicyclohexylcarbodiimide (coupling agent)
DIPEA	*N*,*N*-Diisopropyl-*N*-ethylamine (coupling agent)
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (coupling agent)
Gly	*L*-Glycine
HATU	2-(1*H*-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate (precursor of coupling agent)
HOBT	N-Hydroxybenzotriazole
IL	Ionic Liquid
Leu	*L*-Leucine
Lys	*L*-Lysine
PEG	Poly(ethylene glycol)
Phe	*L*-Phenylalanine
O-*t*-Bu	*t*-Butyl ester (protection for the carboxyl group)
OBzl	Benzyl ester (protection for the carboxyl group)
TMEDA	*N*,*N*,*N'N'*-tetramethylethylendiamine
Z	Benzyloxy-carbonyl (Z) group (protection for the amino group)