Supplementary Material (ESI) for Chemical Communications

Supporting Information

Influence of EDA-π interactions in drug encapsulation using nanospheres

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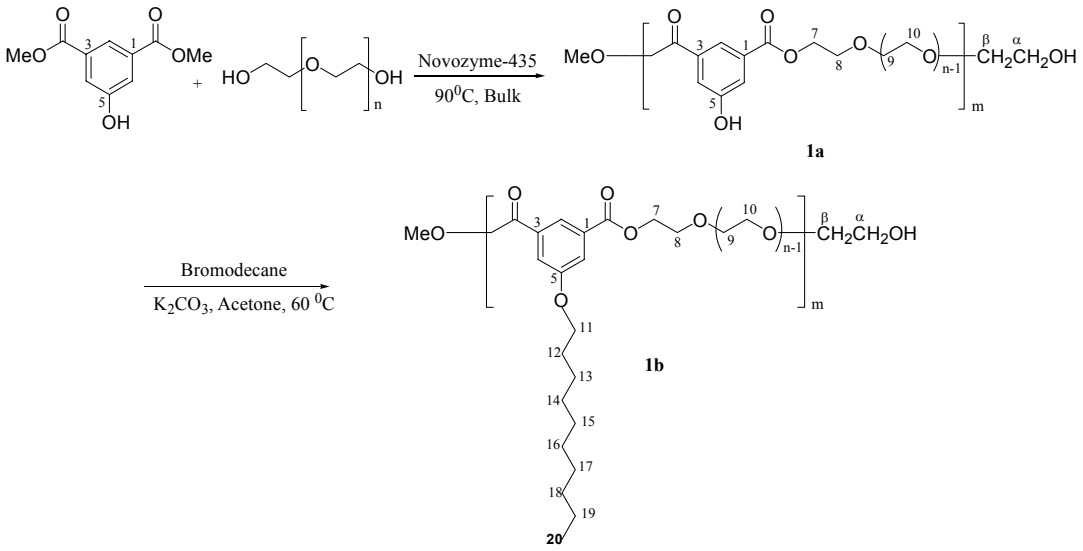
Experimental Section

Materials. Novozyme-435, an immobilized enzyme, was a gift from Novozyme Inc., Denmark and was dried over P_2O_5 under vacuum prior to use. Polyethylene glycol was dried under vacuum for 24 h before use and acetone was dried by distillation over fused potassium carbonate. All other chemicals and solvents were of analytical grade and were used as received unless otherwise noted.

Instrumentation. Gel permeation chromatography (GPC) was used to determine the molecular weights and molecular weight distributions, Mw/Mn of polymer samples. ^{1}H NMR spectra were recorded on Bruker Instrument Inc. DPX 500 spectrometer at 500 MHz. Static light scattering data was collected on a laser light scattering photometer (Wyatt Technology DAWN model F) equipped with a 632 nm He-Ne laser as the light source.

Polymerization: Dimethyl 5-hydroxyisophthalate (1.0 mmol) and PEG 600 (1.0 mmol) were placed in a round bottom flask. To this mixture was added the enzyme (10% by weight w.r.t. total monomers weight) and the reaction vial was then placed in a constant temperature oil bath maintained at 90 ^{o}C under vacuum. The reaction was allowed to proceed for 48 hr, it was then quenched by adding water and filtering off the enzyme and any unreacted isophthalate monomer under vacuum. The filtrate was dialyzed using membrane (MWCO 6000). After the completion of dialysis, the product polymer **1a** was obtained as a white solid by freeze-drying.



Scheme 1. Chemoenzymatic synthesis of amphiphilic polymer **1b**.

^{1}H NMR spectral analysis: ^{1}H NMR spectra were recorded using 5mm tubes and DMSO-d_6 as external standard in WILMAD coaxial insert tubes. All the NMR spectra were recorded at 30 ^{o}C unless otherwise specified.

Poly[poly(oxyethylene-600)-oxy-5-hydroxyisophthaloyl] (1a):

^{1}H NMR Data ($CDCl_3$): δ 3.60-3.79 (*bs*, methylene protons of PEG main chain), 3.86 (*t*, 2H, C-8H), 3.96 (*s*, -$COOCH_3$ end group), 4.50 (*t*, 2H, C-7H), 7.75 (*s*, 2H, C-4H and C-6H) and 8.24 (s, 1H, C-2H); M_n (GPC) 18000 Da.

Coupling of bromodecane with poly[poly(oxyethylene-600)-oxy-5-hydroxyisophthaloyl], 1a:

Polymer **1** and bromodecane (in equimolar quantities) were dissolved in anhydrous acetone and to the resultant solution was added equimolar amount of anhydrous potassium carbonate. The reaction mixture was refluxed and progress of the reaction was monitored by TLC using ethyl acetate in petroleum ether (30%) as solvent. After completion, the potassium carbonate was removed by filtration and the solvent was removed under vacuum to give the product polymer **1b**.

Poly[poly(oxyethylene-600)-oxy-5-decanyloxyisophthaloyl] (1b)

^{1}H NMR Data ($CDCl_3$): δ 0.90 (*t*, 3H, C-20H), 1.30-1.40 (*bm*, CH_2 protons of the side chain), 1.81 (*m*, 2H, C-12H), 3.66-3.69 (*bs*, CH_2 protons of PEG main chain), 3.87 (*t*, 2H, C-8H), 3.96 (*s*, -$COOCH_3$ end group), 4.10 (*t*, 2H, C-11H), 4.51 (*t*, 2H, C-7H), 7.77 (*m*, 2H, C-4H and C-6H) and 8.30 (*s*, 1H, C-2H); M_n(GPC) 18730 Da.

Method for encapsulation of hydrophobic drugs by polymeric nanospheres: The copolymer **1b** and the hydrophobic drug (aspirin) were dissolved in chloroform to obtain 1:5 drug/polymer w/w ratios and mixed for 15 minutes. Organic solvent was removed under vacuum and the highly viscous mixture of drug and polymer obtained was dissolved with an extensive vortexing in water to form nanoparticles. Non-incorporated aspirin was separated by filtration of nanoparticle suspension through a 0.2 μm filter (aspirin crystals as well as the crystals of other insoluble compounds under normal circumstances cannot pass through the filter unless it is solubilized by nanoparticles). For ^{1}H NMR spectral analysis, aspirin was dispersed in aqueous solution at the same concentration as in nanoparticle containing samples by following exactly the same procedure except adding the polymer. In the absence of polymer only a small fraction (less than 1%) of aspirin could be dissolved. The aspirin encapsulation was estimated (20% of nanoparticle weight) by UV spectroscopy using a calibration curve for aspirin in methanol, the efficiency of aspirin encapsulation was found to be 80%. Thus the drug that passes the filter in the presence of polymer must be encapsulated by nanoparticles. The preparation and estimation of % encapsulation of naproxen and other compounds were performed as described above for aspirin.

Figures S1-S8 1H NMR spectra of representative encapsulated and related compounds

Figure S1. ^{1}H NMR spectrum of 2-acetoxybenzoic acid: (a) in D_2O, (b) in nanospheres of co-polymer **1b**.

Figure S2. Full ^{1}H NMR spectrum of 2-acetoxybenzoic acid: (a) in D_2O, (b) in nanospheres of co-polymer **1b**.

Figure S3. ^{1}H NMR spectrum of methyl 2-acetoxybenzoate: (a) in D_2O, (b) in nanosphere of co-polymer **1b**.

Figure S4. Full ^{1}H NMR spectrum of methyl 2-acetoxybenzoate: (a) in D_2O, (b) in nanosphere of co-polymer **1b**.

Figure S5. ^{1}H NMR spectrum of 2-nitrobenzoic acid: (a) in D_2O, (b) in nanosphere of co-polymer **1b**.

Figure S6. ^{1}H NMR spectrum of 3-nitrobenzoic acid: (a) in D_2O, (b) in nanosphere of co-polymer **1b**.

Figure S7. ^{1}H NMR spectrum of 4-nitrobenzoic acid: (a) in D_2O, (b) in nanosphere of co-polymer **1b**.

Figure S8. ^{1}H NMR spectrum of methyl 4-nitrobenzoate: (a) in D_2O, (b) in nanosphere of co-polymer **1b**.

Figure S1. **^{1}H NMR spectrum of 2-acetoxybenzoic acid: (a) in D_2O, (b) in nanosphere of co-polymer 1b.**

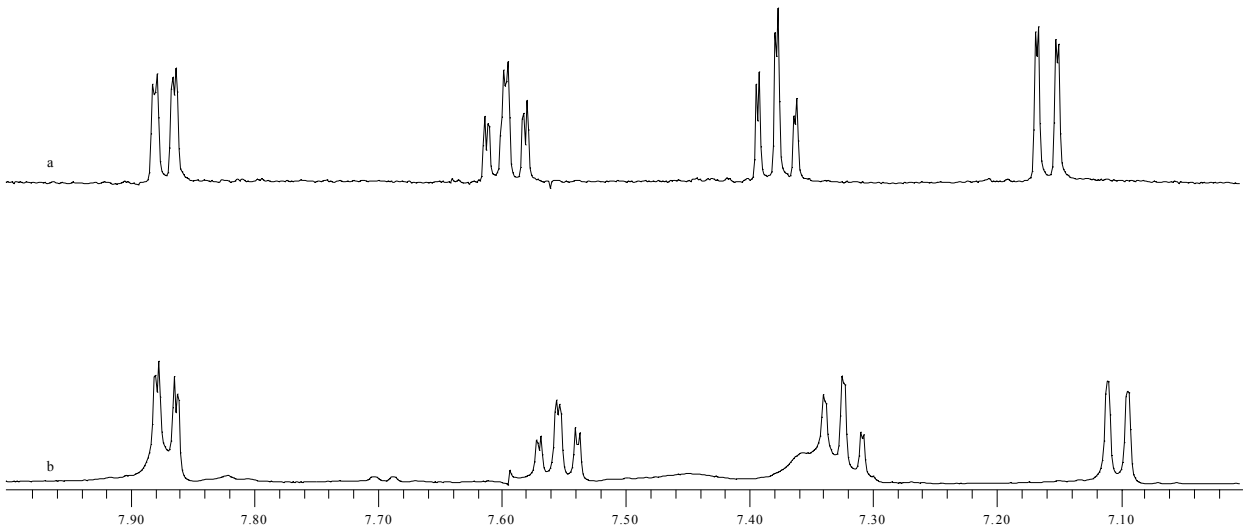


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Figure S2. **Full ^{1}H NMR spectrum of 2-acetoxybenzoic acid: (a) in D_2O, (b) in nanosphere of co-polymer 1b.**

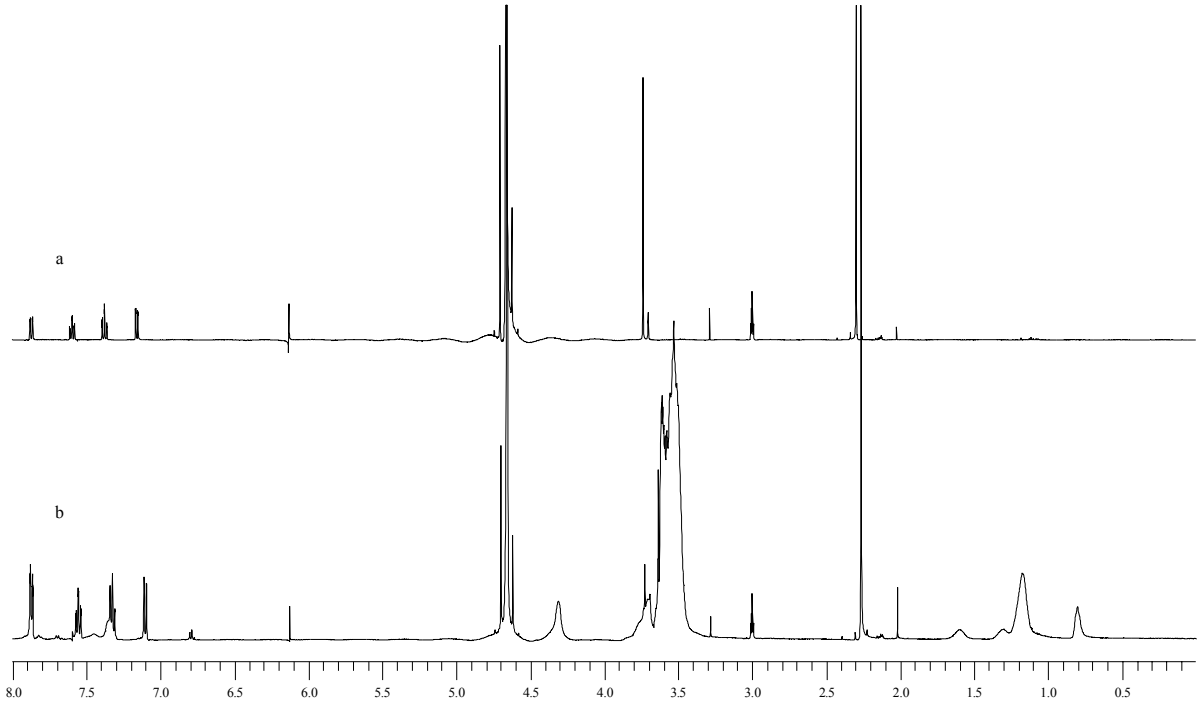

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Figure S3. ^{1}H NMR spectrum of methyl 2-acetoxybenzoate: (a) in D_2O, (b) in nanosphere of co-polymer 1b. .

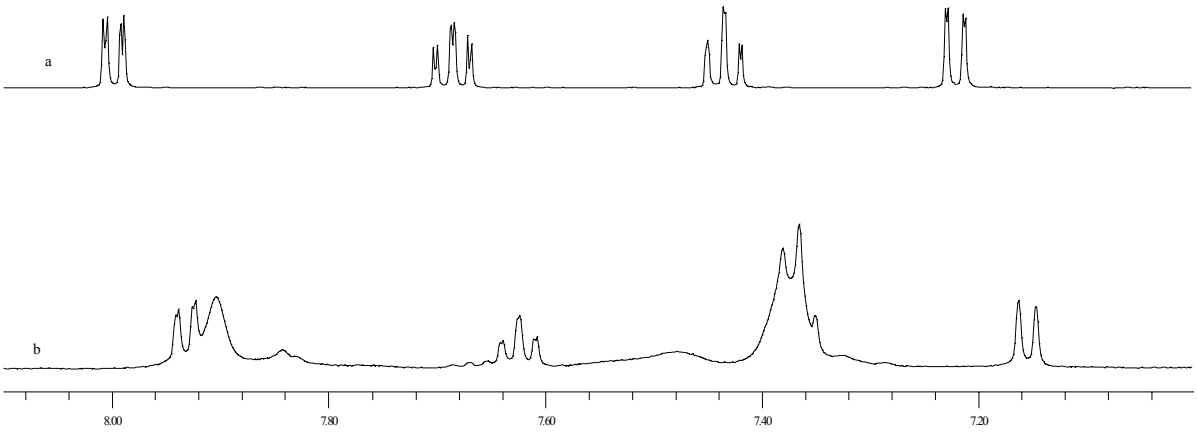

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Figure S4. Full ^{1}H NMR spectrum of methyl 2-acetoxybenzoate: (a) in D_2O, (b) in nanosphere of co-polymer 1b.

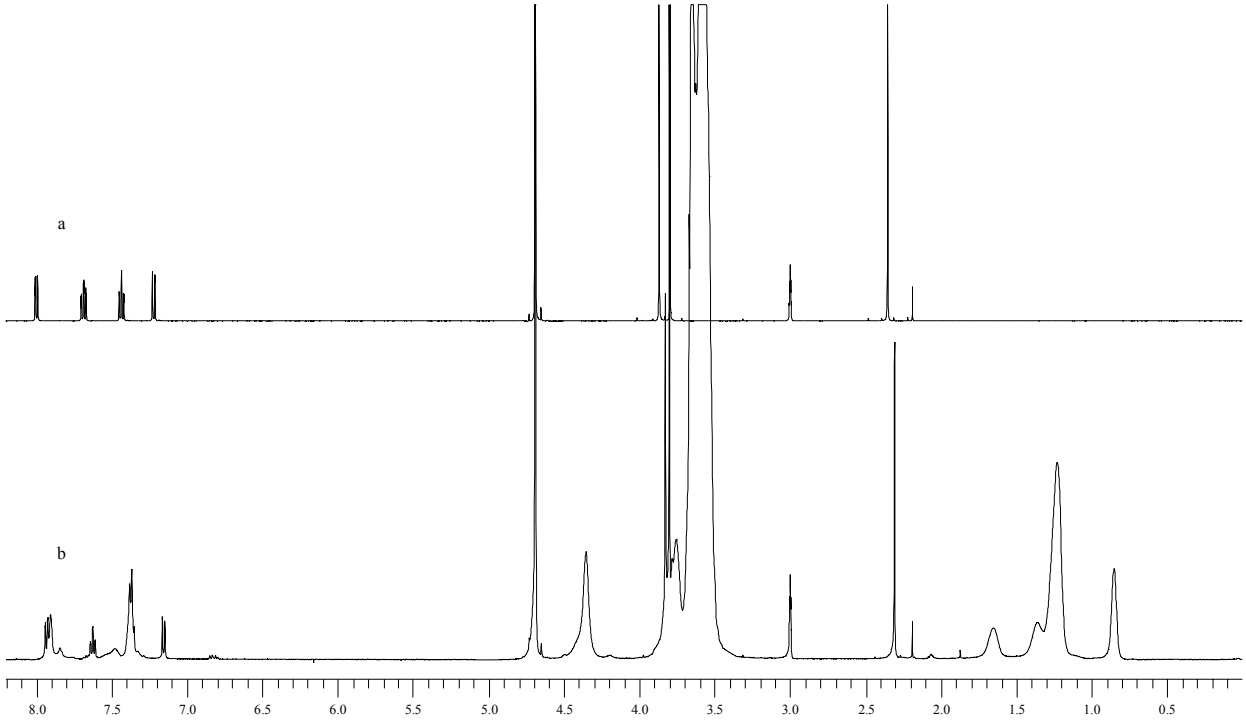

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Figure S5. **^{1}H NMR spectrum of 2-nitrobenzoic acid: (a) in D_2O, (b) in nanosphere of co-polymer 1b.**

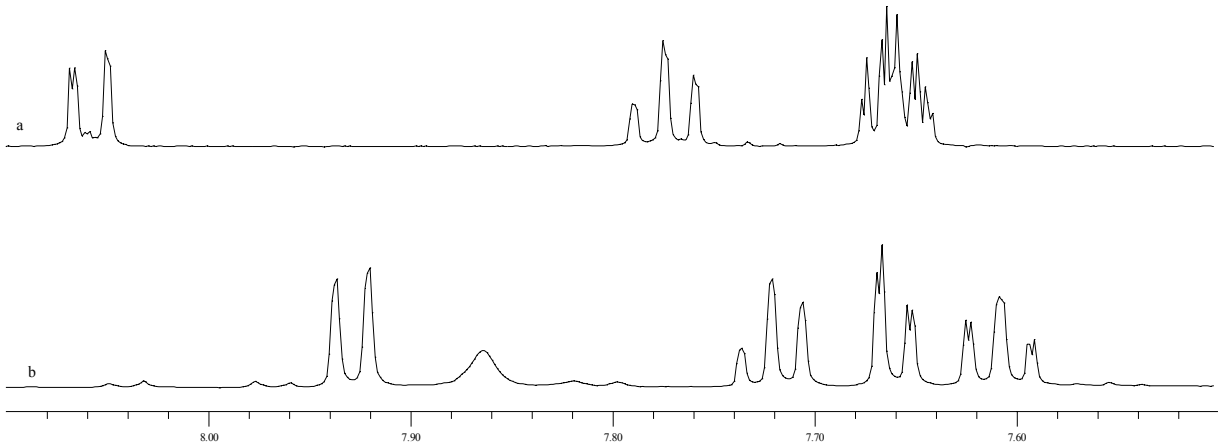

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Figure S6. **^{1}H NMR spectrum of 3-nitrobenzoic acid: (a) in D_2O, (b) in nanosphere of co-polymer 1b.**

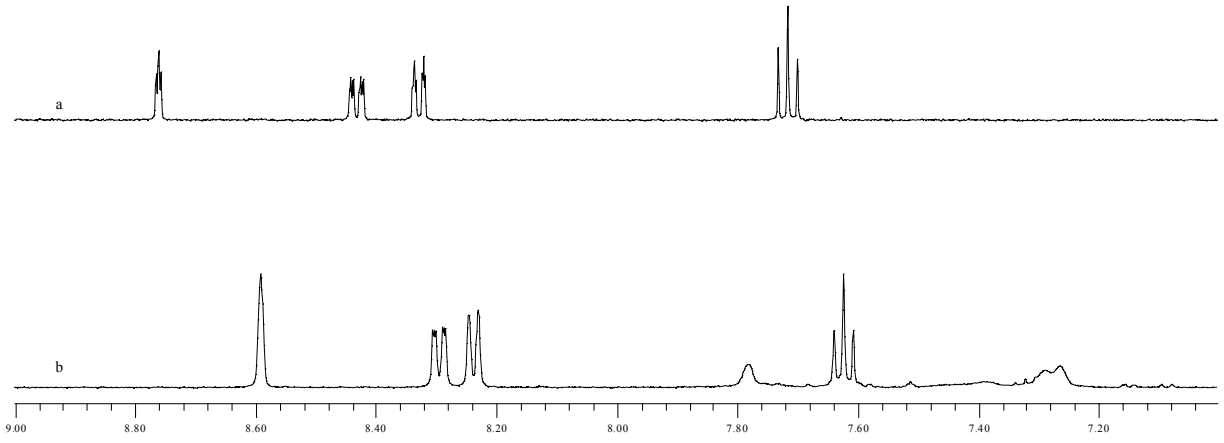

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Figure S7. **^{1}H NMR spectrum of 4-nitrobenzoic acid: (a) in D_2O, (b) in nanosphere of co-polymer 1b.**

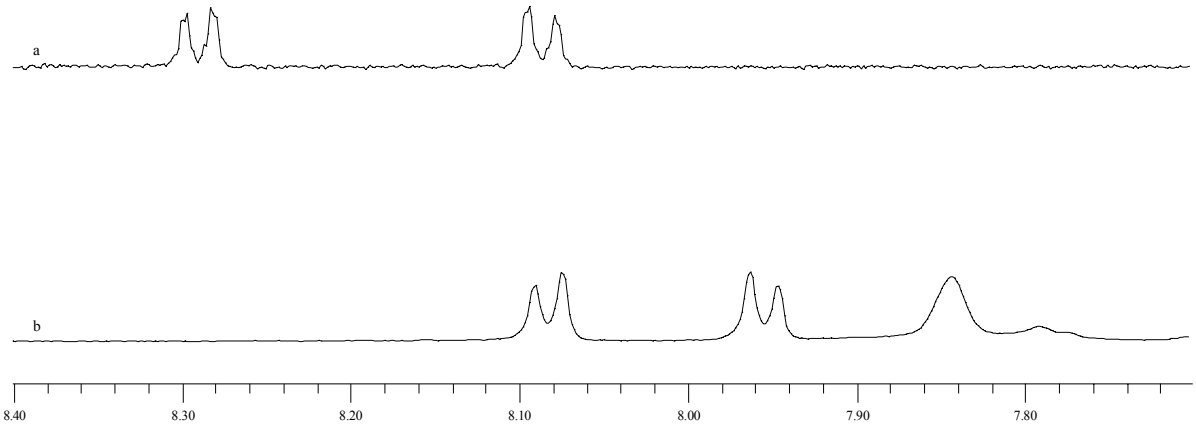

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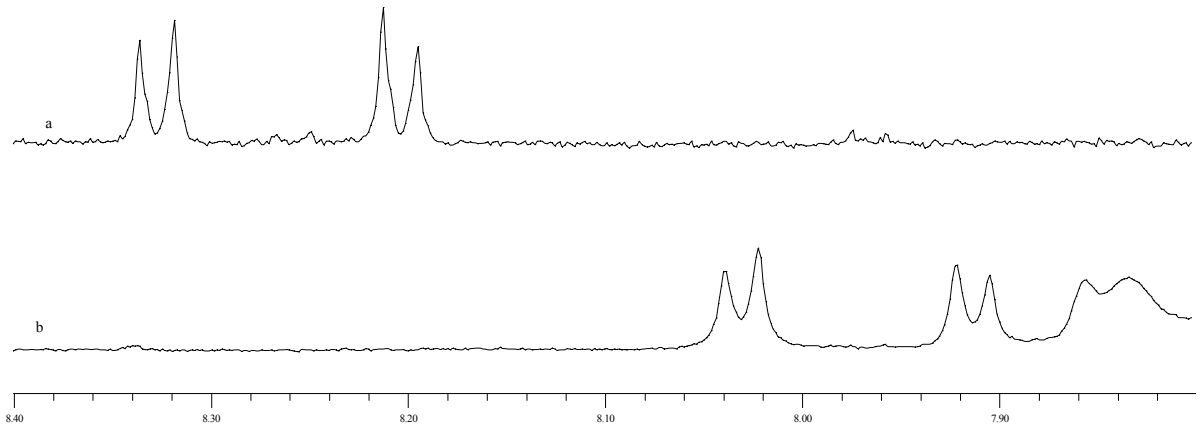
Figure S8. **^{1}H NMR spectrum of methyl 4-nitrobenzoate: (a) in D_2O, (b) in nanosphere of co-polymer 1b.**



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