Electronic Supplementary Material (ESI) for ChemComm.

Supplementary Information

Cyclodextrin-Based Supramolecular Nanoparticles Stabilized by Balancing Attractive Host-Guest and Repulsive Electrostatic Interactions

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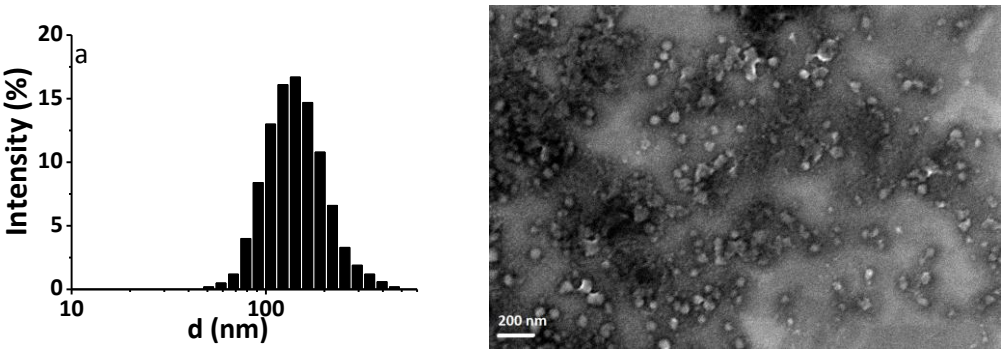


Figure S1. DLS particle size graph (a) and HR-SEM (b) of the SNPs prepared with 10% AdPEG in water.

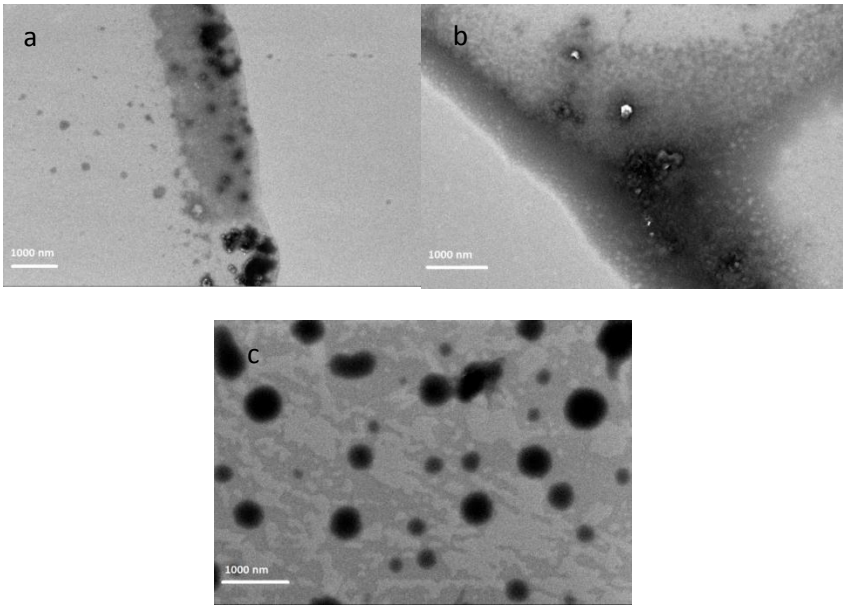


Figure S2. HR-SEM images of a) PiBMA-TBP (1.11 µM), b) PiBMA-CD (1.67 µM), and c) AdPEG (7.5 µM).

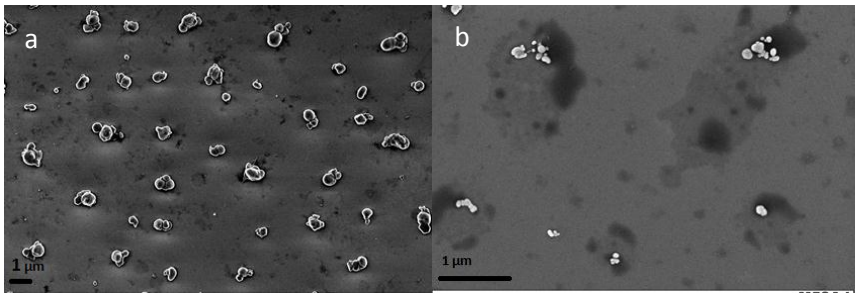


Figure S3. HR-SEM images of a) PiBMA-TBP + PiBMA ([TBP]= 15 µM, [PiBMA]= 1.67 µM), and b) PiBMA-CD + PiBMA ([CD]= 15 µM, [PiBMA]=1.67 µM).

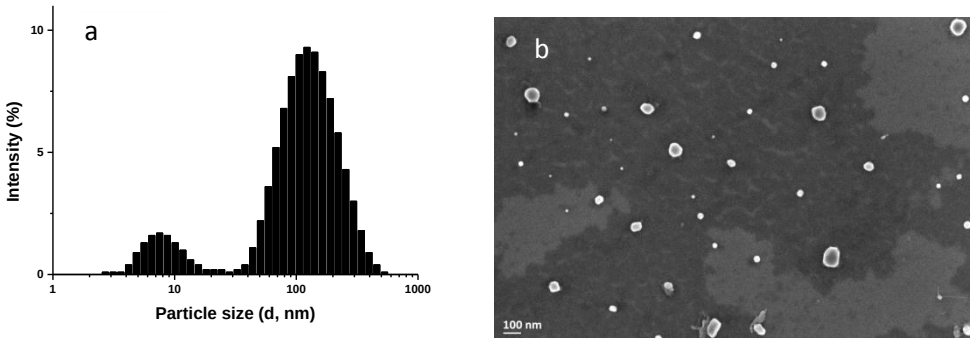


Figure S4. DLS particle size graph (a) and HR-SEM image (b) of the particles prepared with 10% AdPEG in PBS.

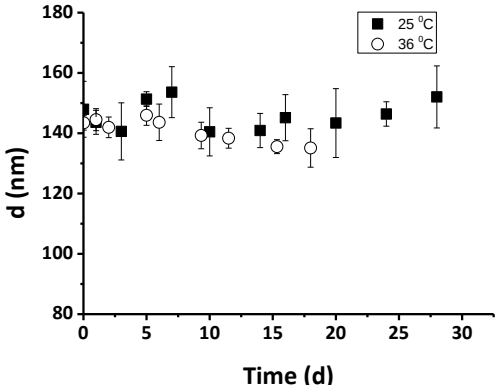


Figure S5. Particle stability in water as indicated by monitoring the particle size by DLS with 10% AdPEG at 25 ˚C and 36 ˚C.

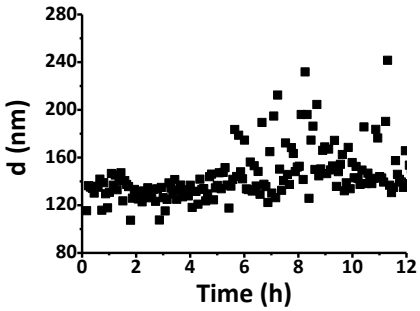


Figure S6. Particle stability in PBS as indicated by monitoring the particle size by DLS with 10% AdPEG at 25˚C.

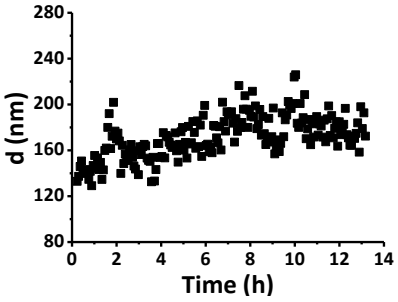


Figure S7. Particle stability in PBS as indicated by monitoring the particle size by DLS with 80% AdPEG at 36˚C.

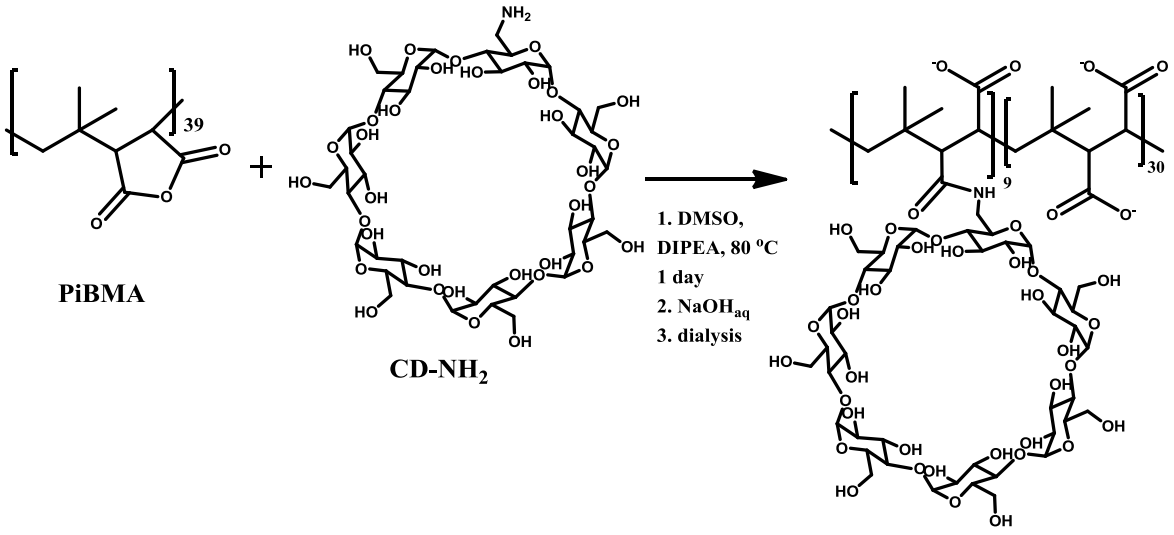
Experimental

1) Materials and Equipment

Starting materials and solvents for the synthesis were obtained from Sigma-Aldrich and used as received. *N,N*-Diisopropylethylamine (DIPEA) was purchased from Biosolve. Deuterated NMR solvents were purchased from Cambridge Isotope Laboratories Inc. Phosphate buffered saline (0.01 M, pH 7.4 at 25 ˚C, 0.138 M NaCl, 0.0027 M KCl) was prepared from Sigma Aldrich powder. 6-monodeoxy-6-monotosyl-β-cyclodextrin, 6-monodeoxy-6-azide- β-cyclodextrin, and 6-monodeoxy-6-monoamino-β-cyclodextrin were synthesized according to literature procedures.[1-3] AdPEG was synthesized as described before.[4] MilliQ water with a resistivity of 18.2 MΩ cm at 25 °C was used in all experiments. ^{1}H-NMR spectroscopy was performed on a Bruker 400 MHz NMR spectrometer. FTIR (ATR) was carried out on a Nicolet™ iS™10 FT-IR spectrometer equipped with a Smart iTR™ Attenuated Total Reflectance (ATR) sampling accessory (diamond plate). Dynamic light scattering (DLS) measurements were performed on a Zetasizer NanoZS (Malvern Instrument Ltd, Malvern, United Kingdom), with a laser wavelength of 633 nm and a scattering angle of 173˚. High resolution scanning electron microscopy (HR-SEM) pictures were taken on a Carl-Zeiss 1500 HR-SEM.

2) Synthesis of the components

a) Synthesis of PiBMA-CD



To a solution of PiBMA (40 mg, 6.66 µmol) in dry DMSO (8 mL), was added a solution of 6-monodeoxy-6-monoamino-β-cyclodextrin (121 mg, 0.1067 mmol) and DIPEA (35 µL, 0.213 mmol) in DMSO (2 mL). The mixture was reacted overnight at 80 ˚C. To the crude reaction mixture, water (10 mL) was added and the unreacted anhydride rings were opened with $NaOH_{aq}$ (0.26 mL 1 M NaOH). Afterwards , the mixture was purified by dialysis (SpectraPor membrane, MWCO 6-8 kD) for 1 week. Pure PiBMA-CD was obtained by freeze-drying (45 mg, 42% yield).The degree of grafting was calculated from the ratio between the CH_3 protons of the polymer and the C_1H of β-CD. **^{1}H-NMR** (400 MHz, D_2O, pH 11): δ 0.25-1.25 (br, 234 H, CH_3), 1.25-3.0 (br m, 136 H, PiBMA backbone), 3.01-4.18 (m, 337 H, $C_{2\text{-}6}H$ of CD), 4.88-5.1 (br, 60 H, C_1H of CD). **FTIR**: 3355 (OH), 1700 (amide), 1665 (COO^-), 1558 (amide), 1371 (COO^-), 1155 (CO), 1079 (CO/CC), 1029 (CO/CC) cm^{-1}.

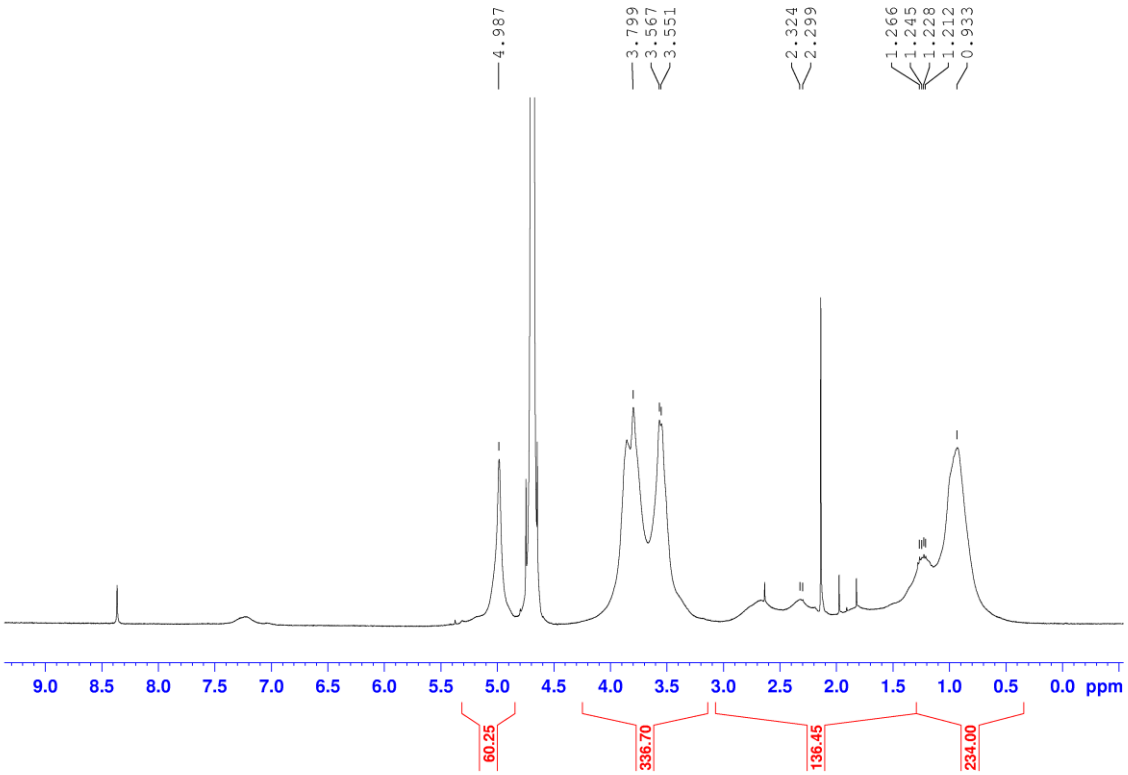
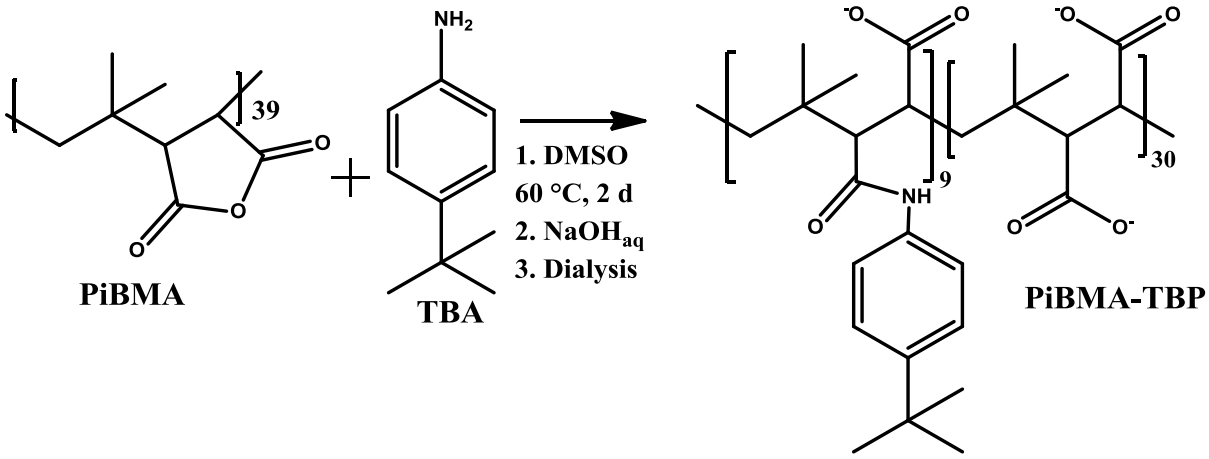


Figure S8. ^{1}H-NMR in D_2O of PiBMA-CD

b) Synthesis of PiBMA-TBP



PiBMA-TBP was synthesized similarly to PiBMA-CD: To a solution of PiBMA (250 mg, 0.042 mmol) in dry DMSO (15 mL), was added a solution of 4-*tert*-butyaniline (64 mg, 0.43 mmol) in DMSO (5 mL). The mixture was reacted overnight at 60 ˚C. To the crude reaction mixture, water (20 mL) was added and the unreacted anhydride rings were opened with 1 M NaOH (1.64 mL). Afterwards , the mixture

was purified by dialysis (Slide-A-Lyzer® dialysis cassette, MWCO 3.5 kD) for 1 week. Pure PiBMA-TBP was obtained by freeze-drying (195 mg, 63% yield). **^{1}H-NMR** (400 MHz, D_2O, pH 11): δ 0.63-1.25 (br d, 317 H, CH_3), 1.30-1.58 (br,39 H, CH_2), 1.60-2.06 (br, 60 H, CH_2), 2.18-2.83 (br, 79 H, CH), 7.23-7.60 (br m, 40 H, Ar-H). **FTIR**: 3388 (OH), 2961 (CH), 1665 (amide), 1556 (COO^-), 1516 (amide), 1469 (CH), 1392 (CO), 1371 (CO), 836 m (ArH) cm^{-1}.

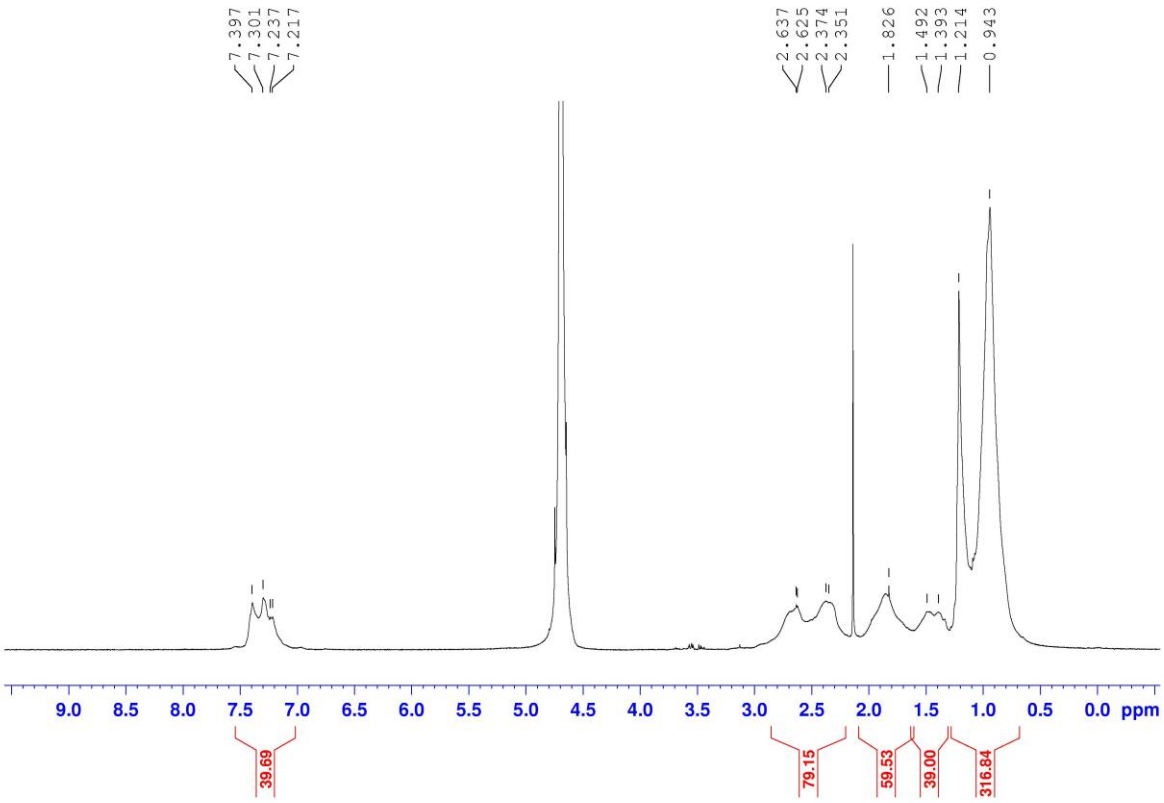


Figure S9. ^{1}H-NMR in D_2O of PiBMA-TBP

3) Preparation of the supramolecular nanoparticles

In water or in PBS: The SNPs were prepared maintaining the host : guest ratio at 1 : 1 at 15 µM CD from stock solutions of PiBMA-CD (6.44 µM), PiBMA-TBP (5.50 µM) and AdPEG (62.50 µM) by mixing the components with a vortex and afterwards they were measured by DLS at different times.

In acetic acid buffer: The SNPs were prepared maintaining the host : guest ratio at 1 : 1 at 15 µM CD from stock solutions of PiBMA-CD (10 µM) and PiBMA-TBP (10 µM) in milliQ water. In order to prepare the particles, 125 µL of the PiBMA-CD and PiBMA-TBP stock solutions were added to 500 µL of acetic acidic buffer (pH 4.2, 0.2 M) containing also 200 mM KCl (final concentration of KCl in the

particles: 100 mM) The samples were vortexed for 30 s and afterwards measured by DLS after 15 min and 4 h.

In KCl: The SNPs were prepared maintaining the host : guest ratio at 1 : 1 at 15 μM CD from stock solutions of PiBMA-CD (10 μM), PiBMA-TBP (10 μM), and AdPEG (90 μM) in milliQ water. In order to prepare the particles, 125 μL of the PiBMA-CD and different amounts of the PiBMA-TBP and AdPEG stock solutions were added to 500 μL of KCl of different concentrations to reach a final concentration of KCl of 100 mM, 300 mM, and 1000 mM. The samples were vortexed for 30 s and afterwards measured by DLS at different times (15 min, 4 h, 7 h, 24 h, and 48 h).

4) DLS measurements

To perform the DLS measurements, the refractive index of the material was fixed to 1.465 and the absorbance to 0.01. The parameters for the dispersant (water or PBS) were taken from the database of the machine. For each measurement, the sample was equilibrated for 2 min. The measurement was set to automatic. The temperature was set to 25 ˚C or 36 ˚C.

5) HR-SEM measurements

The samples were prepared by drop-casting 5 μL of a SNP solution on-to a silicon wafer or a TEM carbon-coated copper grid. After 30 s, excess of water was removed by filter paper. The samples were allowed to dry overnight in a desiccator containing silica gel beads. Original samples and 20x diluted ones were used.

References

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4. H. Wang, S. T. Wang, H. Su, K. J. Chen, A. L. Armijo, W. Y. Lin, Y. J. Wang, J. Sun, K. Kamei, J. Czernin, C. G. Radu and H. R. Tseng, *Angew. Chem. Int. Ed.*, 2009, **48**, 4344.