Supporting Information (SI)

Molecular Spherical Nucleic Acids

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Materials and Instrumentation.

HPLC grade acetonitrile (ACN) was bought from TEDIA (USA). All other reagents and reagent-grade solvents were purchased from Adamas Reagent Co. (China), Sigma-Aldrich Co. (USA), Aladdin Reagent Co. (China), or Sangon Biotech Co. (China), and used as received. Ultrapure deionized (DI) water (18.2 MΩ·cm resistivity) was obtained from a Milipore system (Milli-Q Biocel, USA). DLS data were acquired on a Malvern Zetasizer Nano ZSP (Malvern, UK). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer (Germany). Chemical shifts (δ) were reported in ppm. HPLC purification was carried out on a Waters Breeze 2 HPLC system (USA) coupled to a 2998 PDA detector. MALDI-ToF MS measurements were performed on a Bruker Ultraflextreme mass spectrometer (Bruker Daltonics Inc., USA). Temperature control and mixing during the coupling of

DNA to azide-functionalized cores were achieved using an Eppendorf Thermomixer C instrument (Germany). Gels were imaged on a Fluochem Q imaging system (ProteinSimple Inc., USA). 96-well plates were read using a Spark 10M microplate reader (TECAN, Switzerland). Confocal images were taken on a Nikon TI-E+A1 microscope (Nikon, Japan). Flow cytometry measurements were performed using a Beckman Gallious flow cytometer (Beckman, USA). Atomic force microscopy (AFM) images were taken on a Dimension Icon AFM (Bruker, Germany) using tapping mode on mica substrates. Fourier transform infrared (FT-IR) spectra were recorded on a Varian 2000 spectrometer (USA) in the range 3800-400cm^{-1} and the samples were diluted in KBr and compacted to form thin pellets.

All DNA synthesis reagents were obtained from Glen Research (USA). After synthesis, DNA strands were cleaved from the CPG support using aqueous ammonium hydroxide (28-30% NH_3 basis) at 55 ºC for 17 h, and purified by RP-HPLC equipped with a Waters SunFire C18 column (5 μm, 4.6 × 250 mm), using triethylammonium acetate (TEAA) buffer (0.1 M) and HPLC-grade acetonitrile as mobile phases. MALDI-ToF MS verified the successful syntheses of DNA sequences.

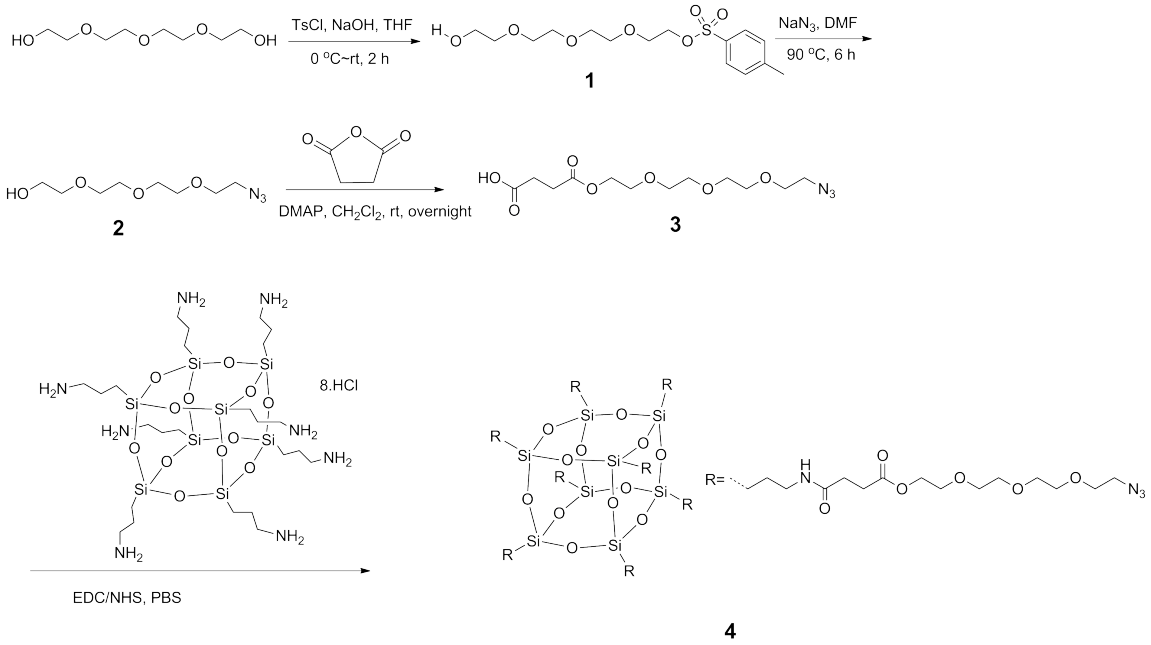
Cell culture. SKOV3 and MCF7 cells were grown in DMEM medium with 10% heat inactivated fetal bovine serum, 1% antibiotics, 1% L-glutamine, and were maintained at 37 °C in 5% CO_2.

Table S1. All sequences used in this study

HER2 antisense	5'-DBCO-TEG-TTT CTC CAT GGT GCT CAC-3'
Fluorescein-labeled HER2 antisense	5'-DBCO-TEG-TTT CTC CAT GGT GCT CAC - fluorescien-3'
Cy3-labeled HER2 antisense	5'-DBCO-TEG-TTT CTC CAT GGT GCT CAC-Cy3-3'
Dabcyl-labeled HER2 sense	5'-Dabcyl-GTG AGC ACC ATG GAG -3'
Scrambled antisense	5'-DBCO-TEG-TTT CGC TGA CTC CAT GTC-3'

Synthesis and characterization of POSS- and C_{60}-based cores

a. Synthesis of POSS-based core



Scheme S1. Synthetic route for POSS-based core (compound **4**).

Tetraethyleneglycol monotosylate (1)

NaOH (1.1 g, 27.5 mmol) was dissolved in water (6 mL) and tetraethylene glycol (34.96 g, 180.0 mmol) was added via 5 mL THF solution. The mixture was cooled using an ice bath, and a THF solution (20 mL) of *p*-toluenesulfonylchloride (3.34 g, 17.5 mmol) was added dropwise over 30 min. The reaction mixture was stirred for 2 h and poured into ice water (300 mL). The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography with silica gel using a mixture of ethyl acetate and hexane (3:1, v:v) to afford compound **1** as a clear oil (4.0 g, 65% yield with reference to *p*-toluenesulfonylchloride).

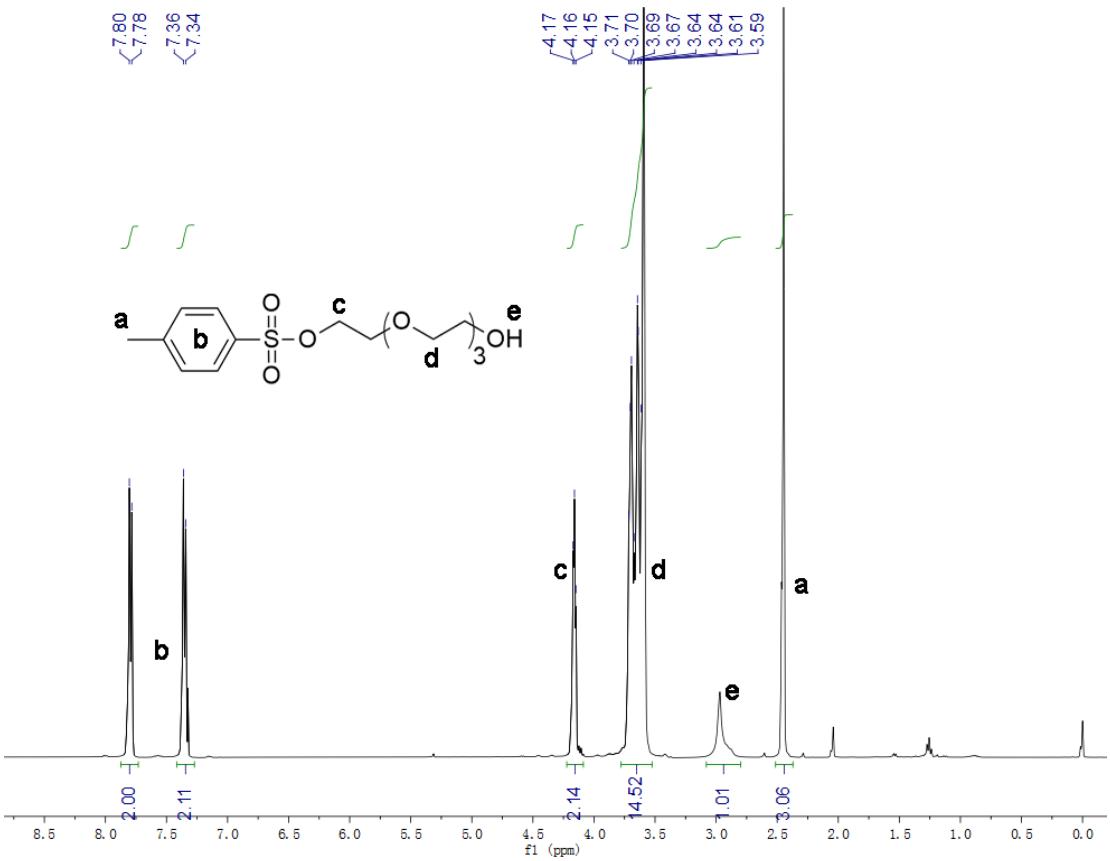


Figure S1. ^{1}H NMR spectrum of compound **1** in $CDCl_3$.

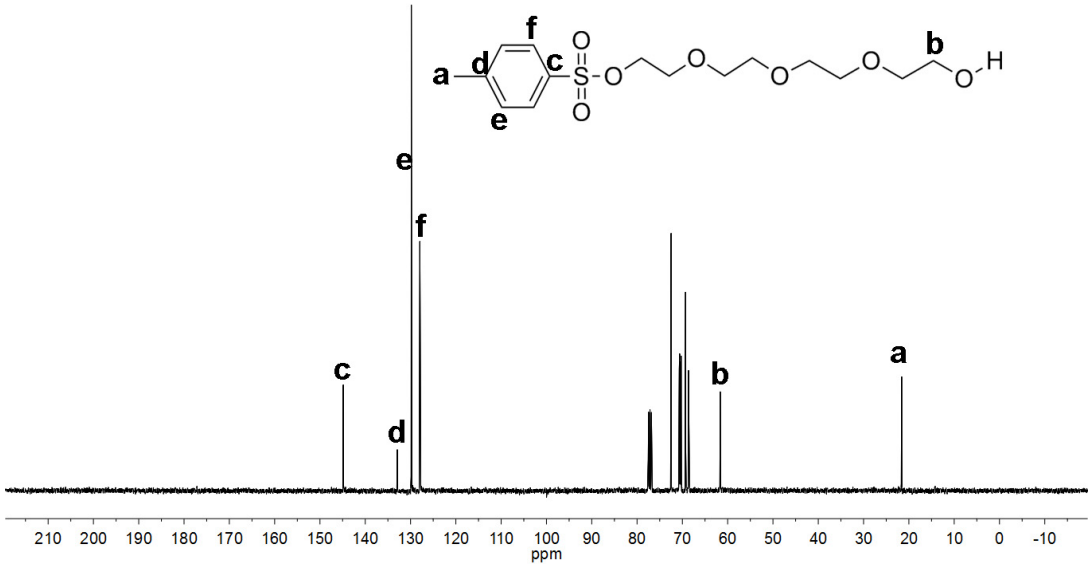


Figure S2. ^{13}C NMR spectrum of compound **1** in $CDCl_3$.

Monoazidotetraethyleneglycol (2)

NaN_3 (0.45 g, 6.9 mmol) was added to a solution of compound **1** (1.75 g, 5.0 mmol) in anhydrous DMF (25 mL) at room temperature. The reaction mixture was stirred at 90 ºC for 6 h, and then concentrated under vacuum. The residue was dissolved in ethyl acetate (150 mL), washed with brine (3×), combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography with silica gel using a mixed eluent of ethyl acetate and hexane (1:1, v:v) to yield **2** as a clear oil (0.75 g, 69%).

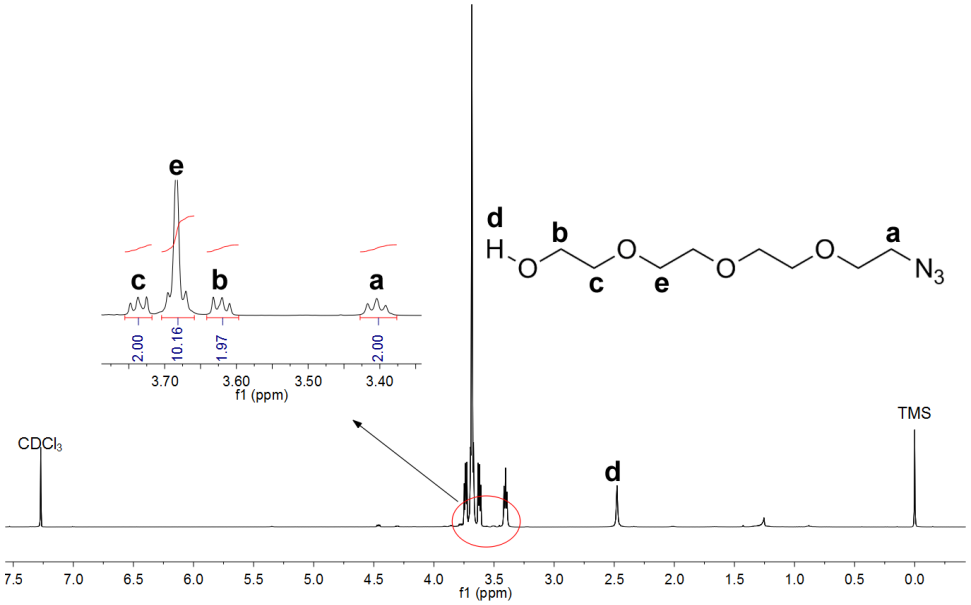


Figure S3. ^{1}H NMR spectrum of compound **2** in $CDCl_3$.

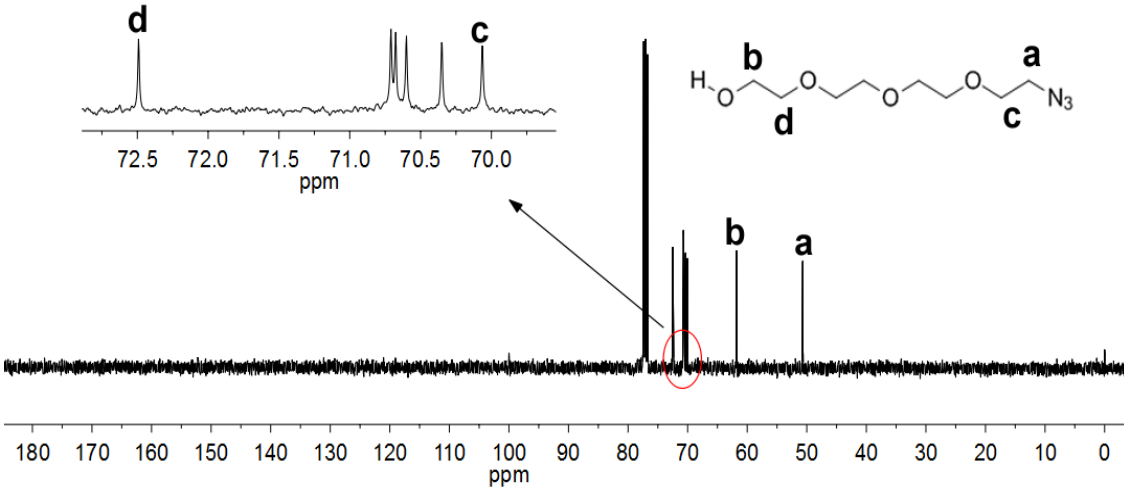


Figure S4. ^{13}C NMR spectrum of compound **2** in $CDCl_3$.

Butanedioic acid 2-{2-[2-(2-Azidoethoxy)ethoxy]ethoxy}ethyl ester (3)

Compound **2** (1.1 g, 5 mmol), 4-dimethylaminopyridine DMAP (122 mg, 1 mmol), and succinic anhydride (0.6 g, 6 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL). The reaction mixture was stirred at room temperature overnight, and quenched with the addition of 10 mL of water. Subsequently, 100 mL of CH_2Cl_2 was added to the mixture, washed with 10% $NaHSO_4$ aqueous solution (3×) and brine (3×). The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography with silica gel using a mixed eluent of ethyl acetate and hexane (2:1, v:v) to afford **3** as a clear oil (1.2 g, 75%).

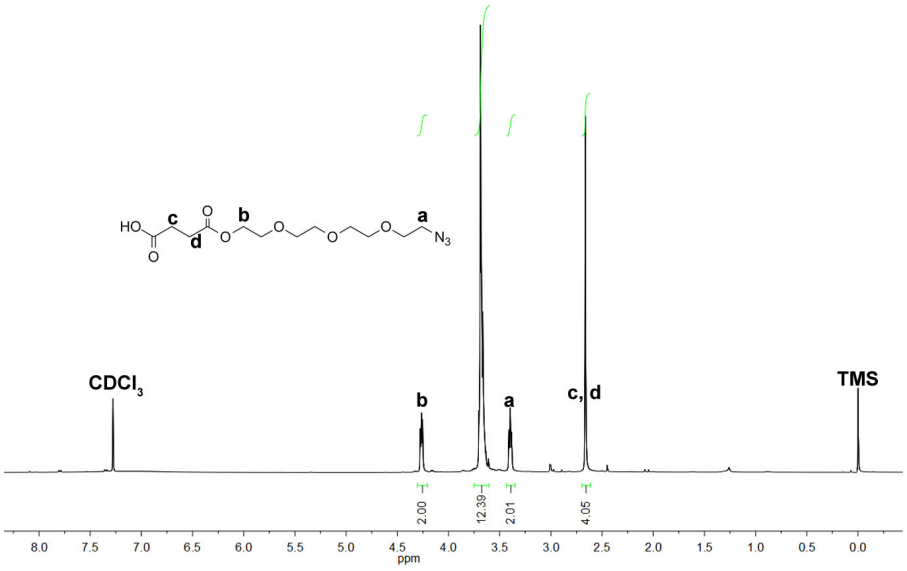


Figure S5. ^{1}H NMR spectrum of compound **3** in $CDCl_3$.

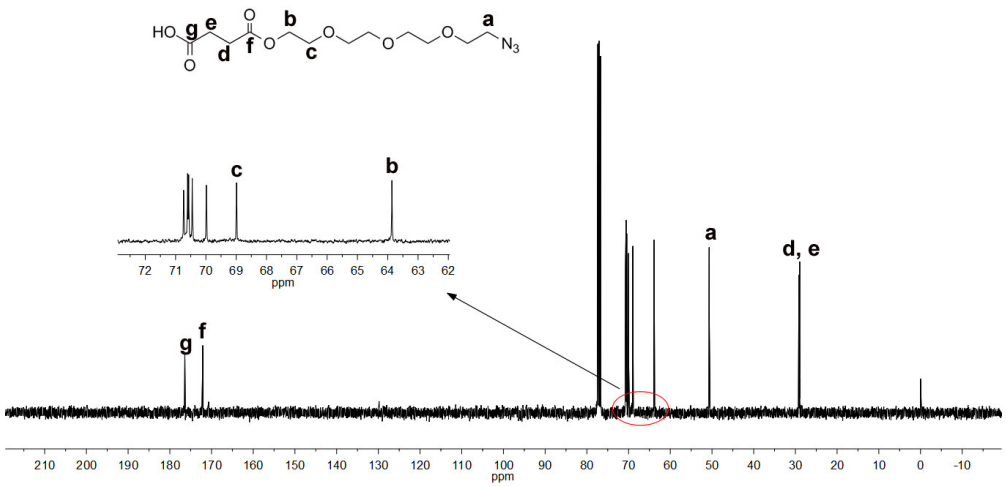


Figure S6. ^{13}C NMR spectrum of compound **3** in $CDCl_3$.

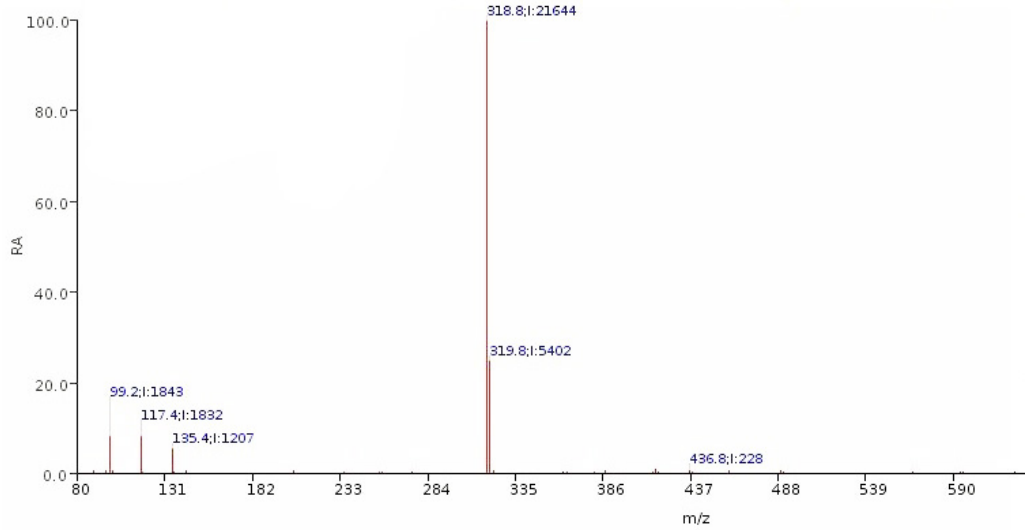


Figure S7. ESI-MS spectrum of compound **3**. $[M-H]^-$ m/z calculated: 318.3, found: 318.8.

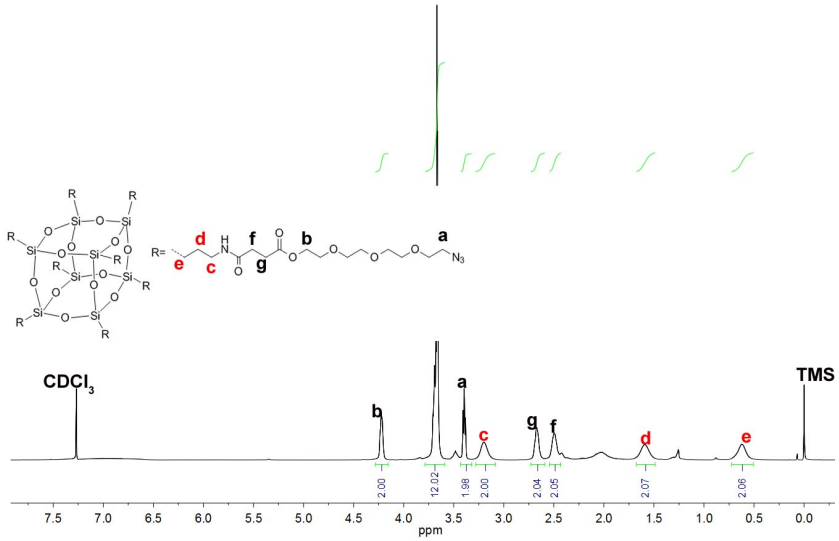


Figure S8. ^{1}H NMR spectrum of compound **4** in $CDCl_3$.

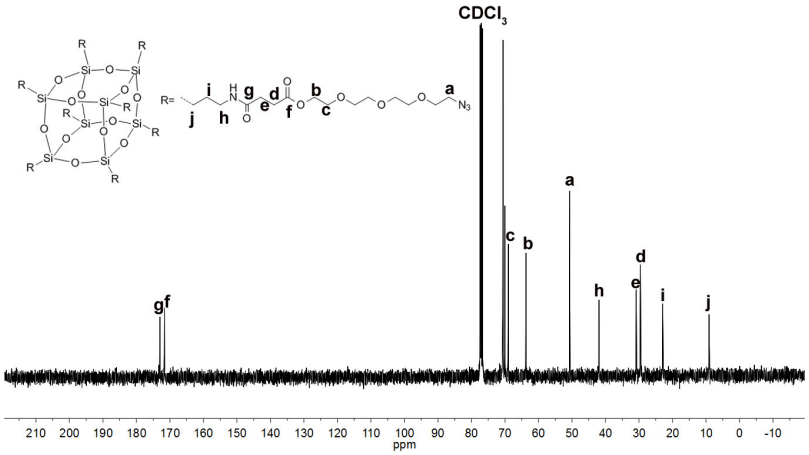


Figure S9. ^{13}C NMR spectrum of compound **4** in $CDCl_3$.

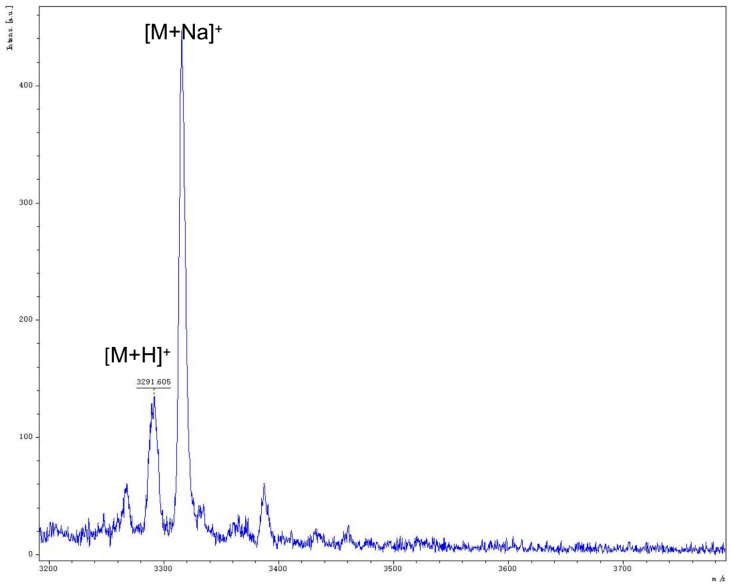


Figure S10. MALDI-ToF MS spectrum of compound **4**. α-Cyano-4-hydroxycinnamic acid (CHCA) was used as the matrix. $[M+H]^+$ m/z calculated: 3290.302, found: 3291.605.

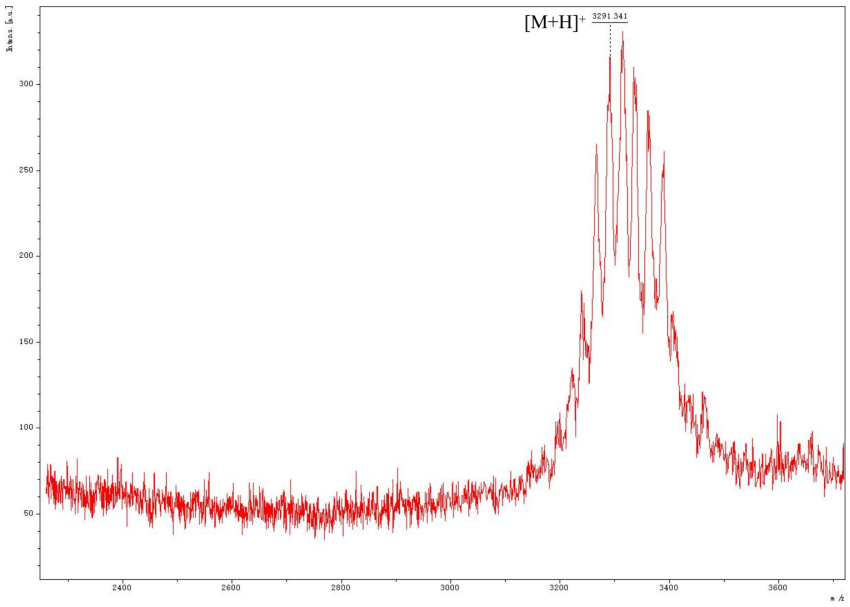
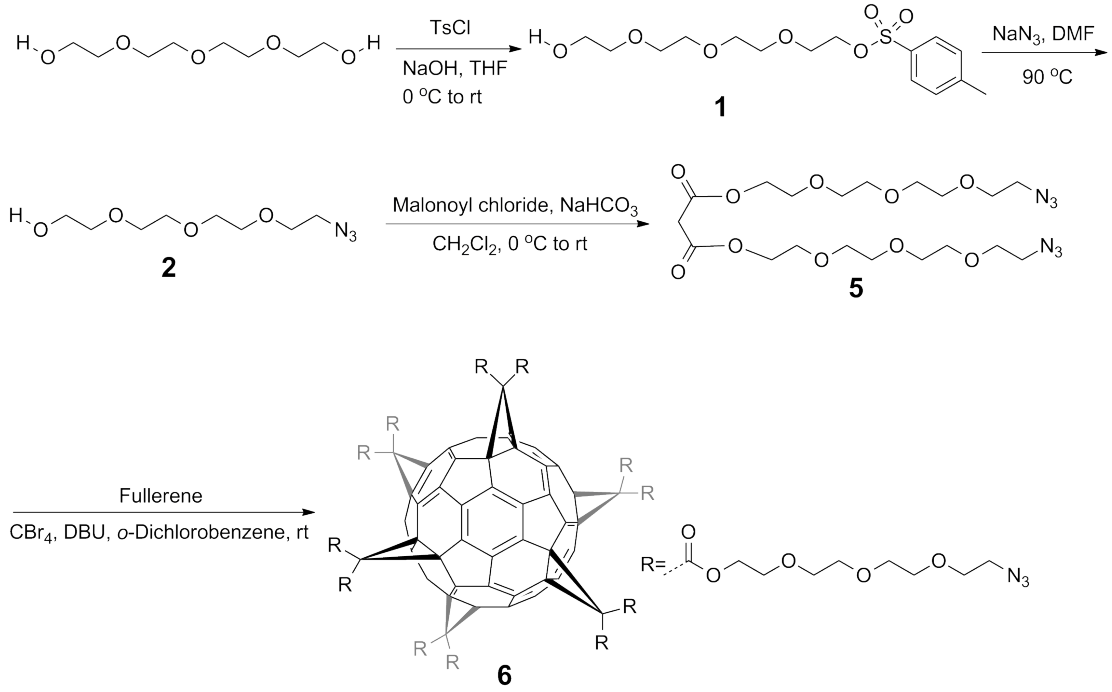


Figure S11. MALDI-ToF MS spectrum of compound **4**. 2,5-Dihydroxybenzoic acid (DHB) was used as the matrix. $[M+H]^+$ m/z calculated 3290.30, found 3291.34. No partial adducts (e.g. with 7 azides) were observed.

b. Synthesis of C_{60}-based core



Scheme S2. Synthetic route for the C_{60}-based core (**6**).

Synthesis of compound 5

A suspension of $NaHCO_3$ (0.4 g, 4.8 mmol) and compound **2** (526 mg, 2.4 mmol) in CH_2Cl_2 (50 mL) was stirred in a three-neck round bottom flask in an ice bath, to which malonyl dichloride (155 mg, 1.1 mmol) in CH_2Cl_2 (50 ml) was dropwise added via dropping funnel over a period of 1 h. When the addition was complete, the mixture was stirred at room temperature for another 12 h, before being washed with water (3× 200 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated at reduced pressure. The crude product was purified by flash chromatography (ethyl acetate:hexane 1:1 v:v) as a clear oil (390 mg, 70% yield).

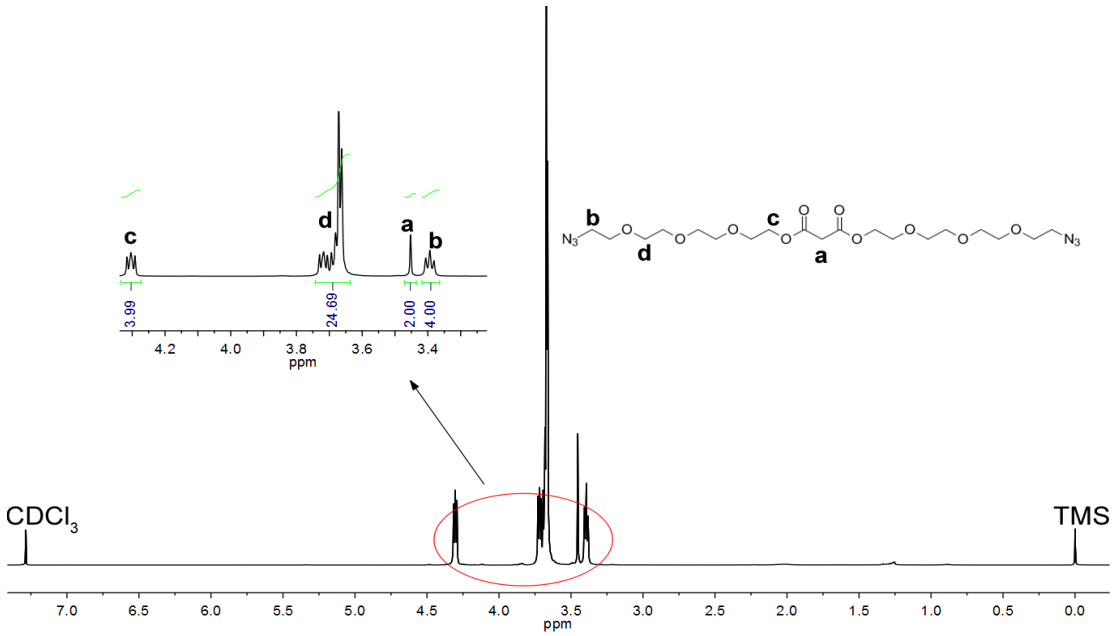


Figure S12. ^{1}H NMR spectrum of compound **4** in $CDCl_3$.

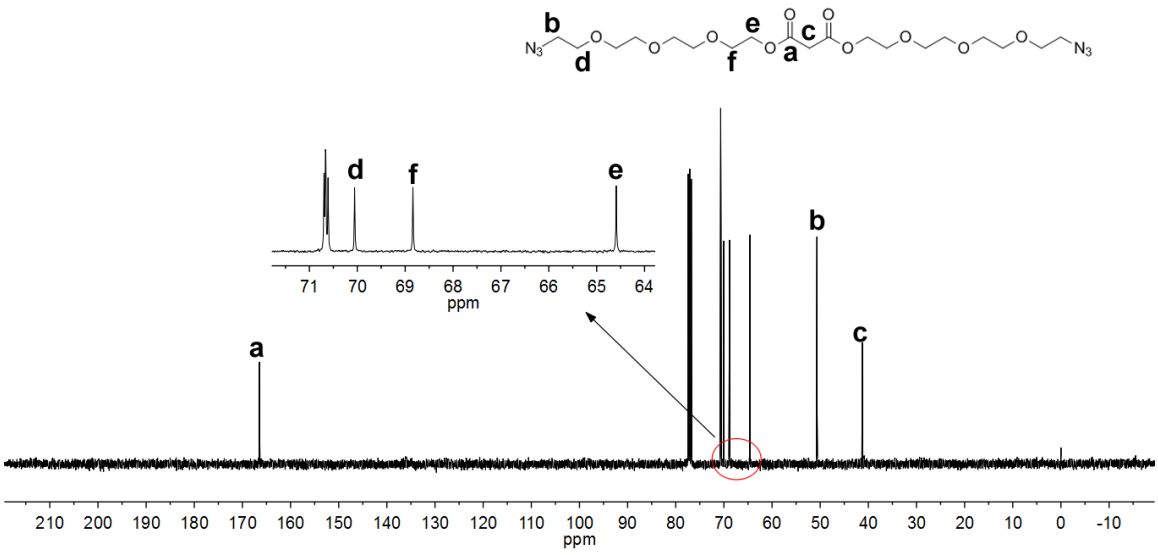


Figure S13. ^{13}C NMR spectrum of compound **4** in $CDCl_3$.

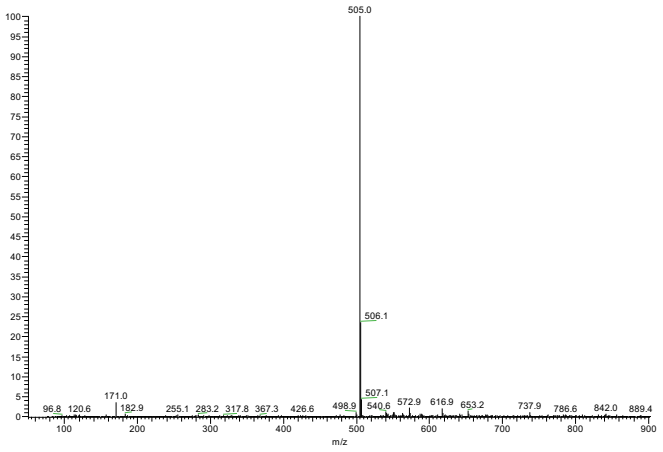


Figure S14. ESI-MS spectrum of compound **5**. $[M-H]^-$ m/z calculated: 505.2, found: 505.0.

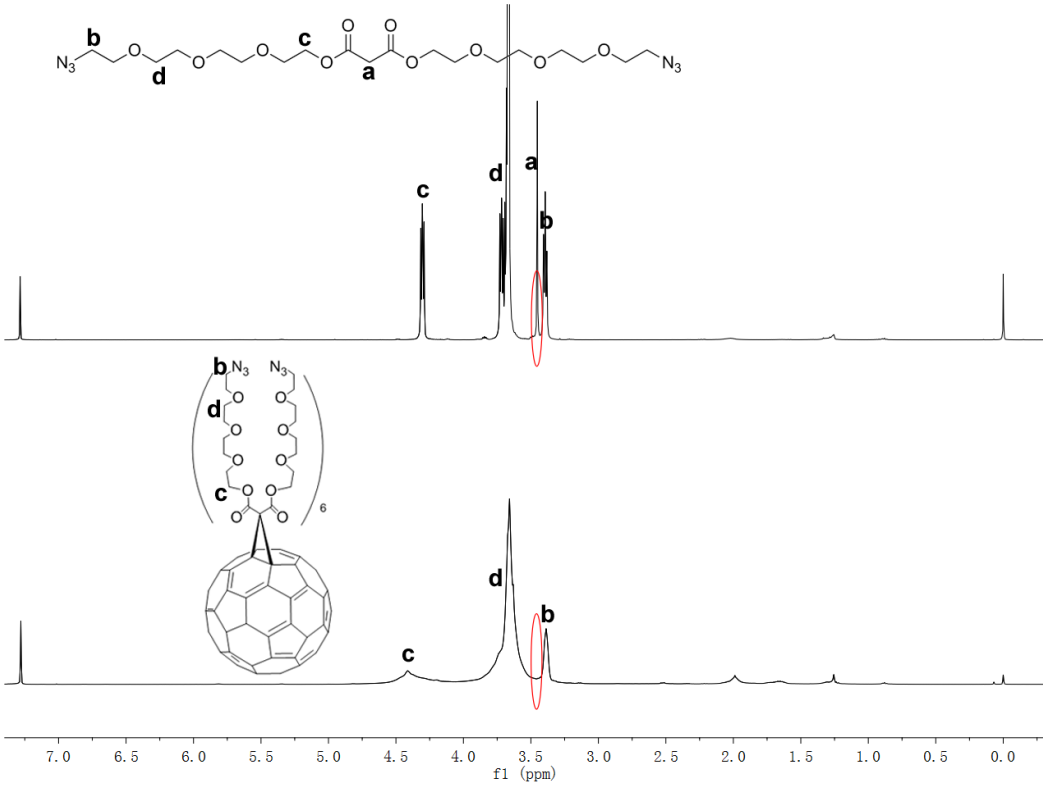


Figure S15. ^{1}H NMR spectra of compounds **5** (top) and **6** (bottom).

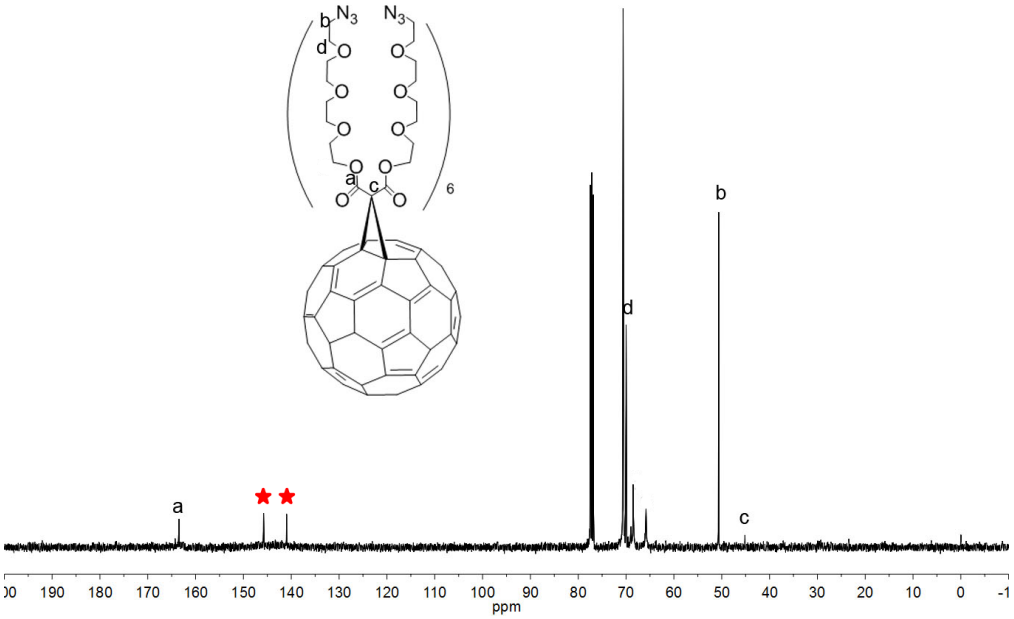


Figure S16. ^{13}C NMR spectrum of compound **6**.

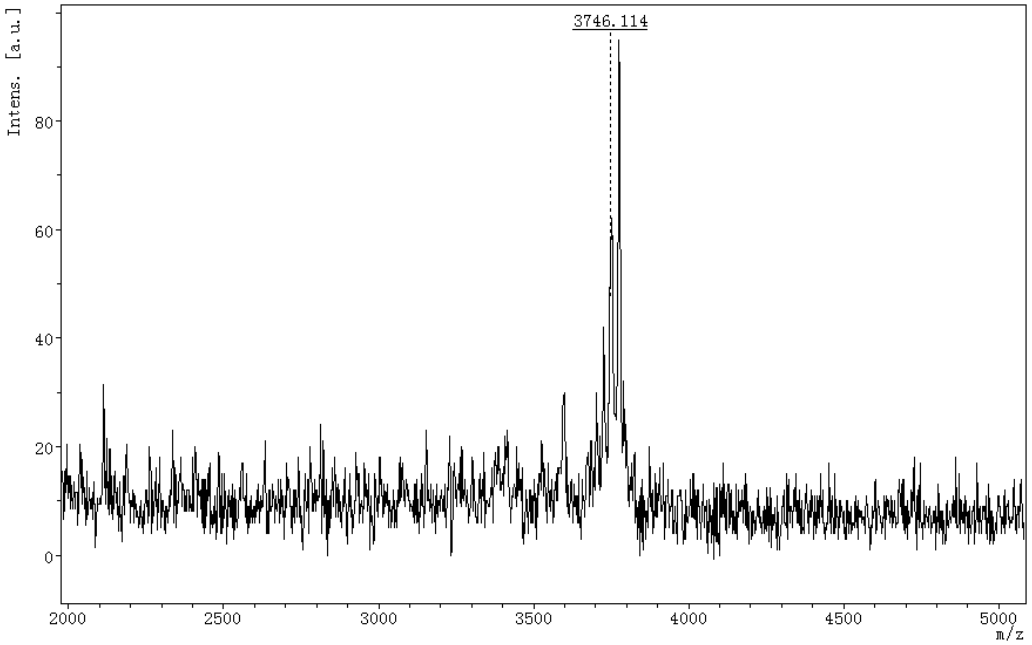


Figure S17. MALDI-ToF MS spectrum of compound **6**. $[M+H]^+$: m/z calculated 3746.316, found 3746.114. Matrix: CHCA.

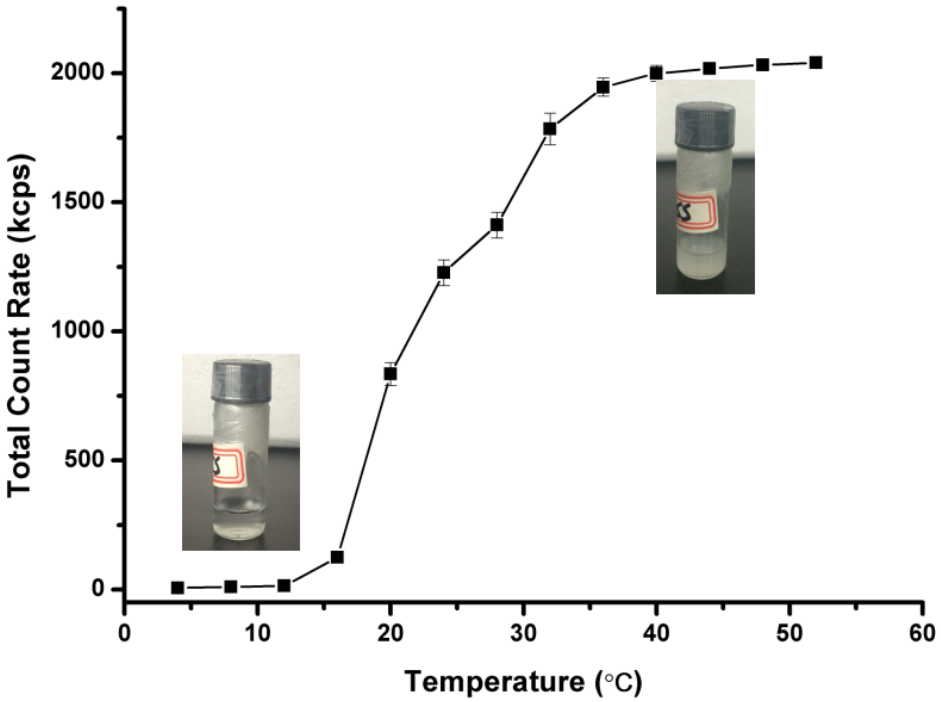


Figure S18. Total light scattering intensity of an aqueous solution of compound **4** (2 μmol/mL) as a function of temperature, showing a lower critical solution temperature of ~24 °C.

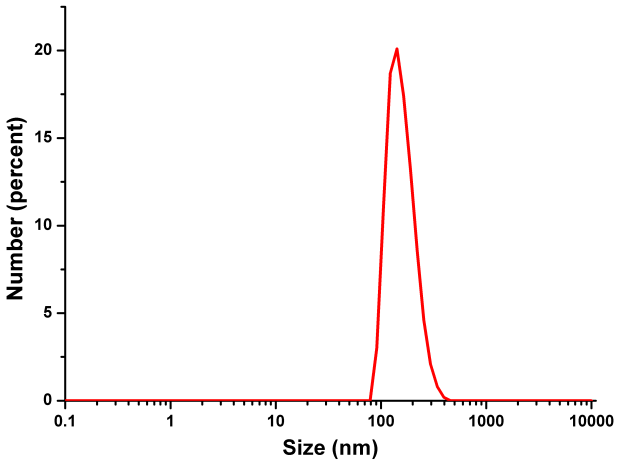


Figure S19. DLS number-average size distribution of compound **6** (2.5 nmol in 100 μL of 1.5 M NaCl solution) at 25 °C, showing aggregates with average hydrodynamic diameter of 160±49 nm.

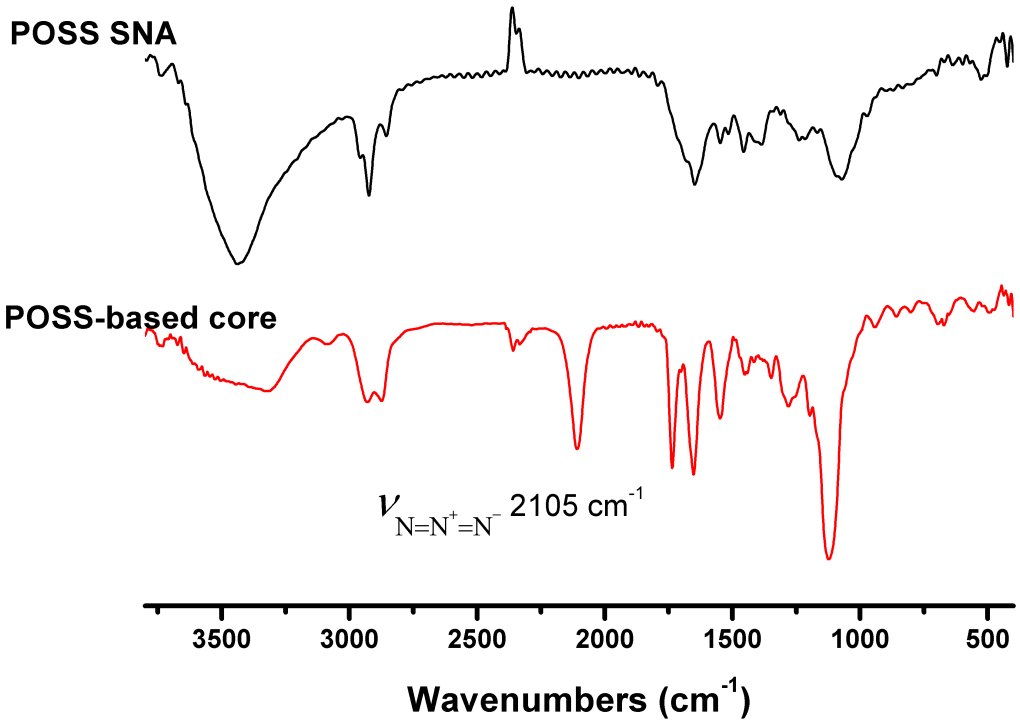


Figure S20. FT-IR spectra of POSS-based core and POSS SNA.

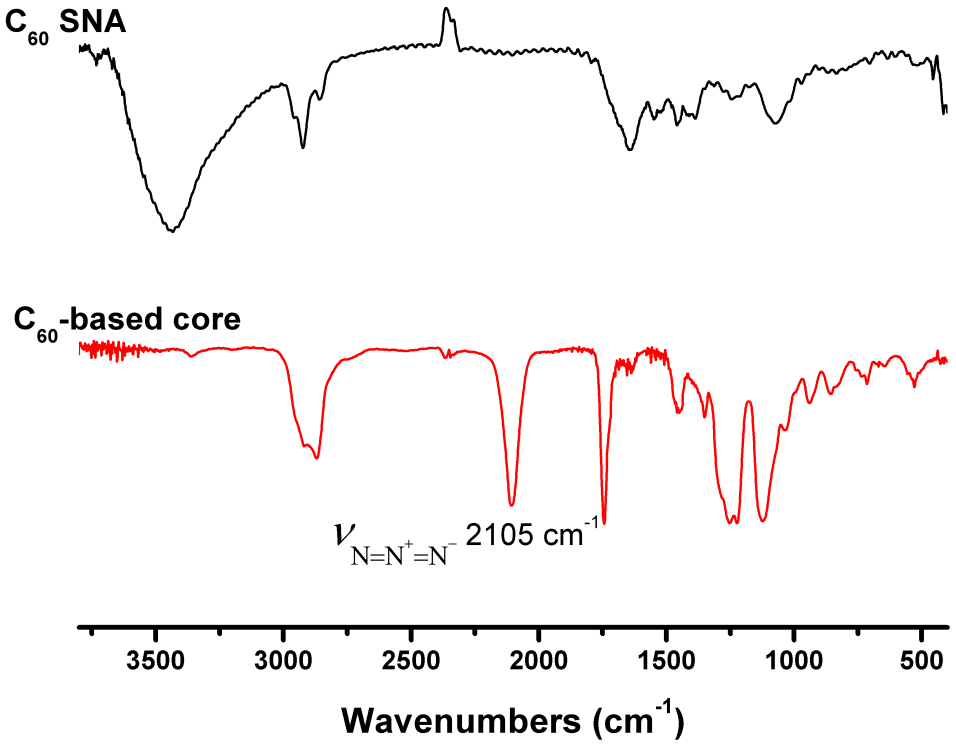


Figure S21. FT-IR spectra of C_{60}-based core and C_{60} SNA.

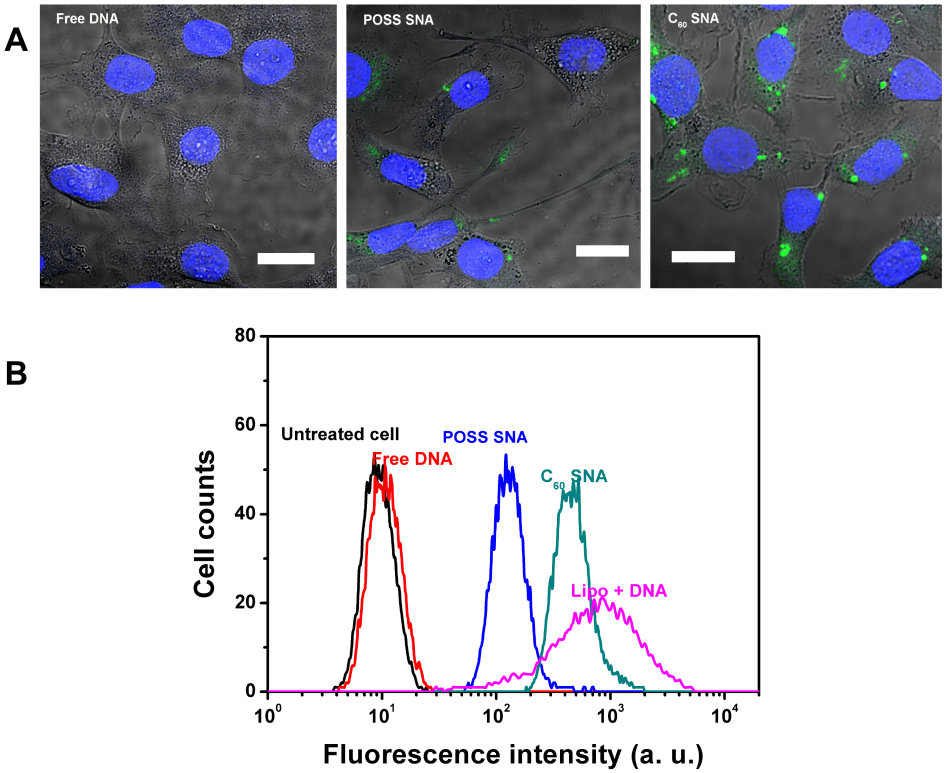


Figure S22. Cellular uptake of molecular SNAs. (A) Confocal microscopy of SKOV-3 cells treated with fluorescein-labeled free DNA and conjugates (green). Cell nuclei were stained with Hoechst (blue). The cells were incubated for 6 h with samples with an equal DNA concentration of 0.5 μM in serum-free medium. Scale bar is 20 μm. (B) Flow cytometry measurement of SKOV-3 cells treated with the samples and the untreated cells.

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