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Supporting Information

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Tunable Hydrophobicity in DNA Micelles: Design, Synthesis, and Characterization of a New Family of DNA Amphiphiles

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Note: SI.#. in the paper refers the corresponding number above.

1. Materials

Solvents and reagents for DNA synthesis were purchased from Novabiochem (Merck, UK) and SAFC (Sigma-Aldrich, Netherlands). Primer SupportTM dC and dG (200 $\mu\text{mol/g}$) from GE Healthcare were used as solid supports during DNA synthesis. Other chemicals were purchased from Sigma-Aldrich (Germany) and used without further purification. During all experiments, ultra pure water (18.2 M Ω), purified by MilliQ-Millipore system (Millipore, Germany) or arium[®] 611 UF (Sartorius, The Netherlands), was used.

2. DNA Synthesis

The modified 5-dodec-1-ynyluracil containing phosphoramidite (**1**, 7 g) was dissolved in CH₃CN (52 mL) to adjust the concentration to 0.15 M, in the presence of 3Å molecular sieve. The acetonitrile solution was directly connected to the DNA synthesizer prior to starting the DNA synthesis. The U2M, U2T and U4T synthesis was performed in 50 μmol scale.

General procedure: after every detritylation step, 1.5 equivalents of the nucleoside phosphoramidite were passed through the column reactor and further recycled for 3 min (coupling and recycling steps). Subsequently oxidation and capping steps were performed.

3. Characterization of DNA Amphiphiles

3.1. Mass spectrometry

Molecular weights of the DNA-amphiphiles were determined using matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) spectrometry. The spectra were recorded on a Bruker MALDI-TOF (Reflex-TOF) mass spectrometer. For the MALDI-TOF mass spectra of the different DNA sequences the following matrix was employed: 20 mg 3-hydroxypicolinic acid, 2 mg picolinic acid, 3 mg ammonium citrate, 0,5 mL of a mixture of ultra pure water/acetonitrile (7:3); ratio sample: matrix = 1:2 (v/v). The concentration of the DNA solution was 20 μM .

Figure S1. MALDI-TOF spectra of the lipid-DNAs. (a) **U2M** (found: 3940 g/mol, calculated: 3938 g/mol). (b) **U2T** (found: 3969 g/mol, calculated: 3968 g/mol). (c) **U4T** (found: 4244 g/mol, calculated: 4244 g/mol)

3.2. Analytical anion exchange (AIEX) chromatography

Analytical AIEX chromatography was performed using a HiTrap Q HP 1 mL column (GE Healthcare) through linear gradient using buffer A (25 mM Tris-HCl, pH 8.0) and buffer B (25 mM Tris-HCl and 1.0 M NaCl, pH 8.0).

Figure S2. AIEX elution graphs of the crude reaction mixtures. (a) U2M. (b) U2T. (c) U4T. (d) Pristine 12mer with same sequence. The product fraction of each crude mixture is marked. Numbers beside the fraction represent the percentage of product area versus total area integrated from the chromatogram.

According to each analytical chromatogram of DNA-amphiphile, HiTrap Q HP 5 mL was used during purification of the crude mixtures.

3.3. UV/Vis spectroscopy

Figure S3. Absorption spectra (not normalized) of **U4T** (blue, $\lambda_{max} = 269$ nm), **U2T** (pink, $\lambda_{max} = 265$ nm), and DNA without modified base (green dashed, $\lambda_{max} = 261$ nm).

4. Characterization of DNA Micelles

4.1. AFM images

Figure S4. Size histograms of ss DNA amphiphile aggregates. (a) **U2M** (5.2 ± 1.3 nm). (b) **U2T** (4.2 ± 2.0 nm). (c) **U4T** (4.2 ± 0.2 nm).

In order to compare the height of the ss- and ds DNA amphiphiles (measured by AFM), the ss and ds materials were prepared under the same conditions:

U2M: A freshly cleaved mica surface was covered with 40 μL of 5 mM MgAc_2 and blown dry after 5 minutes. Subsequently, 50 μL of a ~ 10 μM solution of the material in 500 μM MgAc_2 was deposited on fresh mica and allowed to incubate for 20 minutes. Images were then collected (Table S1, first row).

U2T: A freshly cleaved mica surface was covered with 40 μL of 5 mM MgAc_2 and blown dry after 5 minutes. Subsequently, 50 μL of a ~ 50 μM solution of the material in ultra pure water was then immediately deposited on the surface and allowed to incubate for 20 minutes. Images were collected for ~ 1 hour, and then the excess solution was gently shaken off and replaced with 50 μL ultra pure water, after which these images were collected (Table S1, second row).

U4T: A freshly cleaved mica surface was covered with 40 μL of 5 mM MgAc_2 and blown dry after 5 minutes. Subsequently, 50 μL of a ~ 1.3 μM solution of the material in ultra pure water was then immediately deposited on the surface and allowed to incubate for 20 minutes. Images were then collected (Table S1, third row).

Table S1. AFM images and size histograms of the DNA micelles after and before hybridization

	ss DNA amphiphiles	ds DNA amphiphiles
U2M	<p>Mean: 7.3 ± 1.9 nm</p>	<p>Mean: 6.9 ± 2.2 nm</p>
U2T	<p>Mean: 5.1 ± 1.4 nm</p>	<p>Mean: 7.9 ± 3.6 nm</p>
U4T	<p>Mean: 4.2 ± 0.9 nm</p>	<p>Mean: 6.6 ± 1.2 nm</p>

4.2. DLS size distribution of the DNA amphiphiles after hybridization

Figure S5. Dynamic light scattering (DLS) diameter distributions, analyzed by number. (a) Diameter distribution histograms of ds lipid-DNA micelles. (b) Gaussian-fitted curves (red: ss lipid-DNAs, blue: ds lipid-DNAs) of hydrodynamic size correlation data obtained from DLS measurement.

4.3. CMC determination before and after hybridization

Figure S6. Fluorescence spectra ($\lambda_{\text{ex}} = 339$ nm) of pyrene-loaded U2T micelles (pyrene concentration: 0.6 μM) at different U2T concentrations. Fluorescence spectra of the other pyrene-loaded micelles are not shown (see Tables S2 and S3 for CMC determination of all micellar structures).

Table S2. The change of the intensity ratios (I_3/I_1) from pyrene fluorescence ($\lambda_{\text{exc}} = 339$ nm) for varied concentrations of the ss- and ds lipid-DNAs

DNA-lipids		I_3/I_1 of ss DNA-lipids			I_3/I_1 of ds DNA-lipids ^[b]		
c (g/L) ^[a]	log c	U2M	U2T	U4T	U2M	U2T	U4T
0.0005	-3.30	0.510	0.503	0.513	0.536	0.520	0.543
0.001	-3.00	0.518	0.509	0.503	0.539	0.529	0.539
0.0025	-2.60	0.523	0.520	0.522	0.542	0.532	0.549
0.005	-2.30	0.521	0.521	0.539	0.539	0.531	0.581
0.01	-2.00	0.585	0.572	0.646	0.610	0.580	0.674
0.025	-1.60	0.732	0.728	0.803	0.760	0.741	0.850
0.05	-1.30	0.849	0.842	0.916	0.881	0.862	0.961
0.1	-1.00	0.911	0.934	0.969	0.951	0.920	1.016
0.5	-0.30	0.965	0.979	1.011	1.011	0.969	1.021

[a] In this column, g/L only represents the used concentration of each DNA-lipid. Weight concentration of ds DNA-lipids were omitted for clarity due to the different molecular weights of three cDNAs.

[b] An equimolar cDNA was hybridized with the corresponding lipid-DNA prior to the fluorescence measurement.

Figure S7. The change of the intensity ratio I_3/I_1 from pyrene fluorescence ($\lambda_{\text{ex}} = 339$ nm) as a function of the ds lipid-DNA concentration in ultra pure water (U2M: triangle, U2T: circle and U4T: square).

Table S3. Molar CMC of ss- and ds lipid-DNA micelles

Lipid-DNA	CMC (10^{-6} M)	
	ss	ds
U2M	2.01	2.01
U2T	2.04	2.09
U4T	1.27	1.29