

Supporting Information

A novel class of metal-directed supramolecular DNA-delivery systems

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Experimental

All chemicals were used as commercially supplied. Solvents were distilled under appropriated drying agents. Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer. NMR spectra were recorded on Varian Unity 300 or Varian XL-300 spectrometers. The ^1H chemical shifts are reported relative to the residual protons of the deuterated solvents. Mass spectra were obtained with a Finnigan MAT 95 mass spectrometer with a Finnigan MAT ICIS II operating system at 80 eV (EI). UV-vis spectra were recorded in the visible range (400-800 nm) on a Perkin Elmer Lambda 35 spectrometer. UV WinLab v. 2.85.04 software was used to analyze the spectra.

Synthesis of ligands L_{dt} and L_{ot} . 1-dodecyl-1,4,7-triazacyclononane (L_{dt}) and 1-octadecyl-1,4,7-triazacyclononane (L_{ot}) synthesis were performed using the same procedure. In a 25 mL Schlenk flask under an atmosphere of nitrogen, a mixture of 1,4,7-triazacyclononane (300 mg, 2.31 mmol) and 1.1 equivalents of sodium hydride (60 mg, 2.55 mmol) in 10 mL of dry THF was stirred for 10 minutes. A solution containing 1 equivalent of 1-bromododecane (688 mg, 2.31 mmol) or 1-bromooctadecane (769 mg, 2.31 mmol) was added drop by drop under a nitrogen atmosphere to the reaction flask. The reaction mixture was stirred overnight in an oil bath at 60 °C. Solvent was removed by rotary evaporation and the solid was dissolved in chloroform. The products were isolated using an automated flash chromatography system (Biotage) using a gradient of chloroform-methanol on a silica column. 573 mg (83%) of L_{dt} were obtained as a pale yellow viscous liquid and L_{ot} was obtained as a pale yellow wax like solid, 620 mg (70%). Similar NMR and IR spectra were obtained for both compounds. IR bands (KBr pellet, cm^{-1}) 3405 (N-H), 2918, 2850, 721(C-H); ^1H NMR (CDCl_3 , 300 MHz): δ 2.5-3.4 (m, -NH-CH), 0.8 (t, 3H, CH_3), 1.1-1.7 (m, CH_2).

Synthesis of Cu-complexes 1, 2 and 3. Amphiphilic complexes bis(1-dodecyl-1,4,7-triazacyclononane)copper(II) triflate (**1**) and bis(1-octadecyl-1,4,7-triazacyclononane) copper(II) triflate, (UV-vis λ_{max} = 640 nm in ACN) (**2**) were prepared by dissolving copper(II) trifluoromethanesulfonate, $\text{Cu}(\text{OTf})_2$ (38 mg 0.1 mmol) in 2 mL of acetonitrile and adding 2 equivalents of L_{dt} (60 mg, 0.2 mmol) or L_{ot} (76 mg, 0.2

mmol). The solutions were stirred at room temperature under nitrogen atmosphere for 24 hours. The compounds were isolated by fractional crystallization with diethyl ether at -40 °C. Liposomes of **1** and **2** were obtained were produced by the reverse phase methodology. Water was added to chloroform solutions of the complexes (CHCl₃: H₂O 1:100v/v) and the dispersion was sonicated for 30 minutes while the organic solvent was removed in vacuum. The final volume was adjusted with water to produce 1mM solutions. The solutions were then forced through a 0.4 µm pore-size polycarbonate filter using an extruder apparatus (Avanti Polar Lipids). In order to synthesize bis(1,4,7-triazacyclononane)copper(II) triflate (**3**) 2 equivalents of 1,4,7- triazacyclononane (100 mg, 0.77 mmol) were dissolved in 1 mL of acetonitrile. This mixture was added dropwise to a continued stirred solution of Cu(OTf)₂ (140 mg, 0.38 mmol) in 1 mL of acetonitrile. UV-vis λ_{max} = 620 nm (ACN). The combined mixture turned dark blue. Blue prismatic crystals were obtained by diethyl ether diffusion into a concentrated CH₃CN solution of the complex at room temperature.

Dynamic Light Scattering. Dynamic Light Scattering determinations were performed on a PD2000 DLS Plus (Precision Detectors) at 20 °C, with a scattering angle of 90.0°. The data collected was analyzed using the software Precision Deconvolve Version 4.5. 1mM aqueous dispersions of amphiphilic Cu-complexes **1** and **2** were measured.

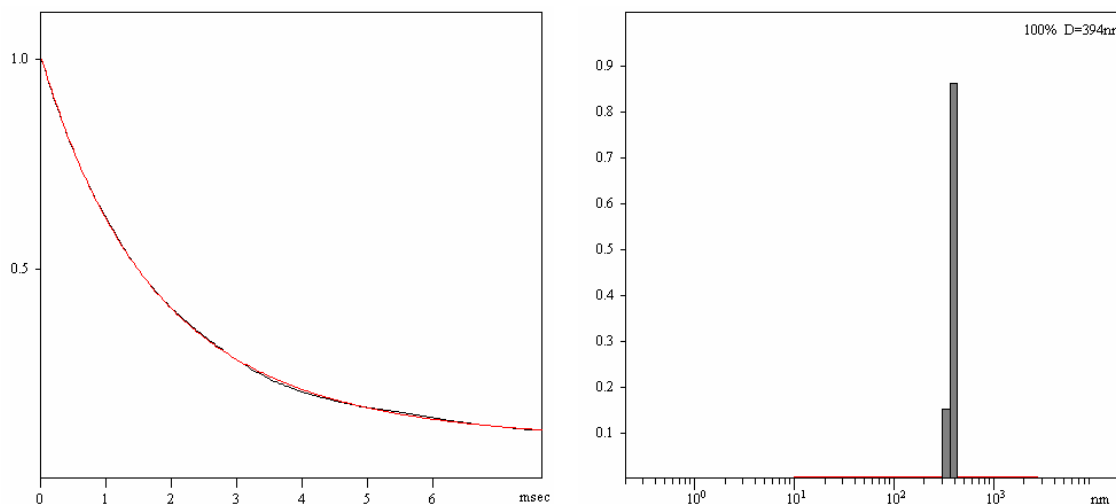


Figure S1. DLS measurement and correlation function of Cu-complex **1**

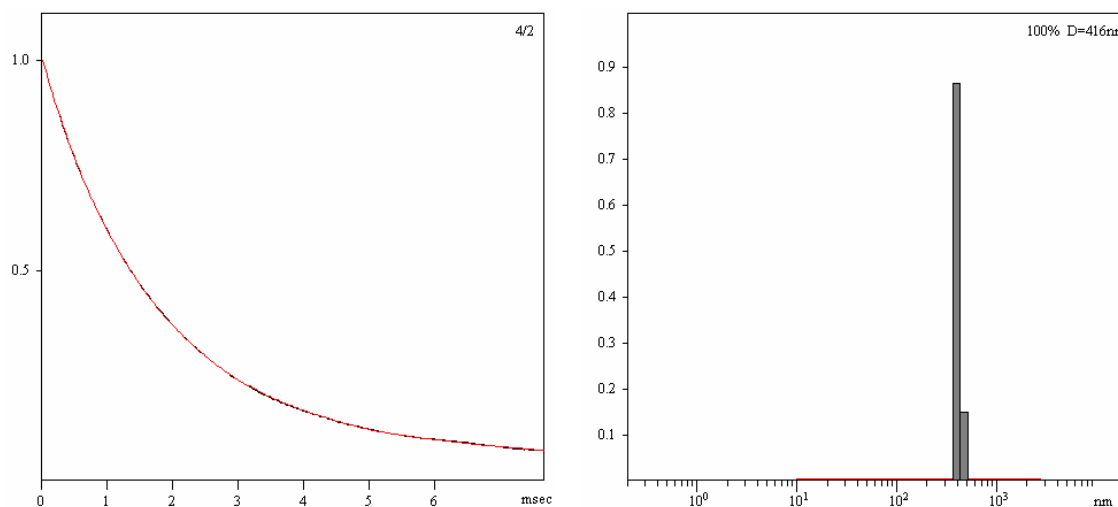


Figure S2. DLS measurement and correlation function of Cu-complex **2**.

Transmission Electron Microscopy. Samples were examined in a Hitachi H-8000 analytical transmission electron microscope. The TEM was operated at 200 kV accelerating potential. A drop of an aqueous 1 mM dispersion of Cu-complex **2** with and without DNA (pEGFP-N1) was placed over a silicon monoxide-coated 200 mesh copper grid and air evaporated.

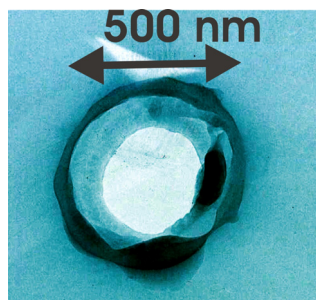


Figure S3. TEM image of Cu-complex **2** with pEGFP-N1.

Critical Micelle Concentration Determination. The critical micelle concentration for the amphiphilic complexes was determined by a dye solubilization method using the fluorescent lipophilic probe nile red¹ (Sigma Aldrich). Fluorescence intensity of nile red solutions with increasing concentration of surfactant were measured at 640 nm on a Fluoroskan microplate reader using an excitation wavelength of 530 nm. The integration time was set to 100 ms. An aqueous stock solution of nile red was prepared dissolving

400 μL of an acetone dye solution (1mg/mL) and adding water for a total volume of 10 mL. 20 μL of Nile red stock solution were added in each well of a 96-well black plate for fluorescence experiments. The concentration of amphiphilic complexes was varied from 0-400 μM using a 1mM stock solution of Cu-complex **1** and from 0-1600 μM using a 4 mM stock solution of Cu-complex **2**. The total volume in each well was adjusted to 50 μL with water. The experiments were performed by triplicate.

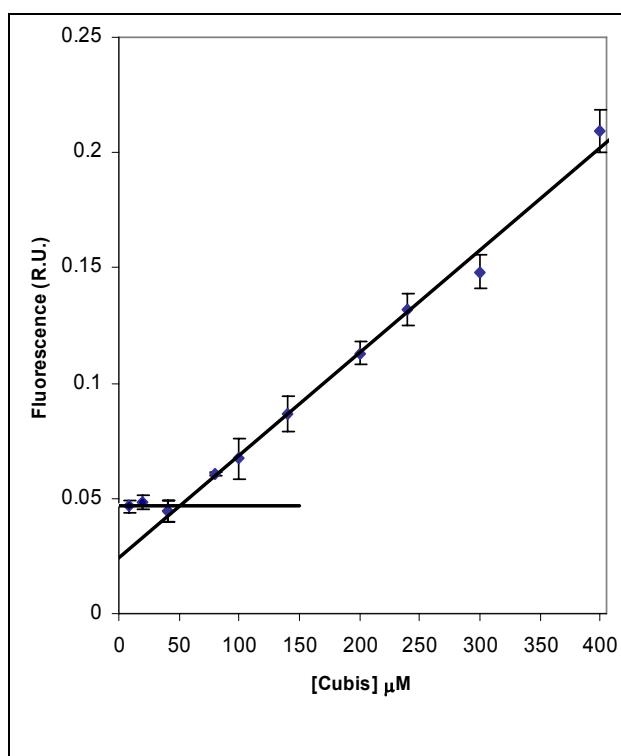


Figure S4. Determination of cmc of Cu-complex **1** (cmc= 50 μM).

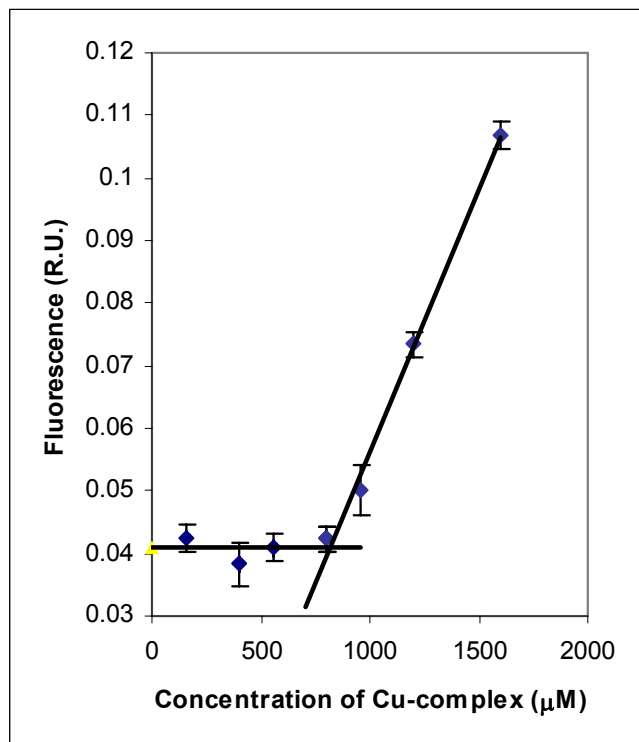


Figure S5. Determination of cmc of Cu-complex **2** (cmc= 800 μM).

Transfection experiments. Human embryonic kidney (HEK) 293T cells (Edge Biosystems, Gaithersburg, MD) were cultured in Dulbecco's modified Eagle's medium (DMEM, Mediatech, Herndon, VA) supplemented with antibiotics and 10% heat inactivated newborn calf serum (Hyclone Laboratories, Logan, UT). pEGFP-N1 green fluorescent protein-encoded plasmid (BD Clontech, Palo Alto, CA) was amplified in *Escherichia coli* and purified with Maxipreps kit (Promega, Madison, WI). Additionally, closed circular DNA plasmid was purified using equilibrium centrifugation in CsCl-ethidium bromide gradients (Sambrook, *et. al.*²).

HEK 293-T cells were cultured in 24-well plates at 40,000 cells/well in a total volume 1 ml of complete media, then incubated to reach about 40 to 50 % of confluence. Cells were washed with DMEM without serum previously to be transfected transiently.

DNA-liposome complexes were produced combining a diluted solutions of DNA with a diluted solution of liposomes (1 μg circular plasmid DNA in 50 μl serum free media with a 50 μL media solution containing 0.5, 1, 2, 3, 4 and 8 μL of a 1mM aqueous solution of

copper complexes **1** and **2**, respectively. After 15 min of incubation 0.4 ml of DMEM without serum were mixed with the complexes and then added to cells. Lipofectin (Invitrogen, Carlsbad, CA) was used as a positive control for transfection. After overnight incubation, wells were monitored by fluorescent microscopy to differentiate transfected (fluorescent) cells from non transfected cells. Experiments were done by triplicate. The transfection efficiency was calculated dividing the number of transfected cells over the total number of cells counted. At least 500 cells were counted by cell.

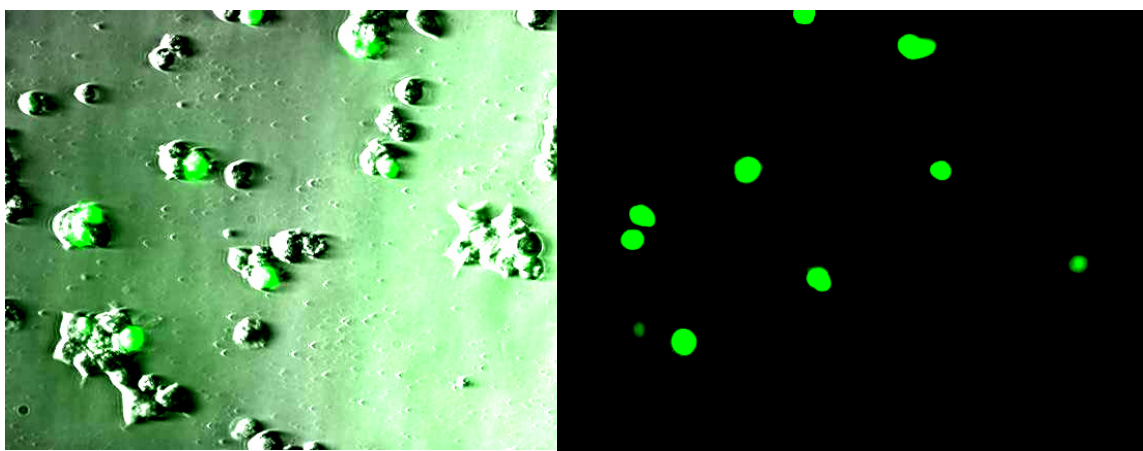


Figure S6. Optical fluorescent microscopy of transfected cells with Cu-complex **1**.

Gel Electrophoresis on Cu complex **1 and pDNA.**

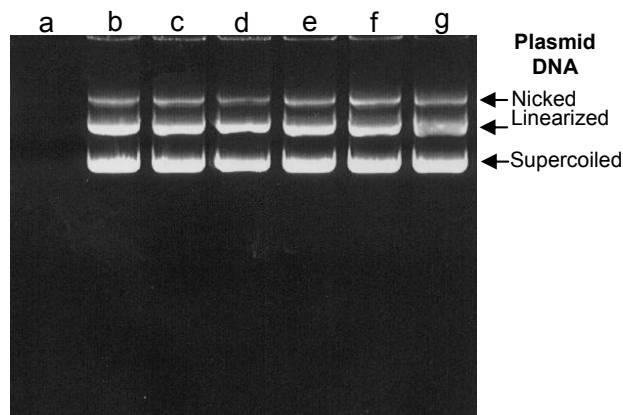


Figure S7. Reaction mixture, 20 μ l total volume, containing final concentration of 500 μ M of **1** in a DNase II buffer plus 1 μ g of DNA pEGFP-N1 were incubated at 37°C by **b**: 0 h, **c**: 0.5 h, **d**: 1 h, **e**: 2 h, **f**: 3 h, respectively. Two controls were included, **a**: Cu complex **1** alone and **g**: DNA pEGFP-N1 alone. Plasmid DNA integrity was analyzed, after the reaction products were separated by 1%-(w/v)-agarose-gel electrophoresis and visualized with UV-light trans-illuminator. The results demonstrated that no degradation products of DNA were observed even after a 3 h incubation time with **1**.

Single-crystal X-Ray Crystallography of Cu-complex 3. [CCDC 638805] A blue prism shaped crystal 0.33 x 0.30 x 0.13 mm in size was mounted on a glass fiber with traces of viscous oil and then transferred to a Nonius KappaCCD diffractometer equipped with Mo K α radiation ($\lambda = 0.71073$ Å). Ten frames of data were collected at 150(1)K with an oscillation range of 1 deg/frame and an exposure time of 20 sec/frame.³ Indexing and unit cell refinement based on all observed reflection from those ten frames, indicated a trigonal **P** lattice. A total of 5097 reflections ($\Theta_{\max} = 27.48^\circ$) were indexed, integrated and corrected for Lorentz, polarization and absorption effects using DENZO-SMN and SCALEPAC.⁴ Post refinement of the unit cell gave $a = 9.4428(2)$ Å, $b = 9.4428(2)$ Å, $c = 24.7664(7)$ Å, and $V = 1912.47(8)$ Å³. Axial photographs and systematic absences were consistent with the compound having crystallized in the Trigonal space group **P3₁ 2 1**.

The structure was solved by a combination of direct methods and heavy atom using SIR 97.⁵ All of the non-hydrogen atoms were refined with anisotropic displacement coefficients. Hydrogen atoms were assigned isotropic displacement coefficients $U(H) = 1.2U(C)$, and their coordinates were allowed to ride on their respective carbons using SHELXL97.⁶ The weighting scheme employed was $w = 1/[\sigma^2(F_o^2) + (0.0304P)^2 + 0.8643P]$ where $P = (F_o^2 + 2F_c^2)/3$. The refinement converged to $R1 = 0.0324$, $wR2 = 0.0739$, and $S = 1.049$ for 2726 reflections with $1 > 2\sigma(I)$, and $R1 = 0.0370$, $wR2 = 0.0765$, and $S = 1.049$ for 2922 unique reflections and 169 parameters.⁷ The maximum Δ/σ in the final cycle of the least-squares was 0.001, and the residual peaks on the final difference-Fourier map ranged from -0.323 to 0.387 e/Å³. Scattering factors were taken from the International Tables for Crystallography, Volume C.^{8,9}

Table S1. Crystal data and structure refinement for Cu-complex 3.

Identification code	Cu complex 3	
Empirical formula	C14 H32 Cu F6 N6 O7 S2	
Formula weight	638.12	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Trigonal	
Space group	P3₁ 2 1	
Unit cell dimensions	$a = 9.4428(2)$ Å	$\alpha = 90^\circ$.

	$b = 9.4428(2) \text{ \AA}$	$\beta = 90^\circ$.
	$c = 24.7664(7) \text{ \AA}$	$\gamma = 120^\circ$.
Volume	$1912.47(8) \text{ \AA}^3$	
Z	3	
Density (calculated)	1.662 Mg/m^3	
Absorption coefficient	1.110 mm^{-1}	
F(000)	987	
Crystal size	$0.33 \times 0.30 \times 0.13 \text{ mm}^3$	
Theta range for data collection	$4.13 \text{ to } 27.48^\circ$.	
Index ranges	$-12 \leq h \leq 12, -10 \leq k \leq 10, -32 \leq l \leq 29$	
Reflections collected	5097	
Independent reflections	2922 [$R(\text{int}) = 0.0331$]	
Completeness to $\theta = 27.48^\circ$	99.0 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.8691 and 0.7108	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2922 / 0 / 169	
Goodness-of-fit on F^2	1.049	
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0324, wR2 = 0.0739$	
R indices (all data)	$R1 = 0.0370, wR2 = 0.0765$	
Absolute structure parameter	0.024(14)	
Largest diff. peak and hole	$0.387 \text{ and } -0.323 \text{ e.\AA}^{-3}$	

Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for Cu complex 3. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
Cu(1)	-575(1)	-575(1)	5000	17(1)
S(1)	-4563(1)	3389(1)	4119(1)	26(1)
F(1)	-4068(4)	2144(3)	3253(1)	83(1)
F(2)	-2090(3)	4470(5)	3465(1)	107(1)
F(3)	-4258(3)	4250(3)	3106(1)	63(1)
O(1)	-6287(2)	2338(3)	4015(1)	42(1)
O(2)	-3817(4)	2693(4)	4440(1)	62(1)
O(3)	-4138(3)	5020(3)	4264(1)	46(1)

O(4)	-8635(3)	0	3333	34(1)
N(1)	-1006(2)	101(2)	4131(1)	23(1)
N(2)	-76(3)	1806(2)	5118(1)	24(1)
N(3)	-2960(2)	-1125(3)	5084(1)	25(1)
C(1)	-517(3)	1846(3)	4132(1)	28(1)
C(2)	576(3)	2734(3)	4613(1)	27(1)
C(3)	-1575(3)	1791(3)	5318(1)	29(1)
C(4)	-2861(3)	71(4)	5490(1)	30(1)
C(5)	-3727(3)	-1048(3)	4566(1)	29(1)
C(6)	-2770(3)	-1043(3)	4069(1)	29(1)
C(7)	-3676(4)	3612(4)	3450(1)	44(1)

Table S3. Bond lengths [Å] and angles [°] for Cu complex 3.

Cu(1)-N(3)#1	2.053(2)
Cu(1)-N(3)	2.053(2)
Cu(1)-N(2)	2.075(2)
Cu(1)-N(2)#1	2.075(2)
Cu(1)-N(1)	2.3377(19)
Cu(1)-N(1)#1	2.3378(19)
S(1)-O(2)	1.422(2)
S(1)-O(3)	1.428(2)
S(1)-O(1)	1.444(2)
S(1)-C(7)	1.821(3)
F(1)-C(7)	1.336(4)
F(2)-C(7)	1.299(4)
F(3)-C(7)	1.312(4)
O(4)-H(4)	0.86(3)
N(1)-C(6)	1.471(3)
N(1)-C(1)	1.473(3)
N(1)-H(1)	0.9300
N(2)-C(2)	1.475(3)
N(2)-C(3)	1.492(3)
N(2)-H(2)	0.9300
N(3)-C(4)	1.481(3)

N(3)-C(5)	1.491(3)
N(3)-H(3)	0.9300
C(1)-C(2)	1.523(4)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.524(4)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.526(4)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900

N(3)#1-Cu(1)-N(3)	95.10(12)
N(3)#1-Cu(1)-N(2)	177.36(9)
N(3)-Cu(1)-N(2)	83.45(8)
N(3)#1-Cu(1)-N(2)#1	83.45(8)
N(3)-Cu(1)-N(2)#1	177.36(9)
N(2)-Cu(1)-N(2)#1	98.08(12)
N(3)#1-Cu(1)-N(1)	102.92(8)
N(3)-Cu(1)-N(1)	80.98(8)
N(2)-Cu(1)-N(1)	79.06(8)
N(2)#1-Cu(1)-N(1)	97.18(8)
N(3)#1-Cu(1)-N(1)#1	80.97(8)
N(3)-Cu(1)-N(1)#1	102.92(8)
N(2)-Cu(1)-N(1)#1	97.18(8)
N(2)#1-Cu(1)-N(1)#1	79.06(8)
N(1)-Cu(1)-N(1)#1	174.33(10)
O(2)-S(1)-O(3)	114.96(16)
O(2)-S(1)-O(1)	115.50(17)
O(3)-S(1)-O(1)	113.47(14)

O(2)-S(1)-C(7)	104.77(14)
O(3)-S(1)-C(7)	103.75(16)
O(1)-S(1)-C(7)	102.27(13)
C(6)-N(1)-C(1)	115.4(2)
C(6)-N(1)-Cu(1)	100.58(14)
C(1)-N(1)-Cu(1)	107.66(14)
C(6)-N(1)-H(1)	110.9
C(1)-N(1)-H(1)	110.9
Cu(1)-N(1)-H(1)	110.9
C(2)-N(2)-C(3)	113.6(2)
C(2)-N(2)-Cu(1)	108.98(15)
C(3)-N(2)-Cu(1)	109.61(15)
C(2)-N(2)-H(2)	108.2
C(3)-N(2)-H(2)	108.2
Cu(1)-N(2)-H(2)	108.2
C(4)-N(3)-C(5)	113.2(2)
C(4)-N(3)-Cu(1)	103.47(15)
C(5)-N(3)-Cu(1)	113.51(15)
C(4)-N(3)-H(3)	108.8
C(5)-N(3)-H(3)	108.8
Cu(1)-N(3)-H(3)	108.8
N(1)-C(1)-C(2)	111.41(19)
N(1)-C(1)-H(1A)	109.3
C(2)-C(1)-H(1A)	109.3
N(1)-C(1)-H(1B)	109.3
C(2)-C(1)-H(1B)	109.3
H(1A)-C(1)-H(1B)	108.0
N(2)-C(2)-C(1)	111.7(2)
N(2)-C(2)-H(2A)	109.3
C(1)-C(2)-H(2A)	109.3
N(2)-C(2)-H(2B)	109.3
C(1)-C(2)-H(2B)	109.3
H(2A)-C(2)-H(2B)	107.9
N(2)-C(3)-C(4)	110.5(2)
N(2)-C(3)-H(3A)	109.6
C(4)-C(3)-H(3A)	109.6

N(2)-C(3)-H(3B)	109.6
C(4)-C(3)-H(3B)	109.6
H(3A)-C(3)-H(3B)	108.1
N(3)-C(4)-C(3)	109.6(2)
N(3)-C(4)-H(4A)	109.8
C(3)-C(4)-H(4A)	109.8
N(3)-C(4)-H(4B)	109.8
C(3)-C(4)-H(4B)	109.8
H(4A)-C(4)-H(4B)	108.2
N(3)-C(5)-C(6)	113.1(2)
N(3)-C(5)-H(5A)	109.0
C(6)-C(5)-H(5A)	109.0
N(3)-C(5)-H(5B)	109.0
C(6)-C(5)-H(5B)	109.0
H(5A)-C(5)-H(5B)	107.8
N(1)-C(6)-C(5)	111.6(2)
N(1)-C(6)-H(6A)	109.3
C(5)-C(6)-H(6A)	109.3
N(1)-C(6)-H(6B)	109.3
C(5)-C(6)-H(6B)	109.3
H(6A)-C(6)-H(6B)	108.0
F(2)-C(7)-F(3)	110.4(3)
F(2)-C(7)-F(1)	107.0(3)
F(3)-C(7)-F(1)	106.0(3)
F(2)-C(7)-S(1)	111.5(2)
F(3)-C(7)-S(1)	111.7(2)
F(1)-C(7)-S(1)	109.9(2)

Symmetry transformations used to generate equivalent atoms:

#1 y,x,-z+1

Table S4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for Cu complex 3. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
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Cu(1)	17(1)	17(1)	20(1)	1(1)	-1(1)	10(1)
S(1)	25(1)	25(1)	28(1)	2(1)	-1(1)	13(1)
F(1)	115(2)	107(2)	64(1)	-20(1)	11(1)	84(2)
F(2)	30(1)	194(3)	59(1)	4(2)	10(1)	29(2)
F(3)	66(1)	81(2)	39(1)	22(1)	-1(1)	34(1)
O(1)	28(1)	37(1)	38(1)	-5(1)	4(1)	0(1)
O(2)	87(2)	88(2)	45(1)	15(1)	-4(1)	69(2)
O(3)	47(1)	29(1)	56(1)	-13(1)	-14(1)	15(1)
O(4)	30(1)	43(2)	35(1)	-13(1)	-6(1)	22(1)
N(1)	26(1)	24(1)	22(1)	1(1)	2(1)	14(1)
N(2)	26(1)	24(1)	26(1)	0(1)	-1(1)	15(1)
N(3)	19(1)	27(1)	28(1)	6(1)	4(1)	11(1)
C(1)	35(2)	25(1)	28(1)	10(1)	4(1)	17(1)
C(2)	30(1)	18(1)	32(1)	4(1)	3(1)	11(1)
C(3)	35(2)	33(1)	28(1)	-3(1)	-1(1)	25(1)
C(4)	31(1)	43(2)	26(1)	2(1)	4(1)	26(1)
C(5)	20(1)	34(1)	30(1)	4(1)	-4(1)	12(1)
C(6)	28(1)	31(1)	24(1)	1(1)	-6(1)	12(1)
C(7)	34(2)	67(2)	36(1)	4(1)	1(1)	29(2)

Table S5. Hydrogen coordinates (x 10⁴) and isotropic displacement parameters (Å²x 10³) for Cu complex 3.

	x	y	z	U(eq)
H(4)	-7740(40)	700(40)	3483(14)	46(10)
H(1)	-409	-111	3877	28
H(2)	728	2283	5382	29
H(3)	-3567	-2172	5226	30
H(1A)	-1506	1954	4146	34
H(1B)	74	2360	3794	34
H(2A)	1685	2903	4546	33
H(2B)	672	3822	4651	33
H(3A)	-2023	2177	5029	34

H(3B)	-1289	2545	5629	34
H(4A)	-2568	-185	5846	36
H(4B)	-3938	4	5524	36
H(5A)	-3812	-45	4564	34
H(5B)	-4849	-1999	4546	34
H(6A)	-2955	-2160	4008	35
H(6B)	-3177	-730	3748	35

Table S6. Torsion angles [°] for Cu complex 3.

N(3)#1-Cu(1)-N(1)-C(6)	63.36(15)
N(3)-Cu(1)-N(1)-C(6)	-29.84(15)
N(2)-Cu(1)-N(1)-C(6)	-114.86(15)
N(2)#1-Cu(1)-N(1)-C(6)	148.25(15)
N(1)#1-Cu(1)-N(1)-C(6)	-163.65(14)
N(3)#1-Cu(1)-N(1)-C(1)	-175.51(15)
N(3)-Cu(1)-N(1)-C(1)	91.29(16)
N(2)-Cu(1)-N(1)-C(1)	6.27(15)
N(2)#1-Cu(1)-N(1)-C(1)	-90.62(16)
N(1)#1-Cu(1)-N(1)-C(1)	-42.52(14)
N(3)#1-Cu(1)-N(2)-C(2)	-168.9(19)
N(3)-Cu(1)-N(2)-C(2)	-112.03(17)
N(2)#1-Cu(1)-N(2)-C(2)	65.80(15)
N(1)-Cu(1)-N(2)-C(2)	-30.00(16)
N(1)#1-Cu(1)-N(2)-C(2)	145.71(16)
N(3)#1-Cu(1)-N(2)-C(3)	-44(2)
N(3)-Cu(1)-N(2)-C(3)	12.81(16)
N(2)#1-Cu(1)-N(2)-C(3)	-169.4(2)
N(1)-Cu(1)-N(2)-C(3)	94.84(17)
N(1)#1-Cu(1)-N(2)-C(3)	-89.46(16)
N(3)#1-Cu(1)-N(3)-C(4)	142.59(18)
N(2)-Cu(1)-N(3)-C(4)	-35.19(15)
N(2)#1-Cu(1)-N(3)-C(4)	-161(2)
N(1)-Cu(1)-N(3)-C(4)	-115.10(16)
N(1)#1-Cu(1)-N(3)-C(4)	60.70(16)

N(3)#1-Cu(1)-N(3)-C(5)	-94.33(18)
N(2)-Cu(1)-N(3)-C(5)	87.89(19)
N(2)#1-Cu(1)-N(3)-C(5)	-38(2)
N(1)-Cu(1)-N(3)-C(5)	7.98(17)
N(1)#1-Cu(1)-N(3)-C(5)	-176.21(17)
C(6)-N(1)-C(1)-C(2)	129.6(2)
Cu(1)-N(1)-C(1)-C(2)	18.3(2)
C(3)-N(2)-C(2)-C(1)	-71.3(3)
Cu(1)-N(2)-C(2)-C(1)	51.1(2)
N(1)-C(1)-C(2)-N(2)	-45.9(3)
C(2)-N(2)-C(3)-C(4)	134.7(2)
Cu(1)-N(2)-C(3)-C(4)	12.6(2)
C(5)-N(3)-C(4)-C(3)	-71.4(2)
Cu(1)-N(3)-C(4)-C(3)	51.9(2)
N(2)-C(3)-C(4)-N(3)	-43.7(3)
C(4)-N(3)-C(5)-C(6)	133.4(2)
Cu(1)-N(3)-C(5)-C(6)	15.8(3)
C(1)-N(1)-C(6)-C(5)	-68.9(3)
Cu(1)-N(1)-C(6)-C(5)	46.6(2)
N(3)-C(5)-C(6)-N(1)	-45.7(3)
O(2)-S(1)-C(7)-F(2)	-55.9(3)
O(3)-S(1)-C(7)-F(2)	65.0(3)
O(1)-S(1)-C(7)-F(2)	-176.8(3)
O(2)-S(1)-C(7)-F(3)	180.0(3)
O(3)-S(1)-C(7)-F(3)	-59.1(3)
O(1)-S(1)-C(7)-F(3)	59.1(3)
O(2)-S(1)-C(7)-F(1)	62.6(3)
O(3)-S(1)-C(7)-F(1)	-176.5(2)
O(1)-S(1)-C(7)-F(1)	-58.2(2)

Symmetry transformations used to generate equivalent atoms:

#1 y,x,-z+1

Table S7. Hydrogen bonds for Cu complex 3 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(4)-H(4)...O(1)	0.86(3)	1.97(3)	2.784(2)	158(3)
N(1)-H(1)...O(4)#2	0.93	2.11	3.023(3)	166.3
N(2)-H(2)...O(1)#3	0.93	2.08	2.990(3)	167.3
N(3)-H(3)...O(3)#4	0.93	2.08	2.987(3)	163.2

Symmetry transformations used to generate equivalent atoms:

#1 y,x,-z+1 #2 x+1,y,z #3 y,x+1,-z+1 #4 y-1,x,-z+1

References

1. Lau, Cheryl; Bitton, Ronit; Bianco-Peled, Havazelet; Schultz, David G.; Cookson, David J.; Grosser, Shane T.; Schneider, James W. J. *Phys. Chem. B.* **2006**, *110*, 9027-9033.
2. Sambrook, J., Fritsch, E.F. & Maniatis, T.; Hrsg. *Molecular Cloning - A Laboratory Manual, 2nd Edition*. Cold Spring Harbour Laboratory Press, **1989**, New York.
3. COLLECT Data Collection Software. Nonius B.V. **1998**.
4. Otwinowski, Z.; Minor, W., *Methods Enzymol.* **1997**, *276*, 307-326.
5. SIR97 (Release 1.02) - A program for automatic solution and refinement of crystal structure. A. Altomare, M.C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A.G. G. Molteni, G. Polidori, and R. Spagna.
6. SHELX97 [Includes SHELXS97, SHELXL97, CIFTAB] - Sheldrick, G. M. (**1997**). Programs for Crystal Structure Analysis (Release 97-2). University of Göttingen, Germany.
7. $R1 = \Sigma (| | F_o | - | F_c | |) / \Sigma | F_o |$, $wR2 = [\Sigma (w(F_o^2 - F_c^2)^2) / \Sigma (F_o^2)^2]^{1/2}$, and $S = \text{Goodness-of-fit on } F^2 = [\Sigma (w(F_o^2 - F_c^2)^2 / (n-p))]^{1/2}$, where n is the number of reflections and p is the number of parameters refined.
8. Maslen, E. N.; Fox, A. G.; O'Keefe, M. A., *International Tables for Crystallography: Mathematical, Physical and Chemical Tables*, Vol. C, Chapter 6, Wilson, A. J. C., Ed.; Kluwer, Dordrecht, The Netherlands, **1992**; 476-516.
9. Creagh, D. C.; McAuley, W. J., *International Tables for Crystallography: mathematical, Physical and Chemical tables*, Vol. C, Chapter 4 Wilson, A. J. C., Ed.; Kluwer, Dordrecht, The Netherlands, **1992**; 206-222.