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Synthesis and Structural Studies of 5,12-Dioxocyclams Capped by 4-Substituted Pyridines Across the Amine Nitrogens

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A series of 4-substituted pyridine-capped 5,12-dioxocyclams was synthesized and fully characterized. The 4-substituent varied from electron-withdrawing groups (NO_2, NO, CN) to electron-donating groups (NHCbz, NH_2). The most versatile substituent was the 4-bromo group, which could be replaced by a variety of groups using Stille, Sonogashira, or Buchwald−Hartig palladium-catalyzed chemistry. Copper complexes of a majority of these capped dioxocyclams were synthesized and characterized as well.

Introduction

Recent research in these laboratories has centered on the synthesis of functionalized 5,12-dioxocyclams as macrocyclic ligands for transition metals.[1,2] Dioxocyclams are intermediate between macrocyclic peptides and macrocyclic polyamines, having two amide and two secondary amine linkages as part of the ring periphery. The amines are nucleophilic and reactive toward a range of electrophiles. The use of bis-electrophiles can result in either linking or capping these macrocycles.[3] The synthesis of pyridine-capped[4] and pyrazine-capped[5] dioxocyclams has recently been reported from these laboratories. These macrocycles provide a rigid, 5-coordinate ligand site for copper and have unusual structural features. The pyrazine-capped system[5] is capable of coordinating metals both inside the macrocyclic cavity and outside the cavity through the remote pyrazine nitrogen, allowing formation of polymetallic coordination oligomers. Coordination oligomers—arrays connected by metal−ligand bonds rather than covalent bonds—are of current interest in the context of self-assembly of supramolecular structures.[6] When the bridging ligands can transmit electronic information, these coordination oligomers can have interesting electronic, magnetic, and optical properties.[7] Dioxocyclams capped with pyridines bearing ligating groups in the 4-position should be able to coordinate to two different metals in a manner similar to that observed with their pyrazine-capped analogues.[5] Synthetic and complexation studies of this new class of capped dioxocyclams are detailed below.

Results and Discussion

Synthesis of Capping Agents. The synthesis of 4-nitro-[8] and 4-cyano-2,6-bis(bromomethyl)pyridine began with oxidation of 2,6-lutidine to the *N*-oxide with either *m*-CPBA[8] or H_2O_2[9] (Scheme 1). Nitration followed by reduction of the *N*-oxide gave 4-nitro-2,6-lutidine, which was overbrominated with NBS and then reduced back to the desired 4-nitro-2,6-bis(bromomethyl)pyridine **1** with diethyl phosphite.[10] This two-step procedure gave substantially better yields (44% vs 11%) than direct, stoichiometric benzylic bromination. *O*-Methylation of lutidine *N*-oxide followed by treatment with aqueous potassium cyanide[11] gave 4-cyano-2,6-lutidine in low

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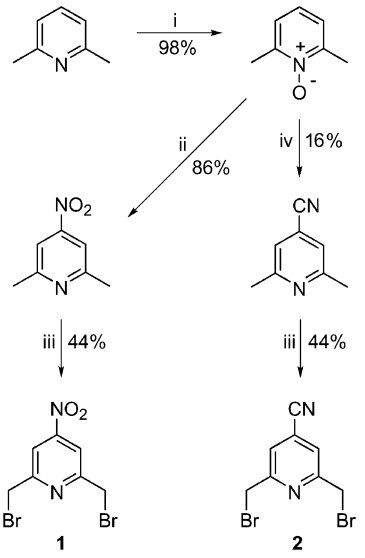
SCHEME 1. Synthesis of 4-Substituted Bis(bromomethyl)pyridines 1 and 2[a]



[a] Reagents and conditions: (i) 30% H_2O_2, glacial AcOH, 80 °C; (ii) HNO_3/H_2SO_4, 130 °C, then PCl_3, $CHCl_3$, 80 °C; (iii) 6.4 equiv of NBS, *hν*, PhH, reflux, then $HP(O)(OEt)_2$, $^iPr_2NEt$, THF, 0 °C; (iv) $(MeO)_2SO_2$, 80−100 °C, then KCN, H_2O, 25 °C.

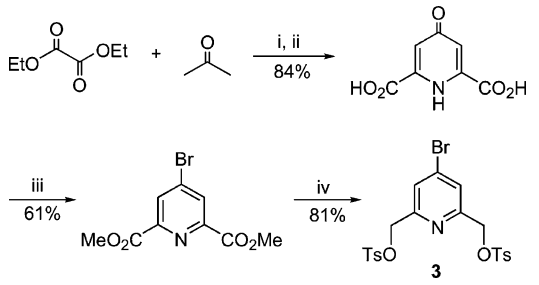
(16% vs 40% reported[11]) yield. The same overbromination followed by diethyl phosphite reduction gave the desired 4-cyano-2,6-bis(bromethyl)pyridine **2** in 44% yield.

Because the yields of benzylic bromination were always low and highly dependent on substrate structure, a more versatile capping agent that would avoid the problematic bromination step as well as provide the opportunity for efficient introduction of a range of functionality in the 4-position was sought. Because of the rich organometallic chemistry available for functionalizing heteroaromatic halides,[12] 4-bromo-2,6-bis(tosyloxymethyl)pyridine **3** was chosen. Treatment of chelidamic acid (commercially available or easily synthesized from diethyl oxalate, acetone, and ammonia) with PBr_5 followed by methanol produced dimethyl 4-bromo-2,6-pyridinedicarboxylate. Reduction followed by tosylation[13] gave **3** in good yield (Scheme 2).

With these materials in hand, capping studies were initiated.

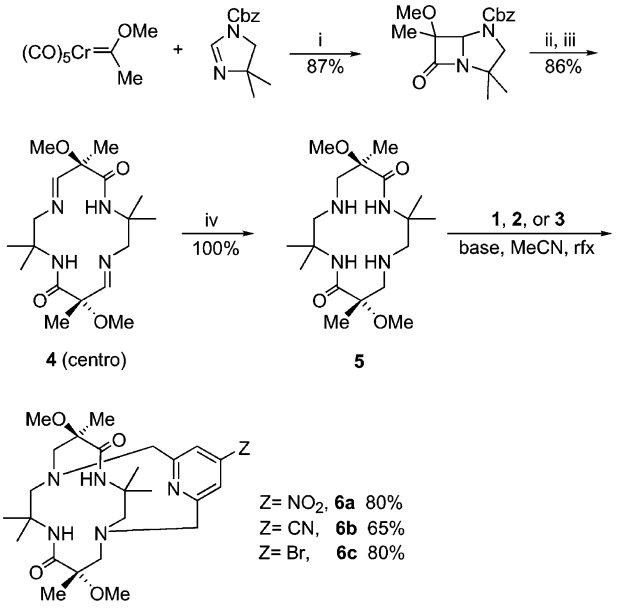
Capping Studies. The desired centrosymmetric dioxocyclam **5** was synthesized as described previously[2e,f] by photolysis of the requisite chromium carbene complex with protected dimethyl imidazoline, followed by deprotection and acid-catalyzed dimerization, producing bisimine **4** as a 1:1 mixture of centro- and C_2-symmetric diastereoisomers. These equilibrate under acid catalysis, and the centrosymmetric diastereoisomer preferentially crystallizes, allowing conversion of the 1:1 mixture completely to the centrosymmetric diastereoisomer **4** after three recrystallizations. Reduction followed by treatment with capping agents **1**−**3** in the presence of sodium carbonate (**1**) or Hünig's base (**2** and **3**) led to

SCHEME 2. Synthesis of 4-Bromobis(tosyloxymethyl)pyridine 3[a]



[a] Reagents and conditions: (i) NaOEt, EtOH, 55 °C, then aq HCl; (ii) 25% aq NH_3, 0 → 25 °C; (iii) PBr_5, $CHCl_3$, reflux, then MeOH; (iv) $NaBH_4$, abs EtOH, 0 → 25 °C, then TsCl, CH_2Cl_2, 40% aq KOH, 0 → 25 °C.

SCHEME 3. Synthesis of 4-Substituted Pyridine-Capped Dioxocyclams 6a−c[a]



[a] Reagents and conditions: (i) *hν*, CH_2Cl_2, 60 psi CO, 35 °C; (ii) H_2, 10% Pd/C, Et_3N, MeOH; (iii) cat. (±)-CSA, CH_2Cl_2, then rxt. CH_2Cl_2/hexanes, cat. (±)-CSA; (iv) $NaCNBH_3$, CH_2Cl_2/MeOH, 0 → 25 °C.

capped dioxocyclams **6a**−**c** in good yield (Scheme 3). Bromomethyl capping agents **1** and **2** capped efficiently at concentrations as high as 0.1 M, while the tosyloxymethyl agent **3** required higher dilution (0.0066 M) to prevent the bridging of two cyclam groups in competition with capping (at 0.1 M, **3** gave 52% of the bridged biscyclam and 41% of the desired capped cyclam).

4-Bromopyridyl-capped cyclam **6c** was a versatile intermediate amenable to further elaboration (Scheme 4). It underwent clean Stille coupling[14] with heteroaryl- and vinylstannanes to give **6d** and **6e**, Sonogashira coupling[15] to give **6f** and **6g**, and palladium-catalyzed amination[16] to give **6h**. Compounds **6d** and **6f** have the desired additional coordinating group external to the

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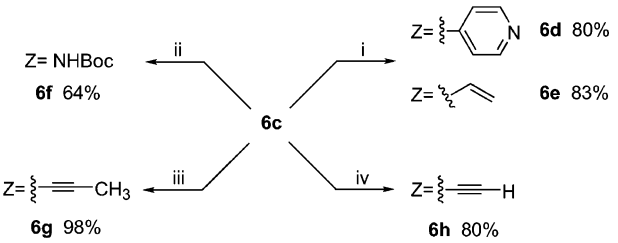
SCHEME 4. Functionalization of 4-Bromopyrine-Capped Dioxocyclam 6c[a]



[a] Reagents and conditions: (i) $ZSnBu_3$, $Pd_2(dba)_3{\cdot}CHCl_3$, Ph_3P, THF, 60−70 °C; (ii) $BocNH_2$, PhONa, $Pd_2(dba)_3{\cdot}CHCl_3$, $^tBu_3P$, $PhCH_3$, 100 °C; (iii) $HC{\equiv}CCH_3$, CuI, $(Ph_3P)_2PdCl_2$, Et_3N, MeCN, 80 °C; (iv) $HC{\equiv}CTMS$, CuI, $(Ph_3P)_2PdBr_2$, Et_3N, MeCN, 80 °C, then KF, MeOH, reflux.

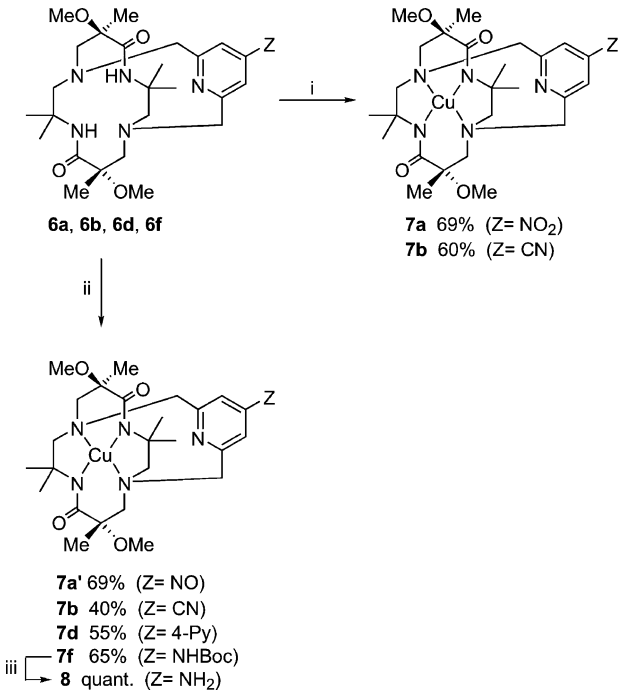
macrocycle, while **6e**, **6g**, and **6h** have functionality suitable for further coupling to generate bis-cyclam structures. (Capped cyclams **6a** (Z = NO_2), **6b** (Z = CN), and **6d** (Z = 4-Py) have been characterized by X-ray crystallography. See the Supporting Information for details.)

Complexation Studies. Introduction of copper into these macrocycles was attempted using previously developed conditions ($Cu(BF_4)_2$, K_2CO_3, MeOH, reflux).[4,5] These proved effective for **7d** (Z = NHBoc), but less so for **6b** (Z = CN). For the 4-nitro compound **7a**, a good yield of copper complex was obtained, but it proved to be the *4-nitroso* complex **7a′** rather than the expected 4-nitro compound **7a**. It is not clear what the reducing agent was, but methanol is the most likely candidate. 4-Nitrosopyridine itself is unstable,[17] although the *N*-oxide is known.[18] Apparently, coordination to copper stabilized this moiety. The desired 4-nitro complex **7a** was obtained by running the reaction in dichloromethane rather than methanol, conditions which also proved to be slightly more efficient for the synthesis of **7b** as well (Scheme 5).

Structural and Spectroscopic Studies. The X-ray crystal structures of complexes **7a′** (Z = NO), **7d** (Z = 4-Py), and **8** (Z = NH_2) were obtained (see the Supporting Information for full details), and key structural features were compared to those of the parent, pyridine-capped cyclam copper complex[4] (Z = H) (Table 1). The nature of the 4-substituent had little effect on coordination sphere about copper. The copper−amine bond lengths (N^2, N^4), copper−amide nitrogen bond lengths (N^1, N^3), and copper−pyridine nitrogen bond lengths (N^5), as well as the nitrogen−copper−nitrogen bond angles, were similar among the complexes, despite substantial differences in the electron-donating or -accepting properties of the 4-substituent. This is likely due to the relative inflexibility of capped cyclams, allowing little variation in structure.

The infrared spectra of all of the complexes showed the expected shift in the position of the amide carbonyl band from 1650 to 1660 cm^{-1} for the free ligand to 1570−1590 cm^{-1} for the complexes. The visible spectra showed an increasing blue shift as the 4-substituent on the pyridine

SCHEME 5. Introduction of Copper(II) into 6a, 6b, 6d, and 6f[a]



[a] Reagents and conditions: (i) $Cu(BF_4)_2$, K_2CO_3, wet CH_2Cl_2, 60 °C; (ii) $Cu(BF_4)_2$, K_2CO_3, MeOH, 60 °C; (iii) 10% HCl/MeOH, then aq $NaHCO_3$, CH_2Cl_2.

group became increasingly electron-withdrawing (**8**, Z = NH_2, $\lambda_{max}(\epsilon)$ 701 nm (90); **7f**, Z = NHBoc, $\lambda_{max}(\epsilon)$ 691 nm (300); **7a′**, Z = NO, $\lambda_{max}(\epsilon)$ 685 nm (90); **7d**, Z = 4-Py, $\lambda_{max}(\epsilon)$ 684 nm (100); **7b**, Z = CN, $\lambda_{max}(\epsilon)$ 670 nm (110); **7a**, Z = NO_2, $\lambda_{max}(\epsilon)$ 658 nm (140)). The ESR spectra were all very similar, with ^{G}ISO values ranging from 2.1318 (Z = 4-Py, **7d**) to 2.1378 (Z = 4-NH_2, **8**) with no apparent correlation to the 4-substituent.

In summary, a series of dioxocyclams capped with 4-substituted pyridines was synthesized and characterized. The 4-bromopyridyl compound **6c** was a versatile precursor to a range of other 4-substituted pyridyl compounds via organopalladium chemistry. Copper(II) complexes of these macrocyclic ligand systems were prepared, and characterized. Studies designed to synthesize oligomers by coordination to other metal complexes through the pyridine 4-substituent are under way.

Experimental Section

Synthesis of 2,6-Bis(bromomethyl)-4-nitropyridine[19] **(1).** A mixture of NBS (125 g, 0.702 mol) and 4-nitro-2,6-lutidine[20] (17 g, 0.11 mol) in benzene (1.0 L) was stirred vigorously at reflux for 3 days with irradiation with visible light. The dark brown mixture was concentrated under reduced pressure. The residue was taken up in diethyl ether and passed through a Celite pad, and the solvent was removed under vacuum to give crude 2,6-bis(tribromomethyl)-4-nitropyridine as a clear dark brown oil (77 g). A portion of the crude material (8.76 g, 11% of the total amount) was dissolved in dry THF (65 mL) and placed in an ice bath under an argon atmosphere. Diisopropylethylamine (6.57 mL, 51.0 mmol) was

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TABLE 1. Comparison of Selected Bond Lengths (Å) and Bond Angles (°) for Pyridine-Capped Copper Dioxocyclam Complexes 7a′, 7d and 8[a]

	bond lengths (Å)					bond angles (deg)		
complex	N^1-Cu	N^2-Cu	N^3-Cu	N^4-Cu	N^5-Cu	N^1-Cu-N^3	N^3-Cu-N^5	N^1-Cu-N^5
Z = H (ref 4)	1.936 (3)	2.102 (3)	1.948 (3)	2.100 (3)	2.125 (3)	157.9 (1)	105.0 (1)	96.9 (1)
	1.954 (3)	2.118 (3)	1.957 (3)	2.138 (3)	2.121 (3)	142.8 (1)	106.8 (1)	110.3 (1)
7a′ (Z = NO)	1.938 (10)	2.117 (9)	1.960 (12)	2.106 (9)	2.087 (10)	153.9 (4)	104.6 (5)	101.5 (5)
7d (Z = 4-Py)	1.951 (9)	2.119 (7)	1.932 (9)	2.099 (7)	2.076 (7)	152.8 (3)	103.7 (3)	103.4 (3)
	1.916 (7)	2.147 (7)	1.921 (8)	2.145 (7)	2.143 (7)	150.9 (3)	103.5 (3)	105.6 (3)
8 ($Z = NH_2$)	1.923 (7)	2.128 (7)	1.907 (7)	2.167 (7)	2.106 (7)	150.1 (3)	103.6 (3)	106.2 (3)
	1.901 (7)	2.147 (7)	1.919 (7)	2.192 (7)	2.105 (8)	150.1 (3)	103.7 (3)	106.2 (3)

[a] Complexes having two sets of entries had two slightly different molecules in the unit cell. Data for both are recorded.

added. Diethyl phosphite (8.88 mL, 51.0 mmol) was added dropwise, and the reaction progress was monitored by TLC (hexanes/EtOAc 9:1, **1**: R_f 0.2). Within 5 min of the end of the addition, the multiple products were converted into a single product. The reaction mixture was poured into ice-cold water. The product was extracted with Et_2O, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography on silica (hexanes/EtOAc 75:25) afforded pure **1** (1.75 g) as a yellowish oil: yield 44%.

Synthesis of 2,6-Bis(bromomethyl)-4-cyanopyridine (2). A mixture of NBS (2.14 g, 12 mmol) and 4-cyano-2,6-lutidine[11] (0.40 g, 3.0 mmol) in CCl_4 (20 mL) placed in a tightly sealed reaction vessel was stirred vigorously at 70 °C for 2 h with irradiation with visible light. The resulting light brown slurry was cooled to room temperature, and insoluble material was removed by filtration through a Celite pad. The clear light brown filtrate was concentrated in vacuo, and the resulting clear yellow oil was redissolved in dry THF (60 mL). The solution, under an argon atmosphere, was placed in an ice bath. Diisopropylethylamine (2.1 mL, 12 mmol) was added followed by dropwise addition of diethyl phosphite (1.54 mL, 12 mmol). The cooling bath was removed, and the reaction progress was monitored by TLC. After ca. 5 h at room temperature, the multiple products were converted into a single product (by TLC). Water (50 mL) was added, and most of the THF was removed under reduced pressure. The resulting slurry was diluted with saturated $NaHCO_3$ (aq) (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (30 g silica; hexanes/EtOAc 85:15) afforded pure **2** (385 mg) as a yellowish crystalline solid: yield 44%; mp 95−96 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61 (s, 2H), 4.54 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.2, 124.2, 122.4, 115.7, 32.0; FT-IR (film) 3073, 2973, 1596, 1557, 1434, 1411, 1247, 1212 cm^{-1}; HRMS (FAB^+, *m*/*z*) calcd for $C_8H_7N_2Br_2^{81}$ ($M + H^+$) 292.8935, found 292.8936.

Synthesis of 4-Bromo-2,6-bis(tosyloxymethyl)pyridine[13] (3). To the dimethyl 4-bromo-2,6-pyridinedicarboxylate[21] (2.20 g, 8.00 mmol) solution in absolute EtOH (20 mL) was added $NaBH_4$ (0.56 g, 15 mmol) portionwise at −5 °C. Upon addition, the previously colorless solution turned orange and then gradually decolorized as the reaction progressed. Several minutes after the last portion of $NaBH_4$ was added, the cooling was removed which resulted in spontaneous warming slightly above room temperature (exothermic reaction). At the point at which the reaction mixture was only slightly colored, it was brought to reflux for 5 min. Solvent was removed under reduced pressure, and then traces of EtOH were removed under high vacuum to give a colorless powder (6.47 g). The crude material was taken up in a precooled (0 °C) mixture of CH_2Cl_2 (40 mL) and KOH (18 g) in water (22 mL). Tosyl chloride (5.8 g, 30 mmol) was added, and the resulting heterogeneous mixture was shaken vigorously until all the solids dispersed. The resulting colorless emulsion was stirred at 0 °C for 45 min and then washed into separatory funnel using CH_2Cl_2 (80 mL) and water (80 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL). The combined organic solutions were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Recrystallization by addition of hexanes to a saturated dichloromethane solution of the crude product afforded pure bistosylate **3** (3.42 g) as colorless flakes: yield 81%; mp 111−112 °C (lit.[13] 110−111 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 8.4 Hz, 4H), 7.42 (s, 2H), 7.33 (d, J = 8.4 Hz, 4H), 5.01 (s, 4H), 2.44 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.7, 145.2, 134.4, 132.4, 129.9, 127.9, 124.3, 70.4, 21.7. FT-IR (film) 1597, 1574, 1367, 1190, 1176, 1096, 1032 cm^{-1}; LRMS (FAB^+, *m*/*z*) 525 ($M + H^+$), 527 ($M + H^+$).

Synthesis of 4-Nitropyridine-Capped Dioxocyclam (6a). A mixture of the dibromide **1** (35 mg, 0.11 mmol), *meso*-dioxocyclam **5** (30 mg, 80 μmol), and Na_2CO_3 (43 mg, 0.41 mmol) was flushed with argon. Acetonitrile (3 mL) was added, and the resulting mixture was stirred at 85 °C for 3 days. The reaction mixture was cooled to room temperature and passed through a pad of Celite using MeCN as eluent. The combined solutions were concentrated under reduced pressure. Flash chromatography on silica (CH_2Cl_2/MeOH 95:5) afforded pure capped dioxocyclam **6a** (33 mg) as a cream colored solid. X-ray quality crystals were obtained by recrystallization from CH_2Cl_2/hexanes (liquid diffusion): yield 80%; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H), 7.69 (s, 1H), 7.65 (s, 2H), 4.38−4.05 (m, 4H), 3.41 (s, 3H), 3.21 (d, 1H, J = 14 Hz), 2.90−2.85 (m, 5H), 2.57 (d, 1H, J = 14 Hz), 2.48 (s, 3H), 2.29 (d, 1H, J = 15 Hz), 1.45 (s, 3H), 1.42 (s, 3H), 1.33 (s, 6H), 1.32 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.2, 172.6, 166.8, 162.1, 155.2, 112.1, 111.8, 82.6, 79.4, 74.6, 72.8, 69.6, 67.4, 65.7, 64.8, 55.9, 54.7, 51.9, 50.4, 26.3, 25.6, 23.5, 23.4, 20.0, 19.2; FT-IR (film) 1660, 1537, 1355 cm^{-1}; HRMS (FAB^+, *m*/*z*) calcd for $C_{25}H_{41}N_6O_6$ ($M + H^+$) 521.3088, found 521.3096. The molecular structure was determined by single-crystal X-ray diffraction.

Synthesis of 4-Cyanopyridine-Capped Dioxocyclam (6b). A mixture of the dibromide **2** (240 mg, 0.83 mmol), *meso*-dioxocyclam **5** (308 mg, 0.83 mmol), and diisopropylethylamine (1.5 mL, 8.5 mmol) in MeCN (12 mL) was stirred at reflux for ca. 3 h until the dibromide could not be detected by TLC (hexanes/EtOAc 8:2, R_f 0.45). The solvent was removed under reduced pressure. The solid residue was dissolved in CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic solutions were dried over Na_2SO_4 and concentrated under vacuum. Flash chromatography on silica (35 g, CH_2Cl_2/MeOH 97:3 → 95:5) afforded pure capped dioxocyclam **6b** (0.27 g) as a yellowish foam. X-ray quality crystals were obtained by recrystallization from CH_2Cl_2/Et_2O: yield 65%; mp 290−291 °C dec; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.76 (s, 1H), 7.62 (s, 1H), 7.20 (s, 1H), 7.17 (s, 1H), 4.24−3.96 (m, 4H), 3.40 (s, 3H), 3.18 (d, J = 13.5 Hz, 1H), 3.03−2.86 (m, 5H), 2.55 (d, J = 14.1 Hz, 1H), 2.50 (s, 3H), 2.26 (d, J = 14.1 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 172.1, 164.6, 160.0, 121.1, 120.9, 120.2, 116.4,

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82.4, 79.2, 74.4, 72.5, 69.0, 67.2, 65.1, 64.5, 55.7, 54.5, 51.7, 50.2, 26.1, 25.5, 23.3 (2C), 19.0; FT-IR (film) 3259, 2959, 2928, 2827, 1660, 1560, 1516, 1453, 1132, 1101 cm^{-1}; LRMS (FAB^+, *m*/*z*) 501 ($M + H^+$). The molecular structure was determined by single-crystal X-ray diffraction.

Synthesis of 4-Bromopyridine-Capped Dioxocyclam (6c). A mixture of the ditosylate **3** (1.34 g, 2.55 mmol), *meso*-dioxocyclam **5** (950 mg, 2.55 mmol), and diisopropylethylamine (4.6 mL, 26 mmol) in MeCN (0.47 L) was stirred at reflux for 2 days until the ditosylate could not be detected by TLC. The solvent was removed under reduced pressure. The solid residue was dissolved in CH_2Cl_2 (0.15 L) and washed with saturated $NaHCO_3$ (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (50 mL). The combined organic solutions were dried over Na_2SO_4 and concentrated under vacuum. Flash chromatography on silica (40 g, CH_2Cl_2/MeOH 97:3) afforded pure capped dioxocyclam **6c** (1.13 g) as an off-white foam. X-ray quality crystals were obtained by recrystallization from hot MeCN: yield 80%; mp 225 °C dec; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.88 (s, 1H), 7.78 (s, 1H), 7.10 (s, 1H), 7.06 (s, 1H), 4.10−3.80 (m, 4H), 3.35 (s, 3H), 3.11 (d, J = 13.5 Hz, 1H), 2.96−2.78 (m, 5H), 2.56−2.46 (m, 4H), 2.25 (d, J = 14.4 Hz, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 172.2, 164.1, 159.6, 133.3, 122.1, 121.8, 82.2, 79.2, 74.2, 72.3, 68.7, 67.1, 64.9, 64.4, 55.6, 54.4, 51.6, 50.0, 26.0, 25.4, 23.2 (2C), 19.0; FT-IR (film) 3248, 2959, 2930, 2826, 1660, 1569, 1518, 1453, 1132, 1103 cm^{-1}. Anal. Calcd for $C_{25}H_{40}N_5O_4Br$: C, 54.15; H, 7.22; N, 12.64. Found: C, 54.24; H, 7.36; N, 12.45.

Synthesis of 4-(4-Pyridyl)pyridine-Capped Dioxocyclam (6d). A solution of the bromide **6c** (500 mg, 0.902 mmol) and tributyl(4-pyridyl)tin[22] (0.45 g, 1.2 mmol) in MeCN (11 mL) placed in a pressure tube was degassed by repeating freeze−pump−thaw sequence four times. $Pd_2(dba)_3$·$CHCl_3$ (47 mg, 45 μmol) was added followed by triphenylphosphine (95 mg, 0.36 mmol), and the resulting clear yellow solution was stirred at 80 °C under argon for 2 days. The reaction mixture was passed through a Celite pad to produce a clear orange solution which was subsequently concentrated in vacuo. The residue was taken up in Et_2O (0.10 L) and 1 M HCl aq (0.10 L). Layers were separated, and the aqueous layer was washed with one more Et_2O portion (0.10 L) to remove all the organotin material. All organic solutions were discarded. The aqueous layer was made basic using concentrated KOH (aq) and extracted with CH_2Cl_2 (3 × 80 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Recrystallization from hot MeCN afforded pure capped dioxocyclam **6d** (400 mg) as colorless needles: yield 80%; mp 270 °C dec; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.06 (s, 1H), 8.74 (s, 1H), 8.72 (s, 1H), 7.96 (s, 1H), 7.53 (s, 1H), 7.51 (s, 1H), 7.18 (s, 1H), 7.15 (s, 1H), 4.28−3.98 (m, 4H), 3.41 (s, 3H), 3.21 (d, J = 13.8 Hz, 1H), 3.02−2.86 (m, 5H), 2.60 (d, J = 14.4 Hz, 1H), 2.51 (s, 3H), 2.35 (d, J = 14.1 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.19 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.0, 172.4, 163.9, 159.3, 150.5, 146.8, 145.5, 121.3, 116.8, 116.5, 82.4, 79.4, 74.4, 72.5, 69.2, 67.2, 65.5, 64.5, 55.8, 54.6, 51.7, 50.1, 26.1, 25.5, 23.4, 23.3, 19.1; FT-IR (film) 3239, 2960, 2930, 2825, 1658, 1593, 1543, 1518, 1454, 1132, 1102 cm^{-1}; HRMS (FAB^+, *m*/*z*) calcd for $C_{30}H_{45}N_6O_4$ ($M + H^+$) 553.3502, found 553.3486. The molecular structure was determined by single-crystal X-ray diffraction.

Synthesis of 4-Vinylpyridine-Capped Dioxocyclam (6e). To a solution of the bromide **6c** (84 mg, 0.15 mmol) in dry, oxygen-free THF (3.0 mL) was added triphenylphosphine (19 mg, 74 μmol) followed by $Pd_2(dba)_3$·$CHCl_3$ (8.4 mg, 8.0 μmol) under argon. The resulting red solution was stirred for 10 min upon which the solution turned yellow-orange. Tributyl(vinyl)tin (66 μL, 0.23 mmol) was added, the reaction vessel was tightly sealed, and the reaction mixture was stirred at 60 °C overnight. The solvent was removed under reduced pressure and the residue purified by flash chromatography (CH_2Cl_2/MeOH 95:5) to afford pure capped dioxocyclam **6e** (62 mg) as a yellowish oil: yield 83%; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.06 (s, 1H), 8.03 (s, 1H), 6.92 (s, 1H), 6.87 (s, 1H), 6.63 (dd, J_1 = 10.8 Hz, J_2 = 17.7 Hz, 1H), 5.94 (d, J = 17.7 Hz, 1H), 5.46 (d, J = 10.8 Hz, 1H), 4.18−3.87 (m, 4H), 3.39 (s, 3H), 3.17 (d, J = 13.5 Hz, 1H), 2.98−2.80 (m, 5H), 2.55 (d, J = 14.4 Hz, 1H), 2.50 (s, 3H), 2.32 (d, J = 14.1 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 172.6, 163.2, 158.6, 146.0, 134.8, 118.7, 116.1, 115.8, 82.4, 79.4, 74.3, 72.4, 69.0, 67.1, 65.4, 64.5, 55.7, 54.6, 51.7, 50.0, 26.0, 25.4, 23.4, 23.2, 19.0; FT-IR (film) 3233, 2956, 2927, 2827, 1659, 1605, 1558, 1519, 1453, 1133, 1103 cm^{-1}; HRMS (FAB^+, *m*/*z*) calcd for $C_{27}H_{44}N_5O_4$ ($M + H^+$) 502.3393, found 502.3394.

Synthesis of 4-(NHBoc)pyridine-Capped Dioxocyclam (6f). The bromide **6c** (50 mg, 90 μmol), *tert*-butyl carbamate (42 mg, 0.36 mmol), freshly prepared sodium phenoxide (42 mg, 0.36 mmol), and $Pd_2(dba)_3$·$CHCl_3$ (4.9 mg, 4.7 μmol) were combined in a screw-cap pressure tube under argon. The mixture was suspended in dry, oxygen-free toluene (2.5 mL). To the resulting dark-red slurry was added 0.05 M $^tBu_3P$ in toluene (0.36 mL, 18 μmol) and the pressure tube was tightly sealed. The reaction mixture was then stirred at 100 °C overnight (16 h). The dark-orange reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, and washed with 5% aq $NaHCO_3$. The aqueous layer was then back-extracted twice with CH_2Cl_2. The combined organic solutions were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography on silica (CH_2Cl_2/MeOH 95:5 → 50:50) afforded capped dioxocyclam **6f** (34 mg) as a colorless solid: yield 64%; mp 165 °C dec; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.08 (s, 1H), 8.27 (s, 1H), 7.14 (s, 1H), 7.08 (s, 1H), 6.86 (s, 1H), 4.14−3.84 (m, 4H), 3.38 (s, 3H), 3.17 (d, J = 13.5 Hz, 1H), 2.98−2.80 (m, 5H), 2.59 (s, 3H), 2.50 (d, J = 9.6 Hz, 1H), 2.32 (d, J = 14.4 Hz, 1H), 1.51 (s, 9H), 1.44 (s, 3H), 1.40 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.19 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.2, 172.6, 163.3, 159.2, 152.0, 146.7, 107.2, 107.1, 82.4, 81.7, 79.5, 74.1, 72.6, 68.8, 66.9, 65.7, 64.6, 55.7, 54.7, 51.7, 50.2, 28.3, 26.1, 25.5, 23.4 (2C), 19.1; FT-IR (film) 3227, 2973, 2931, 2827, 1733, 1653, 1594, 1521, 1456, 1368, 1266, 1233, 1156, 1133, 1104 cm^{-1}; HRMS (FAB^+, *m*/*z*) calcd for $C_{30}H_{51}N_6O_6$ ($M + H^+$) 591.3870, found 591.3878.

Synthesis of 4-(1-Propynyl)pyridine-Capped Dioxocyclam (6g). The bromide **6c** (55 mg, 0.10 mmol) was placed in an argon-flushed pressure tube. After being dissolved in a mixture of dry MeCN (2.0 mL) and dry Et_3N (1.0 mL), the solution was degassed by three freeze−pump−thaw sequences. $(Ph_3P)_2PdCl_2$ (7 mg, 10 μmol) and CuI (9.8 mg, 50 μmol) were added under argon. The pressure tube was fitted with a pressure head,and connected to a propyne tank. The pressure tube was then placed in a liquid nitrogen bath, and propyne (0.7 g, 17 mmol) was condensed into the reaction vessel. The pressure tube was then tightly sealed and placed in a 80 °C bath with stirring (ca. 50 psi of internal pressure developed) for 20 h. The reaction mixture was then passed through Celite and concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc 2:8) afforded pure product **6g** as a yellowish wax (50 mg). X-ray quality crystals were obtained by recrystallization from CH_2Cl_2/MeCN by slow evaporation: yield 98%; mp 236−8 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.98 (s, 1H), 7.94 (s, 1H), 6.89 (s, 1H), 6.86 (s, 1H), 4.12−3.82 (m, 4H), 3.38 (s, 3H), 3.16 (d, J = 13.8 Hz, 1H), 2.98−2.80 (m, 5H), 2.56 (s, 3H), 2.53 (d, J = 13.8 Hz, 1H), 2.29 (d, J = 14.1 Hz, 1H), 2.04 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 172.7, 162.8, 158.3, 133.4, 121.3, 120.9, 91.1, 82.5, 79.6, 74.5, 72.6, 69.1, 67.4, 65.4, 64.7, 55.9, 54.8, 51.9, 50.4, 26.3, 25.7, 23.6, 23.5, 19.3, 4.8; FT-IR (film) 3279, 3207, 2957, 2933, 2827, 2245, 1655, 1601, 1549,

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1519, 1456, 1368, 1263, 1182, 1135, 1104, 1089, 1062 cm^{-1}; HRMS (FAB^+, *m/z*) calcd for $C_{28}H_{44}N_5O_4$ ($M + H^+$) 514.3393, found 514.3395.

Synthesis of 4-(Ethynyl)pyridine-Capped Dioxocyclam (6h). The bromide **6c** (220 mg, 0.397 mmol) and (trimethylsilyl)acetylene (0.28 mL, 2.0 mmol) were combined in an argon-flushed pressure tube. After being dissolved in a mixture of dry MeCN (4.0 mL) and dry Et_3N (4.0 mL), the solution was degassed by three freeze−pump−thaw sequences. $(Ph_3P)_2PdBr_2$ (32 mg, 40 μmol) and CuI (52 mg, 0.27 mmol) were added under argon, and the pressure tube was tightly sealed and placed in a 80 °C bath with stirring for 22 h. The resulting dark-brown reaction mixture was passed through a Celite pad and concentrated in vacuo. The residue was taken up in CH_2Cl_2 and washed with saturated $NaHCO_3$ (aq). The aqueous layer was extracted with CH_2Cl_2. The combined organic solutions were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (CH_2Cl_2/MeOH 93:7) afforded TMS-protected product as a brownish foam (220 mg): yield 96%; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.91 (s, 1H), 7.91 (s, 1H), 6.95 (s, 1H), 6.91 (s, 1H), 4.12−3.82 (m, 4H), 3.36 (s, 3H), 3.13 (d, J = 13.8 Hz, 1H), 2.94−2.78 (m, 5H), 2.52 (s, 3H), 2.49 (d, J = 13.8 Hz, 1H), 2.26 (d, J = 13.8 Hz, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.14 (s, 3H), 1.08 (s, 3H), 0.21 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.0, 172.4, 162.6, 158.1, 132.0, 121.1, 120.7, 102.0, 99.3, 82.2, 79.3, 74.1, 72.4, 68.7, 67.0, 65.1, 64.4, 55.6, 54.5, 51.6, 50.1, 26.0, 25.4, 23.2, 19.0, −0.3. The TMS-acetylene derivative was dissolved in MeOH (10 mL) and treated with KF (44 mg, 0.76 mmol). The resulting brown solution was heated to reflux and then allowed to stand at room temperature for 4 h. The solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2, passed through a Celite pad, and then concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH 93:7) afforded pure terminal alkyne **6h** (159 mg) as a yellowish oil. X-ray quality crystals were obtained by recrystallization from hot MeCN: yield 80%; mp 210 °C dec; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.94 (s, 1H), 7.87 (s, 1H), 7.01 (s, 1H), 6.98 (s, 1H), 4.17−3.85 (m, 4H), 3.40 (s, 3H), 3.25 (s, 1H), 3.18 (d, J = 13.5 Hz, 1H), 2.99−2.81 (m, 5H), 2.59−2.49 (m, 4H), 2.29 (d, J = 14.4 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.9, 172.3, 162.8, 158.3, 131.1, 121.4, 121.0, 82.2, 81.4, 81.0, 79.3, 74.2, 72.3, 68.8, 67.1, 65.1, 64.4, 55.6, 54.5, 51.6, 50.0, 26.0, 25.4, 23.2, 19.0; FT-IR (film) 3242, 2960, 2931, 2827, 2104, 1659, 1599, 1556, 1518, 1453, 1367, 1325, 1132, 1102, 1058 cm^{-1}; HRMS (FAB^+, *m/z*) calcd for $C_{27}H_{42}N_5O_4$ ($M + H^+$) 500.3237, found 500.3238.

General Procedure for the Preparation of Copper(II) Complexes. A ligand **6** (50 μmol), $Cu(BF_4)_2 \cdot 6H_2O$ (85 mg, 0.25 mmol), and K_2CO_3 (0.14 g, 1.0 mmol) were combined in a screw-cap pressure tube. The mixture was suspended in a solvent (MeOH or wet CH_2Cl_2, 5 mL), and the reaction vessel was tightly sealed and placed in 80−100 °C bath with stirring for 1−5 days. The resulting colored slurry was passed through a Celite pad and concentrated in vacuo. For reactions with MeOH as a solvent, the solid residue was triturated with CH_2Cl_2, and passed through a Celite pad again to produce a clear green solution. Purification by flash chromatography on silica (CH_2Cl_2/MeOH, copper(II) complexes **7** reversibly change color from green to purple in contact with silica), and/or by recrystallization.

Copper complex (7a): yield 69%; FT-IR (film) 1576, 1542, 1355 cm^{-1}; UV−vis (MeOH) $\lambda_{max}(\epsilon)$ 658 (1.4×10^2); ESR (CH_2Cl_2/PhH 3:1) 2.1343; HRMS (FAB^+, *m/z*) calcd for $C_{25}H_{39}N_6O_6Cu$ ($M + H^+$) 582.2227, found 582.2231.

Copper Complex (7a′). X-ray quality crystals by recrystallization from CH_2Cl_2/hexanes (slow evaporation): yield 69%; FT-IR (film) 1583, 1358 cm^{-1}; UV−vis (MeOH) $\lambda_{max}(\epsilon)$ 685 (0.9×10^2); ESR (CH_2Cl_2/PhH 3:1) 2.1341. The molecular structure was determined by single-crystal X-ray diffraction.

Copper Complex (7b). X-ray quality crystals by recrystallization from CH_2Cl_2/hexanes (vapor diffusion): yield 60%; mp 200 °C dec; FT-IR (film) 3416, 2918, 1574, 1450, 1365, 1184, 1132, 1074 cm^{-1}; UV−vis (MeOH) $\lambda_{max}(\epsilon)$ 670 (1.1×10^2); ESR (CH_2Cl_2/PhH 3:1) 2.1351; LRMS (FAB^+, *m/z*) 562 ($M + H^+$).

Copper Complex (7d). X-ray quality crystals by recrystallization from CH_2Cl_2/hexanes/EtOAc (slow evaporation): yield 55%; mp 158−160 °C; FT-IR (film) 3238, 2956, 2926, 2855, 1590, 1452, 1368, 1132, 1071 cm^{-1}; UV−vis (MeOH) $\lambda_{max}(\epsilon)$ 684 (1.0×10^2); ESR (CH_2Cl_2/PhH 3:1) 2.1318; LRMS (FAB^+, *m/z*) 614 ($M+ H^+$). The molecular structure was determined by single-crystal X-ray diffraction.

Copper Complex (7f). Purification by flash chromatography (CH_2Cl_2/MeOH 95:5 → 50:50 → 0:100) afforded pure complex **7f** as a green wax: yield 65%; FT-IR (film) 3224, 2925, 1582, 1461, 1451, 1427, 1366, 1260, 1241, 1156, 1084, 1018 cm^{-1}; UV−vis (MeOH) $\lambda_{max}(\epsilon)$ 691 (3×10^2); LRMS (FAB^+, *m/z*) 652 ($M + H^+$).

Copper Complex (8). The copper complex **7f** (7.2 mg, 11 μmol) was dissolved in 10% HCl/MeOH (1 mL) with concominant gas evolution to produce a dark violet solution. The solvent was removed under reduced pressure. The residue was dissolved in saturated $NaHCO_3$ (aq) (10 mL). The resulting clear violet solution was concentrated under reduced pressure. The solid residue was dried under vacuum until the color changed from light violet to light green and was then triturated with CH_2Cl_2 to produce a green solution. Recrystallization from CH_2Cl_2/hexanes afforded pure complex **8** (6.0 mg) as green crystals: yield quantitative; mp 300 °C dec; FT-IR (film) 3308, 2881, 1581, 1447, 1365, 1135, 1090 cm^{-1}; UV−vis (MeOH) $\lambda_{max}(\epsilon)$ 701 (0.9×10^2); ESR (CH_2Cl_2/PhH 3:1) 2.1378; HRMS (FAB^+, *m/z*) calcd for $C_{25}H_{41}N_6O_4Cu$ ($M + H^+$) 552.2485, found 552.2477. The molecular structure was determined by single-crystal X-ray diffraction.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **2** and **6a**,**b**,**d**−**h**. ORTEP diagrams, crystal data and structure refinement parameters, atomic coordinates, bond lengths and bond angles, torsion angles, anisotropic displacement coefficients, and H-atom coordinates for compounds **6a**,**b**,**d**, **7a′**,**d**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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