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The Design and Synthesis of Bis-[4′-Azido-2,2′:6′,2″-Terpyridine Platinum(II)] Complexes with Rigid and Extended Linkers for Studying the Topology of DNA by Photoaffinity Labeling

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A family of bis-[4′-Azido-2,2′:6′,2″-terpyridine platinum(II)] complexes with linear linkers of varying length have been synthesized. They have been designed to bis-intercalate into two DNA duplexes in close proximity, the azido groups allowing the sites of intercalation to be photoaffinity labeled. The linker to Pt(II) bonds are susceptible to cleavage by thiols and cyanide ion, which is a requirement for the intended method of analysis by 2D gel electrophoresis. © 1999 Academic Press

Key Words: bis-intercalators; photoaffinity labeling; molecular rulers; DNA topology.

INTRODUCTION

In order to study the topology of packaged DNA we have designed a family of reagents that should cross-link two DNA duplexes in close spacial proximity. These molecules possess four essential features:

(i) They are bis-intercalators with a rigid and extended linker. By equilibrating them with packaged DNA (e.g., bacteriophage heads, nucleosomes, chromosomes) they should bind to and cross-link two duplexes whose spacial relationship best matches the geometry of the linker since this will provide the greatest binding energy.

(ii) The linker length is variable. This should allow different sets of sites in the packaged DNA to be cross-linked.

(iii) The linker is cleavable at ambient temperature in aqueous solution at neutral pH.

(iv) The intercalators carry a photoaffinity label.

The third and fourth features are required to identify the sites of intercalation using two-dimensional gel electrophoresis. After photoaffinity labeling the DNA will be digested with a restriction endonuclease and the fragments electrophoresed. The

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fragments will then be treated on the gel with the reagent to break the cross-link. Orthogonal electrophoresis under identical conditions will ensure that those fragments that were not cross-linked will be on the diagonal of the 2D-electrophoretogram but those fragments that have been cleaved will generate two off-diagonal spots that can be extracted and sequenced. In this way the sites of intercalation that were cross-linked will be identified.

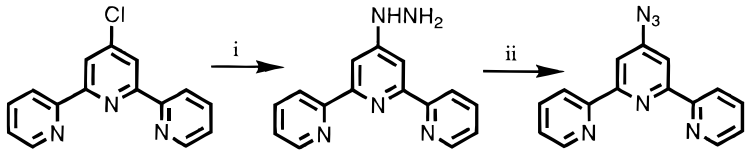
We have shown that 2,2′:6′,2″-terpyridine platinum(II) 4-picoline complexes are potent intercalators of DNA and have selected this moiety for the intercalator groups (*1*). The linkers provide the fourth ligand in the 2,2′:6′,2″-terpyridine platinum(II) complexes and have 4-substituted pyridine groups at each end. Ethynyl and 1,4-phenylene units are used to link the two pyridine groups in a rigid and extended linear configuration. We established at an early stage in the study that thiols and cynanide ion were reagents that would displace pyridine groups, e.g., in the 2,2′:6′,2″-terpyridine platinum(II) 4-picoline complex in aqueous solution at ambient temperature and neutral pH. The photoaffinity labeling group is the azido group. Aryl azides are known to generate nitrenes on photolysis (*2*). Such species are highly reactive and indiscriminate in their behavior and so should react with the first bond they encounter. For this reason they are the functional group of choice for photoaffinity labeling (*3*). Since we expect the reagents to bis-intercalate DNA between helices whose spacial relationship best matches the geometry of the bis-intercalators, the expectation is that at least some of the DNA will become covalently cross-linked at these sites of intercalation on photoactivation.

RESULTS AND DISCUSSION

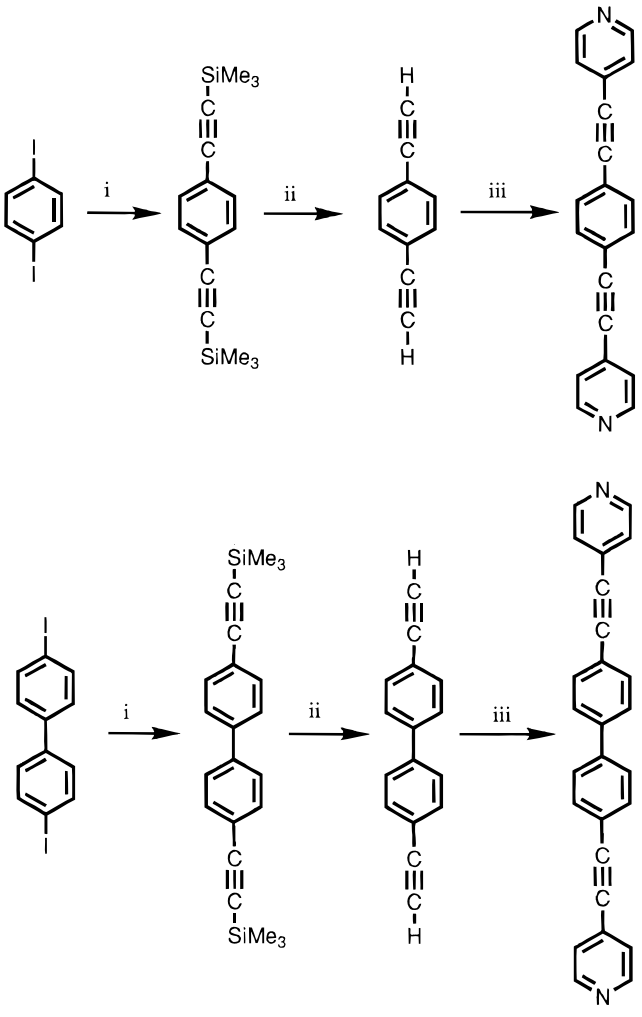
4′-Azido-2,2′:6′,2″-terpyridine was synthesised as outlined in Scheme 1. 4′-Chloro-2,2′:6′,2″-terpyridine reacts cleanly with anhydrous hydrazine to give 4′-hydrazino-2,2′:6′,2″-terpyridine in good yield. It is converted almost quantitatively to 4′-azido-2,2′:6′,2″-terpyridine by treatment with sodium nitrite in aqueous acetic acid.

The shortest linker, 4,4′-dipyridyl, is commercially available. 1,4-Bis(4-pyridyl)butadiyne has been reported previously and the same synthetic route was used (*4*). Longer linkers were made using palladium catalysed coupling chemistry as outlined in Scheme 2 (*5*).

Concern, however, that linkers with increasingly lengthy hydrophobic cores would lack sufficient water solubility as their bis-[4′-azido-2,2′:6′,2″-terpyridine-platinum(II)] complexes led us to consider alternative ways of generating linear rigid linkers. By treating *trans*-diamminedichloroplatinum (II) [transplatin] with 4,4′-dipyridyl and with 1,4-bis(4-pyridyl)butadiyne), the *trans*-diammine bis(4,4′-dipyridyl)



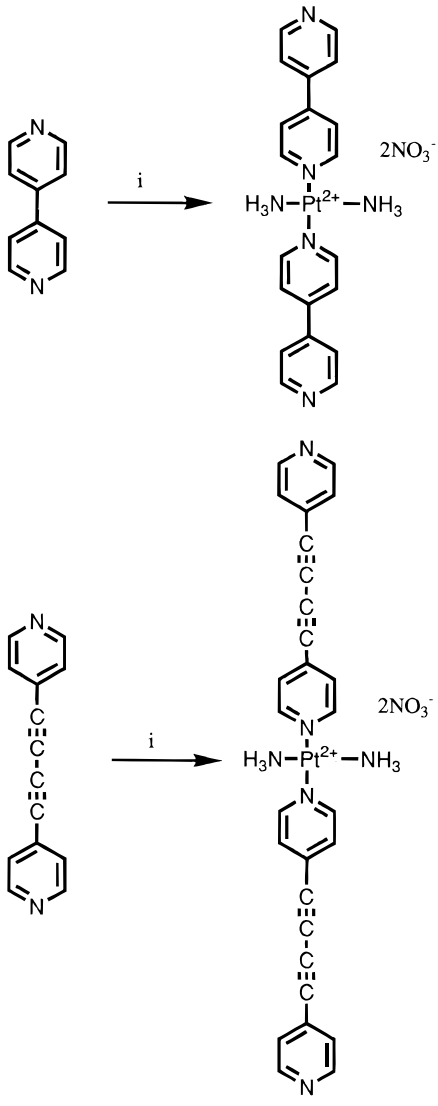
SCHEME 1. Synthesis of 4′-azido-2,2′:6′,2″-terpyridine. Reagents: (i) anhydrous hydrazine, isobutanol; (ii) $NaNO_2$, aq. AcOH.



SCHEME 2. Synthesis of rigid and extended linkers. Reagents: (i) Trimethylsilylacetylene, Cu_2Cl_2, $(Ph_3P)_2PdCl_2$, NEt_3; (ii) Aq. KOH; (iii) $(Ph_3P)_2PdCl_2$, Cu_2I_2, $NHEt_2$, 4-bromopyridine.

platinum (II) and *trans*-diammine bis[1,4-bis(4-pyridyl)butadiyne]platinum(II) complexes were obtained (Scheme 3). This strategy could provide very long linear linkers by using the linkers whose syntheses are outlined in Scheme 2 if required.

The recently developed strategy for the facile platination of 2,2′:6′,2″-terpyridines at ambient temperature was essential for the platination of the thermally labile 4′-azido-2,2′:6′,2″-terpyridine (*6*). Using this approach and the rigid linear linkers, the bis-(4′-azido-2,2′:6′,2″-terpyridine) platinum(II) complexes (**1–4**) shown in Scheme 4 have been prepared. They possess the four features adumbrated above, which are required to study the topology of DNA.

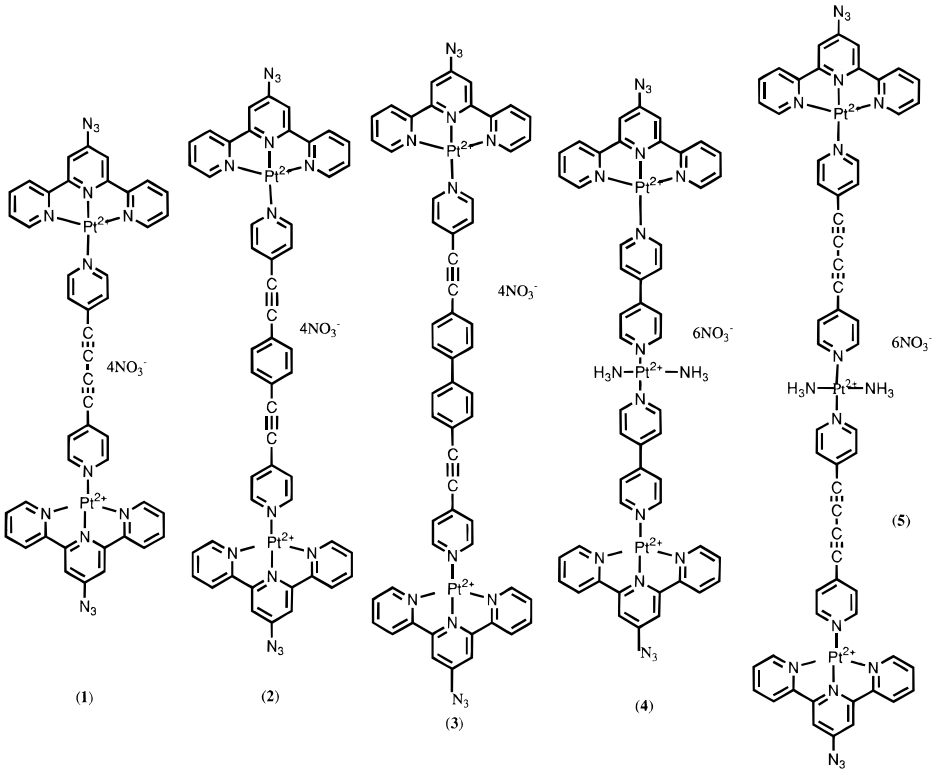


SCHEME 3. Synthesis of *trans*-diammine bis(4,4′-dipyridyl) platinum(II) dinitrate and *trans*-diammine bis[1,4-bis(4-pyridyl)butadiyne]platinum(II) dinitrate. Reagents: (i) *trans*-diamminedichloroplatinum(II), aq.$AgNO_3$.

EXPERIMENTAL

General Methods and Materials

Thin layer chromatography was performed on aluminium sheets precoated with neutral alumina (0.2 mm, Merck Aluminiumoxid, 60 F_{254}) and, unless otherwise indicated, eluted with diethyl ether. Plates were visualized under UV light and stained



SCHEME 4. Bis-[4′-azido-2,2′:6′,2″-terpyridine platinum(II)] complexes with rigid and extended linkers. The distance between the two nitrenes that would be generated on photoactivation are as follows (**1**, 28.2Å), (**2**, 32.5Å), (**3**, 36.8Å), (**4**, 34.1Å) and (**5**, 44.3Å).

to detect terpyridine with $FeCl_2$ solution (saturated solution in 1 M HCl). Melting points were recorded on a Kofler block apparatus and are uncorrected.

Mass spectra were recorded by Dr. R. T. Aplin on a V. G. Biotech Bio-Q spectrometer [electrospray ionisation (ESI)]; the samples were dissolved in methanol:water (1:1 v/v). Values are quoted in *m*/*z* with only the molecular $[M]^+$, fragments of molecular ions, and major peaks being quoted. Routine mass spectra were obtained on a Micromass platform APCI spectrometer. Samples were run in $MeOH/CH_2Cl_2$ (1:1). Routine proton magnetic resonance spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer. Higher field spectra were recorded at 500 MHz by Mrs. E. McGuinness on a Bruker AM500 spectrometer. Coupling constants (J) are recorded in Hertz to one decimal place. Chemicals were purchased from Sigma Chemical Co. Ltd. and Aldrich Chemical Co. and were used without further purification. Solvents were obtained from BDH and Fisons at reagent grade and used without distillation. Sonication was performed in equipment (Model No. SC-120TH, 220 V, 1.2 amps) supplied by Sonicor Instrument Corp. (Copiague, NY).

4′-Hydrazino-2,2′:6′,2″-terpyridine

4′-Chloro-2,2′:6′,2″-terpyridine (600 mg, 2.2 mmol) was dissolved in isobutanol (12 ml) with warming. Excess hydrazine (4 ml) was added. The mixture was then heated to reflux under argon, with stirring, for 30 h. On cooling white crystals precipitated out of solution. These were collected by filtration and washed with a few drops of water to yield analytically pure 4′-hydrazino-2,2′:6′,2″-terpyridine (439 mg, 74%): m.p. 195–197°C; (Found: C, 68.4; H, 4.6; N, 26.6. $C_{15}H_{13}N_5$ requires C, 68.4; H, 4.9; N, 26.6%);ν_{max} (KBr)/cm^{-1} 3329(w, br), 3277(s), 3181(m), 1644(w), 1605(m), 1585(s), 1565(s), 1466(m), 1403(m), 1229(w), 1069(w), 996(m), 864(m); δ_H (200 MHz, $CDCl_3$) 8.69 [d, $^3J(6,5)$ = 4.6, 2H, H-C(6), H-C(6″)]; 8.63 [d, $^3J(3,4)$ = 8.0, 2H, H-C(3), H-C(3″)]; 7.87 [s, 2H, H-C(3′), H-C(5′)]; 7.86 [dt, $^3J(4,5)$ = $^3J(4,3)$ = 7.7, $^4J(4,6)$ = 1.6, 2H, H-C(4), H-C(4″)]; 7.34 [ddd, $^3J(5,4)$ = 7.4, $^3J(5,6)$ = 4.9, $^4J(5,3)$ = 1.3, 2H, H-C(5), H-C(5″)]; 5.81 (s, br, 1H, terpyN*H*.NH_2); 3.83 (s, br, 2H, terpyNH. NH_2); *m/z* (ESI) : 264.26 (100%, $[MH]^+$).

4′-Azido-2,2′:6′,2″-terpyridine

A solution of 4′-hydrazino-2,2′:6′,2″-terpyridine (0.263g; 1.0mmol) in acetic acid (2.0 ml) and water (1.0 ml) was treated dropwise at 0°C with a cold solution of sodium nitrite (0.69 g; 10 mmol) in water (2.0 ml). A cream solid was precipitated. When the addition was complete ether (20 ml) was added and the aqueous layer made alkaline by the addition of solid sodium hydroxide beads. The solid dissolved and the aqueous phase was further extracted with ether (2 × 20 ml). The combined organic extracts were dried and evaporated to give the title compound as a pale yellow brown solid (0.273 g, 99%). Crystallization from methanol-dichloromethane gave pale yellow needles mp. 140–141°C (Found: C, 65.7; H, 3.6; N, 30.5. $C_{15}H_{10}N_3$ requires C, 65.7; H, 3.6; N, 30.6%);ν_{max} (nujol)/cm^{-1} 2109 (N_3); δ_H (200MHz $CDC1_3$) 7.37 (2H, ddd, *J* 1.0, 4.8 and 5.9, terpy H5,5″),7.87 (2H, td, *J* 1.8, 7.8, terpy H4,4″), 8.16 (2H, s, terpy H3′,5′), 8.63 (2H, d, *J* 8.0, terpy H3,3″), and 8.68–8.74 (2H, m, terpy H6,6″); δ_C (50MHz $CDCl_3$) 111.1, 121.3, 124.1, 136.8, 149.1, 150.8, 155.2, 157.1; *m/z* (ESI): 275(MH^+).

1,4-Bis(4-pyridyl)butadiyne

This was prepared by the method of Della Ciana and Haim (*4*) as white crystalline plates, m.p. 208–209°C [lit.(*4*) m.p. 203–205 °C]. δ_H (ppm){200 MHz, $CDC1_3$}: 8.63, AA′m, 4H, H2, H6; 7.38, BB′m, 4H, H3, H5.

Preparation of 4,4″-dipyridyl-1′,4′-diethynylbenzene

1,4-Diethynylbenzene. 1,4-Bis(trimethylsilylethynyl)benzene (*5*) (1.00 g, 3.71 mmol) was dissolved in dichloromethane (15 ml) and methanol (15 ml). Aqueous potassium hydroxide (1 M, 3 ml) was added dropwise with stirring. The mixture was stirred at room temperature for 2.5 h. The organic solvent was removed under reduced pressure. Water (25 ml) was added and the mixture was extracted with ether (3 × 30 ml). The combined ether extracts were dried ($MgSO_4$), decolorized with activated charcoal, and the solvent was removed under reduced pressure to yield 1,4-diethynylbenzene (367 mg, 78%) as a white solid, which was used immediately without further

purification, m.p. 95–96°C. δ_H (ppm){200 MHz, $CDCl_3$}: 7.46, s, 4H, C_6H_4; 3.18, s, 2H, acetylenic H. APCI: m/z 127 (MH+, 14%)

4,4″-Dipyridyl-1′,4′-diethynylbenzene. Bis(triphenylphosphine)palladium(II) chloride (70.2 mg, 0.10 mmol) was added to a stirred suspension of 4-bromopyridine hydrochloride (778 mg, 4.0 mmol), 1,4-diethynylbenzene (252 mg, 2.0 mmol), copper(I) iodide (28.6 mg, 0.15 mmol), and dry diethylamine (15 ml) under an atmosphere of argon. The reaction was stirred for 36 h at room temperature under argon. A further portion of bis(triphenylphosphine)palladium(II) chloride (16.3 mg, 0.023 mmol) was added. The reaction was stirred for a further 48 h. The mixture was filtered through celite using ethyl acetate and concentrated under reduced pressure. The residue was chromatographed on flash silica gel using 5% methanol/dichloromethane as eluant and further purified by chromatography on alumina (grade IV) using 50% ethyl acetate/petroleum ether (40–60°C) as eluant to yield 4,4″-dipyridyl-1′,4′-diethynylbenzene (284 mg, 51%) as a pale yellow solid, m.p. 185–203°C. δ_H (ppm){200 MHz, $CDCl_3$}: 8.64, AA′m, 4H, H2, H6, H2″, H6″; 7.58, s, 4H, C_6H_4; 7.41, BB′m, 4H, H3, H5, H3″, H5″. APCI: m/z 281 (MH+, 100%).

Synthesis of 4″,4‴-Dipyridyl-4,4′-diethynylbiphenyl

4,4′-Diethynylbiphenyl. 4,4′-Bis(trimethylsilylethynyl)biphenyl (*5*) (1.04 g, 2.99 mmol) was dissolved in dichloromethane (15 ml) and methanol (15 ml). Aqueous potassium hydroxide (1 M, 3 ml) was added dropwise with stirring. The mixture was stirred at room temperature for 2.5 h. The organic solvent was removed under reduced pressure. Water (25 ml) was added and the mixture was extracted with ether (3 × 30 ml). The combined ether extracts were dried ($MgSO_4$), decolorized with activated charcoal and the solvent was removed under reduced pressure to yield 4,4′-diethynylbiphenyl (562 mg, 93%) as a white solid which was used immediately without further purification, m.p. 167–169°C. δ_H (ppm){200 MHz, $CDCl_3$} 7.57, s, 8H, 2 × C_6H_4; 3.15, s, 2H, acetylenic H. APCI: 203 (MH+, 15%).

4,4′-Diethynyl-4″,4‴-dipyridylbiphenyl. Bis(triphenylphosphine)palladium(II) chloride (78.2 mg, 0.11 mmol) was added to a stirred suspension of 4-bromopyridine hydrochloride (846 mg, 4.35 mmol), 4,4′-diethynylbiphenyl (440 mg, 2.18 mmol), copper(I) iodide (29.2 mg, 0.15 mmol) and dry diethylamine (30 ml) under an atmosphere of argon. The reaction was stirred for 48 h at room temperature under argon. The mixture was filtered through celite using ethyl acetate and concentrated under reduced pressure. The residue was chromatographed on flash silica gel using 5% methanol/dichloromethane as eluant and further purified by chromatography on alumina (grade IV) using 50% ethyl acetate/petroleum ether (40–60°C) as eluant to yield 4,4′-diethynyl-4″,4‴-dipyridylbiphenyl (310 mg, 20%) as a pale yellow solid, m.p. 205–275°C. δ_H(ppm){200 MHz, $CDCl_3$} 8.63, AA′m, 4H, H2″, H6″, H2‴, H6‴; 7.65, s, 8H, 2 × C_6H_4; 7.41, BB′m, 4H, H3″, H5″, H3‴, H5‴. APCI: *m/z* 357 (MH+, 48%).

Trans-*Diammine bis(4,4′-dipyridyl)platinum(II) dinitrate*

A solution of silver nitrate (36.3 mg, 0.200 mmol) in acetone/water (1:1, 0.5 ml) was added to a suspension of transplatin (30.0 mg, 0.100 mmol) in acetone/water (1:1, 0.5 ml) and sonicated for 24 h. The mixture was centrifuged and the supernatant was added to a solution of 4,4′-dipyridyl (31.2 mg, 0.200 mmol) in acetone (0.5 ml),

maintaining an excess of 4,4′-dipyridyl. The mixture was sonicated for 24 h and then centrifuged to yield *trans*-diamminebis(4,4′-dipyridyl)platinum(II) dinitrate (64.9 mg, 97%) as a white solid. δ_H (ppm){500 MHz, DMSO} 8.90, AA′m, 4H, H2, H6; 8.84, AA′m, 4H, H2′, H6′; 8.25, BB′m, 4H, H3, H5; 7.98, BB′m, 4H, H3′, H5′; 4.73, b s, 6H, NH_3. ESI (CV = 30 V): *m/z* 270.8 (M^{2+}, 60%), 540.3 [$(M\text{-}H)^+$, 33%].

Trans-Diamminebis[1,4-bis(4-pyridyl)butadiyne]platinum(II) dinitrate

A solution of silver nitrate (28.0 mg, 0.165 mmol) in acetone/water (1:1, 0.5 ml) was added to a suspension of transplatin (24.7 mg, 0.082 mmol) in acetone/water (1:1, 0.5 ml) and sonicated for 24 h. The mixture was centrifuged and the supernatant was added to a solution of 1,4-bis(4-pyridyl)butadiyne (37.0 mg, 0.180 mmol) in acetone (0.5 ml), maintaining an excess of 1,4-bis(4-pyridyl)butadiyne. The mixture was sonicated for 24 h and then centrifuged to yield *trans*-diamminebis[1,4-bis(4-pyridyl)butadiyne]platinum(II) dinitrate (64.8 mg, 85%) as a light brown solid. δ_H (ppm) {500 MHz, DMSO}: 8.82, AA′m, 4H, H2, H6; 8.72, AA′m, 4H, H2′, H6′; 7.99, BB′m, 4H, H3, H5; 7.65, BB′m, 4H, H3′, H5′; 4.74, b s, 6H, NH_3. ESI (CV = 20 V): *m/z* 318.7 (M^{2+}, 80%).

Synthesis of Bis-4′-azido-2,2′:6′,2″-terpyridine Platinum(II) Complexes

*Bis(4-pyridyl)butadiyne bis[(4′-azido-2,2′:6′,2″-terpyridine) platinum(II)] tetranitrate (**1**).* A solution of silver nitrate (36.6 mg, 0.218 mmol) in acetone/water (4:1, 0.5 ml) was added dropwise to a suspension of diiodo-1,5-cyclooctadieneplatinum(II) (56.6 mg, 0.102 mmol) in acetone/water (4:1, 0.5 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The silver iodide precipitate was discarded. The supernatant was added to a suspension of 4′-azido-2,2′:6′,2″-terpyridine (22.5 mg, 0.082 mmol) in acetonitrile (0.25 ml). The mixture was vortexed and sonicated for a few minutes and then centrifuged. The supernatant was removed and discarded. The pellet of the 4′-azido-2,2′:6′,2″-terpyridine platinum(II) complex was washed with acetonitrile/ether (1:3, 2 × 1.5 ml) and then dissolved in water (0.75 ml).

A solution of the 1,4-bis(4-pyridyl)butadiyne (9.0 mg, 0.044 mmol) in methanol (0.75 ml) was added to the aqueous solution of the 4′-azido-2,2′:6′,2″-terpyridine platinum(II) complex. The mixture was vortexed and sonicated for 15 min and allowed to stand at room temperature for 30 min. The solution was added dropwise to ether/acetone (1:1, 20 ml) to precipitate the complex. The mixture was centrifuged. The pellet was washed with ether/acetone (1:1, 4 × 20 ml) and then dried to yield the desired complex (44.9 mg, 79%) as an yellow-orange solid. δ_H(ppm){500 MHz, D_2O}: 9.22, AA′m, 4H, H2‴, H6‴; 8.45–8.40, series of multiplets, 8H, H3, H3″, H4, H4″; 8.09, s, 4H, H3′, H5′; 8.07, BB′m, 4H, H3‴, H5‴; 7.87, d, *J* 5.5 Hz, 4H, H6, H6″; 7.72, m, 4H, H5, H5″. ESI (CV = 10 V): *m/z* 272.0 [$(M\text{-}2N_2)^{4+}$, 67%], 279.4 [$(M\text{-}N_2)^{4+}$, 59%], 285.9 (M^{4+}, 100%), 337.0 {[M-Pt(N_3-terpy)]$^{2+}$, 83%}. ν_{max} (nujol) 2121w cm^{-1} (N_3).

*Bis-(4-ethynylpyridyl)-1,4-phenylene bis[(4′-azido-2,2′:6′,2″-terpyridine) platinum(II)] tetranitrate (**2**).* A solution of the 4,4″-dipyridyl-1′,4′-diethynylbenzene (11.8 mg, 0.042 mmol) in methanol (0.75 ml) was added to an aqueous solution of the 4′-azido-2,2′:6′,2″-terpyridine platinum(II) complex prepared on the same scale as above in the preparation of (**1**). The mixture was vortexed and sonicated for 15

min and allowed to stand at room temperature for 30 min. A yellow precipitate formed. The mixture was centrifuged and the pellet washed with ether/acetone (1:1, 3 × 20 ml) to yield the desired complex (33.7 mg) as a yellow solid. The supernatant was added dropwise to ether/acetone (1:1, 20 ml) to precipitate more of the complex which was washed with ether/acetone (1:1, 4 × 20 ml) and then dried to yield the desired complex (18.6 mg) as a yellow solid. The total yield of the product was 52.3 mg (88%). δ_H(ppm){500 MHz, D_2O}: 9.16, AA′m, 4H, H2‴, H6‴; 8.44–8.41, series of multiplets, 8H, H3, H3″, H4, H4″; 8.10, s, 4H, H3′, H5′; 8.01, BB′m, 4H, H3‴, H5‴; 7.91, d, *J* 5.6 Hz, 4H, H6, H6″; 7.80, s, 4H, H2⁗, H3⁗, H5⁗, H6⁗; 7.74, m, 4H, H5, H5″. ESI (CV=10 V): *m/z* 291.0 [$(M\text{-}2N_2)^{4+}$, 42%], 298.1 [$(M\text{-}N_2)^{4+}$, 50%], 305.0 (M^{4+}, 100%), 375.1 {[M-Pt(N_3-terpy)]$^{2+}$, 58%}. ν_{max} (nujol) 2116w cm^{-1} (N_3).

*Bis-(4-ethynylpyridyl)-4,4′-biphenyl bis[(4′-azido-2,2′:6′,2″-terpyridine)platinum (II)] tetranitrate (**3**).* A solution of the 4,4′-diethynyl-4″,4‴-dipyridylbiphenyl (13.0 mg, 0.036 mmol) in methanol (15 ml) was added to an aqueous solution of the 4′-azido-2,2′:6′,2″-terpyridine platinum(II) complex prepared on the same scale as above in the preparation of (**1**). The mixture was vortexed and sonicated for 45 min and allowed to stand at room temperature for 30 min and then concentrated under reduced pressure. The solution was added dropwise to ether/acetone/methanol (65:30:5, 20 ml) to precipitate the complex which was washed with ether/acetone (1:1, 4 × 20 ml) and then dried to yield the desired complex (43.9 mg, 79%) as a bright yellow solid. δ_H(ppm) {500 MHz, D_2O}: 9.06, AA′m, 4H, H2‴, H6‴; 8.48, t, *J* 7.7 Hz, 4H, H4, H4″; 8.42, d, *J* 7.9 Hz, 4H, H3, H3″; 8.03, s, 4H, H3′, H5′; 8.01, BB′m, 4H, H3‴, H5‴; 7.88, d, *J* 5.8 Hz, 4H, H6, H6″; 7.80, m, 4H, H5, H5″; 7.70, m, 8H, H2⁗, H3⁗, H5⁗, H6⁗. ESI (CV = 10 V): *m/z* 310.1 [$(M\text{-}2N_2)^{4+}$, 13%], 317.1 [$(M\text{-}N_2)^{4+}$, 26%], 324.1 (M^{4+}, 100%), 413.1 {[M-Pt(N_3-terpy)]$^{2+}$, 37%}. ν_{max} (nujol) 2120w cm^{-1} (N_3).

Trans-*diamminebis(4,4′-dipyridyl)platinum(II) bis[(4′-azido-2,2′:6′,2″-terpyridine)platinum(II)] hexanitrate (**4**).* A suspension of *trans*-diamminebis(4,4′-dipyridyl)-platinum(II) nitrate (26.6 mg, 0.040 mmol) in water/methanol (1:1, 3.0 ml) was added to an aqueous solution of the 4′-azido-2,2′:6′,2″-terpyridine platinum(II) complex prepared on the same scale as above in the preparation of (**1**). The mixture was sonicated for 5 days at room temperature. The mixture was centrifuged. The supernatant was added dropwise to ether/acetone (1:1, 25 ml) to precipitate the complex. Centrifugation yielded the crude complex as a brown solid (50.8 mg, 67%), which dissolved in water to give a yellow solution. Purification by dissolution in hot methanol/water (1:1) and re-precipitation from ether/acetone (1:1, 20 ml, repeated three times) gave the desired complex as a pale yellow solid. δ_H {500 MHz, D_2O}: 9.37, AA′m, 4H, H2‴, H6‴; 9.14, AA′m, 4H, H2⁗, H6⁗; 8.43–8.42, series of multiplets, 8H, H3, H3″, H4, H4″; 8.34, BB′m, H3‴, H5‴; 8.20, BB’m, 4H, H3⁗, H5⁗; 8.11, s, 4H, H3′, H5′; 7.87, d, *J* 5.7 Hz, 4H, H6, H6″; 7.73, m, 4H, H5, H5″. ESI (CV = 15 V): *m/z* 296.1 {[M-H]$^{5+}$, 47% }. ESI (CV = 20 V): *m/z* 299.2 {[(N_3-terpy)Pt(bip)-N_2]$^{2+}$, 63%}, 312.6 {[(N_3-terpy)Pt(bip)]$^{2+}$, 100%}, 336.4 {[M-Pt(N_3-terpy)-H]$^{3+}$, 33%}. ν_{max} (nujol) 2120w cm^{-1} (N_3).

Trans-*diamminebis[1,4-bis(4-pyridyl)butadiyne]platinum(II) bis[(4′-azido-2,2′:6′,*

*2″-terpyridine)platinum(II)] hexanitrate (**5**).* A suspension of *trans*-diamminebis[1,4-bis(4-pyridyl)butadiyne]platinum(II) dinitrate (30.5 mg, 0.040 mmol) in water/methanol (1:1, 3.0 ml) was added to an aqueous solution of the 4′-azido-2,2′:6′,2″-terpyridine platinum(II) complex prepared on the same scale as above in the preparation of (**1**). The mixture was sonicated for 5 days at room temperature. The mixture was centrifuged. The supernatant was added dropwise to ether/acetone (1:1, 25 ml) to precipitate the complex. Centrifugation yielded the crude complex as a brown solid (69.9 mg, 90%), which dissolved in water to give a yellow solution. Purification by dissolution in hot methanol/water (1:1) and re-precipitation from ether/acetone (1:1, 20 ml, repeated 3 times) gave the desired complex as a pale yellow solid. δ_H {500 MHz, D_2O}: 9.21, AA′m, 4H, H2‴, H6‴; 8.91, AA′m, 4H, H2‴, H6‴; 8.44–8.41, series of multiplets, 8H, H3, H3″, H4, H4″; 8.09, s, 4H, H3′, H5′; 8.04, BB′m, H3‴, H5‴; 7.86, d, *J* 5.8 Hz, 4H, H6, H6″; 7.82, BB′m, 4H, H3‴, H5‴; 7.73–7.70, m, 4H, H5, H5″. ESI (CV = 15 V): *m/z* 315.3 {[M-H]$^{5+}$, 100%}, 336.8 {[(N_3-terpy)Pt($C_{14}H_8N_2$)]$^{2+}$, 71%}, 386.7 {[M-Pt(N_3-terpy)-H]$^{3+}$, 88%}. ν_{max} (nujol) 2120w cm^{-1} (N_3).

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