Synthesis and Characterization of a Series of Achiral and Chiral Mono- and Bis[(dien)Pt(II)I]I Derivatives as Potential DNA and RNA Structure Probes and Anticancer Drugs†

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This paper reports the design, synthesis, and characterization of a series of achirally and chirally substituted diethylenetriamine (dien) and bis(dien) complexes of Pt(II) for study as potential nucleic acid structure and conformation probes. Chiral diisopropyl and achiral tetramethyl derivatives of [(dien)Pt(II)I]I, complexes *R*- and *S*-**1b–d**, were designed to discriminate between B and Z conformations of DNA. Bis([(dien)Pt(II)I]I) complexes with variable length (*n*) methylene linkers, **3a** (*n* = 2–9), and selected chiral tetraisopropyl derivatives, *R*- and *S*-**3b** (*n* = 3,9), were designed to probe the relationship between linker length and steric substitution on the conformation and structure selectivity of interstrand nucleic acid cross-linking. The Pt(II) complexes were prepared from the corresponding amine ligands in almost quantitative yield by a one step synthesis utilizing $Pt(DMSO)_2I_2$. The diisopropyldien ligands *R*- and *S*-**11b** were prepared by a general route in high overall yield from both enantiomers of the amino acid valine via the enantiomeric *N*-tosylisopropylaziridines *R*- and *S*-**8b**. The tetramethyldien ligand **11c** was prepared by the same route starting from the commercially available dimethylaminoethanol **6c**. Bis(dien) ligands, **13a** (*n* = 2–9), in which two dien ligands are linked via the central amine to a variable length linker of two to nine methylene groups were synthesized in high overall yield from *N*-tosylaziridine and the corresponding 1,*n*-diaminoalkane. Bis(diisopropyldien) ligands, *R*- and *S*-**13b** (*n* = 3, 9), were similarly prepared from the corresponding *N*-tosylisopropylaziridines. Selected Pt(II) analogs of the Pt(II) complexes were prepared via $Pd(DMSO)_2Cl_2$.

Introduction

Nucleic acid-binding molecules have found extensive use as chemotherapeutic agents and as probes for the structure of nucleic acids and their complexes with drugs and proteins. Many of these nucleic acid-binding molecules owe their usefulness to their ability to covalently link together or cross-link bases of the same strand (intrastrand) or different strands (interstrand) or different helices (interhelical) (Figure 1). Representative cross-linkers are cisplatin (*cis*-diamminedichloroplatinum(II)),[1] psoralens,[2] and the mitomycins.[3,4] The effectiveness of many anticancer drugs has been attributed to the formation of interstrand cross-links in DNA, a type of damage which is difficult to repair and leads to replication blocks and cell death. Because cross-linkers covalently link nearby nucleic acid strands together, they have also found use in the mapping of the tertiary structures of branched and packaged nucleic acids.[2,4] Unfortunately, most of the known cross-linkers have inherent sequence and conformation specificity, as well as having the property of being inactivated by water or otherwise inefficient, making them unsuitable for many designed drug and probe applications. It would be extremely useful if cross-linkers could be designed with high efficiency and selectivity for a given sequence, nucleic acid conformation, or tertiary structure. Such cross-linkers could be used to target nucleic acid sequences or structures specific to oncogenes and retroviruses or be used to probe the higher order structure of nucleic acid-containing biomolecules.

One approach to the design of a general class of nucleic acid probes and cross-linkers with tailor-made properties and selectivities is to use a known monocovalent nucleic acid binder as a building block. Chemical modification of this building block could result in probes with designed binding specificity. Tethering together two building blocks with a tether of variable length and structure could result in cross-linkers with designed structure or sequence specificity. The ideal nucleic acid building block for such modifications should have low sequence or conformation specificity, react slowly but efficiently in order to allow time for targeting by a sequence or structure specific binding unit, and not be inactivated by water. It should also react irreversibly under standard biological conditions but be easily removable if required for a particular probe application. Recent examples of molecules designed to fulfill some of these criteria are dimeric derivatives of monodentate and bidendate platinum(II) complexes,[5–11] psoralen[4] azidomethidium,[12] CC1065,[13] and anthramycin.[14]

Iodo(diethylenetriamine)platinum(II) iodide or [(dien)Pt(II)I]I, compound **1a**, was chosen as a building block because of what is known about its corresponding chloro complex: (1) it binds monocovalently and irreversibly to DNA with little conformation specificity as evidenced by its lack of preference for either B- or Z-DNA,[15] (2) it can be quantitatively removed

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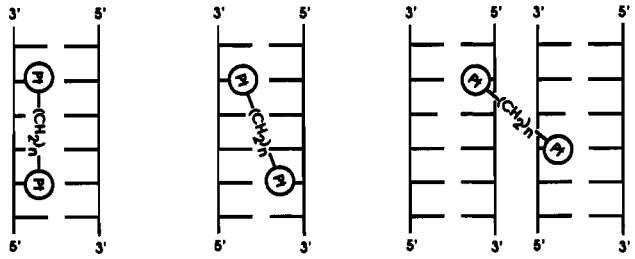
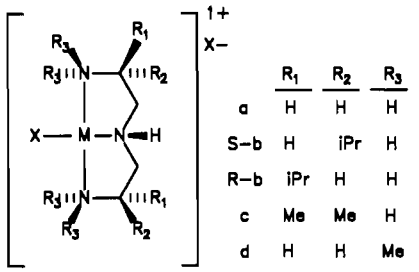


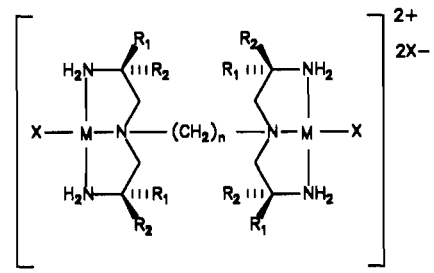
Figure 1. Schematic representation of intrastrand, interstrand, and interhelical cross-linking by a bis Pt(II) reagent.

Chart I



1 M=Pt X=I

2 M=Pd X=Cl



3 M=Pt X=I

4 M=Pd X=Cl

with cyanide or thiourea without damaging the nucleic acid,[16] (3) at drug/base pair ratios of <0.1 it binds to the N-7 position of guanosine, though at higher densities, such as would be the case in the second step of a cross-linking event, it binds to the N-7 position of adenosine,[6,15,17] (4) it is not inactivated by water, (5) the rate-determining step in its binding to DNA is given by its rate of hydrolysis, which is on the order of 1 h in low halide buffers,[16] (6) the reaction mechanism and transition state geometries for nucleophilic substitution at square planar platinum(II) centers are well understood,[18] and (7) its structure makes it readily amenable to synthetic modification. Furthermore, a Pt(II) complex of a bis(dien) ligand with a six-carbon linker had been shown to successfully cross-link an oligonucleotide to its complementary strand.[6]

Herein we report the general and highly efficient synthesis of a series of achiral and chiral derivatives of [(dien)Pt(II)I]I, compounds *R*- and *S*-**1b**, **1c**, and **1d**, for study as potential nucleic acid conformation probes (Chart I). We also report the general and highly efficient synthesis of a series of achiral and chiral bis([(dien)Pt(II)I]I) complexes, compounds **3a** (n = 2–9) and *R*- and *S*-**3b** (n = 3, 9), for study as potential sequence, conformation, and structure selective cross-linkers (Chart I). A selected number of the corresponding Pd(II) complexes have also been prepared as reversible binding analogs of the Pt(II) complexes.

Experimental Section

Materials and Methods. Melting points are uncorrected and were recorded on a Mel-Temp apparatus (Laboratory Devices). Microanalyses were performed by Midwest Microlab (Indianapolis, IN). Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent system on 40–63-μm silica gel from Baker with an elution rate of 2 column in./min. Thin layer chromatography (TLC) was performed on Kieselgel 60 F254 plates from Merck. D- and L-valine, amino alcohols, diamines and other reagents were obtained from the Aldrich Chemical Co. and used without further purification. Ammonia gas was from Matheson Gas Products. Platinum(II) iodide (PtI_2), potassium tetrachloroplatinate(II) (K_2PtCl_4), potassium hexachloroplatinate(IV) (K_2PtCl_6), and palladium(II) chloride ($PdCl_2$) were obtained from Strem Chemicals, Inc. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl. Pyridine was distilled from calcium hydride. Dimethylformamide (DMF) was dried over activated 5-Å molecular sieves. Deuterated dimethylformamide (DMF-d_7, 99 atom % D) was obtained from Cambridge Isotopes and Aldrich. Its proton NMR spectrum revealed water and protiated DMF and was used without further purification. Air and/or moisture sensitive reactions were carried out under an atmosphere of nitrogen with use of flame dried glassware.

Spectroscopy. Proton and carbon spectra were recorded on a Varian XL-300 or Varian VXR-500 spectrometer. Heteronuclear ^{13}C–^1H 2D J-spectroscopy (HET2DJ) was performed at a resonance frequency of 125.7 MHz using standard Varian software with a 2D spectral width (SW2) of 1000 Hz and a number of increments (NI) of 48. Proton-decoupled ^{195}Pt NMR spectra were obtained on a Varian XL-300 spectrometer at 64.4 MHz at 20 °C with a spectral width (SW) of 100 KHz. Samples were dissolved in DMF-d_7 (≈20 mM) and recorded in 5-mm tubes. A line broadening (LB) of 50 Hz was used for platinum complexes containing no ^{14}N substituents. ^{14}N-substituted complexes were processed using a LB of 200 Hz and 2K data points with zero filling to 4K. Spectral data were acquired with a 15-μs pulse (≈42° flip angle) and a repetition time (D1 + AT) of 0.02 s. Chemical shifts were measured relative to 0.2 M K_2PtCl_4 (−1631.0 ppm vs 0.2 M K_2PtCl_6 in D_2O)[19] and are reported as ±10 ppm. Line width in Hz, is given in parentheses. Infrared spectra were recorded on a Perkin-Elmer 283B spectrometer calibrated with polystyrene film and are reported as cm^{-1}. FT-IR spectroscopy was performed on a Perkin-Elmer 1750 spectrometer interfaced to a Perkin-Elmer 7700 Professional computer, and data are reported in cm^{-1}. Ultraviolet (UV) spectra were recorded on a Bausch and Lomb Spectronic 1001 spectrophotometer interfaced to an Apple IIe microcomputer with Bausch and Lomb scanning software, version 2.02 in 1-cm pathlength quartz cells. Electron impact mass spectra (EI) was obtained by Ms. J. Wilking on a Finnigan 9500 GC/MS spectrometer at an ionization voltage of 70 eV and are reported as follows: m/z (species), intensity. Fast atom bombardment mass spectra (FAB) were obtained by Dr. A. Tyler on a VG-ZAB-SE double-focusing mass spectrometer (VG Instruments, Danvers, MA) and is reported as follows: m/z (species). FAB samples are prepared by dispersing the analyte in either glycerol or *m*-nitrobenzyl alcohol and placed on a direct insertion probe. The samples were introduced into the high-vacuum region of the mass spectrometer where they were bombarded with a xenon atom beam of typically 8-keV energy prior to mass analysis. Spectra were acquired by scanning the mass spectrometer over an appropriate mass range and data collected using a VG 11-250J data system. High-resolution mass assignments of ions generated by FAB (HRMS) are made by peak matching sample ions against reference ions from a spectrum of a mixed cesium–rubidium iodide salt. The expected accuracy of this technique is typically better than ±5 ppm. FAB analyses of some of the interstrand cross-linking amines were determined with NaCl added to form $(M + Na)^+$ ion species which appear 22 m/z units higher than the expected $(M + H)^+$ ion. Circular dichroism (CD) spectra were obtained on a Jasco J-500A spectropolarimeter with a Jasco IF 500 interface to a THE personal computer. All spectra were digitized and baseline corrected.

L- and D-Valinol (*S*- and *R*-6b). These were isolated in approximately

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45% yields via borane/dimethyl sulfide and boron trifluoride etherate reduction of L- and D-valine (*S*- and *R*-**5b**) by the method of Smith and Gawley.[20]

Sulfonamide *S*-7b. This was prepared via a modification of the procedure of Ohno et al.[21] A solution of L-valinol, *S*-**6b** (MW 103, 10 g, 97 mmol) in dry pyridine (12 mL) was added dropwise over a period of 1 h to a 0 °C cooled solution of *p*-toluenesulfonyl chloride (MW 190.7, 40.7 g, 213 mmol) in dry pyridine (50 mL) and allowed to stir for an additional 4 h at 0 °C. The reaction was poured into crushed ice (200 g). The aqueous solution was extracted into benzene (1 L) and the combined organic extracts were washed with 5% HCl and saturated NaCl, treated with Celite, decolorizing charcoal, and anhydrous Na_2SO_4, and allowed to stand overnight. The solution was filtered through Celite and concentrated in vacuo yielding a yellow powder. Recrystallization from ethanol gave the desired product in 78% yield (lit.[21] 43.6%) (MW 411, 30 g, 73 mmol) as white crystals. ^{1}H NMR, 300 MHz ($CDCl_3$): (lit.[21]) 7.72 (d, J = 5 Hz, 2 H, ArH), 7.70 (d, J = 4.5 Hz, 2 H, ArH), 7.34 (d, J = 8 Hz, 2 H, ArH), 7.26 (d, J = 8 Hz, 2 H, ArH), 4.91 (d, J = 6.5 Hz, NH), 4.00 (d of d, J = 10, 3.5 Hz, 1 H, C*H*H), 3.80 (d of d, J = 10, 5 Hz, 1 H, CH*H*), 3.17 (m, 1 H, CH), 2.46 (s, 3 H, $ArCH_3$), 2.41 (s, 3 H, $ArCH_3$), 1.85 (m, 1 H, C*H*$(CH_3)_2$), 0.77 (d, J = 7 Hz, 3 H, CH_3), 0.74 (d, J = 7 Hz, 3 H, CH_3). ^{13}C NMR, 125.7 MHz ($CDCl_3$): 145.1, 143.5, 137.3, 132.2, 129.9, 129.0, 127.0, 128.0, 127.0, 69.2, 57.5, 28.8, 21.6, 21.5, 18.8, 17.6. IR (lit.[21]) (KBr): 3270, 2970, 1600, 1445, 1360, 1320, 1290, 1195, 1180, 1160, 1090, 1050, 1020, 985, 965, 950, 895, 845, 815, 790, 705, 665, 630, 550, 540. UV (EtOH): 222 nm (ϵ 22 676 cm^{-1} M^{-1}). MS (FAB): 412 $(M + H)^+$. $[\alpha]^{22}_D$ (c 1.0, C_6H_6): −70.0°.

Sulfonamide *R*-7b. This was prepared as described above. $[\alpha]^{22}_D$ (c 1.0, C_6H_6): +70.0°.

Aziridine *S*-8b. The aziridine *S*-**8b** was prepared via a modification of the procedure of Bulkowski et al.[22] A solution of 20% aqueous KOH (11 mL) was rapidly added to a benzene solution (38 mL) of the sulfonamide *S*-**7b** (MW 411, 15 g, 36 mmol) and magnetically stirred for 2.5 h. The two-phase mixture was washed with saturated NaCl, and the benzene layer was dried over anhydrous Na_2SO_4 and filtered. Concentration in vacuo provided *S*-**8b** as a white crystalline product in 95% yield (MW 239, 1.63 g, 6.8 mmol). The product was homogeneous by TLC. Recrystallization from octane afforded an analytically pure sample as white needles. TLC (30% tetrahydrofuran/hexanes): R_f 0.83. Mp: 85–86 °C. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.76 (d, J = 8 Hz, 2 H, ArH), 7.26 (d, J = 8 Hz, 2 H, ArH), 2.54 (d, J = 7 Hz, 1 H, C*H*H), 2.44 (m, 1 H, NCH), 2.37 (s, 3 H, $ArCH_3$), 2.03 (d, J = 5 Hz, 1 H, CH*H*), 1.33 (m, 1 H, C*H*$(CH_3)_2$), 0.83 (d, J = 7 Hz, 3 H, CH_3), 0.72 (d, J = 6.5 Hz, 3 H, CH_3). ^{13}C NMR, 75.4 MHz ($CDCl_3$): 144.4, 135.1, 129.5, 128.0, 46.2, 32.7, 30.1, 21.6, 19.5, 19.0. IR (KBr): 3049, 2962, 2930, 2892, 2873, 1596, 1494, 1468, 1402, 1369, 1307, 1233, 1159, 976, 887, 813, 725, 700. UV (EtOH): 228 nm (ϵ = 14 446 cm^{-1} M^{-1}). MS (EI): 239 (M^+), 1%; 83 (M^+ − Ts − H), 100%; 69 (M^+ − Ts − CH_3), 100%; 54 (M^+ − Ts − $2CH_3$), 100%. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.25; H, 7.11. Found: C, 60.26; H, 7.27. $[\alpha]^{22}_D$ (c 2.0, C_6H_6): −67.0°.

Aziridine *R*-8b. This was prepared as described above. $[\alpha]^{22}_D$ (c 2.0, C_6H_6): +67.0°.

Amine *S*-9b. To a saturated solution of ammonia in methanol (40 mL) at 0 °C was added dropwise with stirring the aziridine *S*-**8b** (MW 239, 430 mg, 1.8 mmol) over a period of 1 h. Ammonia was bubbled continuously during the addition and for 0.5 h after it was completed. The solution flask was stoppered and allowed to stand for 24 h. The solution was concentrated in vacuo to provide *S*-**9b** as a white solid (MW 256, 452 mg, 1.76 mmol) in 98% yield. Recrystallization from octane afforded an analytical sample as white needles. TLC (50% methanol/ethyl acetate): R_f 0.31. Mp: 87–88 °C. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.75 (d, J = 8.5 Hz, 2 H, ArH), 7.27 (d, J = 8 Hz, 2 H, ArH), 2.93 (m, 1 H, NCH), 2.61 (m, 2 H, CH_2), 2.39 (s, 4 H, $ArCH_3$ and NH), 1.71 (m, 1 H, C*H*$(CH_3)_2$), 0.79 (d, J = 6.5 Hz, 3 H, CH_3), 0.77 (d, J = 6 Hz, 3 H, CH_3). ^{13}C NMR, 125.7 MHz ($CDCl_3$): 143.0, 138.1, 129.5, 126.9, 61.2, 42.3, 29.9, 21.6, 18.8, 18.6. IR (KBr): 3355, 3294, 3082, 2957, 2872, 2775, 1597, 1490, 1462, 1458, 1327, 1156, 1090, 1076, 1020, 1001, 971, 928, 708, 658, 576, 542. UV (EtOH): 229 nm (ϵ = 14 650 cm^{-1} M^{-1}). MS (FAB): 257 $(M + H)^+$. Anal. Calcd for $C_{12}H_{20}N_2O_2S$: C, 56.21; H, 7.81. Found: C, 56.39; H, 8.07. $[\alpha]^{22}_D$ (c 1.0, C_6H_6) +12.0°.

Amine *R*-9b. This was prepared as above. $[\alpha]^{22}_D$ (c 1.0, C_6H_6): −12.0°.

Disulfonamide *S*-10b. This was prepared according to a general procedure for coupling of amines with tosylaziridines.[22] A solution of the aziridine *S*-**8b** (MW 239, 1.50 g, 6.3 mmol) in anhydrous toluene (20 mL) was heated to reflux under an inert atmosphere. The amine *S*-**9b** (MW 256, 1.61 g, 6.3 mmol) in toluene (10 mL) was added dropwise over a period of 2 h. The reaction mixture was refluxed for an additional 14 h. The solution was concentrated in vacuo and recrystallized from toluene to give the coupled product *S*-**10b** as white crystals (MW 495, 2.56 g, 5 mmol) in 82% yield. TLC (30% tetrahydrofuran/hexanes): R_f 0.27. Mp: 121–122 °C. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.76 (d, J = 8.5 Hz, 4 H, ArH), 7.30 (d, J = 8 Hz, 4 H, ArH), 5.10 (br s, 2 H, NH), 2.97 (m, 2 H, NCH), 2.41 (br s, 6 H, $ArCH_3$), 2.44–2.32 (br d of d, 2 H, C*H*H), 2.25 (d of d, J = 12, 4.5 Hz, 2 H, CH*H*), 1.69 (m, 2 H, C*H*$(CH_3)_2$), 0.77 (d, J = 6.5 Hz, 6 H, CH_3), 0.74 (d, J = 7 Hz, 6 H, CH_3). ^{13}C NMR, 75.4 MHz ($CDCl_3$): 143.1, 138.1, 129.5, 127.0, 58.6, 49.5, 30.3, 21.6, 18.7, 18.4. IR (KBr): 3286, 3230, 2953, 2872, 1597, 1494, 1458, 1411, 1324, 1160, 1081, 1040, 1020, 960, 933, 818, 726. UV (EtOH): 230 nm (ϵ = 26 509 cm^{-1} M^{-1}). MS (FAB): 496 $(M + H)^+$. Anal. Calcd for $C_{24}H_{37}N_3O_4S_2$: C, 58.17; H, 7.47. Found: C, 58.27; H, 7.67. $[\alpha]^{22}_D$ (c 1.0, C_6H_6): +26.0°.

Disulfonamide *R*-10b. This was prepared as described above. $[\alpha]^{22}_D$ (c 1.0, C_6H_6): −26.0°.

Diisopropyldien *S*-11b. *S*-**10b** was deprotected via an improvement of the general method of du Vigneaud et al.[23] A solution of the disulfonamide *S*-**10b** (MW 495, 2.9 g, 5.9 mmol) in dry THF (20 mL) and absolute ethanol (25 mL) was cooled to −78 °C under inert atmosphere. Liquid ammonia (200 mL) was added rapidly with good stirring. Sodium metal (MW 23, 3.0 g, 0.13 mol) was added piecemeal over a period of 1 h while the reaction flask was maintained at −78 °C. To assist in stirring, dry THF (10 mL) was added periodically to a final volume of 70 mL in dry THF. The reaction was allowed to come to room temperature and stirred for 12 h. The cloudy white solution was poured into 6 N HCl–ice (50 mL). The aqueous solution was first extracted with benzene (3 × 75 mL) and then concentrated to smaller volume under reduced pressure. The aqueous layer was made strongly basic with sodium hydroxide and concentrated in vacuo. The free amine was extracted with dry benzene (200 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to a yellow oil. Vacuum distillation [97–99 °C (0.1 Torr)] afforded *S*-**11b** (MW 187, 1.0 g, 5.3 mmol) in 91% as a colorless oil which turned pale yellow on standing. ^{1}H NMR, 300 MHz (C_6D_6): 2.45 (m, 4 H, CH_2), 2.27 (m, 2 H, NCH), 1.43 (m, 2 H, C*H*$(CH_3)_2$), 0.97 (br s, 5 H, NH, NH_2), 0.84 (d, J = 6 Hz, 6 H, CH_3), 0.83 (d, J = 6 Hz, 6 H, CH_3). ^{13}C NMR, 125.7 MHz (C_6D_6): 56.9, 54.8, 32.7, 19.7, 17.9. IR (Neat): 3320, 2960, 2870, 1595, 1470, 1390, 1370, 1120, 1105. MS (FAB): 188 $(M + H)^+$.

Diisopropyldien *R*-11b. This was prepared as described for *S*-**11b**.

Sulfonamide 7c. A solution of amino alcohol **6c** (MW 89, 58.8 g, 660 mmol) in dry pyridine (100 mL) was added dropwise to a 0 °C cooled solution of *p*-toluenesulfonyl chloride (MW 190.7, 322 g, 1.68 mol) in dry pyridine (200 mL). The cooling bath was removed and the reaction stirred for 5 h at room temperature. The reaction mixture was poured into crushed ice (400 g) and extracted with benzene (5 × 200 mL). The combined organic extracts were successively washed with 5% HCl, saturated NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Recrystallization from ethanol gave **5c** in 71% yield (MW 397, 186 g, 469 mmol) as white crystals. TLC (30% tetrahydrofuran/hexanes): R_f 0.45. Mp: 101–101.5 °C. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.76 (d, J = 8.5 Hz, 2 H, ArH), 7.71 (d, J = 8.5 Hz, 2 H, ArH), 7.35 (d, J = 8.5 Hz, 2 H, ArH), 7.25 (d, J = 8 Hz, 2 H, ArH), 4.98 (br s, 1 H, NH), 3.86 (s, 2 H, CH_2), 2.45 (s, 3 H, $ArCH_3$), 2.40 (s, 3 H, $ArCH_3$), 1.15 (s, 6 H, CH_3). ^{13}C NMR, 125.7 MHz ($CDCl_3$): 145.1, 143.2, 139.9, 132.6, 129.9, 129.6, 127.9, 126.9, 75.6, 55.5, 24.3, 21.6, 21.4. IR (KBr): 3280, 2990, 1600, 1500, 1450, 1435, 1400, 1370, 1320, 1190, 1180, 1155, 1090, 1035, 1005, 980, 840, 810, 778, 708, 665, 590, 545, 500. UV (EtOH): 220 nm (ϵ = 25 410 cm^{-1} M^{-1}). MS (EI): 212 (M^+ − CH_2-OTs), 32%; 42 (M^+ − CH_2OTs − NHTs), 12%. Anal. Calcd for $C_{18}H_{23}NO_5S_2$: C, 54.41; H, 5.79. Found: C, 53.99; H, 5.94.

Aziridine 8c. **8c** was prepared via a modification of the procedure of Markov et al.[24] A solution of 20% KOH (7.5 mL) was rapidly added to sulfonamide **7c** (MW 397, 2.0 g, 5 mmol) in benzene (40 mL) and stirred for 0.5 h. The two-phase mixture was washed with saturated NaCl and the benzene solution dried over anhydrous Na_2SO_4. Con-

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centration in vacuo provided a white solid homogeneous by TLC. Recrystallization from octane afforded the desired product **8c** (MW 225, 1.02 g, 4.5 mmol) in 91% yield as white needles. TLC (25% tetrahydrofuran/hexanes): R_f 0.75. Mp: 84.5–85.0 °C (lit.[24] 84.0–85.0 °C). ^{1}H NMR, 300 MHz ($CDCl_3$): 7.82 (d, J = 8 Hz, 2 H, ArH), 7.30 (d, J = 8 Hz, 2 H, ArH), 2.40 (s, 2 H, CH_2), 2.39 (s, 3 H, $ArCH_3$), 1.53 (s, 6 H, CH_3). ^{13}C NMR, 75.4 MHz ($CDCl_3$): 143.5, 137.9, 129.3, 127.0, 47.5, 41.7, 22.5, 21.3. IR (KBr): 3490, 3000 br, 1660, 1590, 1320, 1300, 1150, 938, 820, 810, 715, 555, 530. UV (EtOH): 224 nm (ϵ = 12 910 cm^{-1} M^{-1}). MS (EI): 225 (M^+), 0.2%; 70 (M^+ – Ts), 100%.

Amine 9c. This was prepared by the procedure of Markov et al.[24] Twice repeated recrystallization from toluene provided the desired compound in 62% yield (lit.[24] 71.5%) as white crystals. TLC (50% methanol/ethyl acetate): R_f 0.38. Mp: 99.0–100 °C (lit.[24] 99.0–100.0 °C). ^{1}H NMR, 300 MHz, ($CDCl_3$): 7.77 (d, J = 8 Hz, 2 H, ArH), 7.26 (d, J = 8 Hz, 2 H, ArH), 2.56 (s, 2 H, CH_2), 2.41 (s, 3 H, $ArCH_3$), 1.12 (s, 6 H, CH_3). ^{13}C NMR, 125.7 MHz ($CDCl_3$): 142.8, 140.7, 129.5, 127.0, 56.8, 52.4, 25.2, 21.4. IR (KBr): 3390, 2850 br, 1600, 1490, 1470, 1390, 1370, 1320, 1305, 1150, 1090, 1025, 1010, 990, 935, 820, 750, 660, 578, 540. UV (EtOH): 226 nm (ϵ = 17 359 cm^{-1} M^{-1}). MS (FAB): 243 $(M + H)^+$.

Disulfonamide 10c. Amine **9c** (MW 242, 19.0 g, 78.5 mmol) was dissolved in dry toluene (250 mL) and heated to reflux under an inert atmosphere. The aziridine **8c** (MW 225, 17.7 g, 78.6 mmol) was added dropwise in toluene (150 mL) over a period of 1 h. The reaction mixture was refluxed for 14 h, cooled, and concentrated. Purification of the residue by silica gel flash chromatography (eluant: 3:1 benzene–ethyl acetate) and recrystallization from methylene chloride–hexane afforded **10c** (MW 467, 26.8 g, 57.4 mmol) in 73% yield as white crystals. TLC (30% ethyl acetate/benzene): R_f 0.34. Mp: 117.0–118.0 °C. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.79 (d, J = 9 Hz, 4 H, ArH), 7.28 (d, J = 9 Hz, 4 H, ArH), 5.50 (br s, 2 H, NH), 2.54 (s, 4 H, CH_2), 2.41 (s, 6 H, $ArCH_3$), 1.14 (s, 12 H, CH_3). ^{13}C NMR, 75.4 MHz ($CDCl_3$): 142.8, 140.3, 129.4, 126.8, 60.4, 56.7, 26.0, 21.6. IR (KBr): 3360, 3245, 2680, 1595, 1450, 1392, 1325, 1310, 1150, 1090, 1020, 988, 885, 810, 660, 540, 525. UV (EtOH): 225 nm (ϵ = 19 065 cm^{-1} M^{-1}). MS (FAB): 468 $(M + H)^+$. Anal. Calcd for $C_{22}H_{33}N_3O_4S_2$: C, 56.55; H, 7.07. Found: C, 56.42; H, 7.21.

Tetramethyldien 11c. Detosylation was achieved via a general procedure reported by Closson and co-workers.[25] Sodium metal (MW 23, 2.94 g, 0.128 mol) was added to a magnetically stirred (glass-covered bar) solution of naphthalene (MW 128, 16.41 g, 128 mmol) in dry dimethoxyethane (85 mL) under an inert atmosphere at room temperature. After several minutes the solution turned dark green and was stirred for an additional 2 h to assure the anion radical had scavenged any traces of oxygen from the interior of the flask. The sulfonamide **10c** (MW 467, 3.0 g, 6.4 mmol) in dry dimethoxyethane (30 mL) was injected by syringe and the reaction mixture stirred for 12 h. The solution was poured into 6 N HCl–ice (100 mL) and extracted with toluene (5 × 100 mL) and dichloromethane (5 × 100 mL). The aqueous phase was concentrated to a smaller volume and strongly basified by the addition of solid sodium hydroxide. The aqueous solution was placed in a lighter than water liquid–liquid extractor and extracted with ether (500 mL) for 14 h. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the crude ligand. Kugelrohr distillation [95–105 °C (0.1 Torr)] provided **11c** (MW 159, 0.47 g, 2.9 mmol) in 45% yield as a light green oil. NMR revealed that the ligand was contaminated with trace impurities, and attempts at further purification showed no improvement. The sodium–liquid ammonia in ethanol conditions described earlier proved a far superior method in affording the free ligand amines in high yield and purity. This method was never attempted on compound **10c**, since the crude triamine **11c** was used successfully to prepare the desired platinum complex in the ensuing reaction. ^{1}H NMR, 300 MHz (C_6D_6): 2.26 (s, 4 H, CH_2), 1.62 (br s, 5 H, NH_2 and NH), 0.96 (s, 12 H, CH_3). ^{13}C NMR, 75.4 MHz (C_6D_6): 63.3, 50.2, 29.0. IR (Neat): 3300 br, 2970, 2890, 1710, 1650, 1460, 1380, 1230, 1080, 1050, 880. MS (EI): 159 (M^+), 0.3%; 58 (M^+ – $CH_2NHCH_2C(CH_3)_2$, 100%.

General Procedure for the Preparation of Pt(II) and Pd(II) Complexes 1 and 2. *trans*-$Pt(DMSO)_2I_2$ (MW 605, 0.100 g, 0.165 mmol) or *trans*-$Pd(DMSO)_2Cl_2$[26] (MW 333, 0.100 g, 0.300 mmol) was dissolved in DMF (20 mL). One equivalent of the appropriate triamine in DMF (5 mL) was added dropwise. The solution turned light brown or light green in the platinum or palladium reaction, respectively. The solution was allowed to stir for 0.5 h and then concentrated by Kugelrohr distillation to a dark brown oil. Addition of anhydrous ether followed by gentle scratching yielded a light brown solid for both the platinum and palladium complexes. The supernatant was decanted, and the solid was washed with ether several times and dried in vacuo overnight. Isolated yields typically were 85–90%.

***trans*-$Pt(DMSO)_2I_2$.** The neutral Pt(II) sulfoxide complex was prepared via a procedure similar to that used for the preparation of *trans*-$Pd(DMSO)_2Cl_2$.[27] Platinum(II) iodide (MW 449, 0.25 g, 0.56 mmol) was dissolved in dimethyl sulfoxide (5 mL) at 50 °C to give a deep red solution. Addition of anhydrous ether with stirring precipitated the complex as an orange solid. The complex was filtered, washed with ether, and dried in vacuo overnight. The yield was quantitative (MW 605, 0.339 g, 0.56 mmol). Alternatively the complex could be isolated as orange crystals by allowing the red solution to stand at room temperature for several hours. Mp: 217–218 °C decomposition ($-I_2$). ^{1}H NMR, 300 MHz (DMF-d_7): 4.00–3.70 (overlapping br singlets, CH_3), 2.19 (s, 6 H, dissociated DMSO). ^{13}C NMR, 125.7 MHz (DMF-d_7): 54.2, 51.2, 49.0, 48.0, 47.4, 41.2. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): –4048 (189 Hz), –4782 (151 Hz), –4890 (117 Hz), –5108 (107 Hz). IR (KBr): 3425, 3010, 2996, 2909, 1607, 1413, 1292, 1271, 1121, 1027, 929, 707, 679. MS (FAB): 604 $(M - H)^-$, 576 $(M - I + glycerol)^-$, 477 $(M - HI)^-$, 449 $(M - 2DMSO)^-$, 349 $(M - 2HI)^-$. Anal. Calcd for $C_4H_{12}O_2S_2I_2Pt$: C, 7.90; H, 1.98; I, 41.98. Found: C, 8.13; H, 2.09; I, 41.65.

[(dien)Pt(II)I]I 1a. ^{1}H NMR, 300 MHz, (DMF-d_7): 7.38 (br s, 1 H, NH), 5.78–5.32 (br m, 4 H, NH_2), 3.23–2.91 (overlapping br m, 8 H, methylene CH_2). ^{13}C NMR, 125.7 MHz (DMF-d_7): 54.5, 53.6. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): –3140 (588 Hz). IR (lit.[28]) (KBr): 3185, 3115, 3055, 1592, 1450, 1385, 1350, 1310, 1285, 1250, 1150, 1075, 1050, 1020, 1000, 990, 920, 880, 840. UV (lit.[28]) (H_2O): 301 nm (ϵ = 462 cm^{-1} M^{-1}). MS (FAB): 425 $(M - I)^+$. Anal. Calcd for $C_4H_{13}N_3I_2Pt$: C, 8.70; H, 2.36. Found: C, 8.87; H, 2.47.

[(Diisopropyldien)Pt(II)I]I *S*-1b. ^{1}H NMR, 300 MHz (DMF-d_7): 6.72 (br s, 1 H, NH), 5.99 (br d, 1 H, N*H*H), 5.70 (br s, 1 H, N*H*H), 5.19 (triplet, J = 10 Hz, 1 H, N*H*H), 4.60 (doublet, J = 12 Hz, 1 H, N*H*H), 3.31–2.78 (overlapping br m, 6 H), 2.05 (m, 1 H, C*H*$C(CH_3)_2$), 1.95 (m, 1 H, C*H*$C(CH_3)_2$), 1.10 (d, J = 7 Hz, 3 H, CH_3), 1.03 (d, J = 6 Hz, 3 H, CH_3), 1.01 (d, J = 6 Hz, 3 H, CH_3), 0.99 (d, J = 5.5 Hz, 3 H, CH_3). ^{13}C NMR, 125.7 MHz (DMF-d_7): 71.3, 70.2, 57.8, 55.5, 31.2, 28.8, 20.8, 20.4, 19.8. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): –3123 (688 Hz). IR (KBr): 3450, 3180, 3040, 2960, 2870, 1570, 1460, 1390, 1370, 1135, 1090, 1070, 1020. MS (FAB): 509 $(M - I)^+$, 382 $(M - 2I)^+$. Anal. Calcd for $PtC_{10}H_{25}N_3I_2$: C, 18.87; H, 3.93. Found: C, 18.27; H, 3.56.

[(Diisopropyldien)Pt(II)I]I *R*-1b. Prepared as described above. Anal. Calcd for $PtC_{10}H_{25}N_3I_2$: C, 18.87; H, 3.93. Found: C, 18.69; H, 4.03.

[(Tetramethyldien)Pt(II)I]I 1c. ^{1}H NMR, 300 MHz (DMF-d_7): 6.21 (br s, 1 H, NH), 5.50 (d, J = 12 Hz, 2 H, N*H*H), 5.29 (d, J = 11.5 Hz, 2 H, NH*H*), 2.99 (apparent t, J = 11 Hz, 2 H, C*H*H), 2.77 (d of d, J = 12, 4 Hz, 2 H, CH*H*), 1.45 (s, 6 H, CH_3), 1.44 (s, 6 H, CH_3). ^{13}C NMR, 125.7 MHz (DMF-d_7): 66.7, 63.7, 25.4, 25.2. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): –3011 (556 Hz). IR (KBr): 3440, 3420, 3380, 3360, 3220, 3170, 3140, 3080, 2970, 2930, 2900, 1615, 1570, 1470, 1440, 1400, 1380, 1325, 1250, 1220, 1140, 1110, 1060, 1030, 970. MS (FAB): 481 $(M - I)^+$. Anal. Calcd for $C_8H_{21}N_3I_2Pt$: C, 15.79; H, 3.54. Found: C, 15.82; H, 3.99.

[(*N*-Tetramethyldien)Pt(II)I]I 1d. ^{1}H NMR, 300 MHz (DMSO-d_6): 7.35 (br s, 1 H, NH), 3.42–2.58 (overlapping br m, 8 H, methylene CH_2), 2.98 (br s, 6 H, CH_3), 2.89 (br s, 6 H, CH_3). ^{13}C NMR, 125.7 MHz (DMSO-d_6): 69.7, 55.3, 52.1, 50.3. ^{195}Pt NMR, 64.4 MHz (DMSO-d_6): –2894 (582 Hz). IR (KBr): 3100, 2910, 2860, 1455, 1445, 1400, 1280, 1260, 1070, 1005, 980, 950, 860, 770. UV (10% DMF/H_2O): 300 nm (ϵ = 394 cm^{-1} M^{-1}). MS (FAB): 481 $(M - I)^+$, 354 $(M - 2I)^+$. Anal. Calcd for $C_8H_{21}N_3I_2Pt$: C, 15.79; H, 3.54. Found: C, 16.13; H, 3.55.

[(dien)Pd(II)Cl]Cl 2a. ^{1}H NMR, 300 MHz (DMSO-d_6): 7.82 (br s, 1 H, NH), 5.18 (br d, 2 H, N*H*H), 4.76 (br d, 2 H, NH*H*), 2.9–2.6 (overlapping br m, 6 H, CH_2), 2.45 (br s, 2 H, C*H*H). ^{13}C NMR, 125.7

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MHz (DMSO-d_6): 53.1, 48.5. IR (lit.[29]) (KBr): 3200, 3135, 3060, 2890, 1605, 1598, 1465, 1458, 1450, 1442, 1393, 1309, 1152, 1148, 1100. UV (lit.[28]) (H_2O): 330 nm (ϵ = 486.2 cm^{-1} M^{-1}). MS (FAB): 246 (M − Cl)$^+$, 208 (M − 2Cl + 2)$^+$.

[(Diisopropyldien)Pd(II)Cl]Cl *S*-2b. ^{1}H NMR, 300 MHz (DMSO-d_6): 6.76 (br s, 1 H, NH), 5.40 (br d of d, 1 H, N*H*H), 5.04 (br d of d, 1 H, N*H*H), 4.68 (t, J = 9 Hz, 1 H, N*H*H), 4.08 (d, J = 9 Hz, 1 H, N*H*H), 3.00–2.48 (overlapping br m, 6 H, CHN and CH_2), 1.87 (m, 2 H, C*H*C$(CH_3)_2$), 1.70 (m, 2 H, C*H*C$(CH_3)_2$), 0.97 (d, J = 7 Hz, 3 H, CH_3), 0.89 (d, J = 7 Hz, 3 H, CH_3), 0.84 (d, J = 7 Hz, 3 H, CH_3), 0.83 (d, J = 7 Hz, 3 H, CH_3). ^{13}C NMR, 125.7 MHz (DMSO-d_6): 65.9, 65.4, 57.2, 54.1, 30.5, 28.3, 20.7, 20.3, 19.3, 19.3. IR (KBr): 3450, 3090, 3050, 2960, 2870, 1580, 1470, 1395, 1380, 1170, 1130, 1080. UV (H_2O): 331 nm (ϵ = 338.4 cm^{-1} M^{-1}). MS (FAB): 330 (M + Cl + 2)$^+$, 293 (M − 2Cl + 2)$^+$ CD (H_2O): 341.6 nm ($\Delta\epsilon$ = +0.19 cm^{-1} M^{-1}), 303.6 nm ($\Delta\epsilon$ = 0.08 cm^{-1} M^{-1}). Anal. Calcd for $PdC_{10}H_{25}N_3Cl_2$: C, 32.97; H, 6.87. Found: C, 32.00; H, 7.14.

[(Diisopropyldien)Pd(II)Cl]Cl Complex *R*-2b. This was prepared as described above. CD (H_2O): 344.0 nm ($\Delta\epsilon$ = −0.18 cm^{-1} M^{-1}), 305.4 nm ($\Delta\epsilon$ = +0.09 cm^{-1} M^{-1}). Anal. Calcd for $PdC_{10}H_{25}N_3Cl_2$: C, 32.97; H, 6.87. Found: C, 31.34; H, 6.99.11

General Method for Synthesis of Tetrasulfonamides 12. The *N*-tosyl protected hexamine ligands were synthesized by the method of Gauss et al. with slight modification.[30] In a typical procedure 4.5:1 molar ratio of aziridine to aliphatic diamine was used. A 1 M solution of aliphatic diamine in benzene was added dropwise to a 1.5 M solution of tosylaziridine in benzene and allowed to stand for 24 h. The white solid that formed was collected by suction filtration and washed with cold toluene and hexane. The fully protected ligands were homogeneous by TLC and used without further purification. Yields typically were 95–98%. The substituted ligands were prepared by refluxing for 14 h in toluene followed by concentration in vacuo. Purification of the residue by silica gel flash chromatography (90% benzene/10% ether, R_f 0.25) afforded white glass-like amorphous solids with broad melting points in 85–90% yields.

Tetrasulfonamide 12a (n = 2). TLC (50% tetrahydrofuran/hexanes): R_f 0.34. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.75 (d, J = 8 Hz, ArH), 7.26 (d, J = 8 Hz, 8 H, ArH), 6.06 (br s, 4 H, NH), 2.93 (s, 8 H, NHCH_2), 2.54 (br s, 12 H, N$(CH_2)_2$N and NCH_2), 2.39 (s, 12 H, ArCH_3). ^{13}C NMR, 75.4 MHz ($CDCl_3$): 143.3, 136.7, 129.7, 127.2, 54.1, 53.0, 40.9, 21.7. IR (KBr): 3270, 2960, 2920, 2845, 1600, 1450, 1400, 1328, 1155, 1085, 950, 818, 660, 540. UV (THF): 275 nm (ϵ = 20 619 cm^{-1} M^{-1}). MS (FAB): 849 (M + H)$^+$.

Tetrasulfonamide 12a (n = 3). TLC (50% tetrahydrofuran/hexanes): R_f 0.34. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.61 (d, J = 8 Hz, 8 H, ArH), 7.12 (d, J = 8 Hz, ArH), 6.05 (br s, 4 H, NH), 2.69 (m, 8 H, NHCH_2), 2.37 (m, 8 H, NCH_2), 2.25 (s, 12 H, ArCH_3), 2.09 (br t, 4 H, NCH_2-CH_2CH_2N), 1.64 (m, 2 H, NCH_2C$H_2$$CH_2$N). ^{13}C NMR, 125.7 MHz ($CDCl_3$): 143.1, 136.0, 129.7, 127.2, 53.9, 52.2, 41.0, 26.1, 21.5. IR (KBr): 3280, 2950, 2810, 1600, 1450, 1400, 1325, 1155, 1090, 952, 815, 662, 540. UV (THF): 275 nm (ϵ = 21 474 cm^{-1} M^{-1}). MS (FAB): 863 (M + H)$^+$.

Tetrasulfonamide 12a (n = 4). TLC (50% tetrahydrofuran/hexanes): R_f 0.34. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.78 (d, J = 8 Hz, 8 H, ArH), 7.24 (d, J = 8 Hz, 8 H, ArH), 6.04 (br s, 4 H, NH), 2.97 (s, 8 H, NHCH_2), 2.55 (s, 8 H, NCH_2), 2.39 (s, 16 H, ArCH_3 and NCH_2-$(CH_2)_2$CH_2N), 1.53 (s, 4 H, NCH_2C$H_2$$CH_2$N). ^{13}C NMR, 75.4 MHz ($CDCl_3$): 142.8, 137.9, 129.5, 127.1, 55.2, 55.0, 41.5, 26.4, 21.5. IR (KBr): 3280, 2950, 2920, 2830, 1598, 1495, 1455, 1410, 1402, 1385, 1328, 1160, 1080, 938, 818, 712, 670, 660, 585, 535. UV (THF): 275 nm (ϵ = 22 237 cm^{-1} M^{-1}). MS (FAB): 877 (M + H)$^+$.

Tetrasulfonamide 12a (n = 5). TLC (50% tetrahydrofuran/hexanes): R_f 0.34. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.76 (d, J = 8 Hz, 8 H, ArH), 7.26 (d, J = 8 Hz, ArH), 5.99 (br s, 4 H, NH), 2.91 (m, 8 H, NHCH_2), 2.48 (br t, 8 H, NCH_2), 2.39 (s, 12 H, ArCH_3), 2.34 (m, 4 H, NCH_2-$(CH_2)_3$CH_2N), 1.40 (br m, 4 H, NCH_2C$H_2$$CH_2CH_2$$CH_2$N), 1.30 (br m, 2 H, N$(CH_2)_2CH_2$$(CH_2)_2$N). ^{13}C NMR, 125.7 MHz ($CDCl_3$): 143.0, 136.8, 129.6, 127.1, 53.9, 53.8, 41.0, 27.6, 25.0, 21.6. IR (KBr): 3280, 2950, 2930, 2860, 1600, 1495, 1455, 1400, 1325, 1295, 1160, 1088, 950, 818, 660, 542. UV (THF): 275 nm (ϵ = 22 428 cm^{-1} M^{-1}). MS (FAB): 891 (M + H)$^+$.

Tetrasulfonamide 12a (n = 6). TLC (50% tetrahydrofuran/hexanes): R_f 0.34. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.80 (d, J = 8 Hz, 8 H, ArH), 7.27 (d, J = 8 Hz, 8 H, ArH), 6.25 (br s, 4 H, NH), 2.85 (s, 8 H, NHCH_2), 2.49 (s, 8 H, NCH_2), 2.36 (s, 12 H, ArCH_3), 2.23 (br s, 4 H, N$(CH_2)(CH_2)_4(CH_2)$N), 1.42 (br s, 4 H, NCH_2C$H_2$$(CH_2)_2CH_2$$CH_2$N), 1.15 (br s, 4 H, N$(CH_2)_2(CH_2)_2(CH_2)_2$N). ^{13}C NMR, 125.7 MHz ($CDCl_3$): 143.1, 136.7, 129.7, 127.2, 55.0, 54.7, 41.4, 27.7, 27.1, 21.7. IR (KBr): 3295, 3260, 2920, 2860, 1600, 1500, 1450, 1405, 1322, 1160, 1090, 950, 820, 662, 545. UV (THF): 275 nm (ϵ = 22 468 cm^{-1} M^{-1}). MS (FAB): 905 (M + H)$^+$.

Tetrasulfonamide 12a (n = 7). TLC (50% tetrahydrofuran/hexanes): R_f 0.34. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.77 (d, J = 8 Hz, 8 H, ArH), 7.26 (d, J = 8 Hz, 8 H, ArH), 5.95 (br s, 4 H, NH), 2.88 (br s, 8 H, NHCH_2), 2.46 (m, 8 H, NCH_2), 2.39 (s, 12 H, ArCH_3), 2.25 (br t, 4 H, J = 6 Hz, NC$H_2$$(CH_2)_5CH_2$N), 1.42 (m, 4 H), 1.28 (br s, 6 H). ^{13}C NMR, 75.4 MHz ($CDCl_3$): 143.0, 136.8, 129.6, 127.1, 54.2, 53.9, 41.0, 29.4, 27.5, 26.7, 21.6. IR (KBr): 3280, 2930, 1600, 1400, 1325, 1160, 815, 660, 540. UV (THF): 275 nm (ϵ = 22 755 cm^{-1} M^{-1}). MS (FAB): 919 (M + H)$^+$.

Tetrasulfonamide 12a (n = 8). TLC (50% tetrahydrofuran/hexanes): R_f 0.34. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.76 (d, J = 8 Hz, 8 H, ArH), 7.27 (d, J = 8 Hz, 8 H, ArH), 5.67 (br s, 4 H, NH), 2.88 (s, 8 H, NHCH_2), 2.46 (br s, 8 H, NCH_2), 2.40 (s, 12 H, ArCH_3), 2.26 (t, J = 7 Hz, 4 H, NC$H_2$$(CH_2)_6CH_2$N), 1.42 and 1.22 (br overlapping m, 4 H and 12 H, N$CH_2$$(CH_2)_6$$CH_2$N). ^{13}C NMR, 125.7 MHz ($CDCl_3$): 143.2, 136.7, 129.7, 127.2, 53.7, 53.5, 40.9, 29.0, 27.0, 26.5, 21.7. IR (KBr): 3282, 3262, 2930, 2860, 1600, 1497, 1470, 1450, 1400, 1325, 1165, 818, 690, 665, 545. UV (THF): 275 nm (ϵ = 23 700 cm^{-1} M^{-1}). MS (FAB): 933 (M + H)$^+$.

Tetrasulfonamide 12a (n = 9). TLC (50% tetrahydrofuran/hexanes): R_f 0.34. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.76 (d, J = 8 Hz, 8 H, ArH), 7.28 (d, J = 8 Hz, 8 H, ArH), 5.54 (br s, 4 H, NH), 2.88 (br s, 8 H, NHCH_2), 2.52–2.34 (br overlapping t and s, 20 H, ArCH_3 and NCH_2), 2.22 (br t, 4 H, NC$H_2$$(CH_2)_7CH_2$N), 1.72 (br s, 2 H, N$(CH_2)_4CH_2$-$(CH_2)_4$N), 1.40–1.10 (br overlapping peaks, 12 H). ^{13}C NMR, 125.7 MHz ($CDCl_3$): 143.2, 136.6, 129.6, 127.1, 53.7, 53.5, 40.5, 29.1, 28.9, 27.0, 26.0, 21.6. IR (KBr) 3282, 3270, 2925, 2850, 1600, 1450, 1400, 1325, 1160, 1085, 950, 815, 670, 540. UV (THF): 275 nm (ϵ = 23 661 cm^{-1} M^{-1}). MS (FAB): 947 (M + H)$^+$. HRMS (FAB): calcd for $C_{45}H_{67}N_6O_8S_4$ + H, 947.3901; found, 947.3907.

Tetrasulfonamides *R*- and *S*-12b (n = 3). TLC (90% benzene/ether): R_f 0.23. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.84 (d, J = 8 Hz, 8 H, ArH), 7.24 (d, J = 8 Hz, 8 H, ArH), 6.22 (br s, 4 H, NH), 3.19 (m, 4 H), 2.40 (s, 12 H, ArCH_3), 2.56–2.18 (br m, 8 H), 1.94 (m, 6 H), 1.72–1.43 (br overlapping peaks, 4 H), 0.79 (d, J = 7 Hz, 12 H, CH_3), 0.75 (d, J = 7 Hz, 12 H, CH_3. ^{13}C NMR, 125.7 MHz ($CDCl_3$): 142.2, 139.4, 129.3, 127.0, 57.1, 55.5, 50.9, 30.3, 28.6, 21.5, 18.4, 17.3. IR (KBr): 3280, 2965, 1600, br 1450, 1325, 1160, 1026, 815, 705, 660, 580, 540. MS (FAB): 1031 (M + H)$^+$.

Tetrasulfonamides *R*- and *S*-12b (n = 9). TLC (90% benzene/ether): R_f 0.23. ^{1}H NMR, 300 MHz ($CDCl_3$): 7.79 (d, J = 8 Hz, 8 H, ArH), 7.27 (d, J = 8 Hz, 8 H, ArH), 5.28 (br s, 4 H, NH), 3.31 (br s, 4 H), 2.41 (s, 12 H, ArCH_3), 2.46–2.12 (br overlapping peaks, 10 H), 1.93 (m, 4 H, C*H*$(CH_3)_2$), 1.23 (s, 12 H), 1.13 (br s, 4 H), 0.77 and 0.74 (overlapping d, J = 7 Hz, 24 H, CH_3). ^{13}C NMR, 125.7 MHz ($CDCl_3$): 142.9, 138.7, 129.4, 127.0, 56.1, 53.7, 53.3, 30.0, 29.9, 29.9, 27.5, 25.1, 21.5, 17.7, 17.7. IR (KBr): 3260, 2960, 1600, 1450 br, 1330, 1160, 1030, 900, 812, 705, 660, 580, 540. MS (FAB): 1115 (M + H)$^+$. HRMS (FAB): calcd for $C_{57}H_{91}N_6O_8S_4$ + H, 1115.5781; found, 1115.5793.

General Procedure for Detosylation of Tetrasulfonamides. Detosylation of the tetrasulfonamides was performed as described earlier for the disulfonamides monomers with slight modification. Additional sodium metal was added to adjust the mole equivalent per tosyl group to ca. 20:1. The hydrochloride salt and crude amine ligands were all pure by NMR. The crude yields were typically 95–98%. The compounds were further purified by Kugelrohr distillation [>250 °C (0.1 Torr)] to afford clear or light yellow oils in 88–95% yields.

Bis(dien) 13a (n = 2). ^{1}H NMR, 300 MHz (C_6D_6): 2.57 (t, J = 6 Hz, 8 H, C$H_2$$NH_2$), 2.38 (s, 4 H, N$(CH_2)_2$N), 2.27 (t, J = 6 Hz, 8 H, NCH_2), 1.05 (br s, 8 H, NH_2). ^{13}C NMR 125.7 MHz (C_6D_6): 58.6, 53.8, 40.7. IR (Neat): 3360, 3265, 2850 br, 1775, 1598, 1462, 1360, 1300, 1040. MS (FAB): 233 (M + H)$^+$.

Bis(dien) 13a (n = 3). ^{1}H NMR, 300 MHz (C_6D_6): 2.58 (t, J = 5.5 Hz, 8 H, C$H_2$$NH_2$), 2.32 (br t, 4 H, NC$H_2$$CH_2CH_2$N), 2.27 (t, J = 6 Hz, 8 H, NCH_2), 1.49 (quintet, J = 6 Hz, 2 H, NCH_2C$H_2$$CH_2$N), 0.90 (br s, 8 H, NH_2). ^{13}C NMR, 125.7 MHz (C_6D_6): 58.2, 53.1, 40.7, 25.9. IR (Neat): 3350, 3270, 2850 br, 1585, 1455, 1350, 1300, 1030. MS (FAB): 247 (M + H)$^+$.

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Bis(dien) 13a (n = 4). ^{1}H NMR, 300 MHz (C_6D_6): 2.57 (t, J = 6 Hz, 8 H, CH_2NH_2), 2.27 (t, J = 6 Hz, 12 H, NCH_2 and NCH_2-$(CH_2)_2CH_2N$), 1.55–1.25 (m, 4 H, $NCH_2(CH_2)_2CH_2N$), 1.37 (br s, 8 H, NH_2). ^{13}C NMR, 125.7 MHz (C_6D_6): 58.1, 55.0, 40.7, 25.9. IR (Neat): 3250 br, 2900 br, 1650, 1600, 1450, 1365, 1050. MS (FAB): 261 $(M + H)^+$.

Bis(dien) 13a (n = 5). ^{1}H NMR, 300 MHz (C_6D_6): 2.58 (t, J = 6 Hz, 8 H, CH_2NH_2), 2.28 (t, J = 6 Hz, 12 H, NCH_2 and NCH_2-$(CH_2)_3CH_2N$), 1.37 (m, 4 H, $NCH_2CH_2CH_2CH_2CH_2N$), 1.26 (m, 2 H, $N(CH_2)_2CH_2(CH_2)_2N$), 0.97 (br s, 8 H, NH_2). ^{13}C NMR, 125.7 MHz (C_6D_6): 58.2, 55.0, 40.6, 27.9, 25.6. IR (Neat): 3300 br, 2940, 2850 br, 1680, 1600, 1460, 1360, 1300, 1050. MS (FAB): 297 $(M + Na)^+$.

Bis(dien) 13a (n = 6). ^{1}H NMR, 300 MHz (C_6D_6): 2.58 (t, J = 6 Hz, 8 H, CH_2NH_2), 2.28 (t, J = 6 Hz, 12 H, NCH_2 and NCH_2-$(CH_2)_4CH_2N$), 1.45–1.18 (overlapping br m, 8 H, $NCH_2(CH_2)_4CH_2N$), 1.05 (br s, 8 H, NH_2). ^{13}C NMR, 125.7 MHz (C_6D_6): 58.2, 55.0, 40.6, 27.9, 27.7. IR (Neat): 3350, 3260, 2850 br, 1588, 1470, 1350, 1300, 1050. MS (FAB): 311 $(M + Na)^+$.

Bis(dien) 13a (n = 7). ^{1}H NMR, 300 MHz (C_6D_6): 2.58 (t, J = 6 Hz, 8 H, CH_2NH_2), 2.28 (two br overlapping t, J = 6 Hz, 12 H, NCH_2 and $NCH_2(CH_2)_5CH_2N$), 1.40 (br quintet, J = 6 Hz, 4 H, NCH_2-$CH_2(CH_2)_3CH_2CH_2N$), 1.28 (br s, 6 H, $N(CH_2)_2(CH_2)_3(CH_2)_2N$), 0.90 (br s, 8 H, NH_2). ^{13}C NMR, 125.7 MHz (C_6D_6): 58.3, 55.1, 40.7, 30.1, 28.1, 27.9. IR (Neat): 3360, 3280, 2930, 2860, 2800, 1600, 1530, 1360, 1300, 1040 br. MS (FAB): 303 $(M + H)^+$.

Bis(dien) 13a (n = 8). ^{1}H NMR, 300 MHz (C_6D_6): 2.58 (t, J = 5.5 Hz, 8 H, CH_2NH_2), 2.28 (two br overlapping t, J = 6 Hz, 12 H, NCH_2 and $NCH_2(CH_2)_6CH_2N$), 1.40 (br quintet, J = 6 Hz, 4 H, NCH_2-$CH_2(CH_2)_4CH_2CH_2N$), 1.29 (br s, 8 H, $N(CH_2)_2(CH_2)_4(CH_2)_2N$), 0.94 (br s, 8 H, NH_2). ^{13}C NMR, 125.7 MHz (C_6D_6): 58.2, 55.1, 40.6, 30.0, 27.9, 27.8. IR (Neat): 3340, 3280, 2850 br, 1585, 1460, 1448, 1350, 1285, 1035. MS (FAB): 339 $(M + Na)^+$.

Bis(dien) 13a (n = 9). ^{1}H NMR, 300 MHz (C_6D_6): 2.58 (t, J = 6 Hz, 8 H, CH_2NH_2), 2.28 (two br overlapping t, J = 6 Hz, 12 H, NCH_2 and $NCH_2(CH_2)_7CH_2N$), 1.44–1.24 (br overlapping m, 14 H, NCH_2-$(CH_2)_7CH_2N$), 1.00 (br s, 8 H, NH_2). ^{13}C NMR, 125.7 MHz (C_6D_6): 58.2, 55.1, 40.6, 30.1, 30.0, 28.0, 27.8. IR (Neat) 3350, 3280, 2900 br, 1680, 1600, 1465, 1450, 1360, 1300, 1035. MS (FAB): 353 $(M + Na)^+$.

Bis(diisopropyldien) *R*- and *S*-13b (n = 3). ^{1}H NMR, 300 MHz (C_6D_6): 2.68 (m, 4 H, $CHNH_2$), 2.50 (m, 2 H), 2.30 (br d of d, 4 H, $NCHHCH(i\text{-Pr})$), 2.38–2.24 (m, 2 H), 2.19 (d of d, J = 12.5, 3 Hz, 4 H, $NCHHCH(i\text{-Pr})$), 1.63 (m, 2 H, $NCH_2CH_2CH_2N$), 1.48 (m, 4 H, $CH(CH_3)_2$), 1.34 (br s, 8 H, NH_2), 0.92 (d, J = 6 Hz, 12 H, CH_3), 0.91 (d, J = 6 Hz, 12 H, CH_3). ^{13}C NMR, 125.7 MHz (C_6D_6): 60.4, 54.0, 53.7, 32.6, 25.3, 19.6, 18.0. IR (Neat): 3360, 3300, 2900 br, 1585, 1470, 1385, 1368, 1318, 1085, 1075, 1045. MS (FAB): 415 $(M + H)^+$.

Bis(diisopropyldien) *R*- and *S*-13b (n = 9). ^{1}H NMR, 300 MHz (C_6D_6): 2.71 (m, 4 H, $CHNH_2$), 2.54 (m, 2 H), 2.34 (br t, 4 H, NCH-$HCH(i\text{-Pr})$), 2.24 (d of d, J = 12, 3 Hz, 4 H, $NCHHCH(i\text{-Pr})$), 2.29–2.20 (m, 2 H), 1.62–1.44 (br overlapping m, 10 H), 1.46–1.26 (two br overlapping s, 18 H), 0.98 and 0.96 (br overlapping d, J = 6 Hz, 24 H, CH_3). ^{13}C NMR, 125.7 MHz (C_6D_6): 60.3, 55.5, 54.0, 32.7, 30.2, 30.1, 28.0, 27.9, 19.6, 18.1. IR (Neat): 3370, 3310, 2900 br, 1585, 1470, 1385, 1305, 1075, 840. MS (FAB): 499 $(M + H)^+$.

General Procedure for the Preparation of Bis Pt(II) and Pd(II) Complexes. The binuclear metal complexes were prepared via the method described earlier for the synthesis of the mononuclear complexes with slight modification. Two equivalents of *trans*-$Pt(DMSO)_2I_2$ or *trans*-$Pd(DMSO)_2Cl_2$ were used per equivalent of the hexaamine. The desired metal complexes precipitated immediately upon addition of anhydrous ether. The supernatant was decanted and the light brown solid washed with ether several times and dried in vacuo overnight. Isolated yields were 85–90%.

Bis([(dien)Pt(II)I]I) 3a (n = 2). ^{1}H NMR, 300 MHz (DMF-d_7): 5.78 (m, 4 H, N*H*H), 5.34 (m, 4 H, NH*H*), 3.88–3.75 (br m, 8 H, NH_2CH_2), 3.59 (t of d, J = 13, 5 Hz, 4 H, NH_2CH_2CHHN), 3.34–3.18 (two br overlapping m, 8 H, $N(CH_2)_2N$ and NH_2CH_2CHHN). ^{13}C NMR, 125.7 MHz (DMF-d_7): 62.4, 51.5, 49.3. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): 3057 (477 Hz). IR (KBr): 3500 br, 3100 br, 1700, 1650, 1560, 1260, 1160, 1040. MS (FAB): 1003 $(M - I)^+$, 876 $(M - 2I)^+$, 748 $(M - 2I - HI)^+$. Anal. Calcd for $Pt_2C_{10}H_{28}N_6I_4$: C, 10.62; H, 2.48. Found: C, 12.12.; H, 2.71.

Bis([(dien)Pt(II)I]I) 3a (n = 3). ^{1}H NMR, 300 MHz (DMF-d_7): 5.76 (m, 4 H, N*H*H), 5.38 (m, 4 H, NH*H*), 3.84–3.62 (br m, 8 H, NH_2CH_2), 3.43 (overlapping t of d, 4 H, NH_2CH_2CHHN), 3.28–3.10 (br overlapping m, 8 H, NH_2CH_2CHHN and $NCH_2CH_2CH_2N$), 2.31 (m, 2 H, $NCH_2CH_2CH_2N$). ^{13}C NMR, 125.7 MHz (DMF-d_7): 61.1, 51.3, 16.7. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): −3059 (478 Hz). IR (KBr): 3450 br, 3180, 3100, 1660, 1640, 1580, 1460, 1255, 1160, 1040. MS (FAB): 1017 $(M - I)^+$, 889 $(M - I - HI)^+$, 761 $(M - I - 2HI)^+$. Anal. Calcd for $Pt_2C_{11}H_{30}N_6I_4$: C, 11.54; H, 2.62. Found: C, 11.93; H, 2.56.

Bis([(dien)Pt(II)I]I) 3a (n = 4). ^{1}H NMR, 300 MHz (DMF-d_7): 5.72 (m, 4 H, N*H*H), 5.40 (m, 4 H, NH*H*), 3.76–3.52 (br m, 8 H, NH_2CH_2), 3.41 (t of d, J = 13, 5 Hz, 4 H, NH_2CH_2CHHN), 3.20 (quintet, J = 6.5 Hz, 4 H, $NCH_2(CH_2)_2CH_2N$ or NH_2CH_2CHHN), 3.10–2.98 (two br overlapping m, 4 H, NH_2CH_2CHHN or $NCH_2(CH_2)_2$-CH_2N), 1.80 (br s, 4 H, $NCH_2(CH_2)_2CH_2N$). ^{13}C NMR, 125.7 MHz (DMF-d_7): 61.0, 51.2, 51.2, 20.1. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): −3062 (492 Hz). IR (KBr): 3450 br, 3160, 3080, 1655, 1580, 1460, 1258, 1045. MS (FAB): 1031 $(M - I)^+$, 904 $(M - 2I)^+$, 776 $(M - 2I - HI)^+$. Anal. Calcd for $Pt_2C_{12}H_{32}N_6I_4$: C, 12.44; H, 2.76. Found: C, 12.63; H, 2.84.

Bis([(dien)Pt(II)I]I) 3a (n = 5). ^{1}H NMR, 300 MHz (DMF-d_7): 5.75 (m, 4 H, N*H*H), 5.38 (m, 4 H, NH*H*), 3.81–3.50 (br m, 8 H, NH_2CH_2), 3.39 (br t of d, 4 H, NH_2CH_2CHHN), 3.20 (quintet, J = 6 Hz, 4 H, $NCH_2(CH_2)_3CH_2N$ or NH_2CH_2CHHN), 3.12–2.92 (two br overlapping m, 4 H, NH_2CH_2CHHN or $NCH_2(CH_2)_3CH_2N$), 1.83 (br s, 4 H, $NCH_2CH_2CH_2CH_2CH_2N$), 1.45 (br quintet, 2 H, $NCH_2CH_2CH_2$-CH_2CH_2N). ^{13}C NMR, 125.7 MHz (DMF-d_7): 60.0, 54.2, 51.1, 24.3, 21.9. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): −3060 (480 Hz). IR (KBr): 3450 br, 3200, 3080, 1650, 1580, 1465, 1310, 1255, 1155, 1042, 1020. MS (FAB): 1045 $(M - I)^+$, 917 $(M - I - HI)^+$, 790 $(M - 2I - HI)^+$. Anal. Calcd for $Pt_2C_{13}H_{34}N_6I_4$: C, 13.31; H, 2.90. Found: C, 13.11; H, 2.76.

Bis([(dien)Pt(II)I]I) 3a (n = 6). ^{1}H NMR, 300 MHz (DMF-d_7): 5.72 (m, 4 H, N*H*H), 5.42 (m, 4 H, NH*H*), 3.72–3.51 (br m, 8 H, NH_2CH_2), 3.39 (t of d, J = 13, 5 Hz, 4 H, NH_2CH_2CHHN), 3.20 (quintet, J = 6.5 Hz, 4 H, $NCH_2(CH_2)_4CH_2N$ or NH_2CH_2CHHN), 3.08–2.96 (two br overlapping m, 4 H, NH_2CH_2CHHN or NCH_2-$(CH_2)_4CH_2N$), 1.78 (m, 4 H, $NCH_2CH_2(CH_2)_2CH_2CH_2N$), 1.44 (br s, 4 H, $N(CH_2)_2(CH_2)_2(CH_2)_2N$). ^{13}C NMR, 125.7 MHz (DMF-d_7): 60.9, 54.4, 51.2, 26.7, 22.1. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): −3060 (481 Hz). IR (KBr): 3500 br, 3190, 3075, 1460, 1310, 1252, 1153. MS (FAB): 1059 $(M - I)^+$, 931 $(M - I - HI)^+$, 803 $(M - I - 2HI)^+$. Anal. Calcd for $Pt_2C_{14}H_{36}N_6I_4$: C, 14.17; H, 3.06. Found: C, 14.39; H, 3.29.

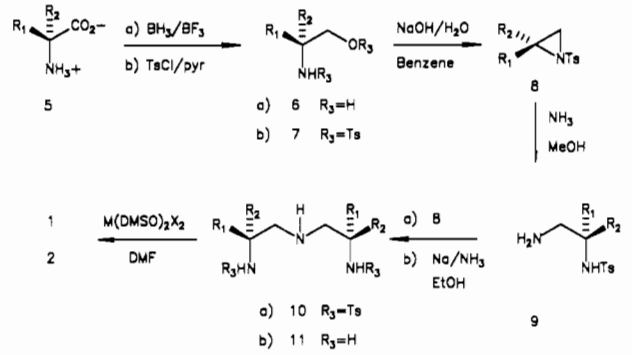
Bis([(dien)Pt(II)I]I) 3a (n = 7). ^{1}H NMR, 300 MHz (DMF-d_7): 5.72 (m, 4 H, N*H*H), 5.38 (m, 4 H, NH*H*), 3.71–3.52 (br m, 8 H, NH_2CH_2), 3.39 (t of d, J = 13, 4 Hz, 4 H, NH_2CH_2CHHN), 3.21 (m, 4 H, $NCH_2(CH_2)_5CH_2N$ or NH_2CH_2CHHN), 3.02 (d of d, J = 12.5, 3 Hz, 4 H, NH_2CH_2CHHN or $NCH_2(CH_2)_5CH_2N$), 1.73 (m, 4 H, $NCH_2CH_2(CH_2)_3CH_2CH_2N$), 1.41 (br s, 6 H, $N(CH_2)_2(CH_2)_3$-$(CH_2)_2N$). ^{13}C NMR, 125.7 MHz (DMF-d_7): 60.9, 54.6, 51.2, 29.6, 27.1, 22.3. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): 3061 (530 Hz). IR (KBr): 3420 br, 3160, 3093, 1460, 1160. MS (FAB): 1073 $(M - I)^+$, 946 $(M - 2I)^+$, 819 $(M - 3I)^+$. Anal. Calcd for $Pt_2C_{15}H_{38}N_6I_4$: C, 15.18; H, 3.28. Found: C, 15.28; H, 3.07.

Bis([(dien)Pt(II)I]I) 3a (n = 8). ^{1}H NMR, 300 MHz (DMF-d_7): 5.71 (m, 4 H, N*H*H), 5.37 (m, 4 H, NH*H*), 3.72–3.52 (br m, 8 H, $NHCH_2$), 3.39 (t of d, J = 13, 5 Hz, 4 H, NH_2CH_2CHHN), 3.20 (br quintet, J = 6.5 Hz, 4 H, $NCH_2(CH_2)_6CH_2N$ or NH_2CH_2CHHN), 3.01 (d of d, J = 12.5, 3 Hz, 4 H, NH_2CH_2CHHN or $NCH_2(CH_2)_6CH_2N$), 1.72 (br s, 4 H, $NCH_2CH_2(CH_2)_4CH_2CH_2N$), 1.36 (br s, 8 H, $N(CH_2)_2$-$(CH_2)_4(CH_2)_2N$). ^{13}C NMR, 125.7 MHz (DMF-d_7): 60.9, 54.5, 51.1, 29.5, 27.3, 22.3. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): 3062 (509 Hz). IR (KBr): 3450 br, 3200, 3090, 2924, 1460, 1310, 1252. MS (FAB): 1087 $(M - I)^+$, 960 $(M - 2I)$· 833 $(M - 3I)^+$. Anal. Calcd for $Pt_2C_{16}H_{40}N_6I_4$: C, 15.82; H, 3.29. Found: C, 16.22; H, 3.37.

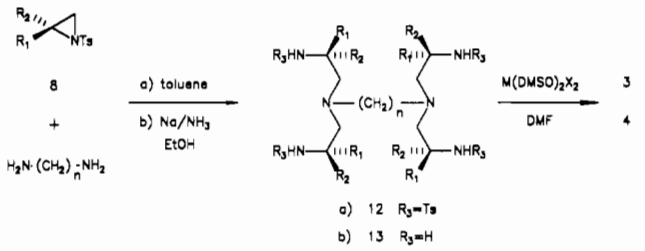
Bis([(dien)Pt(II)I]I) 3a (n = 9). ^{1}H NMR, 300 MHz (DMF-d_7): 5.72 (m, 4 H, N*H*H), 5.39 (m, 4 H, NH*H*), 3.70–3.54 (br m, 8 H, NH_2CH_2), 3.42 (br t of d, J = 12, 5 Hz, 4 H, NH_2CH_2CHHN), 3.24 (m, 4 H, $NCH_2(CH_2)_7CH_2N$ or NH_2CH_2CHHN), 3.10–3.01 (two br overlapping m, 4, NH_2CH_2CHHN or $NCH_2(CH_2)_7CH_2N$), 1.73 (br s, 4 H, $NCH_2CH_2(CH_2)_5CH_2CH_2N$), 1.38 (br s, 10 H, $N(CH_2)_2(CH_2)_5$-$(CH_2)_2N$). ^{13}C NMR, 125.7 MHz (DMF-d_7): 61.0, 54.6, 51.2, 27.3, 22.4. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): −3061 (508 Hz). IR (KBr): 3450 br, 3182, 3090, 2921, 2847, 1463, 1310, 1255, 1165. MS (FAB): 1101 $(M - I)^+$, 971 $(M - 2I)^+$, 847 $(M - 3I)^+$. Anal. Calcd for $Pt_2C_{17}H_{42}N_6I_4$: C, 16.61; H, 3.42. Found: C, 16.53; H, 3.69.

Bis([(diisopropyldien)Pt(II)I]I) *S*-3b (n = 3)). ^{1}H NMR, 300 MHz (DMF-d_7): 5.71 (br d of d, J = 9.5, 4.5 Hz, 2 H, N*H*H), 5.45 (br d, 2 H, NH*H*), 5.18 (t, J = 11.5 Hz, 2 H, N*H*H), 5.05 (br m, 2 H, NH*H*),

Scheme I



Scheme II



3.78–3.10 (br overlapping m, 18 H), 2.06 (m, 4 H, C*H*$(CH_3)_2$), 1.10 (d, J = 5.5 Hz, 6 H, CH_3), 1.08 (d, J = 6 Hz, 6 H, CH_3), 1.05 (d, J = 5.5 Hz, 6 H, CH_3), 1.02 (d, J = 6 Hz, 6 H, CH_3. ^{13}C NMR, 125.7 MHz (DMF-d_7): 68.8, 64.8, 64.6, 61.8, 58.6, 31.6, 31.2, 20.6, 19.9, 19.7, 19.5, 19.4. ^{195}Pt NMR, 64.4 MHz (DMF-d_7): 2964 (479 Hz). IR (KBr): 3450, 3195, 3060, 2960, 1660, 1590, 1582, 1462, 1392, 1185, 1170, 1130, 1060, 1045, 1025, 870. UV (8.7% DMF/H_2O): 302 nm (ϵ = 1303.2 cm^{-1} M^{-1}). MS (FAB): 1185 $(M - I)^+$, 1057 $(M - I - HI)^+$, 929 $(M - I - 2HI)^+$. CD (8.7% DMF/H_2O): 376.6 nm ($\Delta\epsilon$ = –0.48 cm^{-1} M^{-1}), 308.2 nm ($\Delta\epsilon$ = –0.17 cm^{-1} M^{-1}). Anal. Calcd for $Pt_2C_{23}H_{54}N_6I_4$: C, 21.04; H, 4.12. Found: C, 21.38; H, 4.33.

Bis([(diisopropyldien)Pt(II)I]I) *R*-3b (n = 3). CD (8.7% DMF/H_2O): 377.2 nm ($\Delta\epsilon$ = +0.49 cm^{-1} M^{-1}), 308.2 nm ($\Delta\epsilon$ = +0.17 cm^{-1} M^{-1}). Anal. Calcd for $Pt_2C_{23}H_{54}N_6I_4$: C, 21.04; H, 4.12. Found: C, 21.26; H, 4.28.

Bis([(diisopropyldien)Pt(II)I]I) *S*-3b (n = 9). ^{1}H NMR, 300 MHz (DMF-d_7): 5.77 (br m, 2 H, N*H*H), 5.43 (br d, 2 H, NH*H*), 5.24 (br t, J = 11 Hz, 2 H, N*H*H), 5.04 (br m, 2 H, NH*H*), 3.78–3.16 (br overlapping m, 16 H), 2.14–1.72 (two overlapping m, 8 H), 1.35 (br s, 10 H, $N(CH_2)_2(CH_2)_5(CH_2)_2N$), 1.12–0.98 (br overlapping d, 24 H, CH_3). ^{13}C NMR, 125.7 MHz (DMF-d_7): 68.7, 65.2, 64.1, 61.6, 31.6, 30.9, 27.0, 23.7, 19.7, 19.5, 19.2, 19.1. ^{195}Pt NMR 64.4 MHz (DMF-d_7): =2967 (474 Hz). IR (KBr): 3430, 3192, 3040, 2958, 2920, 1655, 1578, 1453, 1390, 1375, 1128, 1084, 870. UV (8.7% DMF/H_2O): 286 nm (ϵ = 1716 cm^{-1} M^{-1}). MS (FAB): 1269 $(M - I)^+$, 1441 $(M - I - HI)^+$. CD (8.7% DMF/H_2O): 374.2 nm ($\Delta\epsilon$ = –0.45 cm^{-1} M^{-1}), 308.2 nm ($\Delta\epsilon$ = –0.24 cm^{-1} M^{-1}). Anal. Calcd for $Pt_2C_{29}H_{66}N_6I_4$: C, 24.93; H, 4.72. Found: C, 25.66; H, 5.01.

Bis([(diisopropyldien)Pt(II)I]I) *R*-3b (n = 9). CD (8.7% DMF/H_2O): 372.8 nm ($\Delta\epsilon$ = +0.45 cm^{-1} M^{-1}), 312.6 nm ($\Delta\epsilon$ = +0.26 cm^{-1} M^{-1}). Anal. Calcd for $Pt_2C_{29}H_{66}N_6I_4$: C, 24.93; H, 4.72. Found: C, 24.27; H, 4.74.

Bis([(dien)Pd(II)Cl]Cl) 4a (n = 2). ^{1}H NMR, 300 MHz (50% DMF-d_7/50% D_2O): 3.90–3.74 (br t of d, J = 12, 6 Hz, 8 H, NH_2CH_2), 3.61 (br t, J = 13 Hz, 4 H, NH_2CH_2CHHN), 3.32–3.14 (two br overlapping m, 8 H, $N(CH_2)_2N$ and NH_2CH_2CHHN). ^{13}C NMR, 125.7 MHz (50% DMF-d_7/50% D_2O): 60.1, 45.5, 45.0. IR (KBr): 3200, 3125, 3060, 2865, 1660, 1598, 1465, 1442, 1385, 1350, 1308, 1150, 1050, 990. UV (H_2O): 341 nm (ϵ = 565.9 cm^{-1} M^{-1}). MS (FAB): 553 $(M - Cl + 2)^+$. Anal. Calcd for $Pd_2C_{10}H_{28}N_6Cl_4$: C, 20.45; H, 4.77. Found: C, 20.68; H, 4.67.

Results

Synthesis of the Dien and Bis(dien) Derivatives. The Pt(II) complexes were prepared by reacting $Pt(DMSO)_2I_2$ with the corresponding dien or bis(dien) derivative, of which dien **11a** and *N*-tetramethyldien **11d** were available commercially. The enantiomeric diisopropyldiens, *S*- and *R*-**11b** were obtained in 60% overall yield from *S*- and *R*-valinol, *S*- and *R*-**6b**, following a general five-step procedure (Scheme I). *S*- and *R*-valinol were obtained in enantiomerically pure form by borane/dimethyl sulfide reduction of *S*- and *R*-valine, compounds *S*- and *S*-**5b**, by the method of Smith and Gawley.[20] Condensation of 2 equiv of *p*-toluenesulfonyl chloride in pyridine with valinol **6b** led to the sulfonamide **7b**. The sulfonamide **7b** was converted to the aziridine **8b** in good yield by a two-phase system of 20% aqueous KOH and benzene. Half of the tosylaziridine was then converted to the amine **9b** by treatment with methanolic ammonia following the procedure of Markov et al.[24] The aziridine **8b** and amine **9b** were then coupled by refluxing in toluene to give the disulfonamide **10b** as the major product. The tosyl groups were removed in approximately 95% yield by sodium reduction in liquid ammonia in the presence of ethanol and diisopropyldien **11b** was isolated by distillation. Tetramethyldien **11c** was prepared by the same route utilized for diisopropyldien starting from the commercially available amino alcohol **6c**.

The bis(dien)s, **3a** (n = 2–9), were prepared by a general two-step procedure outlined in Scheme II. In the first step 4 equiv of *N*-tosylaziridine, **8a**,[22] were treated with one equivalent of 1,*n*-diamine in benzene at room temperature. Detosylation was achieved in yields varying between 88% and 95% by sodium/liquid ammonia in ethanol using the conditions utilized for the detosylation of the disulfonamides. The chiral bis(diisopropyldien)s *S*- and *R*-**3b** (n = 3 and 6) were prepared by the same two step route utilizing the *N*-tosylaziridines *S*- and *R*-**8b**.

Preparation of the Pt(II) and Pd(II) Complexes. The [(dien)-Pt(II)I]I and bis([(dien)Pt(II)I]I) derivatives, compounds **1** and **3**, were isolated in nearly quantitative yield as light brown powders by reacting $Pt(DMSO)_2I_2$ with the corresponding ligands in DMF, followed by removal of the DMF under vacuum. $Pt(DMSO)_2I_2$ was prepared by dissolving PtI_2 in DMSO and then precipitating with ether. The Pt(II) complexes were soluble in DMF and DMSO and only sparingly soluble in water, though they became soluble when converted to the nitrato species with silver nitrate. Attempts to crystallize the platinum complexes were unsuccessful, often leading to oily precipitates. Pd(II) complexes of selected ligands were similarly prepared from $Pd(DMSO)_2Cl_2$. The palladium complexes were found to be freely soluble in water, DMSO and DMF.

Characterization of the Metal Complexes. All complexes gave satisfactory C and H analyses as well as FAB MS data. FAB MS spectra of the complexes were obtained in glycerol matrix and were characterized by an intense ion peak corresponding to the loss of I^- anion. Intense fragment ion peaks corresponding to $(M - I - HI)^+$ and $(M - 2I - HI)^+$, respectively, were also present. Standard IR, UV, and ^{1}H, ^{13}C, and ^{195}Pt NMR spectra were obtained for all the complexes and CD spectra were obtained for all the chiral complexes. Selected ^{13}C NMR, ^{195}Pt NMR, and CD data are presented in Tables I–III.

Discussion

Selection of the Synthetic Targets. The derivatives of [(dien)-Pt(II)I]I were selected in order to determine the extent to which simple alkyl substituents could be used to influence nucleic acid binding selectivity. In particular, we were interested in determining the extent to which steric interactions could be used to discriminate between two well-characterized conformations of DNA, B- and Z-DNA. One of the principal distinguishing features between the B and Z conformations of DNA is the steric environment of the N-7 position of the purine residue, the position to which $[(dien)Pt(II)Cl]^+$ binds. In B-DNA this position lies within the deep, sterically demanding major groove, whereas in Z-DNA this position lies within the shallow major groove which

Table I. ^{13}C NMR Chemical Shifts of Representative Dien and Bis(dien) Derivatives and Their Complexes with Pt(II) and Pd(II)

ligand	$\delta(^{13}C)$ (ppm)	complex	$\delta(^{13}C)$ (ppm)
11a	52.1, 41.5	**1a**	54.5, 53.6
		2a	53.1, 48.5
***S*-11b**	56.9, 54.8, 32.7, 19.7, 17.9	***S*-1b**	71.3, 70.2, 57.8, 55.5, 31.2, 28.8, 20.8, 20.4, 19.8
		***S*-2b**	65.9, 65.4, 57.2, 54.1, 30.5, 28.3, 20.7, 20.3, 19.3, 19.3
13a (n = 2)	58.6, 53.8, 40.7	**3a** (n = 2)	62.4, 51.5, 49.3
		4a (n = 2)	60.1, 45.5, 45.0

Table II. ^{195}Pt NMR Chemical Shifts (±10 ppm) and Line Widths at Half-Peak Height (±5%) for Representative Complexes with Chemical Shifts Relative to the High-Frequency Reference $PtCl_6^{2-}$

compound	$\delta(^{195}Pt)$ (ppm)	line width (Hz)	compound	$\delta(^{195}Pt)$ (ppm)	line width (Hz)
K_2PtCl_6[19]	0	<25	**1c**	−3011	556
K_2PtCl_4[68]	−1631	–	**1d**	−2893	582
cis-DDP[67]	−2048	200	**3a** (n = 3)	−3059	478
1a	−3140	589	***S*-3b** (n = 3)	−2964	479
***S*-1b**	−3123	688			

Table III. Absorption and Circular Dichroism Data for the Chiral Metal Complexes

	UV		CD band 1		CD band 2	
complex	λ_{max} (nm)	ϵ_{max} (cm^{-1} M^{-1})	λ_{max} (nm)	$\Delta\epsilon$ (cm^{-1} M^{-1})	λ_{max} (nm)	$\Delta\epsilon$ (cm^{-1} M^{-1})
***S*-1b**[a]	300	858	375	+0.02	305	−0.07
***R*-1b**[a]			385	−0.01	315	+0.09
***S*-2b**[b]	331	338	342	+0.19	304	−0.08
***R*-2b**[b]			344	−0.18	305	+0.09
***S*-3b** (n = 3)[c]	302	1303	377	−0.48	308	−0.17
***R*-3b** (n = 3)[c]			377	+0.49	308	+0.17
***S*-3b** (n = 9)[c]	300	1716	374	−0.45	308	−0.24
***R*-3b** (n = 9)[c]			373	+0.45	313	+0.26

[a] Conducted in 20% DMF/H_2O, spectra had low signal to noise and were not mirror images of each other. [b] Conducted in H_2O. [c] Conducted in 8.7% DMF/H_2O.

is by comparison much less sterically demanding.[31-33] That alkyl substitution of a dien ligand can influence the rate of substitution at Pt(II) and Pd(II) has already been demonstrated.[18] It was found that *N*,*N*-dimethyl substitution of the terminal nitrogens of $[M(dien)Cl]^+$ led to a substantial decrease in the rate of substition by pyridine. With this in mind, a set of alkyl-substituted derivatives of [(dien)Pt(II)I]I were selected for study. The *N*-tetramethyl derivative **1d** was chosen to be an example of a highly hindered complex and the tetramethyl derivative **1c**,[34] as a less hindered analog.

The enantiomeric diisopropyl derivatives *S*- and *R*-**1b** were chosen to examine the extent to which chirality could play a role in discriminating between different DNA conformations. That enantioselective binding of small molecules could be achieved was first demonstrated by Gabbay utilizing chiral organic intercalators.[35,36] Barton later demonstrated that chiral tris(phenanthroline)ruthenium(II)$^{2+}$ derivatives also show such behavior[37] leading to the development of a series of DNA conformation probes.[38] In the area of covalent binders it was demonstrated that the (+) enantiomer of a racemic mixture of *anti*-benzo[*a*]-pyrenediol epoxides binds selectively to DNA.[39] In contrast, enantioselective binding of a series of chiral derivatives of (ethylenediamine)$PtCl_2$ was never observed.[40] That a metal complex could bind in an enantioselective manner was later achieved with a bis(phenanthroline)dichlororuthenium(II) complex.[41] In order to best insure that enantioselective binding would be achieved in the [(dien)Pt(II)I] system isopropyl substituents were chosen because they are one of the bulkiest side chains of the common amino acids from which we planned to synthesize the ligands.

The bis([(dien)Pt(II)I]I) complexes **3** were chosen based on the fact that the tether would limit the reach of the two platinum centers and hence the types of sequences or structures which could be cross-linked. That a bis([(dien)Pt(II)X]X) complex is indeed able to cross-link DNA was first established by Vlassov and co-workers.[6] They showed that the heterobifunctional reagent $[BrPt(dien)(CH_2)_6(dien)Pt(H_2O)](NO_3)_3$ could be monofunctionally bound to a short oligonucleotide and then sequence-specifically cross-linked to a complementary oligonucleotide, a process they termed complementary-addressed modification.[6,42] In spite of this interesting result, no cross-linking studies of their complex with native duplex DNA were ever reported, nor was the synthesis of other cross-linkers in this series with different length linkers or substituents. We therefore decided to synthesize the series of bis([(dien)Pt(II)I]I) complexes **3a** (n = 2–9) in order to determine the effect of linker length on the conformation and structure specificity of interstrand cross-linking. Enantiomeric bis([(diisopropyldien)Pt(II)I]I) complexes *S*- and *R*-**3a** (n = 3, 9) were selected to determine the extent to which binding selectivity observed for the corresponding [(diisopropyldien)Pt(II)I]I complexes would be enhanced upon dimerization with either a short or long length linker.

Synthesis of the Dien Derivatives. The route used for the preparation of the dien derivatives was similar to that previously used for the synthesis of hexaamine macrocycles.[22] The general idea was to assemble a ligand in a convergent fashion by C–N bond formation via nucleophilic displacements at the ring carbon of *N*-tosylaziridine **8** (Scheme I). As expected, the major products resulted from S_N2 attack at the less hindered site;[24,43] however, formation of minor isomers were observed in the synthesis of **9c** and **10c**, presumably the result of S_N1 attack at the more hindered position of aziridine **8c**. Whereas the coupling steps could be achieved in high yields, it took a long time to find a suitable method for removing the tosyl groups in high yield, a problem which was compounded by the fact that two such groups had to be removed to yield the free amine. Methods employing 48% HBr/phenol,[44] concentrated H_2SO_4,[30,45] 40% H_2SO_4/AcOH,[46] and sodium bis(2-methoxyethoxy)aluminum hydride (SMAH)[47] resulted in either a complex mixture or no reaction.

Detosylation with sodium/naphthalene in dimethoxyethane according to the procedure of Closson and co-workers[25] was at first unsuccessful, leading to what appeared to be a cyclic aminal of acetaldehyde and the dien derivative. Presumably methyl vinyl ether, which is known to form slowly by reaction of sodium naphthalenide with dimethoxyethane,[48] was hydrolyzed upon addition

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of 6 N HCl to the reaction mixture during workup, generating acetaldehyde in the presence of free amine. When the reaction was instead quenched by pouring it into an ice-chilled 6 N HCl solution, the free amine was immediately converted to its hydrochloride salt, and no evidence of aminal formation was detected. However, even with this modification, the dien derivatives were isolated in low to moderate yields (40%–60%) and were still contaminated with unidentifiable impurities, despite changes in temperature, solvent, and reducing agent.

Removal of the tosyl groups was finally achieved in high yield by modifying the sodium/liquid ammonia conditions reported by du Vigneaud.[23] The original procedure failed to give clean deprotection of the series of di- and tetrasulfonamides possibly due to competitive deprotonation of the sulfonamides during the course of the reaction. However, when the reaction was performed in the presence of the proton source ethanol, clean detosylation was observed in every case. Furthermore, cooling the reaction mixture to −78 °C led to isolated yields of 90–95%.

Synthesis of the Bis(dien) Ligands and Derivatives. The first member of the bis(dien) class of amine ligands was synthesized by Schwarzenbach who reacted ethylenediamine with *N*-tosylaziridine, **8a**, to give the tetrasulfonamide **12a** ($n = 2$) which was then detosylated with concentrated H_2SO_4 to give the hexaamine **13a** ($n = 2$) in unreported yield.[30] Since then bis(dien) ligands with three- and four-methylene linkers have been similarly prepared.[49] The bis(dien) ligand with a six-methylene linker was synthesized by Vlassov via an alternate route involving Hoffmann degradation of the tetraamide intermediate obtained from the Michael reaction of 1,6-diaminohexane with acrylamide. By choosing the aziridine route (Scheme II) and utilizing the sodium/liquid ammonia/ethanol procedure in place of sulfuric acid for detosylation, we were able to prepare the bis(dien) ligands **13a** ($n = 2$–9) and the bis(diisopropyldien) ligands *R*- and *S*-**13b** ($n = 3, 9$) in high overall yield, a substantial improvement over the other described procedures.

Initial Attempts at the Preparation of the Pt(II) Complexes. With the synthesis of the ligands in hand, it was initially envisioned that the Pt(II) complexes would be readily prepared by the procedure developed by Watt and Cude for the high yield synthesis of [Pt(dien)I]I, **1a**.[50] This method was reproducible and proceeded in comparable yield in our hands. However, the reaction with the dien and bis(dien) derivatives proceeded in low yields (<20%) and large amounts of unreacted PtI_2 were recovered. Furthermore, C and H analysis revealed that the isolated complexes were not pure and were probably contaminated with unreacted PtI_2. Other methods[51,52] were investigated but yielded oily mixtures. Recently Lippard and co-workers have recounted similar problems in attempts to form Pt(II) complexes derived from substituted 1,2-diaminoethanes using standard procedures due to the precipitation of the intermediate $[PtI_4]^{2-}$ salts.[53] However the addition of DMF as a cosolvent improved the solubility of the reactants and the reaction proceeded smoothly and in high yield.

We reasoned that the failure of the Watt and Cude method for the dien derivatives was most likely due to the poor solubility of these ligands in the water which was used as solvent. We therefore examined the reaction in various polar organic solvents such as acetonitrile, DMSO, and DMF. The reaction in DMSO was particularly interesting. PtI_2 dissolved on slight heating in DMSO to give a deep red solution which when followed by a solution of dien in DMSO immediately turned light green. The sample was concentrated and treated with anhydrous ether whereupon a light brown solid precipitated. The complex was assigned as the DMSO solvolysis product of **1a**, i.e. $[Pt(dien)(DMSO)]I_2$, based on its proton-decoupled ^{13}C NMR spectrum which showed two resonances corresponding to dien and a third corresponding to coordinated DMSO.

Isolation and Characterization of *trans*-$Pt(DMSO)_2I_2$. In order to avoid the formation of DMSO adducts of the Pt(II) complexes attempts were made to isolate the presumed intermediate DMSO complex of PtI_2. It was found that the an orange solid precipitated upon addition of anhydrous ether to the DMSO solution of the PtI_2. Elemental analysis (C H,I) data were consistent with an empirical formula of $Pt(DMSO)_2I_2$. Interestingly, an unsuccessful attempt to prepare $Pt(DMSO)_2I_2$ by reaction of DMSO with aqueous K_2PtI_4 has been reported.[54] Evidence for sulfur coordination comes from the IR bands at 734 and 682 cm^{-1}. These may be assigned to the asymmetric C–S and symmetric C–S stretching frequencies respectively, similar to the sulfur-bonded *cis*-$Pt(DMSO)_2Cl_2$ and *trans*-$Pd(DMSO)_2Cl_2$.[55] If $Pt(DMSO)_2Cl_2$ were an oxygen-bonded complex, the C–S stretching bands would have appeared much weaker (the symmetric stretch is often not observed) and at lower frequencies.[56]

The S–O stretching frequency can provide evidence for the geometric configuration of a square-planar complex. On the basis of symmetry considerations, a cis configuration would give rise to a doublet for the S–O absorption band, whereas a trans isomer would give single IR active S–O peak. The single unsplit S–O stretching frequency at 1121 cm^{-1} suggests a trans assignment of ligands about the platinum(II) center. Since the platinum complexes were eventually prepared in DMF from the precipitated $Pt(DMSO)_2I_2$ complex, the NMR spectrum of the complex was obtained in DMF-d_7 in an attempt to probe its solution state structure. The major peak in both the ^1H and ^{13}C NMR corresponded to uncomplexed DMSO indicating that the complex underwent almost complete solvolysis in DMF. Other minor DMSO-related peaks were also present, suggesting that a complex mixture of species was formed. Four sharp signals appeared in the ^{195}Pt NMR spectrum; the two central peaks being of similar intensity and more intense than the outer two peaks. By comparison, *cis*-$Pt(DMSO)_2Cl_2$ and *cis*-$Pt(DMSO)_2Br_2$ in DMF-d_7 have single ^{195}Pt NMR resonances at −3459 and −3778 ppm relative to K_2PtCl_6. The multiple resonances present in the solution of the iodide complex may be due to different species resulting from ligand exchange[55] or from cis–trans isomerization via bridging iodides or DMSO.[57]

Preparation of the Metal Complexes via $M(DMSO)_2X_2$. The use of *trans*-$Pt(DMSO)_2I_2$ for the preparation of the Pt(II) complexes was first examined for dien. DMF was chosen as the reaction solvent as it was highly polar and aprotic and was expected to be poorly coordinating for the Pt(II) complexes. ^1H NMR spectroscopy indicated that the reaction was over in minutes and both ^{13}C and ^1H NMR spectroscopies indicated that the DMSO ligands had undergone complete solvolysis. Isolation and characterization of the product showed that it was the desired platinum complex **1a**. Reaction with the other dien and bis(dien) derivatives afforded the desired platinum complexes without exception and in excellent yields. When the isolated complexes were examined by ^{13}C NMR in neat DMSO, a substantial amount of platinum-bound DMSO was observed. Not unexpectedly, the *N*-tetramethyldien complex **1d**, the most sterically hindered of the series, was the only Pt(II) complex which did not undergo detectable solvolysis in neat DMSO.

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Attempts to prepare [Pt(dien)Cl]Cl by the reaction of dien with *cis*-$Pt(DMSO)_2Cl_2$ in DMF were unsuccessful. However, when the reaction was performed in DMSO, NMR indicated that a mixture of [Pt(dien)Cl]Cl and $[Pt(dien)(DMSO)]Cl_2$ was formed. The incomplete solvolysis of the chloro complex in DMSO is in accord with the lower lability of the Pt–Cl bond relative to the Pt–I bond which is readily replaced by polar aprotic solvents such as DMSO.[58] This method for the preparation of the Pt(II) complexes was not considered practical since it was not possible to completely remove the DMSO. The successful use of the DMSO complex of PtI_2 in the preparation of the Pt(II) complexes suggested that the Pd(II) complexes might be prepared in a similar manner. There is no report in the literature of $Pd(DMSO)_2I_2$, but the dichloride, *trans*-$Pd(DMSO)_2Cl_2$, is known.[26,27] When the reaction was performed in DMF with the appropriate ligands, the Pd(II) complexes **2a**, *S*-**2b**, *R*-**2b**, and **4a** ($n = 6$) were isolated in excellent yields (85–90%).

^{13}C NMR Spectra of the Metal Complexes. The metal complexes can be viewed as being formed from two fused five-membered rings in which the metal possess square planar geometry as found in crystal structures of similar complexes.[59,60] The nitrogen atoms in the complexes are tetrahedral as they are in the free amines, but the rates for the hydrogen exchange reactions of the N–H bonds and inversion of the secondary and tertiary nitrogen centers are slower.[61] This is also true for the case of nitrogen centers in Pd(II) complexes.[62] Since the ^{13}C NMR spectra of the Pt(II) and Pd(II) complexes were recorded in the absence of base, the rate of inversion of the center nitrogen atom in the chelated ligand is negligible. This accounts for the lower point group symmetry and the observed magnetic nonequivalence of certain alkyl substituents upon complexation. For example, tetramethyldien **11c** possesses three ^{13}C NMR signals; however, coordination of the nitrogens to Pt(II) to form **1c** results in four ^{13}C NMR signals. The achiral dien and bis(dien) derivatives possess C_{2v} symmetry, and this is borne out in the ^{13}C NMR spectra. However upon metal complexation, the symmetry is reduced to C_s with a mirror plane passing through the coordinated halide, metal center, and the central nitrogen of the ligand. This is not true of course for the chiral complexes, which possess C_i symmetry and exhibit a unique ^{13}C NMR resonance for each carbon.

In Table I are listed the ^{13}C NMR chemical shifts for a selected number of dien and bis(dien) derivatives and their changes upon complexation to Pt(II). The methylene carbons α to coordinated nitrogen atoms appear 3–15 ppm downfield relative to the free ligand. This is consistent with the 2–10 ppm downfield shift of ^{13}C resonances in substituted 1,2-diaminoethanes due to Pt(II) binding reported by Reilley and co-workers.[63] The shift can be attributed in part to electron withdrawal of the amine lone pair upon coordination with the metal center or to effects due to changes in the conformation of the ligand upon chelation.[63] Alkyl substituents also shift the carbon resonances downfield.

^1H NMR Spectra of the Metal Complexes. Several interesting features were observed in the 1D ^1H NMR spectra. The amino protons of the free ligands which appear upfield at 1.5–0.9 ppm (C_6D_6) as broad singlets move downfield to 5.0–7.0 ppm (DMF-d_7) and become resolvable upon coordination of the ligands to platinum. The axial secondary amino proton in the mononuclear complexes appears the farthest downfield at ≈6.5 ppm. This is perhaps related to the greater acidity of the N–H group trans to the halide, which results from more effective delocalization of the 2p amido electrons by π bonding to the vacant Pt 6p or Pd 4p orbital upon deprotonation.[64]

The terminal amino protons appear as two sets of multiplets in the achiral metal complexes and can be attributed to a pair of pseudoaxial and pseudoequatorial hydrogens. This is also the case for the tetramethyldien complex **1c**. The methyl signals of both tetramethyldien complexes **1c** and **1d** both appear as a pair of resonances, each corresponding to a pair of pseudoaxial and pseudoequatorial methyl groups. The chiral diisopropyldien complexes **1b** on the other hand, exhibit five separate amino proton ^1H NMR resonances, a result of the absence of any symmetry elements. Also consistent with a lack of symmetry is the fact that the methyl signals appear as four unique doublets, whereas in the free ligands only a pair of doublets is observed, reflecting the diastereotopic nature of these methyls. Four methyl signals were also observed in the case of the chiral Pd(II) complexes. Interestingly, one methyl group always appears to be downfield by about 0.1 ppm relative to the three other methyl groups.

^{195}Pt NMR Spectroscopy of the Metal Complexes. In addition all the platinum complexes were characterized by ^{195}Pt NMR spectroscopy.[65–67] The short T_1 values of ^{195}Pt in these complexes allowed for rapid data acquisition, and typically 30 000 transients were collected in a matter of 10–15 min. ^{195}Pt shifts can be quite sensitive to small changes in the ligand environment around the Pt(II) center (Table II). However, as the ligand becomes more sterically congested near the platinum metal center, there is a pronounced downfield shift of the ^{195}Pt signal. This trend is nicely illustrated in the series of [(dien)Pt(II)I]I derivatives. As the substitution pattern changes from diisopropyl, to tetramethyl, to *N*-tetramethyl, downfield shifts of 18, 129, and 246 ppm are observed relative to the unsubstituted complex. Similar downfield shifts were observed by others for *trans*-$[PtCl_2(amine)(C_2H_4)]$[68] and *trans*-$[PtCl_2(pyridine)(C_2H_4)]$.[69] When the steric bulk increased within a series of *N*-alkyl-substituted amines and 2,6-disubstituted pyridines, downfield shifts on the order of 40[68] and 102 ppm[69] were observed. In the bis([(dien)Pt(II)I]I) complexes, addition of the alkyl chain tether leads to a relatively chain-length-insensitive downfield shift of 80 ppm relative to the parent [(dien)Pt(II)I]I complex. Also in the series of bis([(dien)-Pt(II)I]I) complexes it was found that disubstitution of the dien subunit with isopropyl groups led to an additional 100 ppm downfield shift. This is almost 80 ppm greater than that seen when [(dien)Pt(II)I]I is similarly substituted, possibly a result of the greater crowding introduced by having the tether present.

Electronic and Circular Dichroism Spectroscopy of the Metal Complexes. The complexes exhibit a single absorption band of intermediate intensity (ϵ in the 300–2000 cm^{-1} M^{-1} range) in the 280–340-nm region (Table III). This is indicative of the expected square planar coordination and not trigonal bipyramidal (five) coordination since there are no bands above 370 nm.[70] This is what would be expected since simple alkyl substituents on the dien ligand would probably exhibit little effect on the splitting of the metal d-orbitals.[70,71] It is also interesting to note that the molar ellipticity of the long wavelength CD band of the [(diisopropyldien)Pt(II)I]I complexes changes sign and increases in magnitude on going to the bis([(diisopropyldien)Pt(II)I]I)

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complexes, possibly due to the steric influence of the alkyl tether on the conformation of the ring.

Conclusion

We have described the synthesis of a variety of achiral and chiral alkyl-substituted mono- and bis[(dien)Pt(II)I]I complexes for study as potential nucleic acid conformation and structure probes.[72] As a result of this work we have developed a general method for the preparation of Pt(II) complexes of dien derivatives in essentially quantitative yield via the isolable $Pt(DMSO)_2I_2$ complex. This is the best method that we are aware of for such a purpose and may be generally useful for the preparation of Pt(II) complexes of a wide variety of ligands. In addition, the procedures we have developed for the synthesis of unsubstituted and alkyl-substituted mono- and bis(dien) ligands via coupling of amines with tosylaziridines are superior to those previously described and may be useful for the synthesis of polyamine ligands in general. In particular, the demonstration that chirally-substituted tosylaziridines can be readily obtained from optically active amino acids and used to construct chiral dien and bis(dien) derivatives could find general application to the synthesis of chiral ligands and auxiliaries.

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(72) We have determined the interstrand crosslinking efficiencies for the bis([(dien)Pt(II)I]I) complexes **3a** (n = 2–9)[73] and **3b** (n = 3, 9) and we will report the complete details in due course.

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