Inorg. Chem. **2005**, *44*, 6401–6408

(2,2′:6′,2″-Terpyridine)platinum(II) Complexes Containing (Thioalkyl)dicarba-*closo*-dodecaborane(12) Ligands

Jean A. Todd,[†] Peter Turner,[‡] Erin J. Ziolkowski,[‡] and Louis M. Rendina*[,‡]

School of Chemistry, The University of Sydney, Sydney, NSW 2006, Australia, and School of Chemistry and Physics, The University of Adelaide, Adelaide, South Australia 5005, Australia

Received February 21, 2005

A series of novel platinum(II)–2,2′:6′,2″-terpyridine (trpy) complexes containing (thioalkyl)dicarba-*closo*-dodecaborane(12) (*closo*-carborane) derivatives were prepared by treatment of the labile precursor species [Pt(MeCN)(trpy)](OTf)$_2$ with R(CH$_2$)$_n$SH (R = *closo*-1,2-carborane, n = 0–3; R = *closo*-1,7-carborane, n = 1; R = *closo*-1,12-carborane, n = 1) in the presence of NEt$_3$ to afford brightly colored complexes of the type [PtS(CH$_2$)$_n$R(trpy)]OTf. All products were characterized by means of multinuclear (^{1}H, ^{13}C, ^{11}B, and ^{195}Pt) 1D- and 2D-NMR spectroscopy, ESI-MS, and, for the 1,7-carborane derivative, X-ray crystallography. Preliminary in vitro cytotoxicity studies of selected complexes against human ovarian carcinoma cells are also reported.

Introduction

^{10}B-containing compounds that have the capacity to target DNA are potentially useful agents in the treatment of cancer by means of boron neutron capture therapy (BNCT),[1,2] and numerous classes of compound have been identified. We recently reported a new class of DNA-binding agents that incorporated both platinum and a boron-rich carborane entity, the first examples of platinum(II)−amine complexes containing boron.[3,4] As well as the potential for additive or perhaps synergistic biological effects associated with the DNA-binding reactions of the Pt−B agent coupled with the neutron capture reactions of the ^{10}B nucleus, there is an additional advantage that such agents can be radiolabeled by the use of isotopes such as ^{195m}Pt which would allow their tumor uptake and biodistribution characteristics to be monitored by means of γ imaging following administration into the body ($t_{1/2}$ = 4 d).[5]

DNA metallointercalators are the subject of current research interest,[6] and complexes such as those of platinum(II)−trpy (trpy = 2,2′:6′,2″-terpyridine) possess interesting biological activities which may eventually lead to their exploitation as potential antiprotozoal agents[7] and anticancer drugs.[8,9] Complexes of the type [PtL(trpy)]$^{n+}$ (e.g., L = Cl, 2-hydroxyethanethiolate (het), Me (n = 1); L = 4-picoline (n = 2)) are capable of binding strongly to DNA by intercalation and competitively inhibiting the binding of the well-known intercalator ethidium bromide to DNA.[10−13] While [PtCl(trpy)]$^+$ intercalates and, through the loss of the chloro ligand, also covalently binds to DNA,[12] complexes such as [Pt(het)(trpy)]$^+$ interact predominantly by intercalation, as covalent binding is negligible due to the inert character of the Pt−S bond.[13] Recent work reported by our group included the development of a series (thioalkyl)-*closo*-carborane ligands and their corresponding cationic platinum(II)−trpy complexes, some of which have the capacity to bind to calf-

* To whom correspondence should be addressed. E-mail: rendina@chem.usyd.edu.au. Telephone: 61 2 9351 4781. Fax: 61 2 9351 3329.
[†] The University of Adelaide.
[‡] The University of Sydney.

(1) Hawthorne, M. F.; Lee, M. W. *J. Neuro-Oncol.* **2003**, *62*, 33−45.
(2) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F. G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515−1562.
(3) Woodhouse, S. L.; Rendina, L. M. *Chem. Commun*. **2001**, 2464−2465.
(4) Woodhouse, S. L.; Rendina, L. M. *Dalton Trans*. **2004**, 3669−3677.
(5) Dowell, J. A.; Sancho, A. R.; Anand, D.; Wolf, W. *Adv. Drug Delivery Rev*. **2000**, *41*, 111−126.
(6) Erkkila, K. E.; Odom, D. T.; Barton, J. K. *Chem. Rev*. **1999**, *99*, 2777−2795.
(7) Lowe, G.; Droz, A. S.; Vilaivan, T.; Weaver, G. W.; Tweedale, L.; Pratt, J. M.; Rock, P.; Yardley, V.; Croft, S. L. *J. Med. Chem.* **1999**, *42*, 999−1006.
(8) McFadyen, W. D.; Wakelin, L. P. G.; Roos, I. A. G.; Hillcoat, B. L. *Biochem. J.* **1986**, *238*, 757−763.
(9) Lowe, G.; Droz, A. S.; Vilaivan, T.; Weaver, G. W.; Park, J. J.; Pratt, J. M.; Tweedale, L.; Kelland, L. R., *J. Med. Chem*. **1999**, *42*, 3167−3174.
(10) Arena, G.; Monsu Scolaro L.; Pasternack, R. F.; Romeo, R. *Inorg. Chem*. **1995**, *34*, 2994.
(11) McCoubrey, A.; Latham, H. C.; Cook, P. R.; Rodger, A.; Lowe, G. *FEBS Lett.* **1996**, *380*, 73−78.
(12) Howe-Grant, M.; Wu, K. C.; Bauer, W. R.; Lippard, S. J. *Biochemistry* **1976**, *15*, 4339−4346.
(13) Jennette, K. W.; Lippard, S. J.; Vassiliades, G. A.; Bauer, W. R. *Proc. Nat. Acad. Sci. U.S.A.* **1974**, *71*, 3839−3843.

10.1021/ic050265k CCC: $30.25
Published on Web 08/09/2005

thymus DNA presumably by intercalation of the Pt(trpy) unit.[14] It was the purpose of this research to extend this series to other mononuclear platinum(II)−trpy complexes incorporating (thioalkyl)-*closo*-carborane ligands and to examine the cytotoxicity of selected complexes against tumor cells in vitro. A preliminary communication of this work was reported recently.[14]

Experimental Section

General Synthetic and Analytical Methods. All reactions were performed under an inert atmosphere of dry N_2 utilizing standard Schlenk techniques. All reaction solvents were dried and distilled prior to use. Diethyl ether, dimethoxyethane (DME), and tetrahydrofuran (THF) were dried by distillation from sodium benzophenone ketyl. Toluene and benzene was predried with anhydrous $CaSO_4$, followed by distillation from sodium. CH_2Cl_2 and *n*-hexane were dried by distillation from CaH_2. *N*,*N*-dimethylformamide (DMF) was predried with $MgSO_4$ and anhydrous $CuSO_4$, followed by distillation at reduced pressure.

^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer or a Bruker DPX300 with Oxford 300 MHz magnet at 298 K, except where otherwise indicated. The 200 MHz ^1H NMR spectra were recorded on a Varian Gemini 200 instrument. $^{11}B\{^1H\}$ and $^{195}Pt\{^1H\}$ NMR were recorded on a Bruker DPX400 NMR spectrometer. 2-D NMR spectroscopy experiments were performed on a Bruker Avance DRX 400 MHz NMR instrument. All chemical shifts are reported in ppm, and coupling constants are reported in Hz. ^1H and $^{13}C\{^1H\}$ NMR chemical shifts are relative to tetramethylsilane (TMS). $^{195}Pt\{^1H\}$ and $^{11}B\{^1H\}$ NMR chemical shifts were referenced relative to a sealed external standard of 0.1 M $Na_2[PtCl_6]$ in D_2O and $BF_3{\cdot}OEt_2$, respectively (δ 0.00).

Melting points (uncorrected) were determined using a Kofler hotstage apparatus equipped with a Reichert microscope. Elemental analyses were performed by CMAS (Chemical and Microanalytical Services Pty. Ltd.), Belmont, Victoria, Australia. Electrospray ionization mass spectra (ESI-MS) were obtained by means of a Finnegan LCQ mass spectrometer equipped with Finnegan data processing software, using HPLC grade methanol or 5% DMF/methanol.

Thin layer chromatography (TLC) was performed on Merck DC-Alufolien Kieselgel 60 F_{254} sheets. Visualization of plates was achieved using 254 nm UV light or by staining with either I_2 vapor or a $KMnO_4$ dip solution, followed by heating. Squat and flash column chromatography were performed on Merck Kieselgel 60 (230−400 mesh ATSM) silica gel.

Materials and Methods. $[Pt(MeCN)(trpy)](OTf)_2$,[15] $[PtCl(trpy)]Cl{\cdot}2H_2O$,[16] 1-thiol-1,2-carborane (**18**),[17] 1-(benzylthio)-3-bromoethane (**6**),[18] 1-(benzylthio)-3-bromopropane (**7**),[19] and 1-(thiomethyl)-1,12-carborane (**19**)[20] were prepared according to the literature procedures. 1,2-, 1,7-, and 1,12-carborane were obtained from Katchem (Prauge, Czech Republic) and used without further purification. *nido*-Decaborane was obtained from Strem Chemicals (Newburyport, US), and it was freshly sublimed in vacuo prior to use.

Preparation of Compounds. 1-(Methanedithiolate)-1,7-carborane (1). This preparation was adapted from a related procedure reported by Nachman et al.[20] To a stirred solution of 1,7-carborane (780 mg, 5.40 mmol) in THF (10 mL) at −10 °C was added ^{n}BuLi (3.2 mL, 1.6 M in hexane, 5.12 mmol) dropwise. The reaction mixture was stirred for 1.5 h before a solution of CuBr (149 mg, 1.28 mmol) and LiBr (183 mg, 1.72 mmol) in THF (20 mL) was slowly added. The yellow solution was stirred for 15 min at −10 °C, and then the temperature was reduced to −15 °C and CS_2 (0.4 mL, 6.63 mmol) was added dropwise. The red solution was then allowed to warm to −10 °C. After the solution was stirred for 1.5 h, MeI (0.35 mL, 5.62 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for a further 1.5 h. After workup with KCN (310 mg, 4.76 mmol) and water (10 mL), the solution was extracted with diethyl ether (4 × 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo to give the crude product as yellow crystals. After flash column chromatography (*n*-hexane, $R_f = 0.52$), **1** was obtained as bright-orange crystals (710 mg, 59%). Mp: 51.5−53.5 °C. ^1H NMR (300.13 MHz, $CDCl_3$): δ 3.04 (br, 1H, $C_{cage}H$), 2.58 (s, 3H, SMe). $^{13}C\{^1H\}$ NMR (74.48 MHz, $CDCl_3$): δ 220 ($C_{cage}CSSCH_3$), 54.4 ($C_{cage}H$), 22.8 (SMe), $C_{cage}CSS$ was not observed. $^{11}B\{^1H\}$ NMR (400.21 MHz, $CDCl_3$): δ −4.3 (1B), −7.4 (1B), −10.9 (4B), −13.3 (2B), −16.9 (2B). ESI-MS: *m*/*z* 187.0 ($1,7\text{-}B_{10}C_2H_{11}CS^+$, 100%), 219.0 ($1,7\text{-}B_{10}C_2H_{11}CSS^+$, 42%), 234.9 ($M^+$, 24%).

1-(Thiomethyl)-1,7-carborane (2). This preparation was adapted from a related procedure reported by Nachman et al.[20] To a stirred solution of **1** (310 mg, 1.28 mmol) in toluene (10 mL) was added a solution of 2 M $BH_3{\cdot}SMe_2$ in THF (0.85 mL, 1.7 mmol). The resulting solution was refluxed under an inert atmosphere for 5 h, after which time the orange solution became colorless. When the solution had cooled to room temperature, an excess of concentrated HCl was added (8 mL, 32%) and the mixture was stirred at reflux for 16 h. After cooling, the layers were separated and the aqueous layer was extracted with *n*-hexane (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the crude material was purified by flash column chromatography (*n*-hexane, $R_f = 0.44$) to give **2** as a colorless, low-melting solid (42 mg, 40%). Mp: 25−27 °C. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.95 (br, 1H, $C_{cage}H$), 3.15 (d, $^3J_{HH} = 9.0$ Hz, 2H, CH_2SH), 1.82 (t, $^3J_{HH} = 8.5$ Hz, 1H, SH). $^{13}C\{^1H\}$ NMR (74.48 MHz, $CDCl_3$): δ 55.3 ($C_{cage}H$), 31.0 (CH_2SH); $C_{cage}CH_2$ not observed. $^{11}B\{^1H\}$ NMR (400.12 MHz, $CDCl_3$): δ −3.8 (1B), −9.6 (1B), −10.8 (4B), −13.4 (2B), −15.5 (2B). ESI-MS: *m*/*z* 189.0 ($[M - H]^+$, 100%).

1-(Benzylthio)-2-propyne (3). Sodium (2.50 g, 109 mmol) was dissolved in absolute EtOH (100 mL), and the resulting solution was stirred for 30 min at room temperature. The temperature was then lowered to 0 °C, and benzyl mercaptan (1 mL, 8.48 mmol) was added dropwise to the solution. After stirring of the mixture for 30 min at this temperature, propargyl bromide (8 mL, 85.0 mmol) was added slowly. The solution was then allowed to return to room temperature and stirred for a further 3 h. The reaction was quenched by pouring the cloudy yellow solution into a solution of 2 M HCl (100 mL), and the mixture was extracted with *n*-pentane (4 × 20 mL). The organic extracts were washed with a saturated solution of $NaHCO_3$ (4 × 20 mL) and dried over anhydrous Na_2SO_4. The crude yellow oil was purified by column chromatography (*n*-hexane, $R_f = 0.19$) to give **3** as a yellow oil (1.08 g, 78%). ^1H

(14) Todd, J. A.; Rendina, L. M. *Inorg. Chem.* **2002**, *41*, 3331−3333.
(15) Büchner, R.; Field, J. S.; Haines, R. J.; Cunningham, C. T.; McMillin, D. R. *Inorg. Chem.* **1997**, *36*, 3952−3956.
(16) Howe-Grant, M.; Lippard, S. J. *Inorg. Synth.* **1980**, *20*, 101−105.
(17) Vinas, C.; Benakki, R.; Teixidor, F.; Casabo, J. *Inorg. Chem.* **1995**, *34*, 3844−3845.
(18) Trujillo, D. A.; McMahon, W. A., Jr.; Lyle, R. E. *J. Org. Chem.* **1987**, *52*, 2932−2933.
(19) Palmer, D. C.; Taylor, E. C. *J. Org. Chem.* **1986**, *51*, 846−850.
(20) Ujvary, I.; Nachman, R. J. *Tetrahedron Lett.* **1999**, *40*, 5147−5149.

NMR (300.13 MHz, $CDCl_3$): δ 7.35−7.23 (m, 5H, Ph), 3.87 (s, 2H, $PhCH_2$), 3.08 (d, $^4J_{HH}$ = 2.4 Hz, 2H, SCH_2), 2.29 (t, $^4J_{HH}$ = 2.4 Hz, 1H, C≡CH). $^{13}C\{^1H\}$ NMR (74.48 MHz, $CDCl_3$): δ 137.5 (Ph), 129.0 (Ph), 128.6 (Ph), 127.2 (Ph), 79.9 (*C*≡CH), 71.3 (C≡*C*H), 35.3 ($PhCH_2S$), 22.7 (SCH_2C≡CH).

1-((Benzylthio)methyl)-1,2-carborane (4). A mixture of *nido*-decaborane (769 mg, 6.29 mmol), **3** (978 mg, 6.15 mmol), and MeCN (5 mL, 66 mmol) in toluene (30 mL) was refluxed for 24 h. After cooling the red solution to room temperature, the solvents were reduced in vacuo, and the yellow viscous oil was dissolved in MeOH (15 mL) and left to stand for 18 h at room temperature. After the solvent was removed in vacuo, **4** was obtained as a golden oil (1.65 g, 95%). ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.38−7.27 (m, 5H, Ph), 3.90 (br, 1H, $C_{cage}H$), 3.75 (s, 2H, SCH_2Ph), 3.16 (s, 2H, $C_{cage}CH_2S$). $^{13}C\{^1H\}$ NMR (74.48 MHz, $CDCl_3$): δ 136.4 (Ph), 128.9 (Ph), 128.7 (Ph), 127.8 (Ph), 74.4 ($C_{cage}C$), 59.5 ($C_{cage}H$), 37.4 (SCH_2Ph), 36.9 ($C_{cage}CH_2S$). $^{11}B\{^1H\}$ NMR (400.21 MHz, $CDCl_3$): δ −2.4 (2B), −5.4 (2B), −8.96 (1B), −10.8 (1B), −13.1 (4B).

1-(Thiomethyl)-1,2-carborane (5). A suspension of freshly sublimed $AlCl_3$ (2.6 g, 19.5 mmol) in benzene (30 mL) was stirred at 50 °C for 30 min, after which time the $AlCl_3$ had completely dissolved. A solution of **4** (1.11 g, 3.95 mmol) in benzene (20 mL) was then added dropwise. The reaction mixture was stirred at 50 °C for 24 h, by which time it had become red. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (20 mL). A saturated solution of potassium sodium tartrate (20 mL) was added to the solution and stirred for 30 min. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL), and the combined organic layers were washed with brine (3 × 8 mL). The crude yellow oil was purified by flash column chromatography (10% ethyl acetate/*n*-hexane, R_f = 0.28) to yield **5** as a yellow, low-melting solid (252 mg, 33%). Mp: 44−45 °C. ^1H NMR (300.13 MHz, $CDCl_3$): δ 4.12 (br, 1H, $C_{cage}H$), 3.29 (d, $^3J_{HH}$ = 9 Hz, 2H, $C_{cage}CH_2$), 1.87 (t, $^3J_{HH}$ = 9 Hz, 1H, SH). $^{13}C\{^1H\}$ NMR (74.48 MHz, $CDCl_3$): δ 75.1 ($C_{cage}C$), 59.7 ($C_{cage}H$), 31.7 (CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 74.1 ($C_{cage}C$), 69.8 ($C_{cage}H$), 59.8 (CH_2SH). $^{11}B\{^1H\}$ NMR (400.21 MHz, $CDCl_3$): δ −2.4 (1B), −5.4 (1B), −8.9 (2B), −11.1 (4B), −12.8 (2B). GCEI-MS: *m*/*z* 189.2 ([M − H]$^-$, 100%).

1-(2-(Benzylthio)ethyl)-1,2-carborane (8). 1,2-Carborane (960 mg, 6.65 mmol) was dissolved in DME (25 mL). The solution was cooled to 0 °C, and a solution of ^{n}BuLi (4.32 mL, 1.6 M in hexane, 6.77 mmol) was added slowly. The mixture was stirred at this temperature for 30 min, after which time it was warmed to room temperature and stirred for a further 30 min. The mixture was then cooled to 0 °C, and a solution of **6** (1.02 g, 4.42 mmol) in DME (10 mL) was added dropwise. The resulting yellow solution was allowed to warm to room temperature and stirred for 45 h, by which time the solution had become deep red. After quenching with water, the solution was extracted with diethyl ether (3 × 8 mL) and washed with brine (8 mL), and the solvent removed in vacuo to give a crude golden oil, which was purified by flash column chromatography (*n*-hexane, R_f = 0.35) to give **8** as a colorless solid (612 mg, 47%). ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.34−7.25 (m, 5H, Ph), 3.92 (s, 2H, SCH_2Ph), 3.20 (br, 1H, $C_{cage}H$), 2.86 (t, $^3J_{HH}$ = 6 Hz, 2H, CH_2S), 2.80 (t, $^3J_{HH}$ = 5.8 Hz, 2H, $C_{cage}CH_2$). $^{13}C\{^1H\}$ NMR (74.48 MHz, $CDCl_3$): δ 136.7 (Ph), 127.5 (Ph), 127.1 (Ph), 126.8 (Ph), 72.4 ($C_{cage}C$), 56.5 ($C_{cage}H$), 38.1 (SCH_2Ph), 36.4 (CH_2SCH_2Ph), 24.5 ($C_{cage}CH_2$). $^{11}B\{^1H\}$ NMR (400.21 MHz, $CDCl_3$): δ −2.3 (2B), −5.4 (2B), −9.1 (2B), −10.8 (4B), −13.4 (2B).

1-(3-(Benzylthio)propyl)-1,2-carborane (9). To a solution of 1,2-carborane (900 mg, 6.23 mmol) in DME (20 mL) at 0 °C was added ^{n}BuLi (1.6 M in hexane, 3.8 mL, 6.1 mmol) dropwise with stirring. The mixture was then stirred for 30 min at 0 °C, followed by 30 min at room temperature. The mixture was cooled to 0 °C, and **7** (1.56 g, 6.32 mmol) in DME (10 mL) was added dropwise. The colorless solution immediately became pale yellow. The solution was allowed to return to room temperature and stirred for a further 40 h. After being quenched with H_2O (20 mL), the two layers were separated and the aqueous layer was extracted with diethyl ether (4 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL) and dried with Na_2SO_4, and the solvent was removed in vacuo to give a crude yellow oil. After purification by flash column chromatography (20% diethyl ether/*n*-hexane, R_f = 0.48), **9** was obtained as a yellow oil (717 mg, 46%). ^1H NMR (300.13 MHz, $CDCl_3$): δ 7.35−7.23 (m, 5H, Ph), 3.72 (s, 2H, SCH_2Ph), 3.52 (br, 1H, $C_{cage}H$), 2.38 (t, $^3J_{HH}$ = 5.2 Hz, 2H, CH_2S), 2.17 (m, 2H, $CH_2CH_2CH_2$), 1.78 (t, $^3J_{HH}$ = 6.0 Hz, 2H, $C_{cage}CH_2$). $^{13}C\{^1H\}$ NMR (74.48 MHz, $CDCl_3$): δ 138.0 (Ph), 129.2 (Ph), 128.0 (Ph), 127.6 (Ph), 74.7 ($C_{cage}C$), 61.2 ($C_{cage}H$), 36.4 (CH_2S), 33.7 (SCH_2Ph), 28.8 ($C_{cage}C$), 28.5 ($CH_2CH_2CH_2$). $^{11}B\{^1H\}$ NMR (400.21 MHz, $CDCl_3$): δ −2.3 (1B), −5.71 (1B), −9.29 (2B), −11.6 (4B), −13.1 (2B). ESI-MS: *m*/*z* 307.9 ([M − H]$^-$, 100%).

1-(2-Thioethyl)-1,2-carborane (10). A procedure similar to that used for the synthesis of **5** was followed, using **8** (1.97 g, 6.69 mmol) instead of **4**. The crude yellow oil was purified by flash column chromatography (10% ethyl acetate/*n*-hexane, R_f = 0.42) to give **10** as a colorless solid (315 mg, 23%). Mp: 102−107 °C. ^1H NMR (300.13 MHz, $CDCl_3$): δ 3.67 (br, 1H, $C_{cage}H$), 2.62 (m, 2H, CH_2SH), 2.52 (m, 2H, $C_{cage}CH_2$), 1.47 (t, $^3J_{HH}$ = 8.1 Hz, 1H, SH). $^{13}C\{^1H\}$ NMR (74.48 MHz, $CDCl_3$): δ 74.9 ($C_{cage}C$), 66.7 ($C_{cage}H$), 40.8 (CH_2SH), 29.3 ($C_{cage}C$). $^{11}B\{^1H\}$ NMR (400.21 MHz, $CDCl_3$): δ −2.4 (1B), −5.9 (1B), −9.2 (2B), −11.6 (4B), −14.4 (2B). ESI-MS: *m*/*z* 169.2 ([M − H]$^-$, 100%).

1-(3-Thiopropyl)-1,2-carborane (11). A procedure similar to that used in the synthesis of **5** was followed, using **9** (354 mg, 1.14 mmol) instead of **4**. The crude yellow oil was purified by flash column chromatography (30% diethyl ether/*n*-hexane, R_f = 0.35) to give **11** as a low-melting solid (82 mg, 33%). Mp: 52−55 °C. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.93 (br, 1H, $C_{cage}H$), 2.51 (q, $^3J_{HH}$ = 5.8 Hz, 2H, CH_2SH), 2.37 (t, $^3J_{HH}$ = 5.7 Hz, 2H, $C_{cage}CH_2$), 1.81 (m, 2H, $CH_2CH_2CH_2$), 1.36 (t, $^3J_{HH}$ = 5.8 Hz, 1H, SH). $^{13}C\{^1H\}$ NMR (74.48 MHz, $CDCl_3$): δ 75.1 ($C_{cage}C$), 61.4 ($C_{cage}H$), 36.8 (CH_2SH), 27.1 ($C_{cage}C$), 25.5 ($CH_2CH_2CH_2$). $^{11}B\{^1H\}$ NMR (400.21 MHz, $CDCl_3$): δ −2.3 (1B), −5.8 (1B), −9.4 (2B), −11.7 (4B), −13.3 (2B). ESI-MS: *m*/*z* 185.1 ($1,2\text{-}B_{10}C_2H_{11}CH_2CH_2CH_2^+$, 100%).

(1,2-Carborane-1-thiolato)(2,2′:6′,2″-terpyridine)platinum-(II) Triflate (12). To a stirred suspension of [PtCl(trpy)]Cl·$2H_2O$ (100 mg, 0.19 mmol) in DMF (1 mL) was added a solution of AgOTf (94 mg, 0.36 mmol) in DMF (0.5 mL). The mixture was stirred at room temperature in the absence of light for 48 h. The mixture was then filtered through Celite filter aid to remove the AgCl. A solution of **18** (33 mg, 0.19 mmol) in DMF (1 mL) was then added and the mixture stirred for 2.5 h. Diethyl ether was then added to give an orange precipitate, which was collected by centrifugation, washed with additional diethyl ether, and dried in vacuo to give **12** as an orange powder (61 mg, 45%). ^1H NMR (599.89 MHz, acetone-d_6): δ 9.47 (d, $^3J_{HH}$ = 5.4 Hz, $^3J_{PtH}$ = 27.6 Hz, 2H, H6, H6″), 8.74 (m, 2H, H3′, H5′), 8.68 (m, 3H, H3, H3″ + H4′), 8.58 (td $^3J_{HH}$ = 1.8 Hz, $^3J_{HH}$ = 7.8 Hz, H4, H4″), 8.10 (ddd $^3J_{HH}$ = 1.8 Hz, $^3J_{HH}$ = 5.4 Hz, $^4J_{HH}$ = 7.2 Hz, 2H, H5, H5″), 4.96 (br, $C_{cage}H$). $^{13}C\{^1H\}$ NMR (150.86 Hz, acetone-d_6): δ 159.61 (C2, C2″), 155.38 (C2′, C6′), 153.84 (C6, C6″), 144.30

(C4′), 143.6 (C4, C4″), 130.2 (C5, C5″), 126.7 (C3, C3″), 125.1 (C3′, C5′), 71.0 ($C_{cage}H$). $^{11}B\{^1H\}$ NMR (96.30 MHz, DMF/benzene-d_6): δ −8.0 (2B), −14.2 (br, 6B), −18.1 (2B). $^{195}Pt\{^1H\}$ NMR (64.34 MHz, DMF/benzene-d_6): δ −3140. ESI-MS: *m/z* 603.2 (M^+). Anal. Calcd for $C_{18}H_{22}B_{10}F_3N_3O_3PtS_2$: C, 28.72; H, 2.95; N, 5.58. Found: C, 28.81; H, 2.85; N, 5.60.

(1,2-Carborane-1-methanethiolato))(2,2′:6′,2”-terpyridine)-platinum(II) Triflate (13). Method A. To a stirred solution of **5** (12.5 mg, 0.066 mmol) in acetone (5 mL) was added [Pt(MeCN)-(trpy)](OTf)$_2$ (49.9 mg, 0.065 mmol). After the solution had stirred at room temperature for 20 min, NEt_3 (0.5 mL, 0.201 mmol) was added and the solution stirred for a further 18 h. Diethyl ether (5 mL) was added to precipitate the complex from solution to give **13** as a bright-red, microcrystalline solid (31 mg, 62.5%).

Method B. To a stirred suspension of [PtCl(trpy)]Cl·2H$_2$O (100 mg, 0.19 mmol) in DMF (1 mL) was added a solution of AgOTf (94 mg, 0.36 mmol) in DMF (0.5 mL). The mixture was stirred at room temperature in the absence of light for 48 h. The mixture was then filtered through Celite filter aid to remove the AgCl. A solution of **5** (36 mg, 0.19 mmol) in DMF (1 mL) was then added to the solution, and the mixture was stirred for 1.5 h at room temperature. Diethyl ether was added to the solution, precipitating an off-white solid, which was filtered off and discarded. Additional diethyl ether was added to precipitate the product, which was collected by centrifuging, washed with diethyl ether, and dried in vacuo to give **13** as a bright-red, microcrystalline solid (86 mg, 70%). ^1H NMR (599.89 MHz, acetone-d_6): δ 9.27 (d, $^3J_{HH}$ = 5.9 Hz, $^3J_{PtH}$ = 37.5 Hz, 2H, H6, H6″), 8.62 (m, 2H, H3′, H5′), 8.59 (m, 2H, H3, H3″ + H4′), 8.52 (td, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 1.8 Hz, 2H, H4, H4″), 8.00 (ddd, $^3J_{HH}$ = 1.8 Hz, $^3J_{HH}$ = 5.9 Hz, $^4J_{HH}$ = 9.6 Hz, 2H, H5, H5″), 4.87 (br, 1H, $C_{cage}H$), 3.49 (s, $^3J_{PtH}$ = 37.8, 2H, CH_2S). $^{13}C\{^1H\}$ NMR (50.3 MHz, acetone-d_6): δ 160.0 (C2, C2″), 154.7 (C2′, C6′), 153.3 ($^2J_{PtC}$ = 30.0 Hz, C6, C6″), 143.6 (C4, C4″ + C4′), 130.4 ($^3J_{PtC}$ = 41.9 Hz, C5, C5″), 127.0 ($^3J_{PtC}$ = 31.4 Hz, C3, C3″), 125.4 (C3′, C5′), 66.1 ($C_{cage}C$), 62.2 ($C_{cage}H$), 37.6 (CH_2S). $^{11}B\{^1H\}$ NMR (96.30 MHz, DMF/benzene-d_6): δ −7.8 (1B), −10.6 (1B), −14.1 (2B), −15.6 (2B), −16.8 (2B), −17.5 (2B). $^{195}Pt\{^1H\}$ NMR (64.34 MHz, DMF/benzene-d_6): δ −3135. ESI-MS: *m/z* 618.2 (M^+), 429.4 ($C_{15}H_{11}N_3Pt^+$). Anal. Calcd for $C_{19}H_{24}B_{10}F_3N_3O_3PtS_2$: C, 29.76; H, 3.15; N, 5.48. Found: C, 29.77; H, 3.10; N, 5.43.

(1,2-Carborane-1-(2-ethanethiolato))(2,2′:6′,2”-terpyridine)-platinum(II) Triflate (14). To a stirred solution of **10** (48.3 mg, 0.221 mmol) in acetone (5 mL) was added [Pt(MeCN)(trpy)](OTf)$_2$ (106.1 mg, 0.206 mmol). The solution was stirred at room temperature for 20 min, and NEt_3 (0.5 mL, 0.201 mmol) was added. The solution was then stirred for a further 18 h. Diethyl ether (5 mL) was added to afford **14** as a microcrystalline, red-orange solid (27 mg, 59%). ^1H NMR (300.13 MHz, acetone-d_6): δ 9.31 (d, $^3J_{HH}$ = 7.0 Hz, 2H, H6, H6″), 8.63 (d, $^3J_{HH}$ = 7.3 Hz, 2H, H3′, H5′), 8.51 (d, $^3J_{HH}$ = 7.5 Hz, 2H, H3, H3″), 8.47 (t, $^3J_{HH}$ = 7.2 Hz, 1H, H4′), 8.42 (td, $^3J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 7.8 Hz, 2H, H4, H4″), 7.79 (td, $^3J_{HH}$ = 1.6 Hz, $^3J_{HH}$ = 7.3 Hz, 2H, H5, H5″), 3.74 (br, 1H, $C_{cage}H$), 2.71 (d, 2H, $^3J_{HH}$ = 5.7 Hz, CH_2S), 2.59 (d, 2H, $^3J_{HH}$ = 5.4 Hz, $C_{cage}CH_2$). $^{13}C\{^1H\}$ NMR (74.48 MHz, acetone-d_6): δ 161.8 (C2, C2″), 155.2 (C2′, C6′), 154.3 (C6, C6″), 141.0 (C4, C4″ + C4′), 129.5 (C5, C5″), 127.3 (C3, C3″), 123.5 (C3′, C5′), 72.8 ($C_{cage}C$), 57.9 ($C_{cage}H$), 38.1 (CH_2S), 30.6 ($C_{cage}C$). $^{11}B\{^1H\}$ NMR (400.21 MHz, acetone-d_6): δ −2.2 (1B), −6.1 (1B), −9.6 (2B), −12.6 (4B), −15.8 (2B). $^{195}Pt\{^1H\}$ NMR (85.69 MHz, acetone-d_6): δ −3108. ESI MS: *m/z* 631.6 (M^+, 100%). Anal. Calcd for $C_{20}H_{26}B_{10}F_3N_3O_3PtS_2$·0.5$CH_3CN$: C, 31.48; H, 3.46; N, 6.12. Found: C, 31.36; H, 2.94; N, 6.08.

(1,2-Carborane-1-(3-propanethiolato))(2,2′:6′,2”-terpyridine)-platinum(II) Triflate (15). To a stirred solution of **11** (30.2 mg, 0.145 mmol) in acetone (5 mL) was added [Pt(MeCN)(trpy)](OTf)$_2$ (155 mg, 0.201 mmol). After the solution had been stirred at room temperature for 20 min, NEt_3 (0.5 mL, 0.201 mmol) was added, and the solution was stirred for a further 18 h. Diethyl ether (5 mL) was added to afford **15** as dark-red crystals (60 mg, 67%). ^1H NMR (300.13 MHz, acetone-d_6): δ 9.59 (dd, $^3J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 5.7 Hz, $^3J_{PtH}$ = 49 Hz, 2H, H6, H6″), 8.80 (d, $^3J_{HH}$ = 4 Hz, 2H, H3′, H5′), 8.71 (d, $^3J_{HH}$ = 2.1 Hz, 2H, H3′, H3″), 8.61 (t, $^3J_{HH}$ = 3.5 Hz, 1H, H4′), 8.58 (td, $^3J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, H4, H4″), 8.01 (td, $^3J_{HH}$ = 3 Hz, $^3J_{HH}$ = 6 Hz, 2H, H5, H5″), 2.97 (br, 1H, $C_{cage}H$), 2.74 (t, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2S), 2.61 (t, 2H, $^3J_{HH}$ = 6 Hz, $C_{cage}CH_2$), 1.96 (m, 2H, $CH_2CH_2CH_2$). $^{13}C\{^1H\}$ NMR (74.48 MHz, acetone-d_6): δ 161.1 (C2, C2″), 153.4 (C2′, C6′), 154.5 (C6, C6″), 144.5 (C4, C4″ + C4′), 128.7 (C5, C5″), 126.3 (C3, C3″), 125.1 (C3′, C5′), 77.8 ($C_{cage}C$), 62.6 ($C_{cage}H$), 37.0 (CH_2S), 33.7 ($C_{cage}C$), 30.2 ($CH_2CH_2CH_2$). $^{11}B\{^1H\}$ NMR (400.21 MHz, acetone-d_6): δ −2.1 (1B), −5.0 (1B), −9.0 (2B), −11.1 (4B), −13.8 (2B). $^{195}Pt\{^1H\}$ NMR (85.69 MHz, acetone-d_6): −3142. ESI-MS: *m/z* 645.3 (M^+, 100%). Anal. Calcd for $C_{21}H_{28}B_{10}F_3N_3O_3PtS_2$: C, 30.21; H, 3.55; N, 5.29. Found: C, 30.17; H, 3.59; N, 5.40.

(1,7-Carborane-1-methanethiolato)(2,2′:6′,2”-terpyridine)-platinum(II) Triflate (16). Method A. To a stirred solution of **2** (40 mg, 0.210 mmol) in acetone (5 mL) was added [Pt(MeCN)-(trpy)](OTf)$_2$ (185 mg, 0.244 mmol). The solution was stirred at room temperature for 20 min, and NEt_3 (0.5 mL, 0.201 mmol) was added. The solution was then stirred for a further 18 h. Diethyl ether (5 mL) was added to afford **16** as red needles (79 mg, 49%).

Method B. To a stirred suspension of [PtCl(trpy)]Cl·2H$_2$O (68 mg, 0.13 mmol) in DMF (0.5 mL) was added a solution of AgOTf (64 mg, 0.25 mmol) in DMF (0.5 mL). The mixture was stirred at room temperature in the absence of light for 48 h and then filtered through Celite filter aid to remove the AgCl. A solution of **2** (23 mg, 0.12 mmol) in DMF (0.5 mL) was added to the orange filtrate to give a dark-red solution which was stirred for 5 h at room temperature. Diethyl ether was then added to the solution to precipitate a tan solid, which was removed by filtration. Additional diethyl ether was added to the filtrate, and it was allowed to stand for 12 h at room temperature. The mixture was centrifuged to give dark-red needles of **16**, which were washed with diethyl ether and dried in vacuo (40 mg, 45%). ^1H NMR (599.89 MHz, acetone-d_6): δ 9.18 (d, $^3J_{HH}$ = 5.4 Hz, $^3J_{PtH}$ = 37.5 Hz, 2H, H6, H6″), 8.63 (m, 2H, H3′, H5′), 8.58 (m, 3H, H3, H3″ + H4′), 8.49 (td, $^3J_{HH}$ = 1.2, $^3J_{HH}$ = 7.5 Hz, 2H, H4, H4″), 7.98 (ddd, $^3J_{HH}$ = 1.2 Hz, $^3J_{HH}$ = 5.4 Hz, $^4J_{HH}$ = 7.8 Hz, 2H, H5, H5″), 3.56 ($C_{cage}H$), 3.10 (CH_2S). $^{13}C\{^1H\}$ NMR (75.48 MHz, acetone-d_6): δ 154.3 (C2′ + C6′), 159.7 (C2, C2″), 153.0 ($^2J_{PtC}$ = 21.6 Hz, C6, C6″), 143.5 (C4, C4” + C4′), 130.2 ($^3J_{PtC}$ = 43.1 Hz, C5, C5″), 127.0 ($^3J_{PtC}$ = 32.3 Hz, C3, C3″), 125.4 ($^3J_{PtC}$ = 21.6 Hz, C3′, C5′), 56.2 ($C_{cage}H$), 37.1 (CH_2S). $^{11}B\{^1H\}$ NMR (96.30 MHz, acetone-d_6): δ −3.3 (1B), −10.5 (5B), −3.0 (2B), −14.4 (2B). $^{195}Pt\{^1H\}$ NMR (64.34 MHz, acetone-d_6): δ −3152. ESI-MS: *m/z* 618.2 (M^+), 429.4 ($C_{15}H_{10}N_3Pt^+$). Anal. Calcd for $C_{19}H_{24}B_{10}F_3N_3O_3PtS_2$: C, 29.76; H, 3.16; N, 5.48. Found: C, 29.74; H, 3.16; N, 5.52.

(1,12-Carborane-1-methanethiolato)(2,2′:6′,2″-terpyridine)-platinum(II) Triflate (17). To a stirred solution of **19** (47.9 mg, 0.250 mmol) in acetone (5 mL) was added [Pt(MeCN)(trpy)](OTf)$_2$ (193 mg, 0.251 mmol). After the solution had stirred at room temperature for 20 min, NEt_3 (0.5 mL, 0.201 mmol) was added, and the solution was stirred for 18 h. Diethyl ether (5 mL) was added to afford **17** as an orange microcrystalline solid (98 mg, 71%).

^{1}H NMR (300.13 MHz, DMSO-d_6): δ 9.28 (dd, $^3J_{HH}$ = 0.6 Hz, $^3J_{HH}$ = 6 Hz, $^3J_{PtH}$ = 45 Hz, 2H, H6, H6″), 8.83 (dd, $^3J_{HH}$ = 0.9 Hz, $^3J_{HH}$ = 6 Hz, 2H, H3′, H5′), 8.68 (d, $^3J_{HH}$ = 9 Hz, 2H, H3, H3″), 8.64 (t, $^3J_{HH}$ = 6 Hz, 1H, H4′), 8.49 (td, $^3J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 9 Hz, 2H, H4, H4″), 8.00 (td, $^3J_{HH}$ = 1.5 Hz, $^3J_{HH}$ = 6 Hz, 2H, H5, H5″), 3.25 (s, 2H, CH_2S), 2.83 (s, 2H, $C_{cage}H$). $^{13}C\{^1H\}$ NMR (74.48 MHz, DMSO-d_6): δ 160.3 (C2, C2″), 155.7 (C2′, C6′), 153.4 (C6, C6″), 143.5 (C4, C4″ + C4′), 130.1 (C5, C5″), 127.2 (C3, C3″), 124.9 (C3′, C5′), 55.4 (CH_2S), 31.5 ($C_{cage}H$), $C_{cage}C$ not observed. $^{11}B\{^1H\}$ NMR (400.21 MHz, DMSO-d_6): δ −12.2 (5B), δ −14.5 (5B). $^{195}Pt\{^1H\}$ NMR (64.34 MHz, acetone-d_6): δ −3132. ESI-MS: m/z 459.0 ($C_{15}H_{11}N_3Pt^+$, 100%). Anal. Calcd for $C_{19}H_{24}B_{10}F_3N_3O_3PtS_2$: C, 29.87; H, 3.16; N, 5.48. Found: C, 29.94; H, 2.97; N, 5.60.

X-ray Structure Determination of 16. A red and poorly formed bladelike crystal was attached with Exxon Paratone N to a short length of fiber supported on a thin piece of copper wire inserted in a copper mounting pin. The crystal was quenched in a cold nitrogen gas stream from an Oxford Cryosystems Cryostream. A Bruker-Nonius ApexII-FR591 diffractometer employing graphite-monochromated Mo Kα radiation generated from a rotating anode was used for the data collection. Cell constants were obtained from a least-squares refinement against 8340 reflections located between 5 and 57° in 2θ. Data were collected at 150(2) K with ω and ϕ scans to 57° in 2θ. The data integration and reduction were undertaken with SAINT and XPREP,[21] and subsequent computations were carried out with the WinGX[22] and XTAL[23] graphical user interfaces. A Gaussian absorption correction[21,24] was applied to the data. The structure was solved in the space group $P\bar{1}$ (No. 1) by direct methods with SIR97[25] and extended and refined with SHELXL-97.[26] The asymmetric unit contains three crystallographically independent complex molecules together with three triflate counterions. Significant residual electron density close to the platinum and sulfur sites has been modeled as minor occupancy sites associated with unresolved orientation disorder of the complex molecules. The fully occupied non-hydrogen sites were modeled with anisotropic displacement parameters, and the rest were modeled with isotropic displacement parameters. A riding atom model with group displacement parameters was used for the hydrogen atoms. An ORTEP[27] depiction of one of the cations in **16** with 50% displacement ellipsoids is provided in Figure 1. Crystallographic data are summarized in Table 1.

In Vitro Cytotoxicity Studies. All anticancer screening was performed in the Andrew Durant Drug Testing Facility, Peter MacCallum Cancer Institute (Melbourne, Australia). Details of the sulforhodamine (SRB) assay have been reported previously.[4]

Results and Discussion

Preparation and Characterization of (Thioalkyl)carborane Ligands. A two-step synthesis for 1-(thiomethyl)-1,12-carborane was recently reported by Nachman et al.,[20] and it therefore appeared suitable for adaptation using 1,2- and 1,7-carborane (Scheme 1).

The 1,7-carborane was deprotonated with ^{n}BuLi and treated with CuBr and LiBr followed by CS_2. Addition of MeI, followed by workup and column chromatography gave the dithioester **1** in 59% yield. The $^{11}B\{^1H\}$ NMR spectrum of the product contained five peaks in the range δ −4.3 to −16.9 in the ratio 1:1:4:2:2, which was consistent with a *closo*-1,7-carborane structure. The dithioester **1** was then

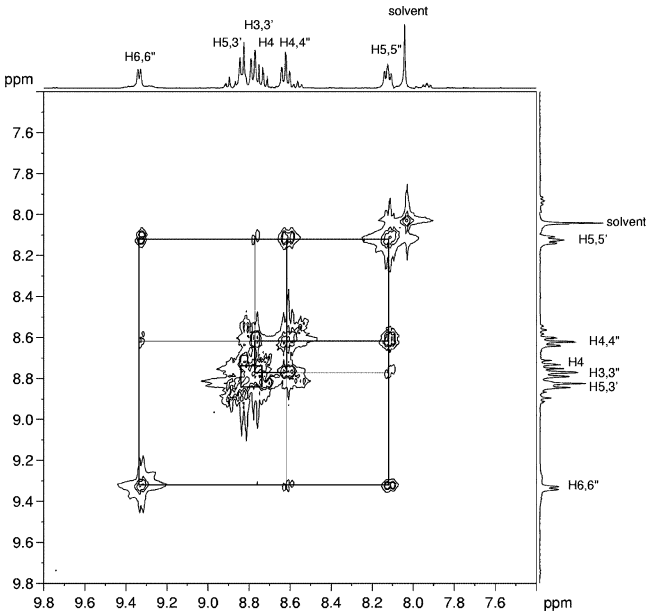


Figure 1. ^{1}H COSY NMR spectrum of **16** showing key couplings and peak assignments for the trpy ligand (solvent = d_7-DMF).

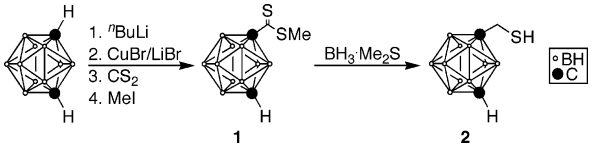
Table 1. Crystallographic Parameters for **16**

formula of the refinement model	$C_{19}H_{24}B_{10}F_3N_3O_{3.33}PtS_2$
model M_r	772.06
cryst system	triclinic
space group	$P\bar{1}$ (No. 1)
a	16.3529(8) Å
b	17.0884(9) Å
c	17.9759(9) Å
α	73.450(3)°
β	76.772(3)°
γ	63.437(2)°
V	4276.6(4) Å^3
D_c	1.799 g cm^{-3}
Z	6
cryst size	0.437 × 0.198 × 0.076 mm
cryst color	red
cryst habit	blade
temp	150(2) K
λ(Mo Kα)	0.710 73 Å
μ(Mo Kα)	5.119 mm^{-1}
T(Gaussian)$_{min,max}$	0.347, 0.727
$2\theta_{max}$	57.46°
hkl range	−22/22, −23/23, −24/24
N	104 700
N_{ind}	22 046 (R_{merge} 0.0980)
N_{obs}	15 963 ($I > 2\sigma(I)$)
N_{var}	1162
resids[a] R1(F), wR2(F^2)	0.0421, 0.1180
GoF(all)	1.147
resid extrema	−2.351, 2.962 e Å^{-3}

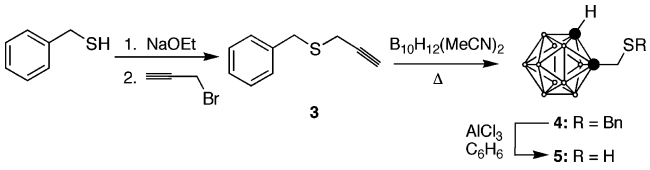
[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\sum w(F_o^2 - F_c^2)^2/\sum(wF_c^2)^2)^{1/2}$ for all reflections $w = 1/[\sigma^2(F_o^2) + (0.05P)^2 + 2.0P]$, where $P = (F_o^2 + 2F_c^2)/3$.

(21) *APEX, SAINT, and XPREP. Area detector control and data integration and reduction software*; Bruker-Nonius Analytical X-ray Instruments Inc.: Madison, WI, 2003.
(22) Win, G. X.; Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837−838.
(23) Hall, S. R., du Boulay, D. J., Olthof-Hazekamp, R., Eds. *Xtal3.6 System*; University of Western Australia: Perth, Australia, 1999.
(24) Coppens, P.; Leiserowitz, L.; Rabinovich, D. *Acta Crystallogr.* **1965**, *18*, 1035−1038.
(25) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1998**, *32*, 115−119.
(26) Sheldrick, G. M. *SHELX97 Programs for Crystal Structure Analysis*; Institüt für Anorganische Chemie der Universität, University of Göttingen: Tammanstrasse 4, D-3400 Göttingen, Germany, 1998.
(27) Johnson, C. K. *ORTEPII. Report ORNL-5138*; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.

Scheme 1



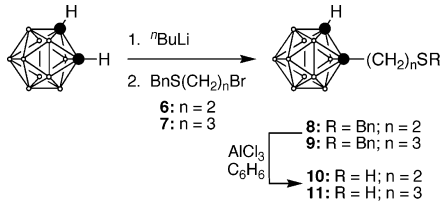
Scheme 2



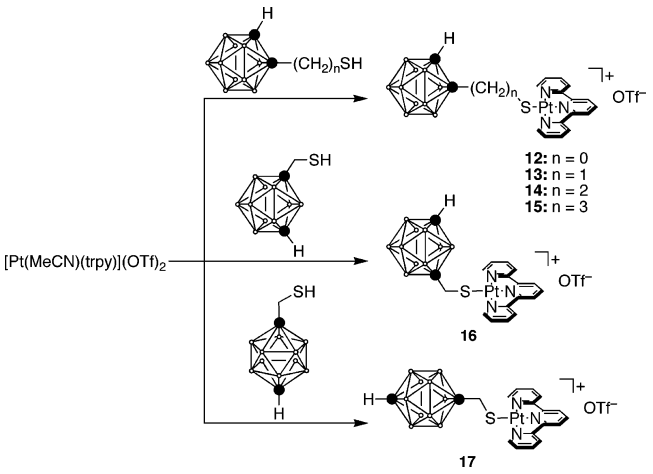
reduced with $BH_3{\cdot}SMe_2$ to afford the thiol **2** in 40% yield. The 1,2-carborane isomer was also prepared by this method, but its yield was found to be consistently less than 5% and a more appropriate synthesis was sought. An alternative three-step synthesis was devised on the basis of the well-known condensation reaction between terminal alkynes and *nido*-decaborane in the presence of MeCN (Scheme 2).[28] In these reactions, protection of the thiol group proved necessary to minimize unwanted side reactions. A benzyl-protecting group was used instead of the *tert*-butyl group,[29] as previous work within our group has demonstrated that higher yields of product may be obtained upon removal of the benzyl group compared with the removal of a *tert*-butyl group.[30] As shown in Scheme 2, the alkyne **3** was refluxed with the MeCN adduct of *nido*-decaborane to afford the carborane derivative **4** in high purity and yield. The ^{1}H, ^{13}C{^{1}H}, and ^{11}B{^{1}H} NMR spectra all agreed with the expected product, and the compound was then treated with freshly sublimed $AlCl_3$ in benzene to remove the *S*-benzyl protecting group by using an adaptation of the method reported by Hermánek et al.[29] The thiol **5** was obtained in 33% yield after column chromatography. The appearance of a triplet at δ 1.87 in the ^{1}H NMR spectrum coupled to a doublet at δ 3.29 ($^3J_{HH}$ = 9 Hz), corresponding to the thiol and methylene protons, respectively, confirmed the removal of the benzyl protecting group. This was also verified by the absence of aromatic signals in both the ^{1}H and ^{13}C{^{1}H} NMR spectra. The ^{11}B{^{1}H} NMR spectrum showed that the *closo*-carborane had remained intact, and GCEI-MS revealed the molecular ion peak (*m*/*z* 189.2, $[M - H]^-$).

Following the same method used to prepare **5**, the carborane derivatives **10** and **11** were synthesized from $B_{10}H_{12}(MeCN)_2$ and 1-(benzylthio)-3-butyne (n = 2) or 1-(benzylthio)-4-pentyne (n = 3), respectively, but this method afforded only low yields of products in our hands. An alternative approach was to incorporate a protected thiol group into the parent 1,2-carborane via its monolithiated intermediate. In this reaction, protection of the thiol group with a benzyl or *tert*-butyl group was required to prevent the slightly acidic thiol from reacting with the lithiated carborane intermediate.

Scheme 3



Scheme 4



A solution of **6** or **7** in DME was added dropwise to a solution of 1,2-carborane which had been treated with 1 equiv of ^{n}BuLi, to give **8** or **9**, respectively, following workup and column chromatography (Scheme 3). ^{1}H, ^{13}C{^{1}H}, and ^{11}B{^{1}H} NMR spectra supported the identity of the purified products. In particular, the signal due to the CH_2Br group in the ^{1}H NMR spectra was shifted upfield by ca. 0.5 ppm, consistent with the replacement of the electronegative halogen atom with a C-bonded carborane.

The benzyl-protected thiol **8** or **9** was then added to a solution of freshly sublimed $AlCl_3$ in benzene to deprotect the thiol group. Following workup and purification by means of flash column chromatography, the ligands **10** and **11** were obtained in reasonable yield. The ^{1}H, ^{13}C{^{1}H}, and ^{11}B{^{1}H} NMR spectra supported the structures of **10** and **11**, with the ^{11}B{^{1}H} NMR spectra containing five peaks in the range δ −2 to −14 in the ratio 1:1:2:4:2, consistent with a *closo*-1,2-carborane cage. ESI-MS also confirmed the nature of the products.

Preparation and Characterization of Platinum(II)−trpy Derivatives. Some of the target platinum(II)−trpy complexes **12**−**17** were originally prepared from [Pt(trpy)(dmf)](OTf)$_2$.[14] However, the relative ease of preparation of [Pt(MeCN)(trpy)](OTf)$_2$ makes it a superior precursor to the related $[Pt(dmf)(trpy)]^{2+}$ species.[15] Thus, the addition of [Pt(MeCN)(trpy)](OTf)$_2$ to acetone solutions containing the ligands **2**, **5**, **10**, **11**, **18**, or **19** containing triethylamine base resulted in an immediate color change from pale-yellow to orange or dark-red, depending on the nature of the thiol ligand, to afford **12**−**17** as microcrystalline solids (Scheme 4).

Complexes **12**−**17** were fully characterized by ^{1}H, ^{13}C{^{1}H}, ^{11}B{^{1}H}, and ^{195}Pt{^{1}H} NMR spectroscopy, as well as ESI-MS and microanalysis. In the ^{1}H NMR spectra for

(28) Bregadze, V. I. *Chem. Rev.* **1992**, *92*, 209−223.
(29) Plesek, J.; Hermanek, S. *Collect. Czech. Chem. Commun.* **1979**, *44*, 2769−2771.
(30) Woodhouse, S. L.; Rendina, L. M. Unpublished results.

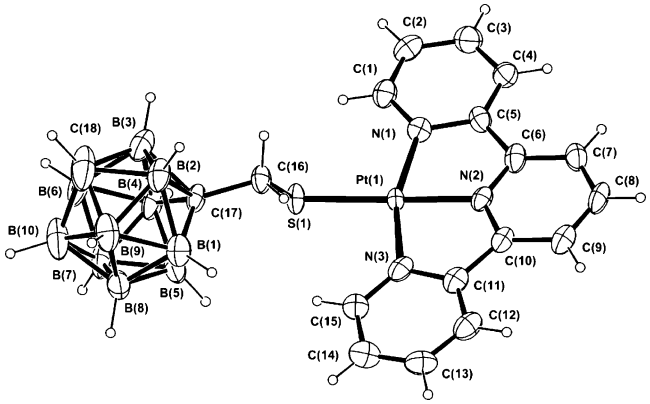


Figure 2. ORTEP34 depiction and atomic numbering scheme of one of the three crystallographically independent cations in **16** with 50% displacement ellipsoids. Selected bond distances (Å): Pt(1)−N(2) = 1.968(4), Pt(1)−N(3) = 1.987(5), Pt(1)−N(1) = 2.018(4), Pt(1)−S(1) = 2.2967(16). Selected bond angles (deg): N(2)−Pt(1)−N(3) = 80.46(17), N(2)−Pt(1)−N(1) = 80.89(17), N(3)−Pt(1)−N(1) = 161.33(17), N(2)−Pt(1)−S(1) = 177.62(13), N(3)−Pt(1)−S(1) = 101.65(13), N(1)−Pt(1)−S(1) = 96.99(13), C(16)−S(1)−Pt(1) = 102.98(17).

12−**17**, there were six distinct aromatic signals observed in addition to the aliphatic and carborane C−H proton resonances. The assignments for the aromatic protons were based on 2-D NMR (COSY, HMBC, and HSQC) methods, and a representative ^{1}H COSY NMR spectrum is presented in Figure 1. ^{195}Pt{^{1}H} NMR spectroscopy also proved useful in characterizing selected complexes. Previous studies have shown that ^{195}Pt{^{1}H} NMR resonances for complexes with a PtN_3S core appear between δ −3100 and −3200 ppm;[31] e.g., the signal for **15** is located at δ −3142 ppm.

Complex **16** was further characterized by means of single-crystal, X-ray diffraction methods (Figure 2), the parameters of which are given in Table 1. The three crystallographically independent complexes are square planar, with metal deviations of 0.018(17), 0.023(18), and 0.038(17) Å from the least-squares planes defined by the four coordinating atoms. In each case the carborane bearing the thioalkyl ligand is canted slightly with respect to the least-squares plane, such that the torsion angles N(3)−Pt(1)−S(1)−C(16), N(6)−Pt(2)−S(2)−C(34), and N(9)−Pt(3)−S(3)−C(52) are 66.7(2), 64.8(2), and 74.3(2)°, respectively. The deviation of the torsion angles from 90° appears to be the result of the proximity of neighboring carborane groups on adjacent complexes. The Pt−N bond lengths range from 1.968(4) to 2.035(4) Å, and the Pt−S bond lengths are 2.2967(16), 2.3005(16), and 2.3006(16) Å. These bond lengths, and the three atom coordination sphere bond angles, are unremarkable with respect to equivalent bonds and angles in platinum complexes having the same coordination motif.[32]

In Vitro Cytotoxicity Studies of Complexes 13 and 15−**17.** Complexes **13** and **15**−**17** were screened against 2008 human ovarian cancer cells and the cisplatin-resistant variant 2008/C13 in vitro. It was expected that some degree of cytotoxicity would be observed in the absence of thermal neutrons if the complexes entered the cells, as the binding of metallointercalators to DNA can result in considerable cytotoxic effects.[8,9] The concentrations (μM) required to achieve 50% inhibition of cell growth (IC_{50}) in each line are presented in Table 2; cisplatin was used as a control.

Table 2. IC_{50} (μM) Values for **13** and **15**−**17** (n = 2)[a]

complex	2008 cell line	C13 cell line
13	1.7	2.1
15	5.3	4.1
16	4.6	5.1
17	26	21
cisplatin	0.6	10

[a] Cell lines were assayed by means of a sulforhodamine B (SRB) assay.

Although cytotoxic effects in the absence of thermal neutrons are not as important for BNCT as an ability to concentrate within tumor cells and bind to DNA,[2] the cytotoxic properties of the complexes may result in an additive or synergistic effect during thermal neutron irradiation. In contrast, a high cytotoxicity is undesirable as this would result in cell death at low platinum concentrations, prior to accumulation of sufficient levels of ^{10}B nuclei within the cells.

Table 2 shows that complexes **13**, **15**, and **16** displayed a consistently higher cytotoxicity than **17** in the 2008 tumor line. This is likely to be a consequence of the significantly lower solubility of **17** in polar environments, as any precipitation of the complex from solution during the incubation period would result in a reduced cytotoxic effect. By comparison of the cytotoxicity of the three isomeric complexes **13**, **16**, and **17**, which differ only in the nature of the carborane, it can be seen that **13** is the most active in these cell lines. This provides strong evidence that subtle changes in the nature of the carborane cage can significantly affect the biological activity of the complexes, probably as a result of the decreased aqueous solubility observed in the complexes on moving from *closo*-1,2- and 1,7- to 1,12-carborane (**13**, **16**, and **17**, respectively). An unexpected result was the lower biological activity of **15** compared with **13**. It was expected that the longer alkyl linker between the carborane and platinum(II)−trpy groups in **15** would facilitate DNA binding by reducing unfavorable steric interactions between the *closo*-carborane cage and DNA.[14] However the lower activity of **15** suggests that this is not the case. Again, the diminished solubility of **15** in polar solvents due to the aliphatic alkyl chain is consistent with this result. Alternatively, another mechanism of action may be responsible for the cytotoxicity of the complexes, e.g. enzyme inhibition.[33]

The similar IC_{50} values obtained for each complex in both the cisplatin-sensitive and cisplatin-resistant lines suggests that, as expected, the mechanism of cytotoxicity differs from that of cisplatin. However, the causes of the observed IC_{50} values cannot be identified until the exact mechanism(s) of cytotoxicity has been determined.

Conclusion

In this work, a series of (thioalkyl)-*closo*-carborane ligands were synthesized with varying alkyl chain lengths and

(31) Fazlur-Rahman, A. K.; Verkade, J. G. *Inorg. Chem.* **1992**, *31*, 2064−2069.
(32) Allen, F. H. *Acta Crystallogr*. **2002**, *B58*, 380.
(33) Becker, K.; Herold-Mende, C.; Park, J. J.; Lowe, G.; Schirmer, R. H., *J. Med. Chem*. **2001**, *44*, 2784−2792.

isomeric carboranes, and a series of novel, brightly colored platinum(II)−trpy complexes containing these ligands were also prepared and fully characterized by means of multinuclear (^{1}H, ^{13}C, ^{11}B, and ^{195}Pt) 1D- and 2D-NMR spectroscopy, ESI-MS and, in the case of **16**, X-ray crystallography. We are currently evaluating the DNA-binding and tumor cell uptake characteristics of selected complexes, and the results of this work will be reported in due course.

Acknowledgment. We are grateful to Dr. C. Cullinane (Peter MacCallum Cancer Institute, Melbourne, Australia) for the cytotoxicity data. We also thank Dr. I. Luck (University of Sydney) for assistance with the recording of ^{11}B{^{1}H} and ^{195}Pt{^{1}H} NMR spectra and Dr. K. Fisher (University of Sydney) for recording the ESI-MS. We are grateful to Johnson-Matthey for the generous loan of K_2-[$PtCl_4$]. Finally, we acknowledge funding from the Australian Research Council and Anti-Cancer Foundation of South Australia.

Supporting Information Available: X-ray crystallographic data files for **16**, including atomic coordinates, bond distances and angles, and thermal parameters, in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

IC050265K