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Synthesis and DNA-Binding Properties of Cationic 2,2′:6′,2′′-Terpyridineplatinum(II) Complexes Containing 1,2- and 1,7-Dicarba-*closo*-dodecaborane(12)

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The first examples of DNA metallointercalators containing a dicarba-*closo*-dodecaborane(12) (carborane) moiety are presented. Treatment of the labile platinum(II) complex [Pt(OTf)(*terpy*)]$^+$ (*terpy* = 2,2′:6′,2′′-terpyridine) with the 1,2-carborane monothiol derivatives 1-HS(CH$_2$)$_n$-1,2-$C_2B_{10}H_{11}$ (n = 0, 1) or the novel 1,7-carborane ligand, 1-HSCH$_2$-1,7-$C_2B_{10}H_{11}$, affords the stable, brightly colored species [Pt(1-S(CH$_2$)$_n$-1,Z–$C_2B_{10}H_{11}$)(*terpy*)]$^+$ (Z = 2, n = 0, 1; Z = 7, n = 1) in good yield and purity. Preliminary DNA-binding experiments with calf-thymus DNA indicate an intercalative interaction by the platinum(II) complexes at high r_f values.

There is considerable interest in the preparation, properties, and structural diversity of late transition metal complexes containing mono- and dithiolato derivatives of polyhedral boranes such as the carboranes (dicarba-*closo*-dodecaboranes-(12)).[1−4] In the case of the 1,2-carborane-1-thiolato ligand, for example, Laguna and co-workers reported the synthesis of the air- and moisture-stable gold(I) species of the type [Au(1-S-$C_2B_{10}H_{11}$)L] (L = PPh$_3$, PPh$_2$Me, SPPh$_3$, AsPh$_3$) and [Au(1-S-$C_2B_{10}H_{11}$)$_2$]$^-$.[2] The analogous dinuclear complexes with bridging bidentate phosphine ligands, [Au$_2$(1-S-$C_2B_{10}H_{11}$)$_2$(μ-L)] (L = dppe, dppp), were also prepared, and a remarkable tetranuclear silver(I) complex, [Ag$_4$(μ_3-1-S-$C_2B_{10}H_{11}$)$_2$(μ-CF$_3$SO$_3$)$_2$(PPh$_3$)$_4$], was characterized by X-ray crystallography.[3] Recently, Grinstaff and co-workers reported the redox and photophysical properties of the platinum(II)−diimine complex [Pt(*dip*)(1-S-$C_2B_{10}H_{11}$)$_2$] and its 1,2-dithiolato analogue [Pt(*dip*)(1,2-S$_2$-$C_2B_{10}H_{10}$)] (*dip* = 4,7-diphenyl-1,10-phenanthroline).[4]

The use of carborane-containing monothiolato ligands in platinum(II)−*terpy* (*terpy* = 2,2′:6′,2′′-terpyridine) complexes that are renowned for their noncovalent DNA-binding properties may lead to the development of novel DNA metallointercalators with potential relevance to boron neutron capture therapy (BNCT).[5] Indeed, organic intercalators such as the acridine dyes,[6] tetracyclines,[7] and phenanthridium analogues[8] linked to carboranes have been prepared for this specific purpose, but to date no examples of carborane-containing DNA metallointercalators are known. Recently, we reported the synthesis of dinuclear platinum(II)−amine derivatives of 1,7-carborane that are capable of targeting plasmid DNA in a covalent manner.[9] Herein we report the first examples of 1,2- and 1,7-carborane complexes based on the platinum(II)−*terpy* chromophore, and we also provide preliminary evidence for intercalative DNA-binding by the complexes.

The 1,7-carborane-containing thiol **2** was prepared by a related method used in the synthesis of the 1,12-carborane isomer (Scheme 1).[10] Thus, reaction of 1,7-carborane with

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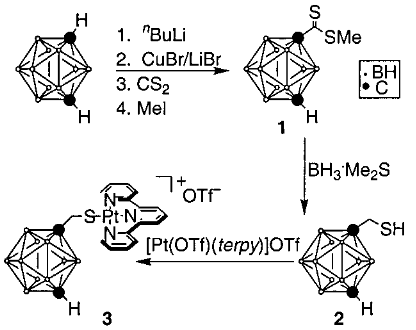
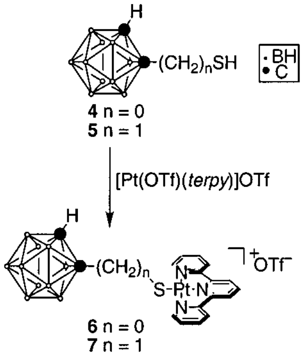
Scheme 1



Scheme 2



ⁿBuLi in the presence of CuBr and LiBr, followed by the addition of CS_2 and MeI, afforded the dithioester intermediate **1** (55%). Reduction of **1** with $BH_3{\cdot}Me_2S$ afforded **2** as colorless crystals in reasonable yield (52%). The addition of 2 equiv of AgOTf to [PtCl(*terpy*)]Cl in DMF solution generated the labile precursor [Pt(OTf)(*terpy*)]OTf, which upon treatment with 1 equiv of the thiol **2**, **4**,[11] or **5**[12] afforded the brightly colored, cationic platinum(II) complex **3**, **6**, or **7**, respectively, in good yield and purity (Schemes 1 and 2).

The complexes were fully characterized by multinuclear (^1H, $^{13}C\{^1H\}$, and $^{11}B\{^1H\}$) NMR spectroscopy and microanalysis. Furthermore, the $^{195}Pt\{^1H\}$ NMR spectra of **3**, **6**, and **7** exhibited the expected singlet resonance in the range δ −3135 to −3152, consistent with a PtN_3S core.[13] Interestingly, **6** and **7** showed no propensity for reduction to platinum metal by the 1,2-carborane entity,[9] a factor that is most likely attributed to the stabilization of the metal center by the electron-rich *terpy* and thiolato ligands.

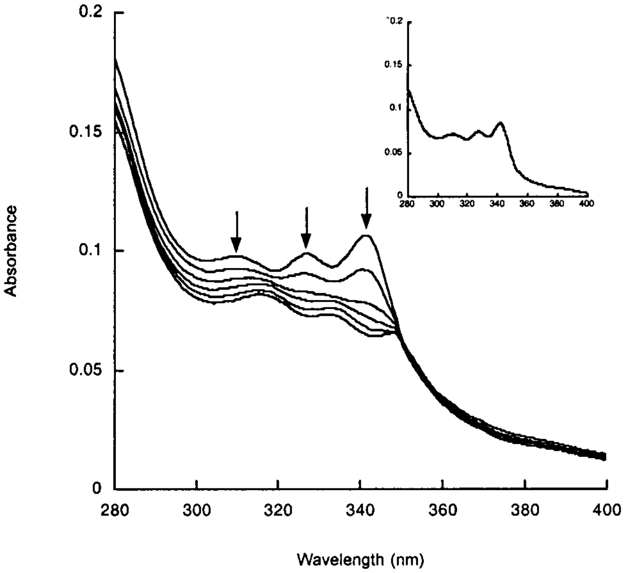


Figure 1. UV−visible spectroscopy experiment. Titration of calf-thymus DNA (1.8, 2.4, 3.4, 3.6, 3.8, and 5.0 μM) with **7** (12.5 μM) in 1 mM phosphate buffer solution containing 20% (*v*/*v*) MeOH at 298 K. Arrows indicate the direction of change upon increasing DNA concentration. The UV−visible spectrum of **7** is also shown (inset).

In order to determine the DNA-binding characteristics of **3**, **6**, or **7**, the UV−visible spectroscopic changes that occurred upon their interaction with calf-thymus DNA were monitored. A typical experiment is presented in Figure 1. Within each series of titration experiments there was a progressive bathochromic shift in the absorbance maxima accompanied by hypochromism with increasing nucleic acid concentrations, features that are characteristic of other platinum(II)−*terpy* metallointercalators.[14,15] Complex **7** exhibited the greatest bathochromic shifts obtained in this study, with the bands at 340, 326, and 309 nm shifted by 9, 6, and 6 nm, respectively (Figure 1). At low r_f values (<2.5),[16] no changes were observed in the spectra of **3**, **6**, and **7**; only at higher r_f values did these shifts occur, most probably the result of unfavorable steric interactions between the carborane moiety and DNA.[17] The spectroscopic changes observed, particularly with **7**, are consistent with extensive intercalation of the platinum(II)−*terpy* chromophore between the base pairs of DNA. Furthermore, all complexes showed a distinct isosbestic point at ca. 349 nm in their spectra, which is consistent with the presence of two distinct forms of the complex in solution, i.e., free and intercalated. At this stage, the spectroscopic titration data cannot be fitted to a suitable binding model using the Scatchard method[18] for the determination of K_{assoc} values. Indeed, deviations from Beer's law are apparent at platinum concentrations greater than 13 μM. This effect is consistent with the aggregation of the complexes in aqueous solution, thus complicating the Scatchard analysis. The formation of similar types of aggregates has been reported previously for related complexes such as $[PtMe(\textit{terpy})]^+$,[15] and, in the case of **3**, **6**, or **7**, the aggregation is probably driven by both the hydrophobicity of the carborane moiety and π-stacking interactions involving the planar platinum(II)−*terpy* moiety.[19] Despite this phenomenon, it is clear from the results of the DNA-binding

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(16) r_f is defined as the molar ratio of Pt added per DNA base pair.

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(19) Experiments that are designed to probe the formation and stability of the proposed assemblies in aqueous solution are planned.

experiments that, at the concentration of complex used in this study (12.5 μM), there must exist a sufficiently high proportion of monomeric species in solution to give rise to the proposed intercalative interactions that are observed with DNA.

In conclusion, complexes **3**, **6**, and **7** represent the first examples of DNA metallointercalators containing a carborane entity. We are currently in the process of preparing analogous complexes containing a carborane moiety tethered to long alkyl chains, in order to determine whether the DNA binding can be enhanced by reducing unfavorable steric interactions between the carborane and the nucleic acid. The results of this work will be reported elsewhere.

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Supporting Information Available: Synthesis and characterization of **1**−**3**, **6**, and **7** and DNA-binding protocol. This material is available free of charge via the Internet at http://pubs.acs.org.

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