Synthesis and reactivity of palladium and platinum diimine complexes containing boronate esters

Arienne S. King, Liliya G. Nikolcheva, Christopher R. Graves, Anna Kaminski, Christopher M. Vogels, Robert H.E. Hudson, Robert J. Ireland, Stephen J. Duffy, and Stephen A. Westcott

Abstract: Condensation of α-diketones (2,3-butanedione, benzil, and acenaphthenequinone) with 3-$H_2NC_6H_4Bpin$ (pin = 1,2-$O_2C_2Me_4$) gave the corresponding boron-containing α-diimines. The addition of these ligands to $[MCl_2(coe)]_2$ (coe = *cis*-cyclooctene, M = Pd or Pt) gave complexes of the type *cis*-MCl_2(α-diimine) in moderate to high yields. The platinum complexes have been examined for their ability to bind to DNA using enzyme digest studies. These complexes were found to bind to single-stranded DNA as well as, or better than, the non-boron containing controls, and showed binding similar to that of cisplatin (*cis*-$PtCl_2(NH_3)_2$).

Key words: boronate esters, diazabutadienes, DNA-binding, platinum.

Résumé : La condensation d'α-dicétones (butane-2,3-dione, benzile, et acénaphtènequinone) avec le 3-$H_2NC_6H_4Bpin$ (pin = 1,2-$O_2C_2Me_4$) conduit à la formation d'α-diimines contenant du bore. L'addition de ces ligands au $[MCl_2(coe)]_2$ (coe = *cis*-cyclooctène; M = Pd, Pt) fournit des complexes du type *cis*-MCl_2(α-diimine) avec des rendements allant de modérés à élevés. Faisant appel à des études de digestion d'enzymes, on a évalué la capacité de ces complexes du platine à se fixer sur l'ADN. Vis-à-vis de l'ADN à brin unique, ces complexes se fixent aussi bien, ou mieux, que les contrôles ne contenant pas de bore et leur taux de fixation est semblable à celui du cisplatine, *cis*-$PtCl_2(NH_3)_2$.

Mots clés : esters de l'acide boronique, diazabutadiènes, fixation de l'ADN, platine.

[Traduit par la Rédaction]

Introduction

Interest in compounds containing boronic acids $[RB(OH)_2]$ or boronate esters $[RB(OR')_2]$ arises from their remarkable versatility in organic synthesis (1) as well as from their potent biological activities (2–11). As part of our ongoing program generating novel boron compounds (12), we decided to examine the synthesis and reactivity of a series of α-diimines containing boronate esters.

1,4-Diazabutadienes (α-diimines) have both been used extensively as ligands for transition metals, owing to their ease of preparation and ability to fine-tune both steric and electronic properties (13). The resulting coordination complexes have been utilized in organic synthesis and catalysis (13–20) and as luminescence labels for the detection and photochemical cleavage of DNA (21). Diazabutadienes have also been used in dehalosilylation – ring-closure reactions of $SbCl_3$ and $BiCl_3$ to give the corresponding 1,2,5-pnictadiazoles (22). Some of the unique chemical and physical properties observed for metal diimine complexes have been attributed to the relatively strong π-acceptor ability of the diazabutadiene ligands, resulting from an energetically low-lying LUMO (23). Although fluorinated α-diimines have recently been prepared (24), to the best of our knowledge no such systems containing boronate esters have been reported. Diimines containing these electron-withdrawing groups would be expected to possess low lying LUMOs, and consequently, be strong π-acceptors. The results of our initial investigations into preparing these compounds, and the corresponding palladium and platinum complexes, are presented herein.

Received 7 June 2002. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 30 August 2002.

A.S. King, **L.G. Nikolcheva**, **C.R. Graves**, **C.M. Vogels**, **S.J. Duffy, and S.A. Westcott.**[1] Department of Chemistry, Mount Allison University, Sackville, NB E4L 1G8, Canada. **R.J. Ireland.** Department of Biology and Biochemistry, Mount Allison University, Sackville, NB E4L 1G7, Canada. **A. Kaminski and R.H.E. Hudson**. Department of Chemistry, The University of Western Ontario, London, ON N6A 5B7, Canada.

[1]Corresponding author (e-mail: swestcott@mta.ca).

Experimental

The reagents and solvents used were obtained from Aldrich Chemicals. NMR spectra were recorded on a JEOL JNM-GSX270 FT-NMR spectrometer. ^1H NMR chemical shifts are reported in ppm and referenced to residual protons in deuterated solvent at 270 MHz. ^{11}B NMR chemical shifts are referenced to external $F_3B{\cdot}OEt_2$ at 87 MHz. ^{13}C NMR chemical shifts are referenced to solvent carbon resonances as internal standards at 68 MHz. Multiplicities are reported as (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad, and (ov) overlapping. Infrared spectra were obtained using a Mattson Genesis II FT-IR spectrometer, and are reported in cm^{-1}. Melting points were measured (uncorrected) with a Mel-Temp apparatus. Microanalyses for C, H, and N were carried out at Desert Analytics (Tucson,

 DOI: 10.1139/V02-145 © 2002 NRC Canada

AZ) and CMA (Vancouver, BC). All reactions were carried out in ambient conditions and the products were found to be stable indefinitely under those circumstances. Polymerization experiments were done by Dr. Marc Kristen (Basell Polyolefin GmbH).[2]

Synthesis

1,4-Bis[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-2,3-dimethyl-1,4-diaza-1,3-butadiene (1a)

An EtOH solution (5 mL) of 3-$H_2NC_6H_4$Bpin (3-APBpin (pin = 1,2-$O_2C_2Me_4$)) (1.67 g, 7.62 mmol) was added dropwise to 2,3-butanedione (0.30 g, 3.48 mmol) in EtOH (3 mL). Following the addition of formic acid (1 drop), the reaction was heated at reflux (4 h) and then stored at 0°C, whereupon a beige precipitate formed, which was collected by suction filtration and washed with hexane (3 × 10 mL). Yield: 1.10 g (65%); mp 225–227°C. IR (Nujol) (cm^{-1}): 2937, 2912, 2856, 1637, 1599, 1570, 1483, 1464, 1417, 1358, 1321, 1265, 1201, 1140, 1076, 966, 901, 881, 849, 804, 779, 714, 706, 671. ^{1}H NMR ($CDCl_3$) δ: 7.54 (d, *J* = 8 Hz, 2H, Ar), 7.36 (ov dd, *J* = 8 Hz, 2H, Ar), 7.22 (br s, 2H, Ar), 6.85 (br d, *J* = 8 Hz, 2H, Ar), 2.11 (s, 6H, N=C(CH_3)), 1.34 (s, 24H, BO_2(CH_3)$_4$). ^{13}C NMR δ: 168.3, 150.5, 130.2, 130 (br, C-B), 128.5, 124.9, 121.6, 83.9, 25.0, 15.5. ^{11}B NMR δ: 31 (br).

1,4-Bis[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-2,3-diphenyl-1,4-diaza-1,3-butadiene (1b)

A CH_2Cl_2 solution (10 mL) of 3-APBpin (1.17 g, 5.35 mmol) was added dropwise to benzil (0.50 g, 2.38 mmol) in methylene chloride (10 mL). Activated molecular sieves (10 g) were added and the reaction was heated at reflux for 24 h. The molecular sieves were removed by suction filtration and washed with CH_2Cl_2 (3 × 10 mL). Removal of the solvent under vacuum gave an oil that was triturated with cold Et_2O (10 mL) to afford a yellow solid. Yield: 0.87 g (60%); mp 224°C. IR (Nujol) (cm^{-1}): 2915, 2856, 1620, 1461, 1376, 1315, 1268, 1142, 1071, 965, 899, 853, 785, 697. ^{1}H NMR ($CDCl_3$) δ: 7.88 (br d, *J* = 8 Hz, 4H, Ar), 7.46–7.35 (ov m, 8H, Ar), 7.06 (ov dd, *J* = 8 Hz, 2H, Ar), 6.97 (br s, 2H, Ar), 6.56 (br d, *J* = 8 Hz, 2H, Ar), 1.26 (s, 12H, BO_2(CH_3)$_4$), 1.22 (s, 12H, BO_2(CH_3)$_4$). ^{13}C NMR δ: 164.4, 148.8, 138.0, 131.0, 130.9, 130 (br, C-B), 128.7, 128.4, 127.8, 126.7, 122.9, 83.6, 24.9, 24.8. ^{11}B NMR δ: 31 (br).

1,4-Bis[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-2,3-acenaphthene-1,4-diaza-1,3-butadiene (1c)

A CH_2Cl_2 solution (10 mL) of 3-APBpin (1.20 g, 5.49 mmol) was added dropwise to acenaphthenequinone (0.50 g, 2.74 mmol) in CH_2Cl_2 (10 mL), in the presence of activated molecular sieves (10 g). The reaction was allowed to proceed at room temperature for 12 days, at which point the sieves were removed by suction filtration and the solution was washed with CH_2Cl_2 (3 × 10 mL). Removal of the solvent under vacuum gave an oily mixture that was triturated with Et_2O (3 × 5 mL) to afford an orange solid. Yield: 1.11 g (70%); mp 245°C. IR (Nujol) (cm^{-1}): 2974, 2882, 2843, 1666, 1644, 1594, 1568, 1461, 1415, 1359, 1315, 1271, 1231, 1143, 1098, 1072, 1045, 964, 943, 871, 850, 783, 703. ^{1}H NMR ($CDCl_3$) δ: 7.85 (d, *J* = 8 Hz, 2H, Ar), 7.69 (d, *J* = 8 Hz, 2H, Ar), 7.55 (s, 2H, Ar), 7.46 (ov dd, *J* = 8 Hz, 2H, Ar), 7.33 (ov dd, *J* = 8 Hz, 2H, Ar), 7.20 (br d, *J* = 8 Hz, 2H, Ar), 6.78 (d, *J* = 8 Hz, 2H, Ar), 1.33 (s, 24H, BO_2(CH_3)$_4$). ^{13}C NMR δ: 161.2, 151.4, 141.8, 131.2, 130.7, 130 (br, C-B), 128.8 (2C), 128.7, 127.7, 124.3, 124.1, 121.2, 83.9, 25.0. ^{11}B NMR δ: 30 (br).

(1,4-Bis[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-2,3-dimethyl-1,4-diaza-1,3-butadiene)dichloropalladium(II) (2a)

To a stirred CH_2Cl_2 solution (10 mL) of [$PdCl_2$(coe)]$_2$ (0.10 g, 0.17 mmol), **1a** (0.18 g, 0.37 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction was allowed to proceed for 18 h, at which point the solvent was removed under vacuum to afford an orange solid, which was then triturated with Et_2O (3 × 10 mL). Yield: 0.19 g (84%); mp 200–202°C (decomp.). IR (Nujol) (cm^{-1}): 2943, 2904, 2870, 1603, 1462, 1427, 1358, 1311, 1269, 1140, 1076, 964, 858, 704. ^{1}H NMR ($CDCl_3$) δ: 7.76 (br d, *J* = 8 Hz, 2H, Ar), 7.54 (br ov m, 2H, Ar), 7.38 (br ov m, 4H, Ar), 2.13 (br s, 6H, N=C(CH_3)), 1.34 (s, 24H, BO_2(CH_3)$_4$). ^{13}C NMR δ: 179.6, 145.0, 134.4, 129.8 (br, C-B), 128.9, 128.3, 126.1, 84.2, 25.1, 21.2. ^{11}B NMR δ: 31 (br). Anal. calcd. for $PdCl_2C_{28}H_{38}N_2B_2O_4$: C 50.51, H 5.77, N 4.21; found: C 49.94, H 5.87, N 4.16.

(1,4-Bis[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-2,3-diphenyl-1,4-diaza-1,3-butadiene)dichloropalladium(II) (2b)

A CH_2Cl_2 solution (5 mL) of **1b** (0.12 g, 0.20 mmol) was added dropwise to a stirred solution of [$PdCl_2$(coe)]$_2$ (0.05 g, 0.09 mmol) in CH_2Cl_2 (10 mL). The reaction was allowed to proceed for 6 h, at which point the solvent was removed under vacuum to afford an orange solid. The solid was triturated with Et_2O (3 × 10 mL). Yield: 0.11 g (77%); mp 214–216°C (decomp.). IR (Nujol) (cm^{-1}): 2937, 2868, 1601, 1462, 1423, 1377, 1358, 1319, 1271, 1142, 1074, 999, 852, 723, 700, 561. ^{1}H NMR ($CDCl_3$) δ: 7.52 (br d, *J* = 8 Hz, 4H, Ar), 7.38 (br d, *J* = 8 Hz, 2H, Ar), 7.08–6.92 (br ov m, 12H, Ar), 1.29 (s, 24H, BO_2(CH_3)$_4$). ^{13}C NMR δ: 178.6, 145.4, 134.0, 132.2, 130.3, 130 (br, C-B), 129.9, 128.7, 127.9, 127.6, 127.3, 84.0, 25.0. ^{11}B NMR δ: 31 (br). Anal. calcd. for $PdCl_2C_{38}H_{42}N_2B_2O_4$: C 57.78, H 5.37, N 3.55; found: C 56.94, H 5.31, N 3.49.

(1,4-Bis[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-2,3-acenaphthene-1,4-diaza-1,3-butadiene)dichloropalladium(II) (2c)

A CH_2Cl_2 solution (5 mL) of **1c** (0.11 g, 0.19 mmol) was added dropwise to a stirred solution of [$PdCl_2$(coe)]$_2$ (0.05 g, 0.09 mmol) in CH_2Cl_2 (10 mL). The reaction was allowed to proceed for 6 h, whereupon removal of the solvent under vacuum afforded an orange solid, which was triturated with Et_2O (3 × 5 mL). Yield: 0.11 g (80%); mp 338°C (decomp.). IR (Nujol) (cm^{-1}): 2967, 2945, 2894, 2871, 2847, 1599, 1579, 1461, 1376, 1359, 1141, 971, 735, 701. ^{1}H NMR

[2] Supplementary material may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada (http://www.nrc.ca/cisti/irm/unpub_e.shtml).

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($CDCl_3$) δ: 8.09 (d, *J* = 8 Hz, 2H, Ar), 7.93 (d, *J* = 8 Hz, 2H, Ar), 7.78 (br s, 2H, Ar), 7.59 (ov dd, *J* = 8 Hz, 2H, Ar), 7.49–7.43 (ov m, 4H, Ar), 6.73 (d, *J* = 8 Hz, 2H, Ar), 1.33 (s, 24H, $BO_2(CH_3)_4$). ^{13}C NMR (in DMF) δ: 177.4, 147.9, 146.1, 135.0, 133.0, 132.2, 131.0 (br, C-B), 129.7, 129.5, 129.1, 126.7, 126.1, 126.0, 84.9, 25.2. ^{11}B NMR δ: 29 (br). Anal. calcd. for $PdCl_2C_{36}H_{38}N_2B_2O_4$: C 56.76, H 5.04, N 3.68; found: C 56.94, H 5.08, N 3.90.

(1,4-Bis[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-2,3-dimethyl-1,4-diaza-1,3-butadiene)dichloroplatinum(II) (3a)

A CH_2Cl_2 solution (5 mL) of **1a** (0.14 g, 0.29 mmol) was added dropwise to a stirred solution of $[PtCl_2(coe)]_2$ (0.10 g, 0.13 mmol) in CH_2Cl_2 (10 mL). The reaction was allowed to proceed for 18 h, at which point the solvent was removed under vacuum to give an oily solid. The mixture was triturated with Et_2O (4 × 5 mL) to afford an orange solid. Yield: 0.15 g (76%); mp 204°C (decomp.). IR (Nujol) (cm^{-1}): 2943, 2908, 2870, 1603, 1462, 1377, 1358, 1313, 1269, 1213, 1142, 1076, 964, 858, 806, 704, 677. ^1H NMR ($CDCl_3$) δ: 7.78 (br d, *J* = 8 Hz, 2H, Ar), 7.56–7.31 (br ov m, 6H, Ar), 1.76 (s, 6H, N=C(CH_3)), 1.33 (s, 24H, $BO_2(CH_3)_4$). ^{13}C NMR δ: 178.1, 145.1, 134.6, 130 (br, C-B), 128.4, 128.1, 126.5, 84.2, 25.1, 21.0. ^{11}B NMR δ: 31 (br). Anal. calcd. for $PtCl_2C_{28}H_{38}N_2B_2O_4$: C 44.58, H 5.09, N 3.71; found: C 44.78, H 5.38, N 3.63.

(1,4-Bis[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-2,3-diphenyl-1,4-diaza-1,3-butadiene)dichloroplatinum(II) (3b)

A CH_2Cl_2 solution (5 mL) of **1b** (0.20 g, 0.33 mmol) was added dropwise to a stirred solution of $[PtCl_2(coe)]_2$ (0.12 g, 0.16 mmol) in CH_2Cl_2 (10 mL). The reaction was allowed to proceed for 4 h, at which point the solvent was removed under vacuum to afford an oil, which was triturated with Et_2O (3 × 5 mL) and hexane (4 × 5 mL) to afford a red solid. Yield: 0.17 g (60%); mp 278°C (decomp.). IR (Nujol) (cm^{-1}): 2945, 2902, 2872, 1603, 1462, 1377, 1358, 1325, 1271, 1144, 1076, 964, 854, 700, 567. ^1H NMR ($CDCl_3$) δ: 7.56 (br d, *J* = 8 Hz, 4H, Ar), 7.41 (br ov m, 4H, Ar), 7.07–6.81 (br ov m, 10H, Ar), 1.29 (s, 24H, $BO_2(CH_3)_4$). ^{13}C NMR δ: 178.3, 145.7, 134.1, 132.9, 131.3, 130 (br, C-B), 129.5, 128.1, 127.8 (2C), 127.2, 84.0, 25.0. ^{11}B NMR δ: 31 (br). Anal. calcd. for $PtCl_2C_{38}H_{42}N_2B_2O_4$: C 51.95, H 4.83, N 3.19; found: C 51.57, H 4.61, N 3.22.

(1,4-Bis[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-2,3-acenaphthene-1,4-diaza-1,3-butadiene)dichloroplatinum(II) (3c)

A CH_2Cl_2 solution (5 mL) of **1c** (0.16 g, 0.27 mmol) was added dropwise to a stirred solution of $[PtCl_2(coe)]_2$ (0.10 g, 0.13 mmol) in CH_2Cl_2 (10 mL). The reaction was allowed to proceed for 4 h, at which point the solvent was removed under vacuum. The resultant oily solid was triturated with Et_2O (3 × 10 mL) to afford a red solid. Yield: 0.17 g (77%); mp 350°C (decomp.). IR (Nujol) (cm^{-1}): 2924, 2855, 1600, 1420, 1358, 1303, 1210, 1145, 967, 856, 777, 703. ^1H NMR ($CDCl_3$) δ: 8.24 (d, *J* = 8 Hz, 2H, Ar), 7.96 (d, *J* = 8 Hz, 2H, Ar), 7.88 (br s, 2H, Ar), 7.67–7.57 (ov m, 4H, Ar), 7.40 (ov dd, *J* = 8 Hz, 2H, Ar), 6.89 (br d, *J* = 8 Hz, 2H, Ar), 1.33 (s, 24H, $BO_2(CH_3)_4$). ^{13}C NMR δ: 175.6, 147.2, 144.5, 135.6, 132.2, 131.0, 130 (br, *C*-B), 129.7, 129.1, 128.8, 126.3, 126.1, 124.5, 84.2, 25.0. ^{11}B NMR δ: 30 (br). Anal. calcd. for $PtCl_2C_{36}H_{38}N_2B_2O_4$: C 50.84, H 4.51, N 3.29; found: C 50.44, H 4.69, N 3.40.

Nuclease digest studies

Binding of the platinum complexes to DNA was investigated using enzymatic degradation of the DNA to nucleosides. Nucleosides were detected using reverse-phase HPLC. The sequence of the model 20-mer DNA strand used in this study (eq. [1]) has two predominant cisplatin-binding-sites: TGGT on one strand and AGGA on the complementary strand. Both the single and the double DNA strands were incubated with each platinum complex, in a 1:3 DNA:Pt molar ratio, for 24 h, in the dark. Samples (2.0 nmol of single-stranded and 1.0 nmol of double-stranded DNA) were digested in series with DNAse I (Amersham Biosciences) (36 U, 4 h), nuclease P1 (Sigma) (10 U, 18 h), and alkaline phosphatase (Promega) (20 U, 4 h), at 37°C, to convert the DNA strand into mononucleosides. The samples were heated to 90°C for 2 min, centrifuged at 10 000 g for 30 s, and then the protein pellet was discarded. The nucleoside composition in each sample was analyzed at 254 nm on a C_{18} column, using a Pro-Star RP-HPLC (Varian). The isocratic solvent system used was Et_3NH–OAc (93%, 20 mM, pH 6.5) and CH_3CN (7%, 1 mL min^{-1}). The areas under the nucleoside peaks were integrated and the G:C ratio analyzed and compared with ANOVA, followed by post-hoc multiple comparisons with Bonferonni's adjustment.

[1] 5′ T C T C C T T C **T G G T** C T C T T C T C 3′
3′ A G **A G G A** A G A C C A G A G A A G A G 5′

Equation [1] illustrates the sequence of the DNA 20-mer used in the binding studies. Possible platinum binding sites are shown in bold type.

Results and discussion

Diimines

Protection of the boronic acid groups in commercially available 3-aminophenylboronic acid (3-$H_2NC_6H_4B(OH)_2$), by transesterification with pinacol ($HOCMe_2CMe_2OH$) to prevent unwanted formation of anhydrides (25), gave quantitative formation of aminoboronate ester 3-$H_2NC_6H_4$Bpin (3-APBpin (pin = $O_2C_2Me_4$)) (12). Unfortunately, the addition of 3-APBpin to glyoxal gave complex product distributions, as evidenced by ^1H NMR spectroscopy, and isolation of the corresponding boron-containing diazabutadiene proved unsuccessful. This result is not surprising as previous studies have shown that glyoxal reacts with electron-deficient amines, such as 3-nitroaniline, to give high yields of 1,2-dihydroxy-1,2-diamino compounds (26). Conversely, we found that reactions of 3-APBpin proceeded smoothly with substituted α-diketones, 2,3-butanedione, benzil, and acenaphthenequinone, to give the corresponding boron-containing α-diimines (**1a**–**1c**) in moderate yields (Fig. 1). All diazabutadienes were characterized by multinuclear NMR spectroscopy. A peak at ca. δ 30 ppm in the ^{11}B NMR spectra is indicative of a three-coordinate boron atom, which suggests that no appreciable intermolecular interaction

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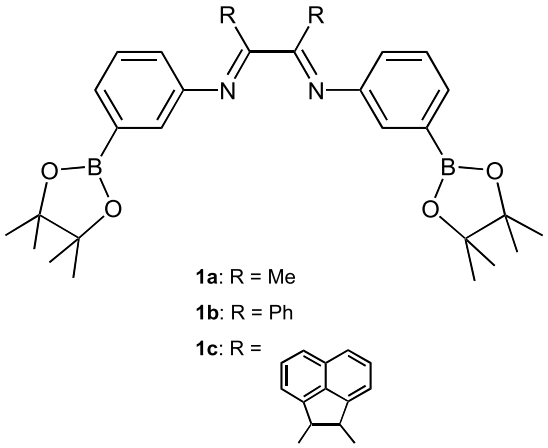
Fig. 1. α-Diimines derived from 3-APBpin.



occurs with the basic imine functionality in solution (27). Although one boron resonance is observed for **1b**, it is interesting to note that two separate peaks are observed for the Bpin methyl groups in the ^{1}H NMR spectra, presumably arising from the perpendicular phenyl groups in the backbone. It is plausible that restricted rotation about the B–C bond causes this loss of symmetry.

Palladium complexes

To examine the potential of these electron withdrawing diimines to act as ligands, we have prepared palladium complexes **2a**–**2c** by the addition of **1a**–**1c** to organic-soluble $[PdCl_2(coe)]_2$ (28, Fig. 2). Indeed, complexes **2a**–**2c** were prepared in high yield and characterized using a number of physical methods, including multinuclear NMR spectroscopy. The boron atom appears to maintain its three-coordinate geometry in solution, as evidenced by a peak at 30 ppm in the ^{11}B NMR spectra. Coincidentally, only one peak is observed for the Bpin methyl groups in the ^{1}H NMR spectra for **2b**.

Electrophilic 1,4-diazabutadiene palladium complexes have found extensive application as catalysts in the polymerization of alkynes (29) and alkenes (14, 30–34). Unfortunately, attempts to catalyze the polymerization of ethylene using complexes **2a**–**2c** proved unsuccessful. Although the addition of electron-withdrawing boronate ester groups should enhance polymerization activities, previous studies have shown that palladium diimine complexes also require bulky substituents in the ortho- position of the *N*-aryl group to be effective catalysts. Indeed, complexes lacking this steric requirement are known to give oligomerization products (14). It appears that the boronate ester groups in **2a**–**2c** are too far removed from the metal center to provide the steric requirement needed for polymerization. Future studies will, therefore, concentrate on designing analogous diimine catalysts derived from 2-APBpin (35).

Platinum complexes

Cisplatin (*cis*-$PtCl_2(NH_3)_2$) is one of the most effective chemotherapeutic agents currently used for the treatment of ovarian, bladder, and testicular cancer (36–44). The drug has to be administered intravenously, however, and has dose-limiting side effects such as severe renal toxicity, neurotoxicity, and emesis, arising, in part, from the low solubility of cisplatin in water. These problems, along with the fact that cancer cells treated with cisplatin acquire resistance to the drug, have resulted in considerable research focussed on the development of a more effective platinum drug that can be administered orally and with reduced side effects. Cisplatin acts by making intra- and interstrand cross-links with DNA, which result in a halt of replication and lead to programmed cell death. Structural analogues of cisplatin, however, react with DNA in a way similar to the parent drug and therefore cause similar biological effects (36). In fact, to be considered for clinical evaluation, a new platinum drug should have an activity different from that of cisplatin and thereby eliminate multi-factorial drug resistance. Therefore, it is highly unlikely that future platinum drug candidates will adhere to the classical structure-activity relationships for cisplatin analogues. Toward this objective, we have prepared platinum complexes (**3a**–**3c**) containing α-diimines by addition to $[PtCl_2(coe)]_2$ (45, Fig. 2). The use of bidentate ligands prevents trans labilization and undesired displacement of the ligands by sulfur and nitrogen donors in biomolecules, interactions that are believed to be responsible for the adverse side effects associated with cisplatin (42).

Interactions of platinum complexes with DNA

As the efficacy of platinum-based anticancer drugs is believed to arise from the coordination of the metal to DNA (43), we decided to examine the binding potential of plati-

Fig. 2. Preparation of metal complexes.

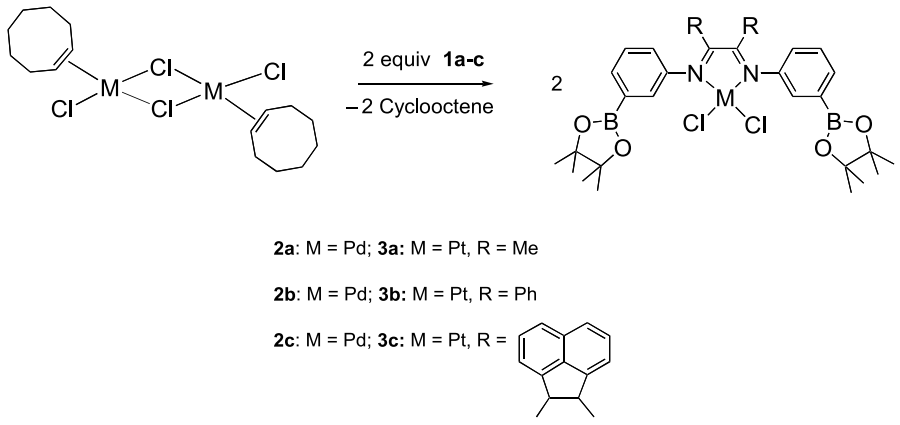


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Fig. 3. The G:C ratio from the nuclease digests of single-stranded 20-mer DNA. Values are mean ±95%CI (n = 10). Complex **4c** is not significantly different from the non-platinum control at $p > 0.05$.

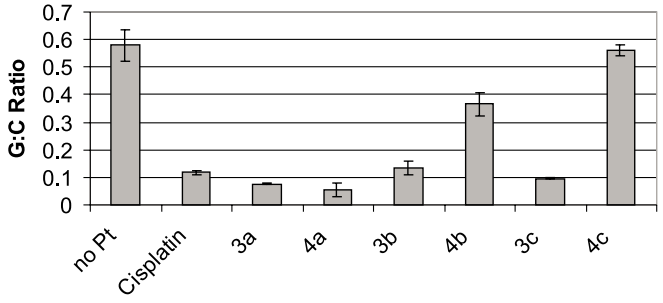
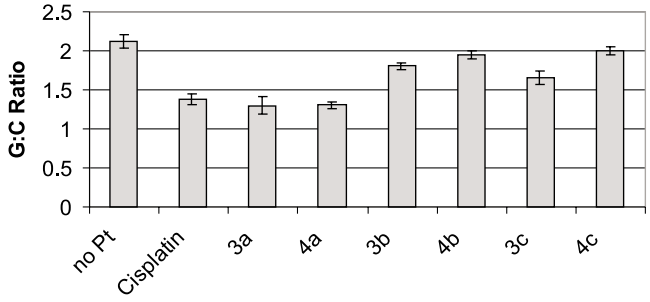


Fig. 4. The G:C ratio from the nuclease digests of double-stranded 20-mer DNA. Values are mean ±95%CI (n = 10). Complexes **3b**, **4b**, and **4c** are not significantly different from the non-platinum control at $p > 0.05$.



num complexes **3a**–**3c** using a 20-bp strand (46). This DNA model contains one preferential binding site (a TGGT motif) in the single strand and a second binding site (AGGA) on the complementary strand. The degree of platinated DNA can be quantified by enzymatically degrading the DNA strand and separating the mononucleosides and Pt-containing dinucleotides using reverse-phase HPLC (47–49). Platinum binding will result in the formation of *cis*-[Pt(diimine){d(GpG)}], and the amount of free guanosine can, therefore, be negatively correlated to the degree of platinated DNA. Cytosine can be used as an internal standard because its concentration is not affected by platinated DNA (50–52).

As expected, the nuclease digest results showed that treatment with cisplatin significantly decreased the G:C ratio (compared to the unplatinated control) in both single-stranded (Fig. 3) and double-stranded DNA (Fig. 4), and confirmed that cisplatin binds well to both types of DNA. The binding affinity for single-stranded DNA was also found to decrease as the size of the backbone of the non-boron diimine compounds (**4a**–**4c**, 14) increased. This result was also evident in the double-stranded samples. It is possible that the larger, more sterically-hindered backbones of **4b** and **4c** do not fit into the binding site and are therefore excluded from the major groove of double-stranded DNA. Remarkably, the boron-containing compounds (**3a**–**3c**) bound to single-stranded DNA as well as, or better than, the non-boron controls, and exhibited binding capabilities not significantly different from those of cisplatin. Binding among the boron complexes could not be correlated with the size of the backbone. These results suggest that the boronate ester may indeed contribute to the increased affinity of these compounds to bind to single-stranded DNA. Compound **3b** showed significant binding to single-, but not to double-stranded DNA; presumably, the flexibility of the DNA single-strand was sufficient to allow access to the binding site, but the complex could not fit into the major groove of the helix in the double-stranded DNA. This binding difference may provide higher selectivity in rapidly dividing cancer cells, where the DNA is replicated at a higher rate, and, as a result, is more often in the single-stranded form. Achieving significant binding to single-, but not to double-stranded DNA, might provide a solution to the problems associated with current platinum therapies. Future work in this area will examine the cytotoxicities of compounds **3a**–**3c**, and relate these findings to binding studies in an effort to design more potent and less toxic platinum complexes for the treatment of cancer.

Conclusion

α-Diimines, derived from the condensation of substituted α-diketones and aminoboronate ester 3-$H_2NC_6H_4$Bpin (pin = $O_2C_2Me_4$), have been prepared in moderate yield and used as ligands for palladium and platinum. The platinum complexes have been studied for their ability to bind to DNA. The boron-containing complexes bound to single-stranded DNA as well as, or better than, the non-boron containing controls, and showed binding not significantly different from that of cisplatin.

Acknowledgements

Thanks are gratefully extended to the Research Corporation (Cottrell College Science Award), Natural Sciences and Engineering Council of Canada (NSERC), Canada Research Chairs program (CRC), the University of Western Ontario, and Mount Allison University for financial support. We also thank Dan Durant (MAU) for expert technical assistance, Dr. Marc Ö. Kristen (Basell Polyolefine GmbH) for conducting polymerization studies, and anonymous reviewers for helpful comments.

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