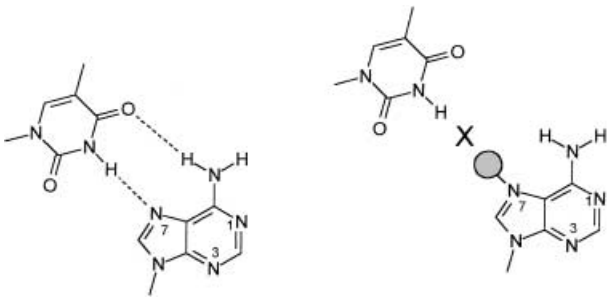
Self-Complementary Metal Complexes Containing a DNA Base Pair**

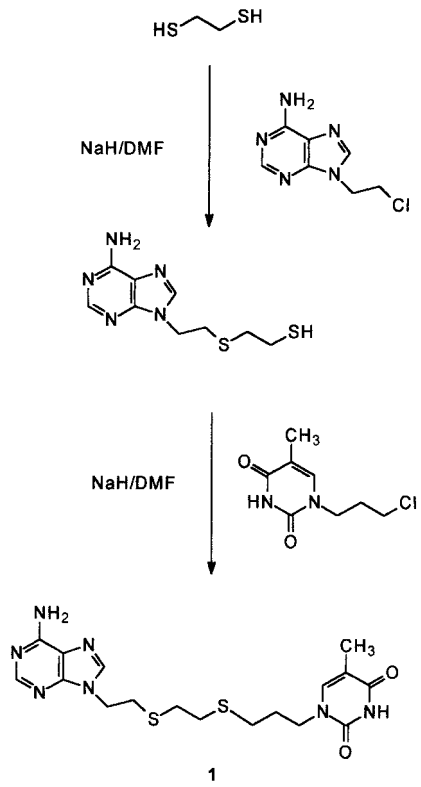
Clayton Price, Benjamin R. Horrocks, Annabelle Mayeux, Mark R. J. Elsegood, William Clegg, and Andrew Houlton*

DNA-type interactions such as hydrogen bonding and aromatic stacking can be used to control the molecular assembly of synthetic compounds in solution and in the solid state.[1] As nucleobases can bind metal ions, base-pairing interactions can be used directly in their complexes.[2] However, in some instances prediction of the resulting assembly is difficult because certain key hydrogen-bond acceptor sites are also preferred for metal-ion binding. This is especially true for the adenine – thymine (AT) pair, in which there are numerous possibilities for interactions which involve two hydrogen bonds (for example, $A_{WC}\cdots T$, $A_H\cdots T$, $A_H\cdots A_H$, $A_{WC}\cdots A_{WC}$, $A_{WC}\cdots A_H$, $T\cdots T$, etc.; where WC and H denote Watson – Crick and Hoogsteen faces). The thermodynamically favored arrangement is the Hoogsteen AT pattern, which involves A-N7[3] (Scheme 1, left). However, since this is also the preferred site for metal-ion binding (right), this pairing mode is often unavailable. Recently, we have been developing the chemistry of chelate-tethered nucleobase strands that can give atypical coordination at the nucleobase.[4] In particular we were able to rationally synthesize A-N3-bound complexes. Such compounds should be capable of undergoing a Hoogsteen interaction with thymine and thus assemble in a predictable manner. Here we demonstrate this with the synthesis of a bis-nucleobase ligand strand **1** containing A and T as substituents.[5, 6] The dithioether **1** reacts with Pd^{II} and Pt^{II} to give cationic A-N3-bonded complexes **2** and **3**. Furthermore, the complexes assemble in the solid state in the predicted manner.



Scheme 1.

The synthesis of the dithioether ligand strand **1** is summarized in Scheme 2 and involves two successive deprotonation/alkylations of 1,2-dithioethane with 9-(2-chloroethyl)adenine[4b] and 1-(3-bromopropyl)thymine,[6a] respectively, to give **1** in 34% yield. The compound is moderately soluble in methanol, DMSO, and DMF.



Scheme 2. Synthesis of **1**.

Reaction of **1** with $[PdCl_2(MeCN)_2]$ in refluxing MeCN/MeOH or $K_2[PtCl_4]$ in H_2O/EtOH gives monocationic complexes $[PdCl(\mathbf{1})]^+$ (**2**) and $[PtCl(\mathbf{1})]^+$ (**3**), which were isolated as BF_4^- salts by addition of a saturated aqueous solution of $NaBF_4$. The resulting complex salts are soluble in water and DMSO. The ^1H NMR spectrum in [D$_6$]DMSO shows marked shifts of individual signals relative to **1**. Most dramatic, perhaps, is the effect on the A-N6H$_2$ signal, which moves significantly downfield and the splitting of which indicates restricted rotation about the exocyclic amino group upon complexation (**1**: $\delta = 7.23$; **2**: $\delta = 8.37, 8.46$; **3**: $\delta = 8.47, 8.57$). Also apparent was the effect of slow inversion at sulfur on some signals (for example, A-H2: **1**: $\delta = 8.16$; **2**: $\delta = 8.36, 8.37$; **3**: $\delta = 8.41, 8.43$; A-H8: **1**: $\delta = 8.14$; **2**: $\delta = 8.26, 8.28$; **3**: $\delta = 8.28, 8.29$). This was also seen in the ^{195}Pt NMR spectrum of **3**, which contains two signals ($\delta = -2137, -2124$) in a 1:2 ratio. Coordination to A-N3 can also be deduced from the downfield shift for the protons on C10 (**1**: $\delta = 4.36$; **2**: $\delta = 5.00, 5.16$; **3**: $\delta = 5.07, 5.13$). This effect is characteristic for N3 binding.[4a,c,d,f, 7] Complexation has little effect, however, on the positions of the thymine group signals (for example, T-N3H: **1**: $\delta = 11.28$; **2**: $\delta = 11.30$; **3**: $\delta = 11.29$).

Based upon these spectroscopic data and the known binding modes for adenine-only analogues[4] of **1** it was anticipated that the dithioether group and the A-N3 site would coordinate to the metal ions. X-ray crystallography[8] confirms this for both **2** and **3** (Figure 1), which are

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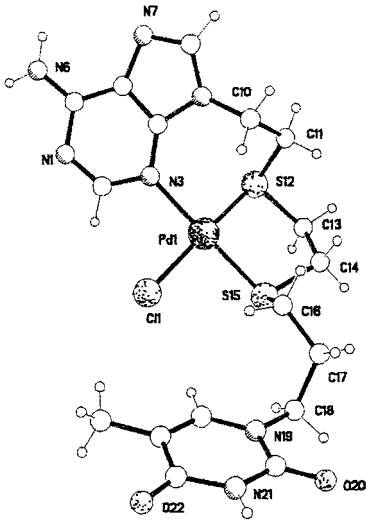

Figure 1. Molecular structure of the cation in **2**. Selected bond lengths [Å]: Pd1-N3 2.051(7), Pd1-S12 2.267(2), Pd1-S15 2.261(2), Pd1-Cl 2.315(2). The Pt complex **3** is isostructural. Pt-N3 2.058(4), Pt-S12 2.2562(12), Pt-S15 2.2583(12), Pt-Cl 2.3225(12). The angles between the adenine and thymine planes is 67.8 (**2**) and 68.6° (**3**).

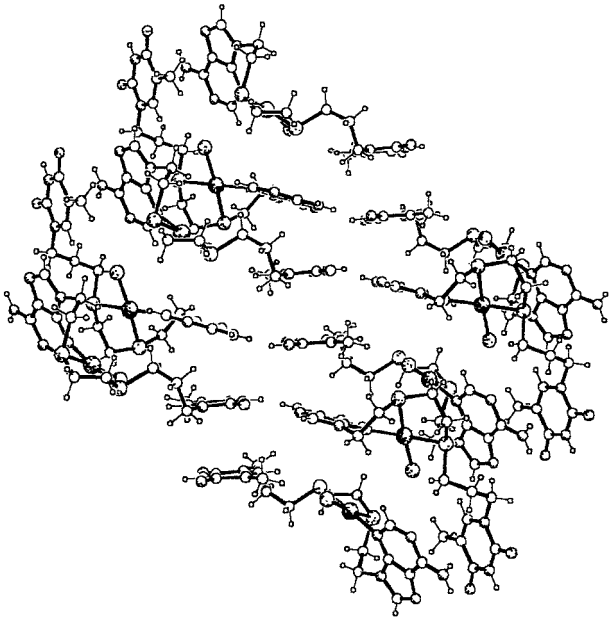

Figure 3. $\pi-\pi$ stacking interactions between base pairs in **2** occur in ATTA sequence. Interplanar T···T distance about 3.394 Å; interplanar angle A···T 19°.

isostructural. In each complex the central metal ion has a slightly distorted square-planar geometry, and **1** acts as a tridentate ligand. The coordination forms five- and seven-membered chelate rings, and the nucleobase is inclined at an angle of 46.2° in **2** and 45.7° in **3**. The angle between the coordinated A and the pendant T is 67.8° in **2** and 68.6° in **3**. Compound **3** is a rare example of a Pt–N3 adenine complex.[7] Interestingly, this type of binding was recently observed in the reaction of the antitumor drug *trans*-[$PtCl_2$\{(*E*)-HN=C(O-Me)Me\}$_2$] with the ribonucleotide r(ApG) in the formation of a 1,2-intrastrand adduct.[7b]

Analysis of the molecular packing reveals the expected Hoogsteen base pairing between cations ($O4_T\cdots N6_A$ 2.940, $N3_T\cdots N7_A$ 2.886 Å; Figure 2). Infinite base-paired chains are formed by translational symmetry and have a repeat distance of 14.8 Å. The crystal symmetry produces antiparallel alignment of neighboring chains. Further interactions between the nucleobases involve dimers of stacked AT pairs that are slipped so as to form ATTA sequence runs with typical separations for $\pi-\pi$ stacking (Figure 3).

In summary, controlling the metal ion nucleobase binding pattern by using a chelating group enables the synthesis of base-pairing complexes that assemble in a predictable arrangement. We are currently investigating further complexation reactions of **1** with regards to metal–ligand stoichiometry and metal ion coordination geometry. In particular it is envisaged that dinucleobase duplex and triplex structures can be assembled by analogy with simple bis- and trischelate complexes.

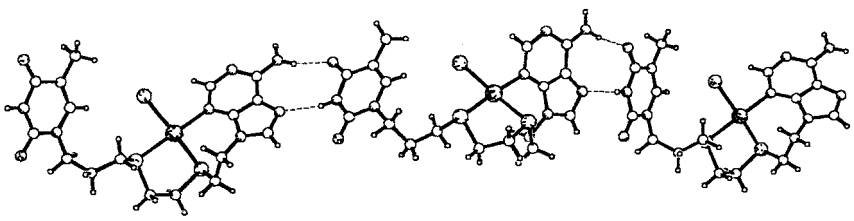

Figure 2. Hoogsteen base pairs formed between complex cations in **2**. A···T interplanar angle is 19°.

Experimental Section

1: NaH (0.12 g, 5.06 mmol) was added to a solution of 1,2-ethanedithiol (0.48 g, 0.42 mL, 5.06 mmol) in dry DMF (100 mL), and the mixture stirred until hydrogen evolution ceased. 9-(2-Chloroethyl)adenine (1.00 g, 5.06 mmol) was added and the mixture was allowed to stir. After 16 h a second equivalent of NaH was added (0.12 g, 5.06 mmol), and the mixture was again stirred until H_2 evolution ceased. A solution of 1-(3-bromopropyl)thymine (1.25 g, 5.06 mmol) in dry DMF (100 mL) was added, and the suspension was stirred for a further 16 h. The solution was filtered (Celite) and taken to dryness under reduced pressure, water (100 mL) was added, and the slurry was extracted into dichloromethane (3×300 mL). The organic extracts were dried (Na_2SO_4), and after evaporative removal of the solvent the crude product was purified by column chromatography (matrix 60 silica) with 15% EtOH in dichloromethane as eluent. Yield: 0.72 g, 34%. ^{1}H NMR ([D_6]DMSO, TMS): $\delta=1.62$ (s, 3H, Thy-CH_3), 1.85 (m, 2H, H17), 2.51 (t, 2H, H16), 2.70 (m, 4H, H13, H14), 3.04 (t, 2H, H11), 4.35 (t, 2H, H18), 4.36 (t, 2H, H10), 7.23 (br s, 2H, H6), 7.54 (s, 1H, Thy-*H*6), 8.14 (s, 1H, Ade-*H*8), 8.16 (s, 1H, Ade-*H*2), 11.28 (s, 1H, Thy-N*H*3); MS: *m*/*z*: 422 [*M*+H]; elemental analysis (%) calcd for $C_{17}H_{23}N_7O_2S_2$: C 48.32, H 5.49, N 23.20; found: C 48.40, H 5.29, N 22.37.

2: To a refluxing solution of $PdCl_2$ (0.038 g, 0.21 mmol) in MeCN (10 mL) was added dropwise a methanolic solution (10 mL) of ligand **1** (0.088 g, 0.21 mmol), and the mixture was refluxed overnight. The cooled solution was taken to dryness under reduced pressure, and the resultant solid residue dissolved in hot water (50 mL). The mixture was filtered to remove undissolved solids and concentrated to a minimum volume in vacuo. Addition of a saturated aqueous solution of $NaBF_4$ precipitated **2** as a yellow solid, which was washed with water, ethanol, and diethyl ether and pump dried. Yield 0.09 g, 66%. ^{1}H NMR ([D_6]DMSO, TMS): $\delta=1.76$, 1.77 (s, 3H, Thy-CH_3), 2.15 (m, 2H, H17), 3.17 (m, 2H, H16), 3.26 (d, 1H, H13′), 3.49 (m, 2H, H14, H14′), 3.61 (d, 1H, H13), 3.65 (m, 1H, H11′), 3.76 (m, 1H, H11), 3.81 (m, 2H, H18), 5.00 (d, 1H, H10′), 5.16 (m, 1H, H10), 7.54 (s, 1H, Thy-*H*6), 8.26,

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8.28 (s, 1H, Ade-*H*8), 8.36, 8.37 (s, 1H, Ade-*H*2), 8.37, 8.46 (br s, 2H, Ade-N6H_2), 11.30 (s, 1H, Thy-N3*H*); MS: *m*/*z*: 562.0 [Pd(**1**)Cl]$^+$; elemental analysis (%) calcd for **2**·3H_2O: C 28.99, H 4.12, N 13.92; found: C 28.13, H 3.97, N 13.14. A small quantity of crystals of **2** suitable for single-crystal X-ray diffraction studies were grown by slow cooling of a hot aqueous solution.[9]

3: Same procedure as for Pd analogue **2**, except that $K_2[PtCl_4]$ (0.074 g, 0.182 mmol) in aqueous solution was used as starting material, and to this was added dropwise a hot ethanolic solution of **1** (0.076 g, 0.182 mmol), and the mixture refluxed overnight. The cooled solution was taken to dryness under reduced pressure, and the resultant solid residue dissolved in hot water (50 mL). The mixture was filtered to remove undissolved solids and concentrated to a minimum volume in vacuo. The addition of a saturated aqueous solution of $NaBF_4$ precipitated **3** as a white solid, which was washed with water, ethanol, and diethyl ether and pump dried. Yield 0.093 g, 69.3%. ^{1}H NMR ([D$_6$]DMSO, TMS): δ = 1.78, 1.81 (s, 3H, Thy-CH_3), 2.13, 2.23 (m, 2H, H17), 3.04 (m, 1H, H16), 3.10 (m, 1H, H16), 3.22 (d, 1H, H13′), 3.36 (m, 1H, H14), 3.39 (m, 1H, H14′), 3.62 (d, 1H, H13), 3.73 (m, 1H, H11′), 3.82 (m, 1H, H11), 4.74 (m, 2H, H18), 4.81, 5.07 (d, 1H, H10′), 5.13 (m, 1H, H10), 7.51, 7.53 (s, 1H, Thy-*H*6), 8.28, 8.29 (s, 1H, Ade-*H*8), 8.41, 8.43 (s, 1H, Ade-H2), 8.47, 8.57 (br s, 2H, Ade-N6H_2), 11.29 (s, 1H, Thy-N3*H*); MS: *m*/*z*: 652.0 [Pt(**1**)Cl]$^+$; elemental analysis (%) calcd for **3**·2H_2O: C 26.35, H 3.51, N 12.65; found: C 27.07, H 3.98, N 12.71. Crystallization by slow cooling of a hot aqueous solution of **3** yielded a few single crystals, some of which were suitable for diffraction studies.[9]

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[8] a) Crystal data for **2**: $C_{17}H_{32}ClF_3N_7O_{6.5}PdS_2Si_{0.5}$, M_r = 715.51, monoclinic, space group *I*2/*a*, *a* = 24.3737(16), *b* = 7.9006(5), *c* = 29.2031(19) Å, β = 97.894(2)°, *V* = 5570.3(6) Å^3, *Z* = 8, ρ_{calcd} = 1.706 g cm^{-3}, Mo$_{K\alpha}$ radiation, λ = 0.71073 Å, μ = 1.00 mm^{-1}, *T* = 160 K. 18467 measured reflections were corrected for absorption; 4903 were unique (R_{int} = 0.0451, $\theta \le 25.0°$); *R* = 0.0829 (*F* values, $F^2 > 2\sigma$), R_w = 0.1771 (F^2 values, all data), GOF 1.312 for 350 parameters, max./min. residual electron density 2.58/ – 1.47 e Å^{-3}. b) Crystal data for **3**: $C_{17}H_{32}ClF_3N_7O_{6.5}PtS_2Si_{0.5}$, M_r = 804.20, monoclinic, space group *I*2/*a*, *a* = 24.4619(10), *b* = 7.9190(3), *c* = 29.1288(10) Å, β = 98.073(2)°, *V* = 5586.7(4) Å^3, *Z* = 8, ρ_{calcd} = 1.912 g cm^{-3}, synchrotron radiation at Darebury Laboratory station 9.8, λ = 0.6942 Å, μ = 5.36 mm^{-1}, *T* = 160 K. 18024 measured reflections were corrected for absorption; 6866 were unique (R_{int} = 0.0360, $\theta \le 27.5°$); *R* = 0.0388 (*F* values, $F^2 > 2\sigma$), R_w = 0.1053 (F^2 values, all data), GOF 1.185 for 350 parameters, max./min. residual electron density 2.49/ – 1.19 e Å^3. c) The anion in both crystal structures wass identified as SiF_6^{2-}, generated by etching of the glass by the aqueous BF_4^- ions. Detailed evidence is available from the authors. d) Programs: standard Bruker AXS control and integration software and SHELXTL. CCDC-170471 (**2**) and CCDC-170472 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Dearomatizing Disrotatory Electrocyclic Ring Closure of Lithiated *N*-Benzoyloxazolidines**

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Aromatic amides—both naphthamides and benzamides—can be dearomatized in a cyclization reaction triggered by a benzylic lithiation α to the amide nitrogen.[1] The reaction has been optimized for the synthesis of functionalized cyclohexadienes **4** and cyclohexenones from amides **1**, and both the benzamide and naphthamide versions of the reaction (Scheme 1) have been employed in the synthesis of important members of the kainoid family of cyclic amino acids.[2]

Superficially, the mechanism of this cyclization appears to be an intramolecular conjugate addition reaction[3] of the benzylic anionic center into the electron-deficient *ortho* position of the aromatic ring, with the product stereochemistry arising from the preference of the phenyl group for the *exo* face of the forming bicyclic ring system. However, under this interpretation, the cyclization of the lithiated benzamide **2** has at least some (Baldwin-disfavored) 5-*endo-trig* character,[4] and the cyclization of a 2-naphthamide **2** (R^1, R^2 = benzo) rather more.

An attractive alternative rationalization, illustrated in the box in Scheme 1, is that the cyclization is pericyclic and

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