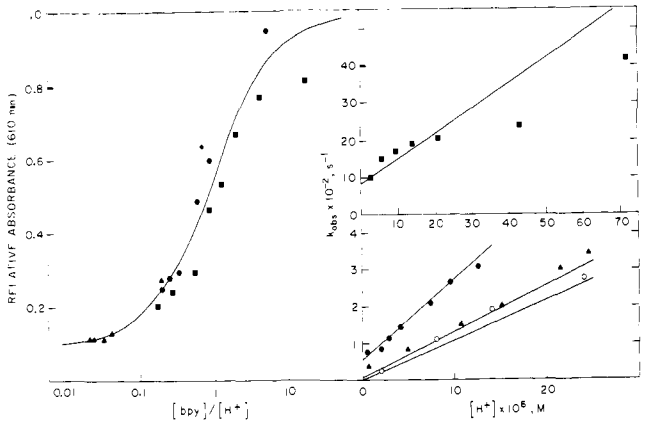

Figure 1. Dependence of equilibrium (left) and kinetics (right) of hydride formation from $Co(bpy)_3^+$ on H^+ and bpy concentrations. The absorbing species is $Co(bpy)_3^+$ (at $(0.3-1.0) \times 10^{-6}$ M). ○, 0.02 M Co(II), 0.002 M total bpy (1.2×10^{-7} M free bpy), 0.1 M ionic strength (no equilibrium data); ▲, 0.005 M Co(II), 0.0016 M total bpy (4.6×10^{-7} M free bpy), 0.04 M ionic strength; ●, 0.001 M Co(II), 0.001 M total bpy (2.5×10^{-6} M free bpy), 0.03 M ionic strength; ■, 0.001 M Co(II), 0.002 M total bpy (1.2×10^{-5} M free bpy), 0.03 M ionic strength. All solutions contained 0.02 M acetate–acetic acid and were deoxygenated with argon. The 1:1 Co(II) to bpy solution contained 0.3 M ethanol; the others contained 0.26 M 2-propanol. (Note: k_{obsd} values at high [bpy] and $[H^+]$ (upper right-hand corner) have not been corrected for the fact that under these conditions eq 1 is comparable in rate to eq 2.)

centration of free bipyridine. Remarkably, however, the slopes also increase with [bpy] and the rate law for the equilibration is given by eq 3 with $a = 1.0 \times 10^7$ M^{-1} s^{-1} and $b = 5.0 \times 10^{12}$ M^{-2}

$$k_{obsd} = (a + b[bpy])([H^+] + ([bpy]/K_2)) \quad (3)$$

s^{-1}. The reaction proceeds by parallel (a and b) paths. The two terms in $[H^+]$ are the forward components of the rate of approach to equilibrium while the two terms in $[bpy]/K_2$ are from the reverse rates.

The magnitude and concentration dependence of the b term in eq 3 suggests the sequence eq 4–7[12] in which the formation of

$$bpy + H^+ \overset{fast}{\rightleftharpoons} (bpy)H^+ \quad (4)$$

$$Co(bpy)_3^+ + (bpy)H^+ \overset{slow}{\rightleftharpoons} Co(bpy)_3^{2+} + (bpy)H\cdot \quad (5)$$

$$(bpy)H\cdot + H^+ \overset{fast}{\rightleftharpoons} (bpy)H_2^{+}\cdot \quad (6)$$

$$(bpy)H\cdot/(bpy)H_2^{+}\cdot + Co(bpy)^{2+}/Co(bpy)_2^{2+} \xrightarrow{fast} Co(bpy)_2(H_2O)H^{2+} \quad (7)$$

(bpy)H· (eq 5) is the rate-determining step in the forward direction. In terms of this mechanism, $b = K_4k_5$ and the b values used in calculating the lines in Figure 1 were obtained from the values reported previously:[9] $K_4 = 2.6 \times 10^4$ M^{-1}, $k_5 = 1.8 \times 10^8$ M^{-1} s^{-1} ($K_6 = 1 \times 10^8$ M^{-1}).

Although the a term in the rate law is of the form expected if eq 2 is an elementary reaction (i.e., $k_2 = 1.0 \times 10^7$ M^{-1} s^{-1}), the fact that (bpy)H· production is implicated for the b term suggests an analogous process for the a term, i.e., eq 4 and 6–9, in which rapid preequilibrium eq 8 is maintained by the reverse

$$Co(bpy)_3^+ \overset{fast}{\rightleftharpoons} Co(bpy)_2^+ + bpy \quad (8)$$

$$Co(bpy)_2^+ + (bpy)H^+ \overset{slow}{\rightleftharpoons} Co(bpy)_2^{2+} + (bpy)H\cdot \quad (9)$$

of eq 1. In this mechanism $a = K_4K_8k_9$. The magnitude of $K_8 = 1.3 \times 10^{-7}$ M, and k_9 is estimated as 3×10^9 M^{-1} s^{-1} from the $Co(bpy)_2^{2+/+}$ and $(bpy)H^{+/0}$ $E°$ values (−1.03[8] and −0.97 V,[9] respectively) and the fact that both couples undergo very rapid electron exchange[8,9] ($\sim 1 \times 10^9$ M^{-1} s^{-1}). Thus $K_4K_8k_9$ is estimated as 1×10^7 M^{-1} s^{-1}, and this route is sufficiently rapid to account quantitatively for the a term. Thus conventional Brønsted proton-transfer paths are not detected in this system. They could, nevertheless, be relatively rapid: our observations impose a limit of $<10^7$ M^{-1} s^{-1} for reaction of either $Co(bpy)_3^+$ or $Co(bpy)_2^+$ with H_3O^+.

The above considerations suggest that the generation of (bpy)H· via reduction of $(bpy)H^+$ by $Co(bpy)_3^+$ or $Co(bpy)_2^+$ is the rate-determining step in $Co(bpy)_2(H_2O)H^{2+}$ formation. Thus actual assemblage of the hydride—presumably via reaction of $Co(bpy)^{2+}$ or $Co(bpy)_2^{2+}$ with (bpy)H· or $(bpy)H_2^{+}$· (eq 7)—must be extremely facile. The reaction could involve H atom transfer or sequential electron and proton transfer, with either possibly coupled to substitution of (bpy)H· on Co(II). Finally, the generality of the free radical route to hydrides is of some interest. Such routes likely obtain in other Co(I) polypyridine systems, being facilitated by the similarity of the reduction potentials for $CoL_n^{2+/+}$ and $LH^{+/0}$ couples,[9] the rapidity of electron transfer among these couples, and (probably) the relatively high substitutional lability of the Co(II) species.[13] Whether or not such routes prevail with other metal centers or other reducible ligands remains to be demonstrated.

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(12) Given the buffer and Co(II) concentrations used, eq 6 is probably rapid compared to eq 7. Thus reaction of either (bpy)H· or $(bpy)H_2^{+}$· with Co(II) (eq 7, $Co(bpy)^{2+}$ or $Co(bpy)_2^{2+}$) is a possibility.

(13) Hydride formation mechanisms in other Co(I) polypyridine systems are currently under study as are the routes via which the hydrides react with water to give H_2. Hydride formation via H-atom abstraction from organic radicals finds precedent in the $Co(CN)_5^{3-}$/alkyl halide systems (Chock, P. B.; Halpern, J. H. *J. Am. Chem. Soc.* **1969**, *91*, 582).

A d(GpG)-Platinated Oligonucleotide Can Form a Duplex with a Complementary Strand

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In the cell, DNA appears to be the primary target of the active aquated forms of the antitumor drug *cis*-$[PtCl_2(NH_3)_2]$ (*cis*-DDP),[2] and the cytotoxicity of the drug could result of a particular bifunctional binding of the *cis*-$Pt^{II}(NH_3)_2$ moiety.[3] It has been shown, using enzymatic digestion methods, that platinum cross-links between adjacent guanines are formed upon reaction of DNA with *cis*-DDP[4,5] and represent more than 50% of the lesions.[5] This is in agreement with the results obtained by enzymatic restriction

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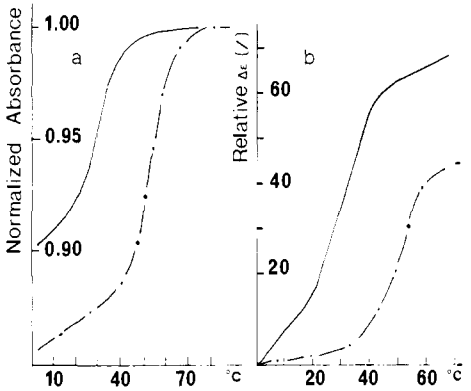

Figure 1. (a) Variation of the normalized absorbance (absorbances are normalized by dividing by the absorbance at 80 °C) of (**1** + **2**) at 258 nm (-·-) and (**1**[Pt] + **2**) at 260 nm (—) vs. temperature (actual temperature progression: 0.5 °C per min). Solutions: cacodylate buffer 8 mM pH 7.6, NaCl 1 M, EDTA 2 mM; (**1** + **2**) 2.3×10^{-5} M, (**1**[Pt] + **2**) 8×10^{-6} M oligomer strand concentrations. (b) Variation of the relative value of $\Delta\epsilon((\Delta\epsilon_0 - \Delta\epsilon_T)/\Delta\epsilon_0)$ ($\Delta\epsilon_0$ and $\Delta\epsilon_T$ are the differential absorptions at 0 and T °C respectively) at 285 nm vs. temperature of (**1** + **2** (-·-) and (**1**[Pt] + **2**) (—). Solutions: cacodylate buffer 10 mM pH 7, NaCl 0.2 M; (**1** + **2**) 1.8×10^{-5} M, (**1**[Pt] + **2**) 2×10^{-5} M oligomer strand concentrations.

techniques[6] and by the studies of oligonucleotide models, which pointed to the facile N7–N7 platinum chelation by two adjacent guanines.[7-10] Many studies of the perturbation of DNA secondary structure and stability, induced by the binding of the *cis*-$Pt^{II}(NH_3)_2$ moiety, have revealed a strong distortion of the DNA duplex suggesting the disruption of several base pairs.[11-14] It is known that the d(GpG)-chelated *cis*-$Pt^{II}(NH_3)_2$ adducts of the self-complementary hexanucleotides d(A-G-G-C-C-T) and d(T-G-G-C-C-A) do not form a duplex structure.[9,10] We here report preliminary results which show that the d(GpG)–platinum adduct of the octanucleotide d(G-A-T-C-C-G-G-C) (**1**), *cis*-[Pt-$(NH_3)_2$(d(G-A-T-C-C-G-G-C)-*N7*(6),*N7*(7))]$^{5-}$ hereafter called **1**[Pt], gives a duplex with the complementary decanucleotide d(G-C-C-G-G-A-T-C-G-C) (**2**). The melting temperature of the (**1**[Pt] + **2**) duplex (10^{-5} M) is 30 °C and there are eight imino protons involved in hydrogen bonding between the two strands.

The deoxyoligonucleotides **1** and **2** were synthesized from dimers by a phosphotriester method in solution, as reported previously.[15] The **1**[Pt] adduct was prepared by the stoichiometric reaction of *cis*-DDP or *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ with the octamer **1** in previously described conditions.[10] **1**[Pt] was the major complex formed and was separated by preparative HPLC.[16] Its structure

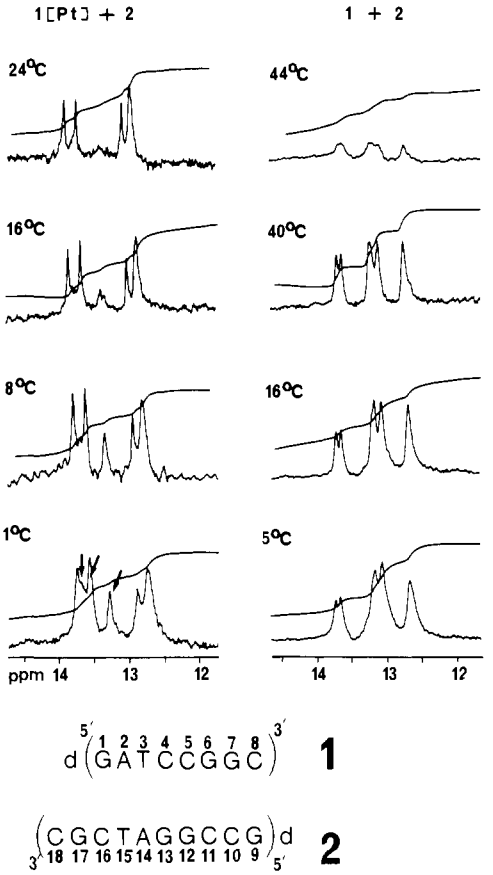

Figure 2. 12–14.5 ppm region of the 400-MHz ^{1}H NMR spectra of (**1** + **2**) (right) and (**1**[Pt] + **2**) (left) at different temperatures. Chemical shifts are relative to $TSPd_4$ (sodium 3-(trimethylsilyl)-1-propionate-*2,2,3,3-d*$_4$). Samples: phosphate buffer 10 mM pH 6.9 in H_2O/D_2O 90/10, NaCl 0.2 M; (**1** + **2**) 2.3×10^{-3} M, (**1**[Pt] + **2**) 8×10^{-4} M. The spectra were recorded on a Bruker WM-400, by using a time-shared "soft" pulse to reduce the water signal.[25] The arrows indicate the 13.7, 13.6, and 13.30 ppm signals first affected by the temperature increase. The numbering of the bases is indicated at the bottom of the figure.

is unambiguously assigned by the usual methods;[9,10,17] i.e.: (i) high-pressure gel permeation chromatography[10] and atomic absorption spectroscopy coupled with the UV absorption of the complex[18] show that **1**[Pt] is monomeric and contains one platinum atom; (ii) 400-MHz ^{1}H NMR allows the assignment of the platinum binding sites from the analysis of the pH dependence of the chemical shifts of the nonexchangeable base protons,[19] in agreement with the H8 downfield shifts of the coordinated guanines.[8-10,17]

In order to assess the possibility of duplex formation between the platinated octamer **1**[Pt] and the complementary decamer **2**,

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(16) Reverse-phase HPLC analyses were performed on a Beckman 421 liquid chromatograph with 254-nm detection, on a Waters C18 μ-Bondapak column, using a 10^{-2} M aqueous $CH_3CO_2NH_4$ solution as eluant A and a 10^{-2} M $CH_3CO_2NH_4$ solution in $H_2O/CH_3OH/CH_3CN$ (5:4:1) as eluant B. Both solutions were brought to pH 7.0 by NH_4OH addition. The preparative separations were performed in the same conditions.

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(18) From the UV absorption of the adduct, an approximate ϵ_{max}/Pt molar extinction coefficient of 64 000 was calculated. This value compared to that of ~60 000 for the unplatinated octamer shows that one platinum is bound per oligonucleotide molecule.

(19) Among the four purine H8, three are exchanged with D_2O at basic pH. The plots of the chemical shifts vs. pH show that the lower field one, experiencing the fastest exchange, belongs to the N7-platinated G(7) (pK_a-(N1–H) = 8)[7c] and the others to the N7-platinated G(6) (pK_a(N1–H) = 8.5) and the free G(1) (pK_a(N1-H) = 9.7). The C-H6, A-H8, and A-H2 curves show the protonation of the free C-N3 and A-N1 sites (pK_a(N3) = 4.3, pK_a(N1) = 3.5). Platinum binding by the **1** G(1), giving a loop, can be excluded because the adjacent adenosine H8, H2, and H1′ are respectively little and not affected by the metal chelation.

we investigated the effect of temperature on the (**1**[Pt] + **2**) and (**1** + **2**) equimolar mixtures.

Both relative absorbance vs. temperature curves for (**1** + **2**) and (**1**[Pt] + **2**) (Figure 1a) present a sigmoidal shape, with respective melting temperatures of 55 and 28 °C at 2.3×10^{-5} and 8×10^{-6} M oligomer strand concentrations. (**1**[Pt] + **2**) shows less cooperativity than (**1** + **2**). That the observed melting profile of (**1**[Pt] + **2**) does not reflect the partial self-pairing of any of the two strands is ascertained by comparison with the curves of **1**[Pt] and **2** alone.[20]

The circular dichroism spectra of (**1** + **2**) and (**1**[Pt] + **2**) belong to the B DNA type,[21] the latter showing a larger differential absorption in the 270-290-nm region. The relative $\Delta\epsilon_{285}$ vs. temperature plots for (**1** + **2**) and (**1**[Pt] + **2**) (Figure 1b) show respective melting temperatures of 50 and 30 °C at 1.8×10^{-5} and 2×10^{-5} M oligomer strand concentrations. These T_m values are in agreement with those of the UV melting profiles. Here too, none of the $\Delta\epsilon_{285}$ vs. temperature curves for **1**[Pt] and **2** alone exhibit a sigmoidal profile.[22]

The NMR spectra of the exchangeable imino protons (G-N1H and T-N3H) of (**1** + **2**) and (**1**[Pt] + **2**) in water[23,24] are shown in Figure 2 at different temperatures. For (**1** + **2**) the integration gives eight imino protons. The lower field group (2 H) is assigned to the two A-T base pairs (2-15 and 3-14, see Figure 2 for the numbering) based on the nuclear Overhauser effects between these protons and the two A-H2. The two higher field groups of signals (4H and 2H) belong to the G-C base pairs.[26] All these signals are little affected by raising the temperature up to 40 °C. But at 44 °C, they experience a general broadening and disappear at 50 °C. For (**1**[Pt] + **2**) at low temperature, the signal pattern is completely different. It is noteworthy that there are still eight imino protons involved in hydrogen bonding.[26] Compared to (**1** + **2**), four G-C imino protons are moved: three are downfield shifted, two overlapping with the A-T's, and one is upfield shifted, overlapping with the two high field G-C's. Raising the temperature from 1 to 24 °C affects the three signals at 13.7, 13.6, and 13.30 ppm. At 30 °C all the signals have disappeared, and this agrees with the lower UV and CD T_m obtained for (**1**[Pt] + **2**) compared to (**1** + **2**). Three G-C imino protons of (**1**[Pt] + **2**) are involved in fraying of the duplex, which should first affect the (6-11), (7-10), and (8-9) base pairs of the platinated end if one takes into account the stabilization of the other end by the unpaired G(17) and C(18) bases of the decamer strand.[27,28] Therefore the three downfield shifted G-C imino protons should correspond to the G-platinated (6-11) and (7-10) pairs and to the distorted terminal (8-9) pair. The upfield shifted G-C imino proton could be assigned to the (5-12) pair because of the perturbation due to the adjacent platinum chelate. These assignments are tentative and are in agreement with preliminary results obtained by other workers.[29]

In conclusion, our preliminary results show that a d(GpG)-*cis*-$Pt(NH_3)_2$ chelate on a short oligonucleotide does not preclude duplex formation with a complementary strand. In our case, melting occurs at a temperature lower than 37 °C, but the duplex is quite short, and the platinated sequence is next to the helix end. This suggests that d(GpG)-platinum chelation should not induce a large distortion of the DNA duplex. This distortion might be quite similar to that of a kink[30] or of a region of systematically bent B DNA,[31] and this would raise the question of its detection by the repair enzymes.[32]

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Measurement of the Thermochromic Equilibrium Constant of a Nonthermochromic Compound: 1,1′-Dimethylbianthrone

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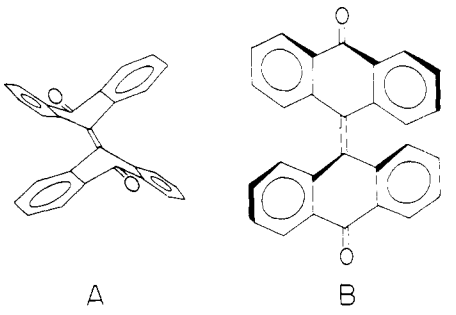
Bianthrone [Chemical Abstracts name: 10-(10-oxo-9-(10*H*)-anthracenylidene)-9(10*H*)-anthracenone (**1**)] is a thermochromic substance that exists at room temperature as a yellow A form. As solutions of **1** are heated, a significant fraction is converted to the green B form whose enthalpy is 3.0 kcal/mol greater than A.[1] Substituents larger than fluorine at the 1- and 1′-positions prevent thermochromicity.[2] It is likely that bulky substituents destabilize B more than A causing the energy difference to be too high to allow formation of detectable quantities of B at temperatures below decomposition.[3] Until now no means of measuring this energy difference has been available. We have developed an indirect electrochemical technique and have found $K_{AB} = [B]/[A] = 8 \times 10^{-6}$ at 373 K ($\Delta G_{A \rightarrow B} = 8.7$ kcal/mol)



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