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A Palladium-mediated DNA Base Pair of a β-C-Nucleoside Possessing a 2-Aminophenol as the Nucleobase

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An approach we have used in this study for the incorporation of metal ions into DNA, is the direct modification of a DNA base itself, turning it into a metal-chelating nucleobase wherein two nucleobases are paired through metal coordination. Herein we report the X-ray crystal structure of a synthetic intermediate 6 for the aminophenol-bearing nucleoside 3 and its metal coordination properties with Pd^{2+}. The anomeric configuration of the nucleoside was unequivocally determined to be β-form by the X-ray analysis of 6; the structure has been resolved by direct methods (S1R97) and expanded using Fourier techniques (DIRDIF94) using 2628 independent reflections with $I>2.00\,\sigma(I)$ and 425 parameters. Final R (R_w) was 0.037 (0.043): orthorhombic, space group $P2_12_12_1$ (#19) with $a=16.562(1)$ Å, $b=16.933(1)$ Å, $c=11.205(1)$ Å, and $V=3142.2(4)$ Å^3; $D_c=1.369$ g/cm^3 for $Z=4$, and molecular weight 647.65. This result is consistent with the tentative assignment by our previous ^{1}H NOE differentiation experiments. Detailed ^{1}H NMR studies showed that the nucleoside forms a stable 2:1 complex with Pd^{2+} with concomitant deprotonation of its phenolic proton. Although there are two possible structures (*cis* or *trans*) for the square-planar Pd^{2+} complex, the ratio of *cis* to *trans* was approximately 1:1. The electrospray ionization time-of-flight mass spectrum of the complex also provided clear evidence for the 2:1 complexation.

Keywords: Artificial DNA; Metal-assisted base pairing; Palladium complex; 2-aminophenol

INTRODUCTION

Replacement of the hydrogen-bonded base pairing of natural DNA by alternative base pairing modes is expected to lead not only to expansion of genetic alphabet, but to novel DNA structures and/or functions based on the controlled and periodic spacing of the building blocks along the helix axis. In recent years we and others have envisioned the placement of charged metal complexes in the interior of the DNA helix [1–7]. Our approach for the incorporation of metal ions into DNA framework is

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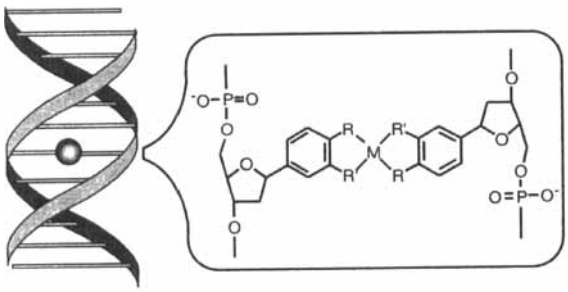


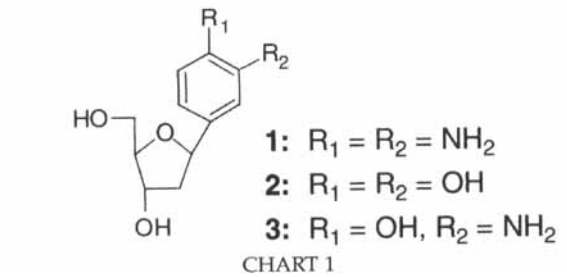
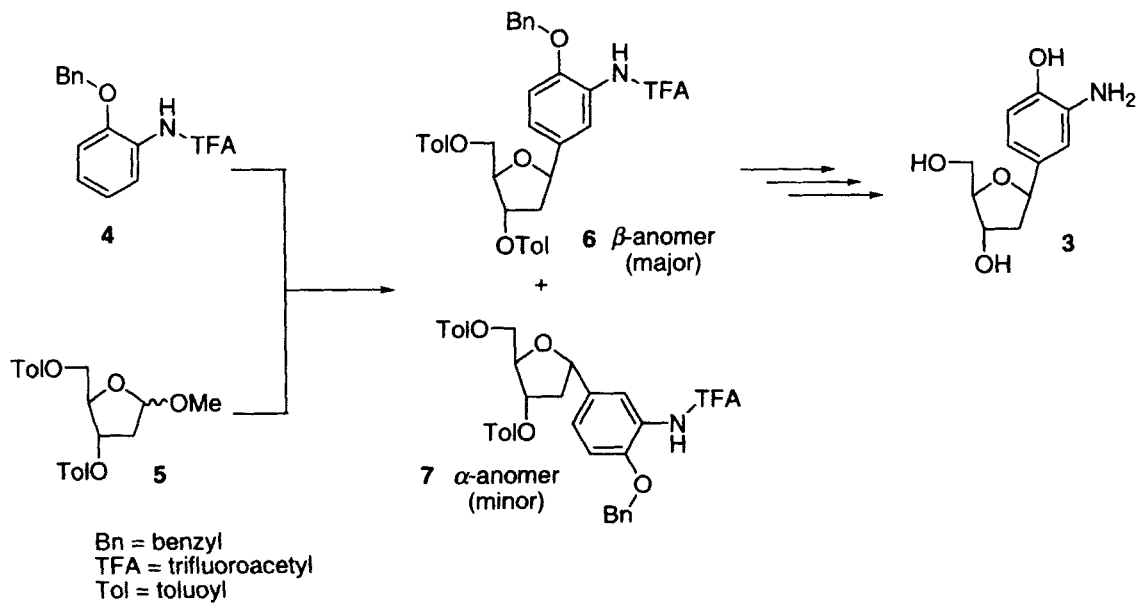


CHART 1

the direct modification of a DNA base itself, converting it into a metal-chelating nucleobase wherein two nucleobases are paired through metal coordination. We have recently reported that the synthesis of three kinds of metal-chelating nucleosides, **1**–**3**, possessing a metal-chelating site (an *o*-phenylenediamine, a catechol, or a 2-aminophenol, respectively) as the nucleobase moiety (Chart 1) [1–4]. The nucleosides **1** and **2** have been found to form a stable 2:1 complex with a Pd^{2+} ion [1] and a borate ion [3], respectively. Herein we report the X-ray crystal structure of a synthetic intermediate **6** for the nucleoside **3**, the determination of its anomeric configuration, and its metal coordination properties with Pd^{2+}. These results provide critical information that could prove useful in predicting the structure of metal-assisted base pairs incorporated into oligo-DNA.

RESULTS AND DISCUSSION

Scheme 1 depicts a schematic representation of a synthetic route for the β-C-nucleoside **3** which has a 2-aminophenol as the nucleobase [4]. A Friedel–Crafts approach was used to build up the carbon skeleton of the nucleoside **3**. In this reaction, β-C-nucleoside **6** was found to be produced with high selectivity (α-**7**:β-**6**=1:10). The anomeric configuration of each anomer has



SCHEME 1

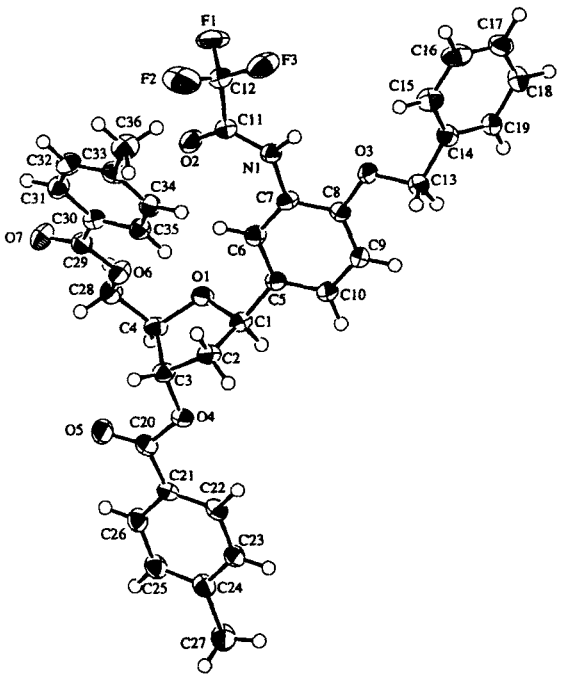


FIGURE 1 The X-ray crystal structure of β-anomer **6**.

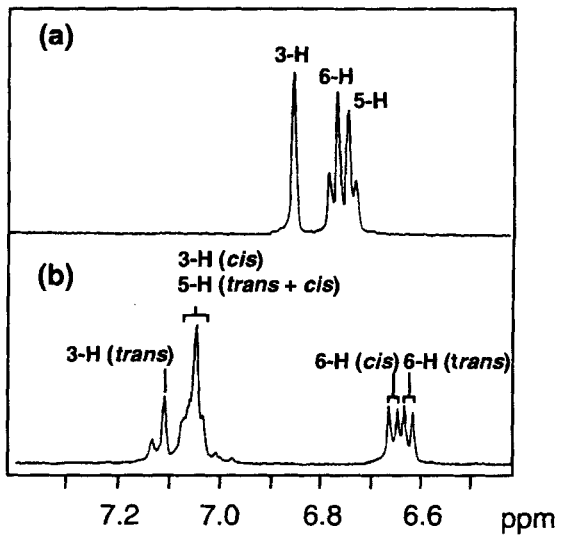
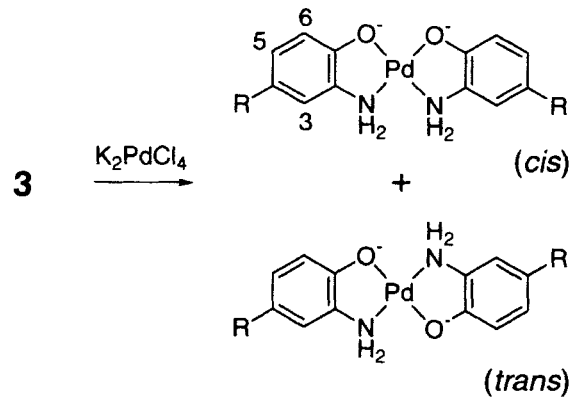


FIGURE 2 500 MHz ^{1}H NMR spectra of nucleoside **3** in the absence or presence of K_2PdCl_4; [**3**] = 2.0 mM, $[Pd^{2+}] = 0$ and 1.0 mM for (a) and (b), respectively, $[NaHCO_3] = 2.0$ mM in D_2O–CD_3OD (4:1) at room temperature.

been tentatively assigned by the 1′-H–2′-H coupling constant trend in the ^{1}H NMR spectra, which was compared with those for related β-*C*-nucleosides [8–11]. The trend in the coupling constants $J_{1'-2'\alpha} = 5.1$ and $J_{1'-2'\beta} = 11.0$ Hz for the major product is consistent with the trends reported for β-*C*-nucleosides. ^{1}H NOE differentiation experiments also strongly supported this result as previously reported [4]. The β configuration of the anomer **6** was unequivocally confirmed by the X-ray crystal structure (Fig. 1). The corresponding dihedral angles for 1′-H–2′α-H and 1′-H–2′β-H obtained from the X-ray structure of **6** were found to be 36.7 and 158.9°, respectively. Application of the Karplus relationship empirically adjusted for nucleosides [12] predicts $J = 5.9$ and 9.6 Hz, respectively, indicating that the ring conformation of the ribose in solution is very similar to that in the solid state.

Complexation between the nucleoside **3** and Pd^{2+} in D_2O–CD_3OD in the presence of $NaHCO_3$ was investigated by ^{1}H NMR spectroscopy. Proton resonances in the aromatic region for **3** in the presence of an equimolar amount of $NaHCO_3$ to neutralize released protons upon complexation are compared with those of a mixture of **3** and K_2PdCl_4 at the ratio of 2:1 in D_2O–CD_3OD (4:1). As shown in Fig. 2, dramatic changes of the chemical shifts were observed upon complexation with Pd^{2+}. Two sets of signals for 3-H and 5-H begin to appear at significantly lower field with an increased intensity in proportion to increasing concentration of Pd^{2+}, whereas the two sets of signals for 6-H appear at higher field, compared with those for the nucleoside **3**. The complexation was complete when the concentration of Pd^{2+} reached almost half the concentration of **3** (Fig. 2(b)). From COSY measurements (data not shown), each signal was assigned as shown in Fig. 2. Although there are two possible structures (*cis* or *trans*) for the square-planar Pd^{2+} complex, considering the *trans*-effect that should occur between the two phenolates bound to Pd^{2+} in the *trans*-complex, one set of the signals for 6-H appeared at higher field (6.62 ppm) is assignable to the 6-H of the *trans*-complex with higher electron density. The ratio of *cis* to *trans* was



SCHEME 2

approximately 1:1. In addition to the results of ^{1}H NMR titration experiments implying the 2:1 complexation between **3** and Pd^{2+}, (Scheme 2) the ESI-TOF mass spectrum of the complex in the positive mode provided clearer evidence for the composition ratio as shown in Fig. 3. The signals were centered at m/z 555.09 (Fig. 3(b)) correspond to the +1 charged cationic species, $[Pd(\mathbf{3}\text{-}H)_2 + H]^+$, which gave excellent agreement with the theoretical isotopic distribution (Fig. 3(a)). These results establish that the nucleoside **3** form a stable 2:1 complex with Pd^{2+} with concomitant deprotonation of its phenolic proton.

The present study demonstrates that a β-C-nucleoside containing 2-aminophenol as a "chelator" moiety provides an alternative metal-mediated DNA base pair. Site-specific incorporation of this novel DNA base pair into oligo-DNA will be reported elsewhere.

MATERIALS AND METHODS

^{1}H NMR spectra referenced to 3-(trimethylsilyl)-propionic-2,2,3,3-d_4-acid sodium salt were recorded on a Bruker DRX500 (500 MHz) spectrometer. Electrospray ionization time-of-flight (ESI-TOF) mass spectra were recorded on a Micromass LCT spectrometer.

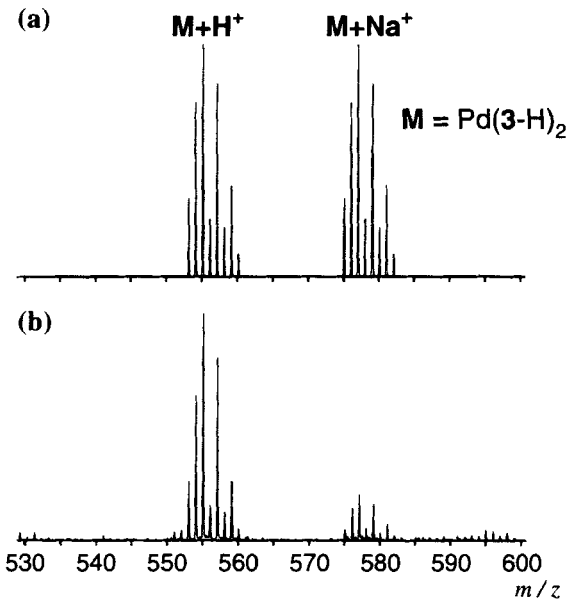


FIGURE 3 ESI-TOF mass spectrum in the positive mode for the 2:1 complex between **3** and Pd^{2+} (m/z 530–600); (a) the theoretical isotopic distribution for $[M + H]^+$ and $[M + Na]^+$ and (b) the experimental isotopic distribution, where M = $Pd(3\text{-}H)_2$.

Compound **6** was prepared according to the previously reported literature [4]. The structural determination was made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Cu-Kα radiation at -130.0 ± 1°C to a maximum 2θ value of 136.5°. The structure was solved by direct methods (SIR97) [13] and expanded using Fourier techniques (DIRDIF94) [14]. The non-hydrogen atoms were refined anisotropically. Crystal data for **6**, $C_{36}H_{32}NO_7F_3$: F.W. = 647.65, crystal dimensions $0.30 \times 0.30 \times 0.10\,mm^3$, orthorhombic, space group $P2_12_12_1$ (#19), $a = 16.562(1)$ Å, $b = 16.933(1)$ Å, $c = 11.205(1)$ Å, $V = 3142.2(4)$ Å^3, $Z = 4$, $\mu = 8.99\,cm^{-1}$, $D_c = 1.369\,g/cm^3$, min/-max transmission = 0.72/0.91. $2\theta < 136.5°$, $R(R_w) = 0.037$ (0.043) for 2628 ($R_{int} = 0.050$) independent reflections out of a total of 35198 reflections with $I > 2.00\ \sigma(I)$ and 425 parameters. The good-of-fit on F^2 is 1.03, and the residual electron density (min./max) is $-0.18/0.21/e^-/Å^3$.

Solutions for ^1H NMR studies at room temperature were prepared as follows: nucleoside **3** (2.0 mM), K_2PdCl_4 (0–1.0 mM), and $NaHCO_3$ (2.0 mM) in 0.5 ml D_2O–CD_3OD (4:1).

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