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Synthesis of a redox active analogue of adenine†

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Abstract

An analogue of adenine **3**, in which the aminopyrimidine moiety is annulated to a cyclopentadienyl ring of ferrocene, was synthesized from ferrocenecarboxaldehyde. The key intermediate in this synthesis was 2-aminoferrocenenitrile, which was prepared regio- and stereoselectively. An X-ray crystallographic structure study of **6**, a derivative of **3** obtained by acetylation, confirmed the structure of the product.

Keywords: ferrocenes; pyrimidine; nucleic acid analogues.

In the duplex structure of DNA the bases are π-stacked. This raises the interesting question of whether there can be rapid, long-range conduction of electrons through the π-system.[1] To address this controversial issue metal redox centers have been intercalated into the π-stack[2] or covalently attached to the sugar moieties[3] and the β-values for electron transfer determined to evaluate the conductivity through the π-stack. The rate of electron transfer has been shown to depend on the nucleotide sequence and π-stacking of the base moieties, electron donor and electron acceptor.[4] In this communication a new approach for evaluating electron transfer through oligonucleotides is outlined involving a nucleotide base modified so as to covalently attach a metal redox center properly oriented to overlap the π-stack and the synthesis of the modified base presented.

Nucleoside **1** is an analogue of 2′-deoxyadenosine **2**, which could be selectively introduced into an oligonucleotide sequence. Because the amino pyrimidine ring in **1** is the same as in **2**, hydrogen bonding to thymine, important for base-pairing and formation of a duplex structure, should occur. Furthermore, the CpFe moiety should be correctly positioned for overlap with the π-stack of a duplex oligonucleotide and, since ferrocene undergoes reversible one-electron transfer on oxidation, **1** should behave analogously. Incorporating two such moieties into an

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† Dedicated with best wishes to Professor Harry H. Wasserman, a renowned teacher, scholar and editor, on the occasion of his 80th birthday.

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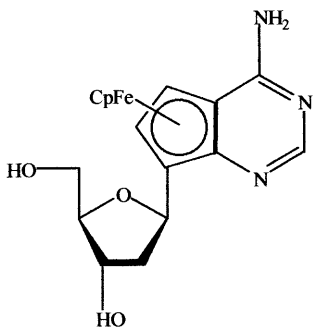
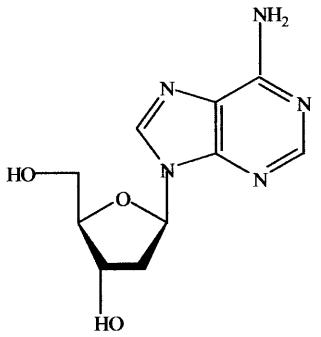
oligonucleotide should allow the assessment of electron-transfer rates in mixed valence duplex structures.[5] This communication reports a regio-and enantioselective synthesis of **3** which has planar chirality.



1



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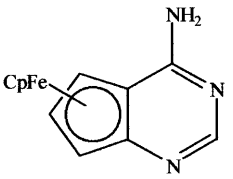
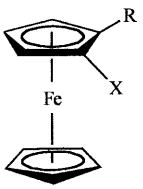
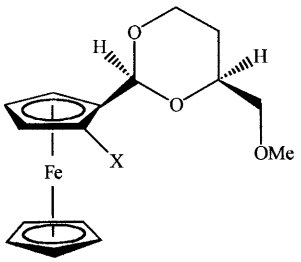


3

Retrosynthetic analysis revealed that amino nitrile **4a** is a promising precursor to **3** because treatment of analogous amino nitriles with formamidine provides 4-amino pyrimidines.[6] Furthermore, **4a** could be synthesized regioselectively from an appropriate ferrocene derivative by directed *ortho*-metalation.[7] The directing group could be an amine derivative or a carboxylic acid derivative, which subsequently could be converted either to the desired nitrile or, after Curtius or analogous rearrangement, to the amino group.



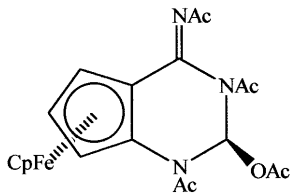


4a, R=CN, X=NH_2;
b, R=CHO, X=CO_2Me;
c, R=CH=NOH, X=CO_2Me;
d, R=CN, X=CO_2Me;
e, R=CN, X=CO_2H;
f, R=CN, X=$NHCO_2$ tBu;
g, R=CN, X=$NHCO_2CH_2Ph$;
h, R=CN, X=N=CHOMe

5a, X=H;
b, X=NH_2;
c, X=CO_2Me

The method that proved successful[8] for the synthesis of **4a** starts with ferrocenecarboxaldehyde. Kagan and co-workers[10] reported the enantioselective deprotonation of **5a**, a readily obtained derivative of ferrocenecarboxaldehyde which bears a chiral auxiliary. Furthermore, transmetalation of the lithiated derivative to give a higher order cuprate followed by amination with *O*,*N*-bis (trimethylsilyl) hydroxylamine afforded **5b** in 36% yield. However, only traces of this product were formed under these conditions in our hands. Consequently, an alternative route for introducing the amino group was developed. Kagan and co-workers[10] reported formation of **5c** in 43% yield on treatment of **5a** with base and methyl chloroformate sequentially. Conditions were found which resulted in raising the yield of this reaction to 51–62%. Ketal **5c** was hydrolyzed with *p*-toluenesulfonic acid to ester–aldehyde **4b** in 85% yield.[11] The aldehyde moiety in **4b** was then converted to a cyano group in two steps. Aldehyde **4b** formed oxime **4c** in 78% yield, which on dehydration with *N*,*N*′-dicyclohexylcarbodiimide in

benzene at reflux produced nitrile **4d** in 88% yield. The ester group in **4d** was hydrolyzed with aqueous sodium hydroxide in THF to acid **4e** in 77% yield. Reaction of acid **4e** with diphenylphosphoryl azide[12] and triethylamine in *t*-butyl alcohol yielded the protected amine **4f**. However, the acidic conditions needed to hydrolyze the protecting group decomposed the expected product **4a**. Replacement of *t*-butyl alcohol with benzyl alcohol in the Curtius rearrangement of **4e** resulted in the formation of **4g** in 17% yield, which on hydrogenolysis in the presence of hydrogen and 10% palladium-on-carbon gave the desired amino nitrile **4a** in 75% yield. Treatment of **4a** with formamidine acetate, under conditions in which anthranilonitrile gave 4-aminoquinazoline in 86% yield, resulted only in decomposition. However, the desired cyclization product could be obtained from **4a** in two steps.[13] Imino ether **4h** was formed from **4a** on treatment with trimethylorthoformate and *p*-toluenesulfonic acid. Treatment of the crude product with gaseous ammonia in methanol gave the desired air-sensitive product **3**, in 49% yield, whose structure was determined spectroscopically (IR, ^{1}H and ^{13}C NMR, and mass spectra).[14] In addition, reaction of this material with excess acetic anhydride and triethylamine produced **6** as red crystals suitable for X-ray crystallographic analysis. The structure was unequivocally established by this analysis.[15] The thermal ellipsoid drawing of this material is shown in Fig. 1. Compound **6** is derived from **3** by acetylation of all of the nitrogen atoms, nucleophilic addition of acetate ion to C(2) and double bond isomerization.



6

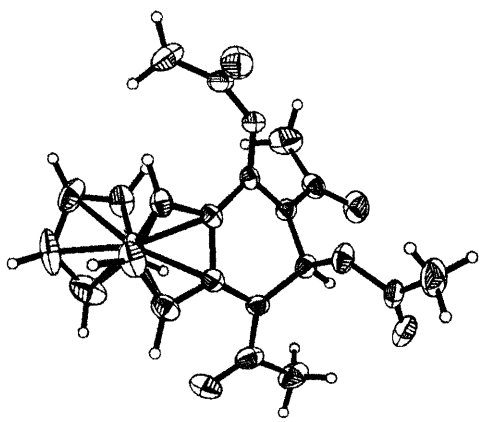


Figure 1. Thermal ellipsoid drawing of **6**

Acknowledgements

The X-ray crystallographic structure of **6** was determined at the Molecular Structure Laboratory of the University of Arizona using a diffractometer provided by NSF grant CHE 9610374.

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11. The structures of all new compounds were confirmed spectroscopically (IR, ^{1}H NMR, ^{13}C NMR, MS) and by elemental analysis or high resolution MS. The reported yields are for isolated, pure compounds.
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14. IR ($CHCl_3$) 3300–3100 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.9 (s, 5), 4.3 (br, 1), 4.65 (br, 1), 5.2 (br, 1), 8.2 (s, 1); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 56.7, 63.9, 69.6, 156.2, 170.2; MS m/z 253, 254; HRMS calcd for $C_{12}H_{12}N_3Fe$: 254.0381. Found: 254.0376.
15. Crystallographic data for **6** have been deposited with the Cambridge Crystallographic Data Centre.