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# Nucleosides, Nucleotides and Nucleic Acids

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# Synthesis of (Dicarbonyl)(η⁵-cyclopentadieny1)iron -Derived Nucleoside Phosphonate Esters

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# Synthesis of (Dicarbonyl)(η<sup>5</sup>-cyclopentadienyl)iron -Derived Nucleoside Phosphonate Esters

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#### Abstract

New methods for generating phosphonate linkages in oligonucleotides are under investigation. Among reagents that react selectively with phosphite triesters and H-phosphonates are  $(dicarbonyl)(\eta^5$ -cyclopentadienyl)( $\eta^2$ -olefin)iron complexes. We have found that  $(dicarbonyl)(\eta^5$ -cyclopentadienyl)( $\eta^2$ -ethylene)iron reacts with 5'-O-dimethoxytritylnucleoside 3'-phosphite esters to yield  $(dicarbonyl)(\eta^5$ -cyclopentadienyl)iron(ethyl)phosphonates. The  $(dicarbonyl)(\eta^5$ -cyclopentadienyl)iron-derived nucleoside phosphonates are stable to the conditions commonly used to construct oligonucleotides by phosphoramidite methodology.

Oligonucleotides based on methylphosphonate or other non-ionic linkages between nucleoside units have been of particular interest as anti-sense molecules for inhibiting mRNA function.<sup>1</sup> The introduction of alkyl phosphonate linkages during oligonucleotide construction requires alkyl phosphonamidite derivatives of each of the four deoxyribonucleosides. Attempts to derivatize the phosphite triester linkage during oligonucleotide construction by Arbuzov type reactions using alkyl halides have generally proven ineffective.

The goal of our research is the development of new construction techniques for oligonucleotides substituted at phosphorus. We are addressing the problem of modifying the phosphodiester backbone to inhibit nuclease degradation and enhance transport through cell membranes, while at the same time providing sites for the attachment of linker arms to DNA/RNA binding and/or cleaving molecules. Specifically we have been investigating new methods for generating phosphonate linkages in oligonucleotides during the course of automated synthesis. Instead of alkyl halides we have focused on metal activated alkenes. Among reagents that react selectively with phosphite triesters and H-phosphonates are (dicarbonyl)( $\eta^5$ -cyclopentadienyl)( $\eta^2$ -olefin)iron complexes.<sup>2</sup> We have found that (dicarbonyl)( $\eta^5$ -cyclopentadienyl)( $\eta^2$ -ethylene)iron fluoroborate (1) reacts with 5'-O-dimethoxytritylnucleoside 3'-phosphite esters 2 and 3 to yield phosphonium salts 4 and 5 which are readily transformed to (dicarbonyl)( $\eta^5$ -

cyclopentadienyl)iron(ethyl)phosphonates, 6 and 7 by reaction with LiCl in DMSO at room temperature. The protected mononucleotides and dinucleotides shown in the scheme were synthesized and characterized by <sup>1</sup>H, <sup>31</sup>P NMR spectroscopy and IR.

The (dicarbonyl)( $\eta^5$ -cyclopentadienyl)iron-derived phosphonates were tested and appear to be stable to the conditions commonly used to construct oligonucleotides by phosphoramidite methodology. To evaluate the reactivity of (dicarbonyl)( $\eta^5$ -cyclopentadienyl)( $\eta^2$ -ethylene)iron towards H-phosphonates the reaction of the model compound diethyl hydrogen phosphonate in the presence of triethylamine was examined. The product was the expected diethyl (dicarbonyl)( $\eta^5$ -

cyclopentadienyl)iron(ethyl)phosphonate, which indicates that this reaction could be extended to the modification of nucleoside derived H-phosphonates.

One additional major concern was whether (dicarbonyl)( $\eta^5$ -cyclopentadienyl)( $\eta^2$ -ethylene)iron fluoroborate (1) would react with the protected nucleosides at other sites, particularly at ring nitrogens. Transition metal complexes such as (dicarbonyl)( $\eta^5$ -cyclopentadienyl) (tetrahydrofuranyl)manganese and tricarbonylhexadienyliron cation are known to react with nucleic acid bases and nucleosides leading to structures wherein the nitrogen atoms on the bases serve as ligands for the metals. 3,4 However, model reactions with 3'-O-levulinyl-5'-O-dimethoxytritylthymidine, 3'-O-acetyl-5'-O-dimethoxytrityl-6N-benzoyl-2'-deoxyadenosine and (1) showed no changes in the characteristic carbonyl stretching frequencies of the iron complex. In contrast the reactions with phosphite ester are complete within a few minutes at room temperature as judged by the disappearance of the two carbonyl peaks at 2083 and 2046 cm<sup>-1</sup> and the appearance of two new peaks at around 2000 and 1950 cm<sup>-1</sup>.

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