A ferrocene nucleic acid oligomer as an organometallic structural mimic of DNA

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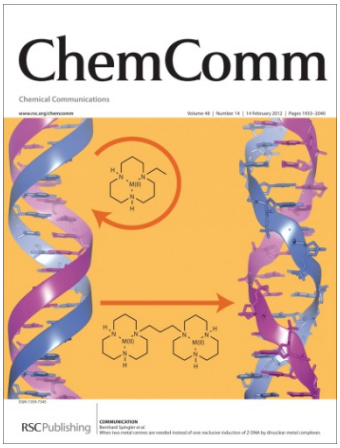

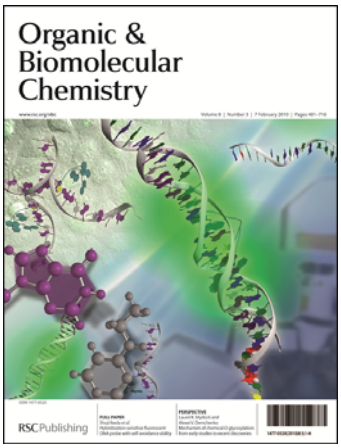

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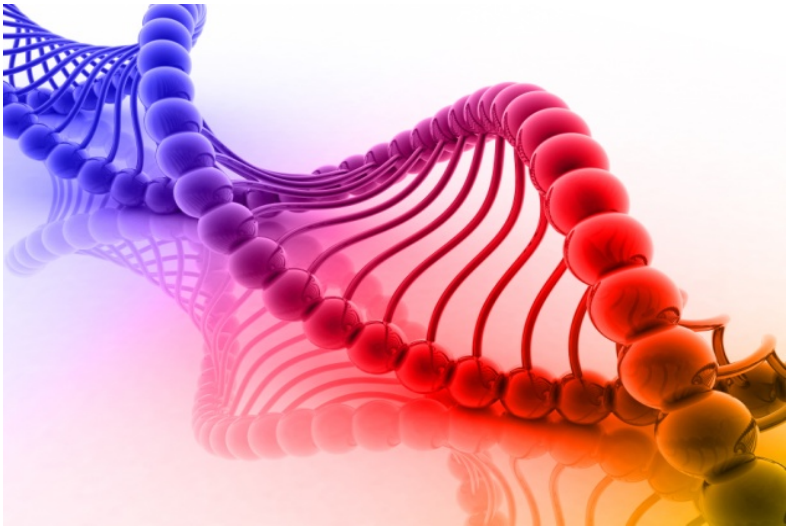

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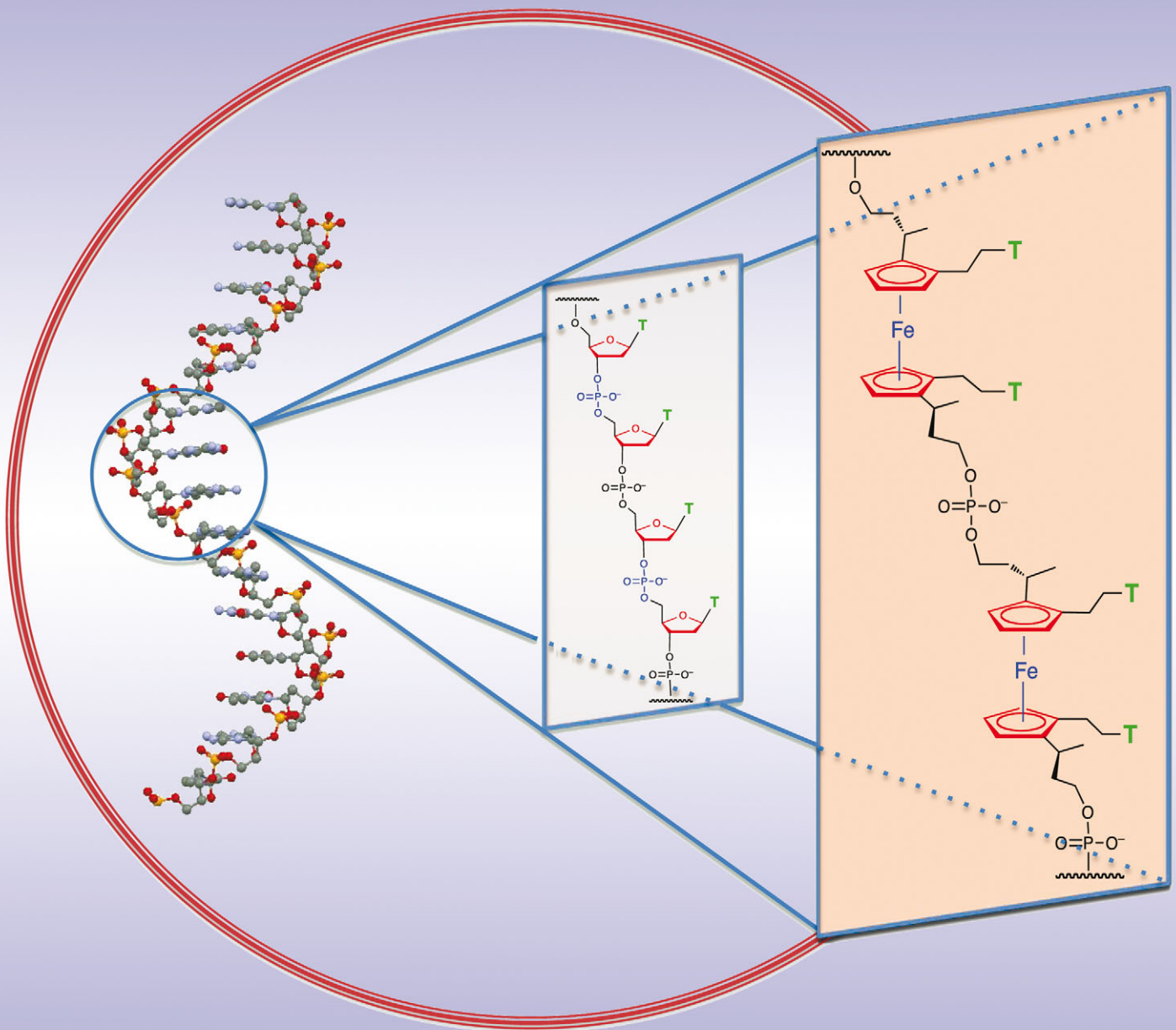

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COMMUNICATION

A ferrocene nucleic acid oligomer as an organometallic structural mimic of DNA†‡

Huy V. Nguyen, Zheng-yun Zhao, Antoine Sallustrau, Sarah L. Horswell, Louise Male, Andrea Mulas and James H. R. Tucker*

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The design, synthesis and electrochemical behaviour of an oligomer consisting of linked thymine-functionalised ferrocene units are reported, which, as a so-called form of ferrocene nucleic acid (FcNA), acts as a structural mimic of DNA.

For several decades, chemists have been interested in the modification and mimicry of nucleic acids to complement and add function to that which nature can offer.[1] From a conceptual point of view, the design of a structural mimic of a nucleic acid is quite straightforward if one considers the replacement of one or more of the three repeating units of the nucleic acid polymer (sugar, phosphate linker and nucleobase) with suitable alternatives. One of the more successful analogues so far, in terms of potential medical applications, is the family of peptide nucleic acids (PNA),[2] where the sugar–phosphate backbone in DNA is replaced with a pseudopeptide backbone.

There are now many examples of organic synthetic mimics of nucleic acids,[1–3] but as part of the diverse field of metallopolymers,[4] metal-containing analogues have also been developed, with perhaps the most striking being the replacement of the nucleobase itself with metal-coordinating ligands,[5] allowing metal coordination to trigger the assembly of duplexes and triplexes. However an alternative approach to a metal-containing analogue of a natural nucleic acid would be to make the metal an integral component of the backbone. In other words, the nucleobases would be retained but the backbone would consist of a repeating metal-based unit, akin to the pseudopeptide unit in PNA. An obvious candidate in this respect is ferrocene, not least because the gap between its cyclopentadienyl (Cp) rings (3.3 Å) is very similar to that between adjacent base pairs in B-DNA (3.4 Å). Furthermore, it has well characterised electrochemical behaviour and its use is widespread in various areas of bioorganometallic chemistry and biomolecular sensing.[6,7]

School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. E-mail: j.tucker@bham.ac.uk; Fax: +44 (0)121 414 4403; Tel: +44 (0)121 414 4422

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‡ Electronic supplementary information (ESI) available: Synthetic procedures for **2–13**, NMR spectra and relevant HPLC traces, X-ray data, details of the oligomer synthesis and its characterisation, electrochemical data. CCDC 896623. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc36428j

However, as described above, the creation of a so-called strand of ferrocene nucleic acid (FcNA) would require the replacement with ferrocene of a structural component of the backbone of a nucleic acid, rather than its use as a tag to,[6b,c] or a linker group within,[7] an existing nucleic acid structure.

Our initial strategy in the design of such an oligomer has been to replace an entire sugar–phosphate–sugar motif (*i.e.* a dinucleotide unit) in DNA with one ferrocene moiety, as depicted in Fig. 1. In other words, two furanose rings are replaced by two Cp units, and a linking phosphodiester group is replaced with an iron atom. In this design, each unit is bridged by a second phosphodiester unit, which carries a negative charge to impart water solubility. Therefore a strand of this type would carry half the charge of a DNA strand containing the same number of nucleobases, due to the replacement of every other phosphodiester group with an iron atom. Herein we report the synthesis and characterisation of such an oligomer, **(Fc-TT)$_8$**, containing eight ferrocene units

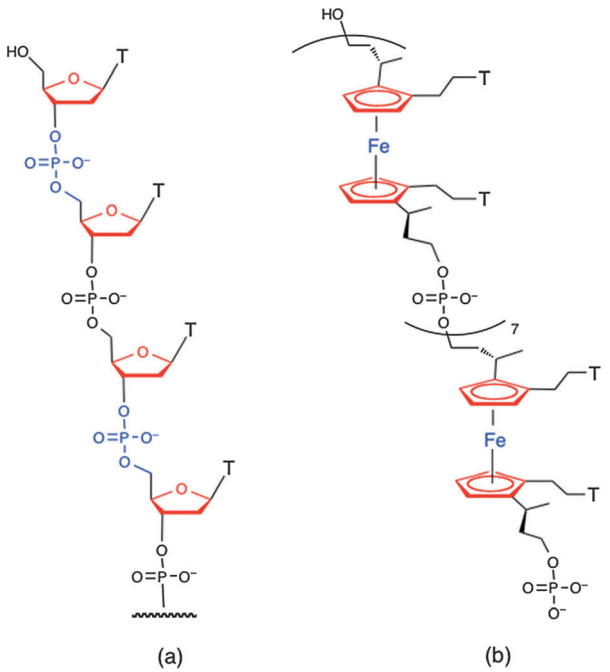
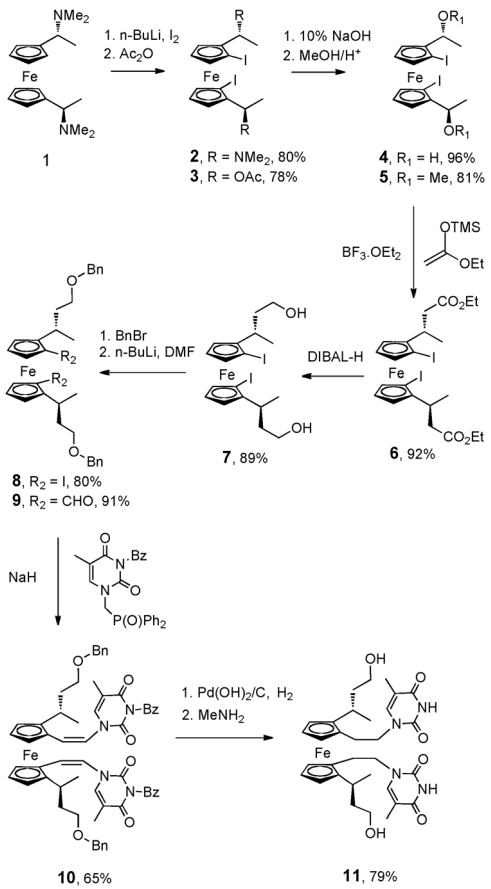


Fig. 1 The structure of (a) DNA (b) a form of FcNA reported in this work, **(Fc-TT)$_8$**, where T represents the nucleobase thymine.

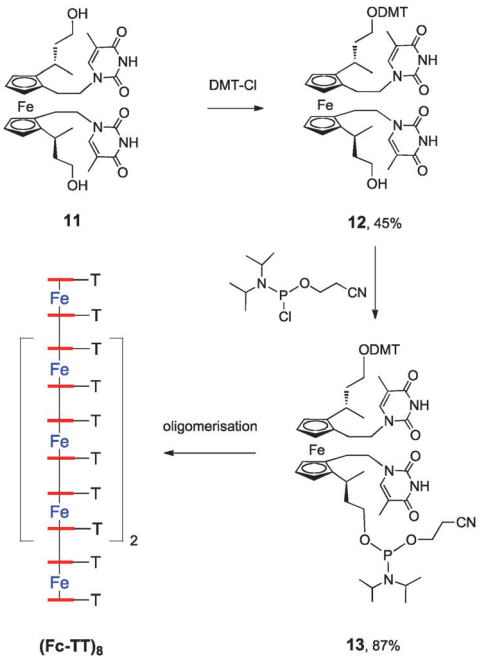
and sixteen thymine nucleobases, and we give a preliminary account of some of its spectroscopic and electrochemical properties.

In order to synthesise the target oligomer, it was necessary to synthesise a tetra-substituted ferrocene monomer prior to oligomerisation, as outlined in the synthetic schemes in Schemes 1 and 2.‡ Several factors were taken into account in designing the route. First of all, to allow chemical synthesis on an automated nucleic acid synthesiser, a suitable phosphoramidite would be required which meant the route would proceed *via* a diol for tritylation followed by phosphitylation. Secondly, in this form of a ferrocene nucleic acid, both Cp units would form part of the backbone, with one alcohol and one nucleobase positioned on each ring, so the retention of C_2 symmetry as far as possible in the synthesis would minimise unwanted side reactions. Finally, each tetra-substituted ferrocene would contain two centres of planar chirality and therefore the chosen route would have to ensure good control over product stereochemistry.

Having noted the effective use by others of a three-carbon linker group on each Cp to connect ferrocenes together between DNA fragments,[7] the same spacer length was chosen for this study. However in order to ensure good control over stereochemistry, two centrally chiral stereocentres were also introduced into these arms by starting the synthesis with the ferrocenyl bis-amine **1**.[8] This allowed diastereoselective *ortho*-lithiation and iodination to afford the known[9] tetrasubstituted **2** containing two planar chiral centres, the enantiopurity of



Scheme 1 The synthetic route taken towards the tetra-substituted ferrocene diol **11**.



Scheme 2 The synthetic route taken towards **(Fc-TT)$_8$** (shown in a ladder representation), starting from ferrocene diol **11**.

which was confirmed by chiral HPLC.§ This compound was then converted *via* **3** and **4** to the bis-ether **5**, which was treated with silyl ketene acetal and boron trifluoride etherate to give the bis-ester **6**. The X-ray crystal structure of this compound (Fig. 2) clearly shows the expected stereochemistry of the four chiral centres (*S*, *S*, S_p, S_p).

The two ester groups were then reduced to afford the bis-alcohol **7** containing the two desired three-carbon linker arms. However these groups required protection through benzylation before conversion to the bis-aldehyde **9**, which was then subjected to a Horner–Wittig reaction with the benzoyl protected thymine phosphine oxide, as described previously.[10] The double bonds of the major product from the reaction, compound **10**, were then reduced and the benzyl groups removed simultaneously through hydrogenation. In the same pot, the two thymines were then deprotected with methylamine to give the diol **11**.

The tetrasubstituted ferrocene diol could now be functionalised in the usual manner,[7,11] firstly through tritylation with

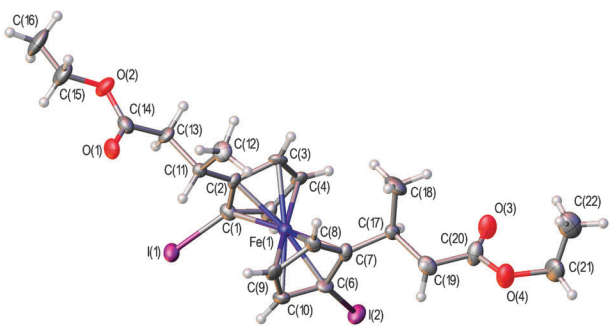


Fig. 2 X-Ray crystal structure of **6** with ellipsoids drawn at the 50% probability level. The structure contains two crystallographically independent molecules with only one being shown for clarity. The methyl group C(16)/C(16′) is disordered over two positions and the minor positions have been omitted for clarity.

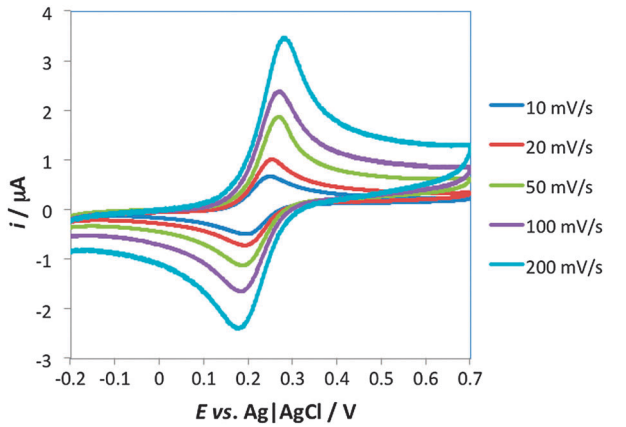


Fig. 3 Cyclic voltammograms of **(Fc-TT)$_8$** at various scan rates (conditions: concentration 0.1 mM, 10 mM sodium phosphate buffer, 100 mM NaCl) at RT.

4,4′-dimethoxy trityl chloride to give **12** and then through phosphitylation with 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite to give compound **13** (Scheme 2). The monomer was then oligomerised on an automated nucleic acid synthesiser starting from a 3′-phosphate controlled pore glass (CPG) support to give the desired target **(Fc-TT)$_8$**. The product was purified by reversed-phase HPLC and characterised by analytical HPLC and ESI‡ mass spectrometry, giving the correct *m*/*z* values for its various charge states.

The **(Fc-TT)$_8$** oligomer is readily soluble in aqueous phosphate buffer at physiological pH (10 mM sodium phosphate buffer, 100 mM NaCl). Its UV/vis spectrum gives the expected band at *ca.* 260 nm, which is largely due to absorption by the sixteen thymine nucleobases, and a small band attributed to the ferrocene d–d transition at 435 nm.¶ The oligomer has also been characterised by cyclic voltammetry, giving a quasi-reversible wave centred at 212 mV ± 5 mV *vs.* Ag/AgCl at potential scan rates between 10–200 mV s^{-1} (Fig. 3). This redox wave can be readily ascribed to Fc/Fc^+ redox processes within the oligomer,‖ its potential being not too dissimilar to the range of potentials observed for related oligomers in the literature,[7] in which each ferrocene unit is bis-functionalised with two linker arms only.

To conclude, the bioorganometallic oligomer presented here, **(Fc-TT)$_8$**, is the first example from a new family of artificial nucleic acids that contain a backbone consisting of repeating nucleobase-tagged ferrocene units. The potential and scope of FcNA in its various stereoisomeric and structural forms, for example through its binding or electrochemical behaviour, has yet to be established and will be the subject of future work.

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Notes and references

§ The opposite enantiomers of several compounds along the synthetic route were also made to check chiral purity by HPLC, as described in the ESI.‡

¶ A CD signal is also observed in this absorbance region, meriting a separate and more detailed study of the chiral properties of this and related oligomers.

‖ The anodic and cathodic current intensities, as well as digital simulations of the CVs, indicate a multiple electron transfer process within the redox wave of **(Fc-TT)$_8$** under the conditions used. More detailed studies on the electrochemical behaviour of these strands will be reported in due course.

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