Directing spatial disposition of ferrocene around homoadenine tetrads†

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Received (in Cambridge, UK) 5th February 2008, Accepted 28th February 2008
First published as an Advance Article on the web 28th March 2008
DOI: 10.1039/b802051e

We report synthesis and crystallographic studies of a ferrocenyl conjugate of adenine, where the hydrogen bonding interactions promote and stabilize nucleobase homotetrad formation.

The chemical stability and electroactive behavior of ferrocene has been extensively used for its conjugation to a diverse array of biotic and abiotic molecules catapulting an emerging area of bioorganometallic chemistry.[1] However, ferrocene conjugation to nucleobases, nucleosides and nucleic acids is a relatively unexplored domain compared to the studies of its interaction with amino acids and peptides and more recently, with peptide nucleic acids.[2] As nucleobases offer well-studied skeletons in terms of hydrogen bonding and supramolecular assembly,[3] hierarchical structures of ferrocene–nucleobase conjugates may offer exciting design avenues and potential applications.[3a]

We have extensively reported on adenine–metal ion interactions in the solid state and also in synthetic polymeric matrices.[4] Recent results in these studies have revealed the formation of adenine–silver quartets that are stabilized by hydrogen bonding and metal–ligand interactions. As nucleobases exhibit a tendency to self-associate with the help of Watson–Crick and Hoogsteen hydrogen bonds, we decided to explore the possibility of arranging ferrocene around nucleobase templates.

3-Bromopropionic acid chloride was used for ferrocene acylation, which upon base-catalyzed alkylation resulted in the formation of modified ferrocenylated-adenine (**1**) (Fig. 1a).‡ Compound **1**, when crystallized from a chloroform–methanol mixture, revealed a monoclinic unit cell in the *C*2/*c* space group (Fig. 1b). The various possibilities of hydrogen bonding interactions engendered in adenine supported the formation of defined hierarchical structures in the crystal lattice and are worth being discussed in detail.

Neatly packed adenine ribbons were observed when viewed along the *b*-axis (Fig. 2a). These ribbons exhibit further interaction with another ribbon, running parallel to each other, with the help of weak CH···O hydrogen bonds *via* the carbonyl oxygen, which is simultaneously bonded to C8-H and C11-H of different adenine moieties in the crystal structure (Fig. 2b). These interactions allow connectivities between

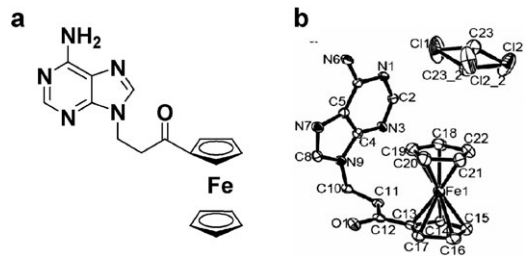

Fig. 1 (a) Molecular structure of **1**; (b) ORTEP diagram of **1** is drawn at 50% probability label (chloroform molecule is disordered). Hydrogen atoms are omitted for clarity.

ferrocenylated adenine ribbons to reveal a complex motif, which permits π–π stacking of two adjacent ferrocene units in three dimensional space. Some recent examples of simple adenine ribbons, without appendages, have appeared in the literature.[5] The various hydrogen bonding distances and bond angles are given in the ESI.†

A remarkable aspect of the lattice structure concerns a homoadenine tetrad where four ferrocenylated adenine moieties reveal formation of a quartet structure with the help of N6–H and N9–C–H sites as hydrogen bond donors, while N1, N3 and N7 acting as hydrogen bond acceptors. This tetrad is stabilized with the help of eight hydrogen bonds which are invoked both from the Watson–Crick and Hoogsteen faces of the modified adenine nucleobase. Notably, a adenine dimer is formed *via* intermolecular hydrogen bonding (2.13 Å) through the Watson–Crick face, whereas the Hoogsteen face of one of the adenines in the FcA–FcA base pair hydrogen bonds to the N3 nitrogen and elicits weak hydrogen bonding to the C–H of

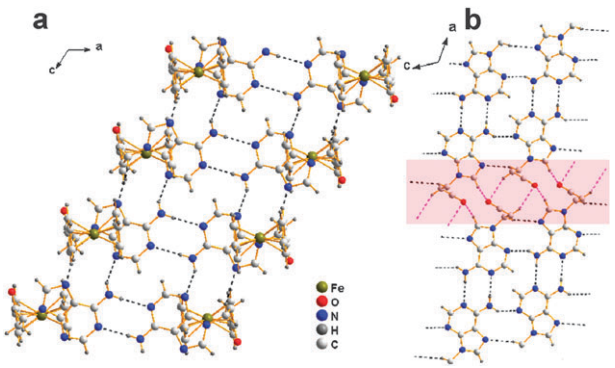

Fig. 2 (a) View of ferrocenylated adenine ribbons when viewed along the *b*-axis; (b) interconnection of two adenine ribbons (ferrocene units are omitted for clarity) by intermolecular CH···O hydrogen bonds (drawn as pink fragmented bonds and highlighted).

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† Electronic supplementary information (ESI) available: Summary of structural refinement parameters, hydrogen bonding table, additional representations of crystal lattice as figures for conjugate **1** and crystallographic data in CIF or other electronic format for CCDC 654334. See DOI: 10.1039/b802051e

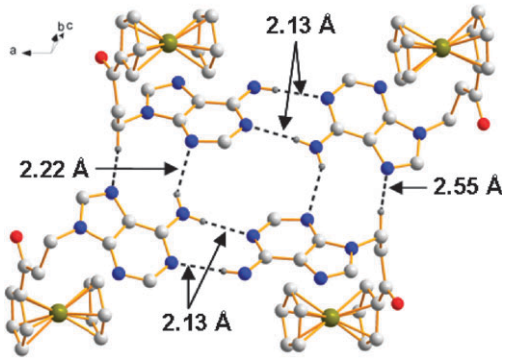


Fig. 3 Ferrocenylated-adenine (FcA) homotetrad formation with the help of eight hydrogen bonds (shown by fragmented bonds; H atoms not involved in the tetrad formation are omitted for clarity).

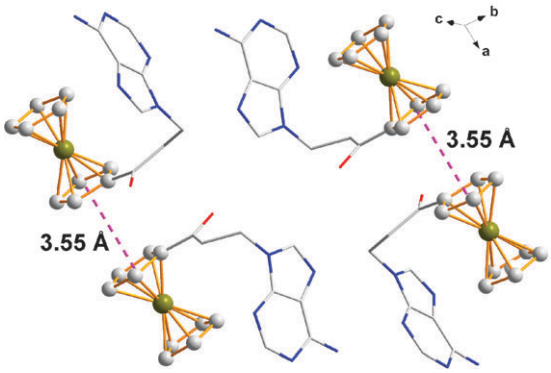


Fig. 4 The arrangement of ferrocene units in the crystal structure of **1**, inset view shows the strong π–π stacking between substituted Cp rings, distance is measured from the centre of the Cp ring (adenine moieties and H atoms are omitted for clarity).

the linker of the ferrocenyl appendage at the N9 position to afford a base tetrad (Fig. 3). Further confirmation of the dimer was obtained from the HRMS data (Calcd: 773.1463, Found: 773.1470 for $[2Fc–Ad + Na]^+$), while a mass peak corresponding to a quartet structure, from a weakly bonded dimer, was not detected.

One of the interactions observed in the solid state structure of **1** is the π–π stacking between the substituted Cp rings of ferrocenyl appendages as shown in Fig. 4. In addition, we were also able to detect CH–π weak interactions which are well known to affect the conformation of molecules.[6] Thus, we decided to check the conformational preference of the ferrocene unit with respect to the purine ring about the C10–C11 bond.

On a closer inspection, it appears that **1** adopts a synclinal arrangement along C10–C11 bond due to the dominant CH–π interaction (within ~2.9 Å, Fig. 5). The corresponding dihedral angle between the ferrocenyl unit and adenine is 68° (Fig. 5b). Interestingly, the highlighted H atom in **1** is directed more towards the five membered ring of adenine rather than the six membered ring, which is supported by theoretical calculations that suggest favourable interactions with five membered rings.[7] The angle C–H–X, where X is the centroid of the corresponding ring, for **1** is 161° and 124° for five and six membered rings, respectively. It was possible to detect the

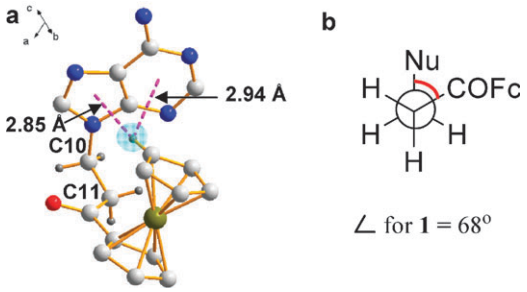


Fig. 5 (a) CH–π interaction shown by the fragmented bonds which are drawn from the centre of corresponding ring in **1** to the highlighted hydrogen atom; (b) shows the dihedral angle between adenine and the ferrocenyl moiety along the specified bond (C10–C11).

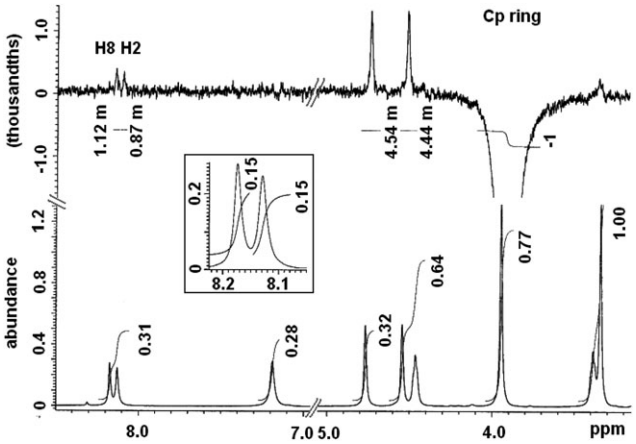
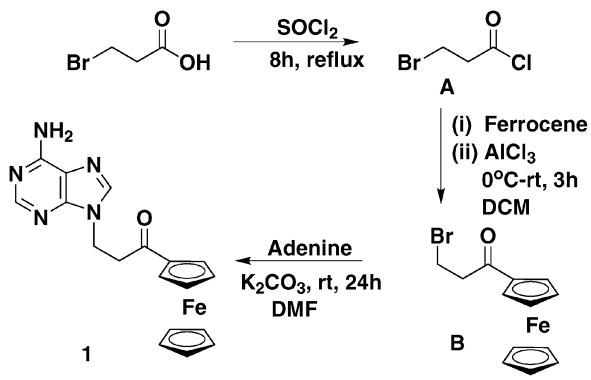


Fig. 6 NOE enhancements for H2 and H8 protons upon irradiation of the unsubstituted Cp ring protons (inset shows the integration of H2/H8 protons in ^{1}H NMR).



Scheme 1

proximal nature of the Cp hydrogens with respect to the H2 and H8 hydrogens of adenine using NOE experiments.[8] A marked NOE enhancement was observed when hydrogens of the unsubstituted Cp ring, not having the acyl substituent, were irradiated (Fig. 6). These observations suggest that individual Cp rings of ferrocene adopt an almost eclipsed conformation and the Cp–Fe–Cp axis is nearly parallel to the plane of the nucleobase, which can be partly attributed to stabilization due to CH–π interactions.

In conclusion, we have reported the synthesis and crystal structure of an adenine–ferrocene conjugate, the nucleobase forms a ribbon-like motif with the help of intermolecular hydrogen bonds and these ribbons are further connected by CH···O hydrogen bonding, thus forming a network of adenine ribbons. Hydrogen bonding, π–π stacking and CH–π interactions play an important role in the stability of the homoadenine tetrad structure, which enables ferrocenyl moieties to adopt an interesting spatio-temporal arrangement in the lattice superstructure.

We thank the Single Crystal CCD X-ray facility at IIT-Kanpur; CSIR, for S. P. Mukherjee Fellowship (J.K.). This work is supported by *Bioinorganic Chemistry Initiative*, DST, India.

Notes and references

‡ **General**: All reactions were performed under nitrogen atmosphere by using standard Schlenk techniques, while the workup was performed in the air. All solvents were distilled following standard procedures prior to use. 3-Bromopropanoic acid and adenine were purchased from Sigma-Aldrich, Mumbai, India, whereas anhydrous aluminium chloride, thionyl chloride, and ferrocene were purchased from Spectrochem, Mumbai, India, and used as supplied. ^{1}H and ^{13}C NMR spectra were recorded on JEOL-JNM LAMBDA 400 model operating at 400 and 100 MHz, respectively. ^{1}H and NOE spectra of **1** were recorded on JEOL ECX-500 model operating at 500 MHz. HRMS mass spectra were recorded at IIT Kanpur, India, on Waters Q-Tof Premier Micromass HAB 213 mass spectrometer using capillary voltage 2.6–3.2 kV.

Synthesis of 3-bromopropanoyl chloride (A): 10 ml thionyl chloride was added to 5 g of 3-bromopropanoic acid at room temperature then the reaction mixture was refluxed for eight hours under nitrogen atmosphere. The solvent was evaporated under reduced pressure and **A** was obtained as a light yellow viscous liquid (4.5 g, yield 80%) which was used in the next step without further characterization. The synthetic scheme of conjugate **1** is given in Scheme 1.

Synthesis of 3-bromo-1-ferrocenylpropan-1-one (B): To a solution of ferrocene (4.0 g, 1.0 mol) in dichloromethane (50 ml), **A** was added (3.69 g, 1.0 mol) slowly at 0 °C under nitrogen atmosphere. After this, aluminium chloride (3.01 g, 1.05 mol) was added in small portions at such a rate that the reaction mixture remains below 5 °C. The appearance of a deep blue colour indicates that the reaction was occurring. This addition requires about 20 min, and after its completion stirring was continued for 30 in an ice-water bath and then at room temperature for 2 h. After this time the reaction mixture was cooled again in an ice bath and 50 ml of chilled water was added cautiously which resulted in a two-phase mixture. This was then vigorously stirred for 30 min. This mixture was then transfered into a separating funnel and the organic layer was collected. The aqueous layer was extracted twice more with 20 ml portions of dichloromethane. The combined dichloromethane solutions were washed twice with 50 ml portions of 10% aqueous sodium hydroxide and dried over sodium sulfate. It was then evaporated at reduced pressure and column chromatographed over neutral alumina (petroleum ether/chloroform, 85 : 15), yielding 3.53 g. (51%) of **B** as a viscous, reddish liquid, which gradually solidifies. HRMS: $(M+1)^+$ calculated: 320.9577, found: 320.9563; M.P. = 66 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) 3.28 (t, J = 6.60 and 6.56 Hz, 2H, CH_2), 3.71 (t, J = 6.60 and 6.56 Hz, 2H, CH_2), 4.23 (s, 5H, Cp ring), 4.52 (s, 2H, two aromatic CH), 4.77 (s, 2H, two aromatic CH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) 25.98, 42.29, 69.19, 69.88, 72.52, 78.23, 200.55.

Synthesis of 3-(6-amino-9H-purin-9-yl)-1-ferrocenylpropan-1-one (1): To a solution of adenine (0.5 g, 1.0 mol) in 20 ml of dry DMF was added K_2CO_3 (0.61 g, 1.2 mol) and **B** (1.18 g, 0.99 mol) and the reaction mixture was stirred for 24 h at room temperature under a nitrogen atmosphere. The solvent was then removed under reduced pressure and the residue was purified by column chromatography over neutral alumina (chloroform/methanol, 95 : 5), affording 0.35 g. (25.48%) of **1** as red color solid. HRMS: $(M+1)^+$ calculated: 376.0861, found: 376.0829; Decomposes above 190 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 3.39 (s, 2H, CH2), 3.95 (s, 5H, Cp ring), 4.46 (s, 2H, CH2), 4.54 (s, 2H, Cp ring), 4.77 (s, 2H, Cp ring), 7.19 (s, 2H, NH2), 8.13 (s, 1H, C8-H), 8.17 (s, 1H, C2-H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) 37.96, 38.32, 68.89, 69.27, 72.21, 78.41, 141.24, 152.20, 155.86, 200.58.

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