Organometallic Chemistry

Structures of ferrocenylalkyl derivatives of adenine

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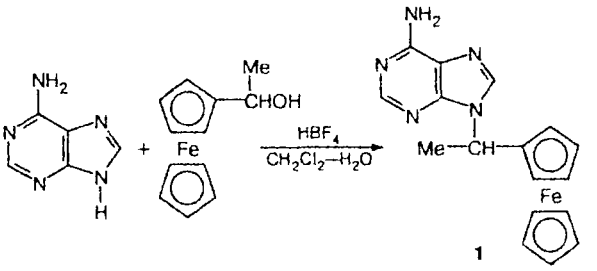
9-(α-Ferrocenylethyl)adenine was prepared by the reaction of adenine with α-hydroxyethylferrocene in a two-phase aqueous-organic medium in the presence of HBF_4. The structure of the resulting compound was established by X-ray diffraction analysis.

Key words: adenine, ferrocenylalkylation, α-hydroxyethylferrocene; 9-(α-ferrocenylethyl)adenine, X-ray diffraction analysis.

It is known that alkylation of purine bases yields 3-, 7-, or 9-alkyl-substituted derivatives.[1—4] The ratio of these derivatives depends on the nature of the alkylating agent and on the reaction conditions. Previously, we obtained ferrocenylalkyl derivatives of adenine using different versions of the ferrocenylalkylation reaction.[5,6] The assignment of these compounds to particular isomers was made based on the ^1H NMR spectral data on the values of the differences between the chemical shifts $|\Delta\delta|$ of the signals for the protons at the C(2) and C(8) atoms of the heterocycle as is customary for alkyl and aralkyl derivatives of adenine.[2,3] For example, for adenine substituted at position 9, the value of $|\Delta\delta|$ is 0—0.1. The corresponding value for the 3-substituted derivative is 0.6—0.7. However, in the case of the ferrocenylethyl derivative of adenine, the value of $|\Delta\delta|$ depends substantially on the nature of the solvent ($|\Delta\delta|$ 1.26, 0.28, and 0 in benzene-d_6, acetone-d_6, and DMSO-d_6, respectively).[6] In this connection, the aim of this work was to establish the structures of ferrocenylalkyl derivatives of adenine by X-ray diffraction analysis.

The reaction of adenine with α-hydroxyethylferrocene proceeds in a two-phase aqueous-organic system in the presence of HBF_4 (Scheme 1).[5]

Scheme 1



In the molecule of product **1** (Fig. 1), the ferrocenylethyl group is attached at position 9 of the adenine fragment. The ferrocenyl fragment is bent away from the plane of the heterocycle. The bond lengths in **1** are similar to those in other ferrocenylalkyl derivatives of nitrogen bases.[7,8] The C(9)—N(9) bond (1.490(5) Å) is slightly elongated compared to the mean value (1.469 Å) typical of $C(sp^3)$—N bonds with the three-coordinate nitrogen atom,[9] and it is longer than the $C(CH_3)$—N(9) bond in 9-methyladenine[10] or the $C(CH_2)$—N bond in 2-ferrocenyl-1-ferrocenylmethylbenzimidazole[8] (1.459 Å). This may be one of the factors that favor the

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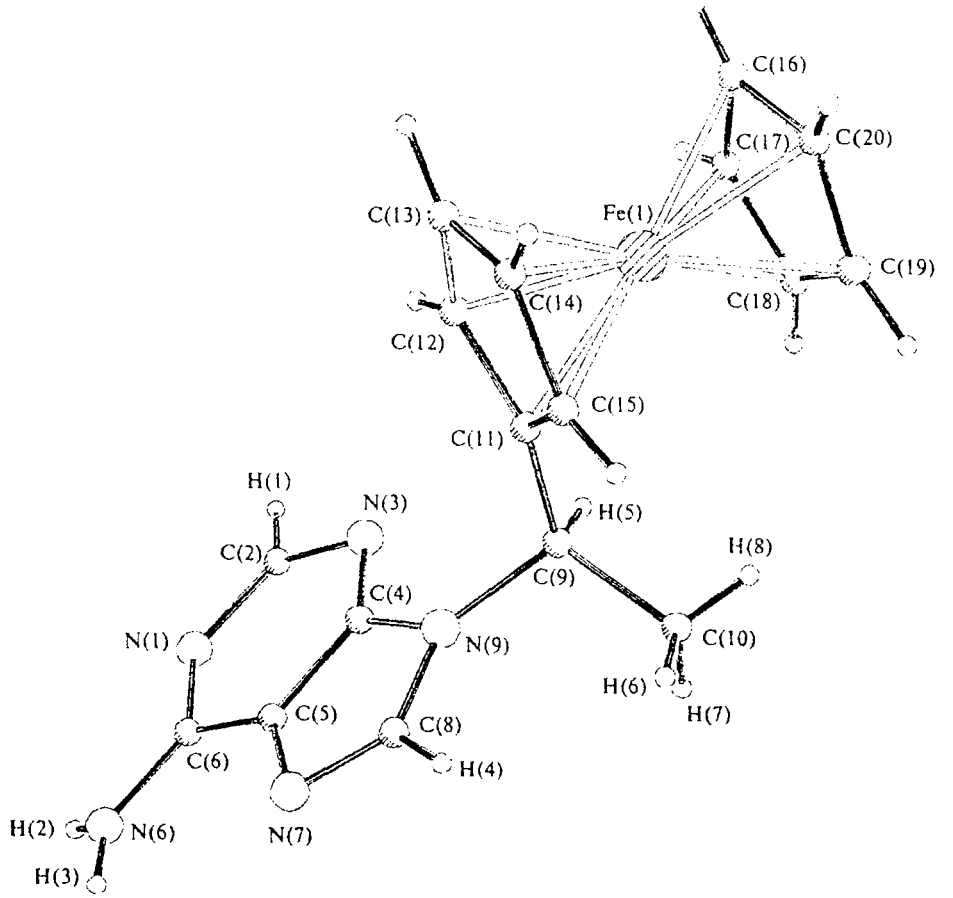

Fig. 1. Molecular structure of 9-(α-ferrocenylethyl)adenine (**1**).

cleavage of the C(9)—N(9) bond, which is manifested in the high reactivity of 9-(α-ferrocenylethyl)adenine. Previously,[6] we have demonstrated that this compound is an efficient ferrocenylalkylating reagent, for example, with respect to benzotriazole.

The cyclopentadienyl rings in the ferrocenyl fragment are coplanar (the dihedral angle between their planes is 0.9°) and form an angle of 111.9° with the plane of the adenine nucleus. The Fe atom is located symmetrically with respect to the Cp rings at distances of 1.644(5) and 1.653(6) Å. The C(8)—N(9)—C(9)—C(10) and C(8)—N(9)—C(9)—C(11) torsion angles are 42.43° and −83.66°, respectively. The molecular geometry of the adenine fragment agrees well with the geometries of adenine trihydrate[11] and 9-methyladenine.[10]

In the crystal, molecules **1** are linked into doubled ribbons *via* intermolecular hydrogen bonds with the participation of the H atoms of the amino groups and the N(3)″ atoms (Fig. 2). The parameters of the hydrogen bonds are as follows: N(3)″...H(3), 2.42(5) Å;

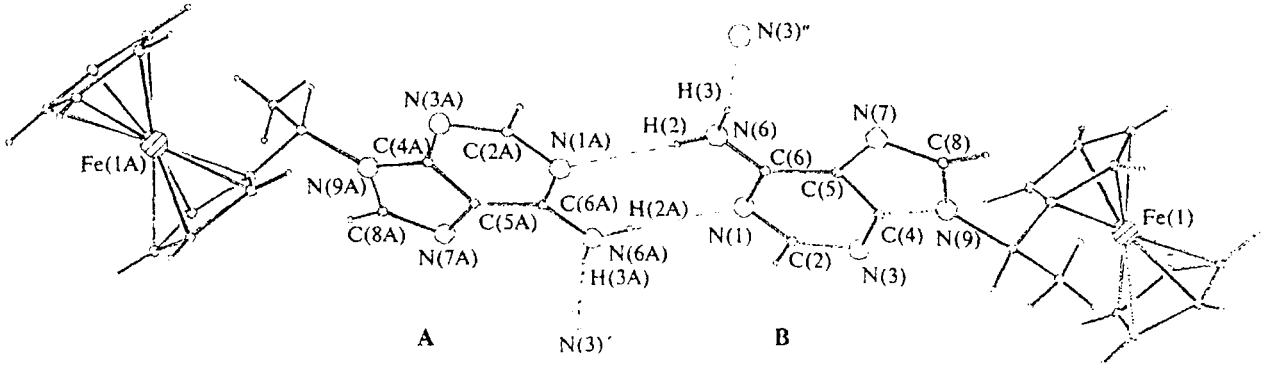

Fig. 2. Structure of the fragment of the ribbon formed by two symmetrically related molecules **1**.

Table 1. Atomic coordinates ($\times 10^4$) and isotropic equivalent temperature factors (B_{eq}) in the structure of **1**

Atom	x	y	z	B_{eq}/Å^2
Fe(1)	5747(1)	−1280(1)	6696(1)	40(1)
N(1)	9234(3)	−3869(3)	9110(2)	44(1)
N(3)	8711(3)	−2184(3)	8078(2)	42(1)
N(6)	9138(4)	−3847(3)	10835(3)	51(1)
N(7)	8121(4)	−1360(3)	10597(2)	53(1)
N(9)	8034(3)	−529(3)	9074(2)	43(1)
C(2)	9076(4)	−3285(4)	8248(3)	45(1)
C(4)	8434(3)	−1658(3)	8939(2)	36(1)
C(5)	8500(3)	−2149(3)	9879(3)	37(1)
C(6)	8957(3)	−3300(3)	9965(3)	37(1)
C(8)	7852(5)	−423(4)	10074(3)	56(1)
C(9)	7858(4)	373(3)	8282(3)	41(1)
C(10)	8416(5)	1531(4)	8646(4)	56(1)
C(11)	6449(4)	441(3)	7935(2)	40(1)
C(12)	5812(5)	−365(4)	7271(3)	49(1)
C(13)	4496(5)	7(5)	7125(3)	64(1)
C(14)	4319(5)	1025(5)	7700(4)	65(1)
C(15)	5525(4)	1291(4)	8199(3)	49(1)
C(16)	5279(6)	1673(5)	5244(3)	67(1)
C(17)	6559(6)	1210(4)	5333(3)	62(1)
C(18)	7304(5)	1928(4)	5965(3)	57(1)
C(19)	6501(5)	2842(4)	6277(3)	56(1)
C(20)	5242(5)	2696(4)	5841(4)	64(1)

N(1A)...H(2), 2.32(5) Å; N(6)...N(3)″, 3.280 Å; N(6)...N(1A), 3.104(5) Å; the N(6)—H(3)—N(3)″ and N(6)—H(2)—N(1A) angles are 171(4)° and 173(4)°, respectively. The chains are formed *via* N(6)—H(3)...N(3)″ hydrogen bonds (and *via* analogous symmetrically related N(6A)—H(3A)...N(3)′ hydrogen bonds). These chains are linked into ribbons *via* cyclic N(6)—H(2)...N(1A) hydrogen bonds (and *via* analogous symmetrically related N(6A)—H(2A)...N(1) hydrogen bonds). In the ribbons, molecules **1** are arranged in a head-to-head fashion, and the ferrocenyl substituents form the outer surfaces of the ribbons. The N(7) atom of the adenine fragment is not involved in hydrogen bonding. The plane of the adenine fragment of one molecule (**A**, see Fig. 2) is parallel to the corresponding plane of the other molecule (**B**). The distance between these planes is 0.88 Å.

Therefore, ferrocenylalkylation of adenine with α-hydroxyethylferrocene in a two-phase system in the presence of HBF_4 afforded 9-(α-ferrocenylethyl)adenine. The results obtained in this work allow one to judge with higher assurance the structures of other derivatives of adenine.[6] For example, the reactions of adenine with hydroxymethylferrocene (in the two-phase system in the presence of HBF_4) and with trimethyl(ferrocenylmethyl)ammonium iodide (boiling in water) also afforded 9-substituted derivatives of adenine because their ^{1}H NMR spectra are analogous to those obtained[5,6] for compound **1**.

As expected, the X-ray diffraction data are indicative of the considerable role of hydrogen bonds in the formation of supramolecular structures of ferrocenylalkyl derivatives of nucleic bases. Because of this, when studying

Table 2. Bond lengths (d) and bond angles (ω) in molecule **1**

Bond	d/Å	Bond	d/Å	Bond	d/Å	Bond	d/Å
Fe(1)—C(11)	2.030(3)	Fe(1)—C(14)	2.049(5)	N(9)—C(4)	1.372(5)	C(12)—C(13)	1.421(7)
Fe(1)—C(19)	2.039(4)	N(1)—C(2)	1.343(5)	N(9)—C(9)	1.490(5)	C(13)—C(14)	1.415(8)
Fe(1)—C(12)	2.039(4)	N(1)—C(6)	1.359(5)	C(4)—C(5)	1.382(5)	C(14)—C(15)	1.416(6)
Fe(1)—C(15)	2.040(4)	N(3)—C(2)	1.334(5)	C(5)—C(6)	1.404(5)	C(16)—C(17)	1.416(8)
Fe(1)—C(16)	2.041(4)	N(3)—C(4)	1.343(4)	C(9)—C(11)	1.503(5)	C(16)—C(20)	1.423(8)
Fe(1)—C(13)	2.041(5)	N(6)—C(6)	1.333(5)	C(9)—C(10)	1.520(6)	C(17)—C(18)	1.390(7)
Fe(1)—C(17)	2.041(4)	N(7)—C(8)	1.308(5)	C(11)—C(15)	1.414(5)	C(18)—C(19)	1.407(6)
Fe(1)—C(20)	2.043(4)	N(7)—C(5)	1.389(5)	C(11)—C(12)	1.425(5)	C(19)—C(20)	1.406(7)
Fe(1)—C(18)	2.046(5)	N(9)—C(8)	1.368(5)				

Angle	ω/deg	Angle	ω/deg	Angle	ω/deg	Angle	ω/deg
C(11)—Fe(1)—C(19)	121.1(2)	C(13)—Fe(1)—C(20)	125.3(2)	C(8)—N(9)—C(9)	128.4(3)	N(9)—C(9)—C(10)	110.1(3)
C(19)—Fe(1)—C(12)	155.6(2)	C(11)—Fe(1)—C(18)	107.9(2)	C(4)—N(9)—C(9)	126.1(3)	C(11)—C(9)—C(10)	113.6(3)
C(19)—Fe(1)—C(15)	109.0(2)	C(12)—Fe(1)—C(18)	120.2(2)	N(3)—C(2)—N(1)	130.1(4)	C(15)—C(11)—C(12)	108.0(4)
C(11)—Fe(1)—C(16)	162.0(2)	C(15)—Fe(1)—C(18)	126.2(2)	N(3)—C(4)—N(9)	127.7(3)	C(15)—C(11)—C(9)	127.1(3)
C(12)—Fe(1)—C(16)	124.7(2)	C(13)—Fe(1)—C(18)	155.0(2)	N(3)—C(4)—C(5)	126.7(3)	C(12)—C(11)—C(9)	125.0(4)
C(15)—Fe(1)—C(16)	155.9(2)	C(19)—Fe(1)—C(14)	126.5(2)	N(9)—C(4)—C(5)	105.5(3)	C(13)—C(12)—C(11)	107.6(4)
C(19)—Fe(1)—C(13)	162.8(2)	C(16)—Fe(1)—C(14)	120.8(2)	C(4)—C(5)—N(7)	111.3(3)	C(14)—C(13)—C(12)	108.2(4)
C(16)—Fe(1)—C(13)	107.5(2)	C(17)—Fe(1)—C(14)	155.6(2)	C(4)—C(5)—C(6)	117.6(3)	C(13)—C(14)—C(15)	107.9(4)
C(11)—Fe(1)—C(17)	124.9(2)	C(20)—Fe(1)—C(14)	108.1(2)	N(7)—C(5)—C(6)	131.1(3)	C(11)—C(15)—C(14)	108.3(4)
C(12)—Fe(1)—C(17)	107.2(2)	C(18)—Fe(1)—C(14)	163.3(2)	N(6)—C(6)—N(1)	119.2(3)	C(17)—C(16)—C(20)	107.8(5)
C(15)—Fe(1)—C(17)	162.2(2)	C(2)—N(1)—C(6)	117.8(3)	N(6)—C(6)—C(5)	123.3(4)	C(18)—C(17)—C(16)	108.4(5)
C(13)—Fe(1)—C(17)	120.5(2)	C(2)—N(3)—C(4)	110.2(3)	N(1)—C(6)—C(5)	117.5(3)	C(17)—C(18)—C(19)	107.9(5)
C(11)—Fe(1)—C(20)	155.7(2)	C(8)—N(7)—C(5)	102.8(3)	N(7)—C(8)—N(9)	114.8(3)	C(20)—C(19)—C(18)	109.0(4)
C(12)—Fe(1)—C(20)	162.2(2)	C(8)—N(9)—C(4)	105.5(3)	N(9)—C(9)—C(11)	110.3(3)	C(19)—C(20)—C(16)	106.8(4)
C(15)—Fe(1)—C(20)	121.0(2)						

the mechanism of antitumor action of ferrocenylalkylazoles, which we have found previously,[12] it is necessary to take into account not only the possibility of ferrocenylalkylation of nucleic bases of DNA[6] by these compounds but also the possible formation of hydrogen and intercalation bonds between ferrocenylalkylazoles and bases of DNA.[13]

Experimental

The reaction of adenine with α-hydroxyethylferrocene was carried out according to a known procedure.[5] The reaction mixture was chromatographed on Al_2O_3 (acetone as the eluent). The thoroughly dried compound was crystallized from methanol with the addition of a small amount of hexane at −12 °C. 9-(α-Ferrocenylethyl)adenine (**1**) (M = 347.21) was obtained as yellow crystals, the yield was 30%, m.p. 194–196 °C. Found (%): C, 58.62; H, 4.96; N, 20.12. $C_{17}H_{17}FeN_5$. Calculated (%): C, 58.79; H, 4.89; N, 20.17.

X-ray diffraction study of compound 1 was carried out on an automated CAD-4 diffractometer (Mo-Kα radiation, μ = 9.6 cm^{-1}). Crystals are monoclinic, at 20 °C a = 10.252(5) Å, b = 11.468(5) Å, c = 13.428(6) Å, β = 92.19(4)°, V = 1577.7 $Å^3$, d_{calc} = 1.462 g cm^{-3}, space group $P2_1/c$, Z = 4; the R factor is 0.0655 using 2509 reflections with $I > 2\sigma(I)$. The atomic coordinates are given in Table 1. The bond lengths and bond angles are listed in Table 2.

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