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Synthesis and properties of some 1,1′-bis [*N*-formyl-*N*′-substituted thiourea]ferrocene derivatives: crystal structure of 1,1′-bis [*N*-formyl-*N*′-*p*-chlorophenylthiourea]ferrocene

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Abstract—A series of 1,1′-bis[*N*-formyl-*N*′-substituted thiourea]ferrocene derivatives was synthesized through the reaction of 1,1′-bis[formyl isothiocyanate]ferrocene and various primary amines, with high yields after simple and convenient purification. All the compounds were characterized by elemental analysis, IR and ^{1}H NMR spectra. Intramolecular hydrogen bonding between the formyl carbonyl group and the proton attached to N′ was found to be common in this kind of compound. Cyclic voltammetric analysis revealed that the substituents on the N′ atom affect the electrochemical behaviour of the ferrocenyl group *via* the intramolecular hydrogen bonded ring. The crystal structure of 1,1′-[*N*-formyl-*N*′-*p*-chlorophenylthiourea]ferrocene was determined showing the character of the intramolecular hydrogen bonding. © 1997 Elsevier Science Ltd. All rights reserved.

Keywords: ferrocene; acyl thiourea; intramolecular hydrogen bonding; electrochemistry.

Many acyl thiourea compounds have been widely studied for their insecticidal, antibacterial and pesticidal activities and promoting effect on plant growth [1,2]. It has been found that intramolecular hydrogen bonding is common in *N*-ferrocenoyl-*N*′-monosubstituted thiourea derivatives, which form a novel kind of polychelate ligand ready to complex with transition metal ions [3,4]. Whether intramolecular hydrogen bonding exists in 1,1′-disubstituted acyl thiourea ferrocene compounds is still another question to be investigated. In an extensive study, 1,1′-bis[*N*-formyl-*N*′-substituted thiourea]ferrocene derivatives were synthesized through the reaction of 1,1′-bis[formyl isothiocyanate]ferrocene with various primary amines. The existence of intramolecular hydrogen bonding was confirmed by IR ^{1}H NMR spectra and single crystal X-ray diffraction.

EXPERIMENTAL

All reagents and solvents were of analytical or chemical grade quality. Acetone was dried by refluxing with P_2O_5 for 3–4 hours after treatment with anhydrous potassium carbonate. KSCN was baked before use. Aromatic amines were vacuum distilled or recrystallized. Aliphatic amines were used directly without further purification.

Elemental analysis (C, H, N) were performed on a CHN-Corderm7-3 autoanalyser. Melting points were determined on a PHMK melting point apparatus (from Germany) and are uncorrected. ^{1}H NMR spectra were recorded on a Jeol FX-90QNMR, spectrometer, using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. IR spectra were carried out with a Nicolet-FT-IR5-DX infrared spectrophotometer. X-ray diffraction data were obtained using an Enraf Nonius CAD4 diffractometer with graphite-monochromated Mo-K_α radiation ($\lambda = 0.071073$ nm). The crystal belongs to the monoclinic, space group $P2_1/n$, $a = 8.435(1)$, $b = 23.088(8)$, $c = 13.307(3)$ Å, $\beta = 95.70(1)°$, $V = 2597(2)$ Å^3, $z = 4$, $D_c = 1.575$ g cm^{-3}, $\mu = 9.804$ cm^{-1} and $F(000) = 1248$. A total of 3240 independent reflections was collected in the range $4.0 < \theta < 46.0°$ by 2θ–θ scan, at room temperature (299 ± 1 K), of which 1690 were accepted as observable [$I \geqslant 3\sigma(I)$]. The intensities were fully corrected

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for Lp factors and empirical absorption. The crystal structure was solved by direct phase determination method (MULTAN82). One independent Fe atom was located on an E map. The other non hydrogen atoms were found in the successive difference Fourier syntheses. The hydrogen atoms were not included in the refinement and calculations of structure factors. The coordinates and anisotropic thermal parameters of non-hydrogen atoms were refined by full-matrix least-squares methods and converged to $R = 0.053$ and $R_w = 0.061$ with unit weights. The highest electron density on the final difference Fourier map was found to be 0.45 e Å^{-3}. All calculations were performed on a PDP11/44 computer using the SDP-PLUS program system.

Cyclic voltammetric experiments were performed on a BAS-100B electrochemical analyser equipped with a three electrode assembly with 0.1 mol dm^{-3} TBAFB (Bu_4NBF_4) as support electrolyte and CH_2Cl_2 as solvent. The working electrode was a ϕ 1.5 mm platinum disk embedded in a cobalt glass seal and was polished consecutively with polishing alumina and diamond suspensions between runs. The 0.1 M $AgNO_3/Ag$ (in 0.1 M Bu_4NBF_4-DMSO) was the reference electrode. A platinum filament was used as an auxiliary electrode.

Synthesis of 1,1′*-bis(formyl isothioncyaate)ferrocene* (I)

KSCN (0.533 g, 5.5 mmol) was dissolved in acetone (15 cm^3) and added dropwise to the 20 cm^3 acetone solution of 2.5 mmol $Fc(COCl)_2$ and refluxed for 30 min. The red acetone solution of $Fc(CONCS)_2$ was obtained on filtration of KCl and used *in situ* for the following reactions without further separation and purification.

Reaction of aromatic amines and aminoferrocene with I

Taking *p*-chloroaniline as an example. *p*-Chloroaniline (0.65 g, 5 mmol) dissolved in acetone (20 cm^3) was added dropwise to the acetone solution of 2.5 mmol $Fc(CONCS)_2$ and a red solid rapidly appeared. The mixture was refluxed for 2 h and the red powder obtained by filtration was washed with acetone. A total of 1.39 g was collected, yield 91%.

Reaction of aliphatic amines with I

Taking isopropyl amine as an example. An acetone solution of isopropyl amine (5 mmol) was added to the aforesaid acetone solution of $Fc(CONCS)_2$ and refluxed for 5 h. After removal of acetone by distillation, the residue was dissolved in the minimum amount of $CHCl_3$, and 0.96 g orange–red crystal was eluted from a neutral Al_2O_3 (200–300 mesh) chromatographic, column, yield 81%.

RESULTS AND DISCUSSION

General characterization

Analytical and physical data for the 11 compounds are given in Table 1. Compounds **1**–**3** are very soluble in acetone, diethyl ether, chloroform and dichloromethane and are soluble in benzene and hot alcohol, but are insoluble in petroleum ether. Compounds **4**–**9** can be dissolved in DMF, DMSO and other non-protic solvents.

Reactivity of I *towards primary amines*

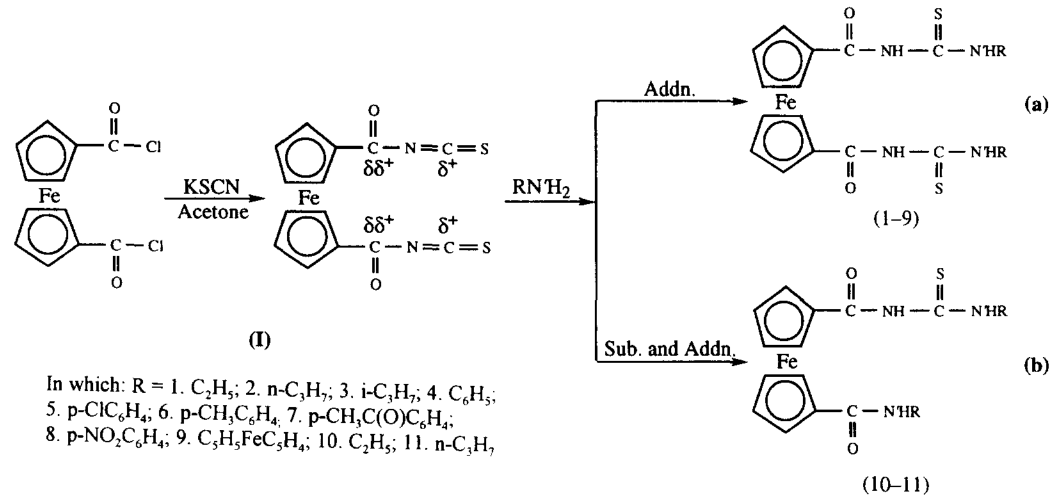
The intermediate 1,1′-bis[formyl isothiocyanate] ferrocene (**I**) was synthesized and reacted with aliphatic amines *in situ* under mild condition. There are two competing reactive sites in **I** as shown in Scheme 1.

If RNH_2 attacks the carbon atom in the isothiocyanate group ($C^{\delta+}$), addition of RNH_2 to the C=N double bond takes place, resulting in the thiourea product. An alternative site for RNH_2 to attack is

Table 1. Physical properties and elemental analysis for compounds **1**–**11**

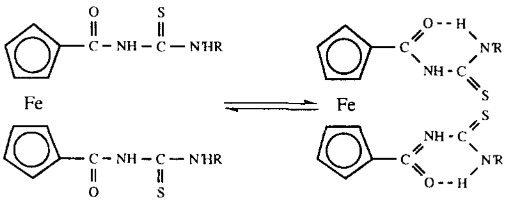
Compound	M.p. (°C)	Yield (%)	Colour	Elemental analysis (%)^a C	H	N
1	178–9	70	orange-red	48.4(48.4)	5.0(5.0)	12.4(12.5)
2	88–9	68	red	50.8(50.6)	5.6(5.5)	11.8(11.8)
3	165–6	81	orange-red	50.6(50.6)	5.8(5.5)	11.8(11.8)
4	192–4	89	red	57.4(57.6)	4.1(4.1)	10.2(10.3)
5	195–7	91	orange-red	51.2(51.1)	3.4(3.3)	8.9(9.2)
6	198–9	92	orange-red	58.8(58.9)	4.6(4.6)	9.9(9.8)
7	196–8	88	orange-red	57.8(57.1)	4.2(4.2)	8.7(8.4)
8	212(dec.)	85	red	49.2(49.4)	3.2(3.2)	13.5(13.3)
9	184(dec.)	84	orange-yellow	53.8(54.0)	3.8(3.7)	7.4(7.4)
10	139–40	-	red	52.7(52.7)	6.5(6.5)	10.8(10.8)
11	148–50	-	red	54.9(54.9)	6.1(6.1)	9.9(10.1)

^{a}Calculated values are given in parentheses.



In which: R = 1. C_2H_5; 2. n-C_3H_7; 3. i-C_3H_7; 4. C_6H_5; 5. p-ClC_6H_4; 6. p-$CH_3C_6H_4$; 7. p-$CH_3C(O)C_6H_4$; 8. p-$NO_2C_6H_4$; 9. $C_5H_5FeC_5H_4$; 10. C_2H_5; 11. n-C_3H_7

Scheme 1.



Scheme 2.

the carbonyl carbon atom ($C^{\delta\delta+}$). In this case, the isothiocyanate group is substituted by the amino group, thus the amide product is anticipated. Unlike its monosubstituted ferrocene derivative analogue, whose reaction with primary amines gave only the addition product, the reaction of (**I**) with aliphatic amines involved competition between addition and substitution. Both products were isolated through column chromatography. In the case of aromatic primary amines, owing to their lower nucleophilicity, they were reacted with (**I**) under reflux. The products precipitated from the solution directly. No substitution took place and only the addition form was collected.

IR spectra

The medium–strong $\nu_{C=O}$ band in the IR spectra of all the compounds appears at about 1671 cm^{-1}, apparently decreasing in wavenumber compared with the ordinary carbonyl absorption (1710 cm^{-1}) (see Table 2). This is interpreted as being a result of its conjugate resonance with the ferrocenyl group and the possible formation of intramolecular hydrogen bonding with N′—H. In addition, the abnormal intensity ratio between $\nu_{C=O}$ and δ_{CNH} (1515–1550 cm^{-1}, vs) bands revealed that intramolecular hydrogen bonding might exist in this kind of compound (as shown in Scheme 2) [5]. No ν_{S-H} absorption was observed in the region 2600–2500 cm^{-1}, indicating that the compounds do not exist in the thioenol form. The ν_{C-N} band appears at about 1269 cm^{-1} and is much weaker than $\nu_{C=O}$ and δ_{CNH} in intensity. It is presumed to be the mixed vibration of δ_{OCN} and ν_{N-H}. A strong band at about 1319–1355 cm^{-1} is assigned to the stretching vibration of the thione group. There is a weak or medium intensity singlet peak at 3300 cm^{-1} in the IR spectra of compounds **1**–**9**, indicating the presence of the secondary amino group. It is attributed to ν_{N-H}, whereas the $\nu_{N'-H}$ band shifts to 3010–3230 cm^{-1} and becomes broad and weak because of the intramolecular hydrogen bond formation. In the IR spectra of compounds **10** and **11**, there are three ν_{N-H} absorptions at 3279, 3246 and 3164 cm^{-1}, respectively, and two $\nu_{C=O}$ bands, one very strong at 1630 cm^{-1} and the other comparatively weak at about 1671 cm^{-1}. With respect to other regions, there is little difference compared with compounds **1**–**9**. All of the above facts support structure (b) in Scheme 1, in which one side chain gives the addition product while the other undergoes substitution.

Nujol IR spectra were also recorded and it was shown that there are no ν_{O-H} and ν_{S-H} bands. This indicates that compounds **1**–**11** exist in the keto-thione form.

^{1}H *NMR spectra*

In the ^{1}H NMR spectra of compounds **1**–**9** (Table 3), the signals of the cyclopentadienyl protons shift downfield owing to their proximity to the carbonyl group with δ_{ortho} (4.74–5.46) > δ_{meta} (4.48–4.78), displaying the characteristics of AA′BB′ coupling, since the two Cp rings are in the same chemical environment. There are two kinds of Cp rings in compound **9**, with four being monosubstituted and two unsubstituted. The former gives AA′BB′ coupling and altogether five Cp bands are observed. δ_{N-H} appears at 8–9 ppm. The downfield δ 12.50 peak is assigned to

Table 2. IR spectral data (cm^{-1}) for **1**–**11**

Compound	ν_{N-H}	$\nu_{N'-H}$	δ_{CHN}	$\nu_{C=O}$	$\nu_{C=S}$	ν_{C-N} C(O)—N	ν_{C-N} —C(S)—N
1	3263m	3200–3164w	1516vs 1548vs	1671s	1355w	1269m	1171s
2	3263m	3200–3100w	1507vs 1548vs	1671s	1335w	1269m	1171s
3	3312m	3222–3156w	1515vs 1548vs	1663s	1340m	1269m	1146s
4	3312s	3010w	1524vs	1671s	1351m	1269s	1163vs
5	3304m	3017w	1524vs	1663s	1327m	1269s	1155s
6	3312m	3100w	1524vs	1671m	1352m	1269m	1163vs
7	3279m	3107w	1530vs	1671s	1335m	1269s	1146s
8	3263m	3115w	1516vs	1671s	1335s	1278m	1155s
9	3271w	3148w	1507vs	1663s	1319w	1269m	1155s
10	3279m 3246w	3164m	1557vs 1507vs	1671s 1622vs	1352w	1269m	1179s
11	3279m 3246s	3164m	1557vs 1507vs	1680s 1630vs	1352w	1269m	1155m

vs: very strong; s: strong; m: middle; w: weak.

Table 3. ^1H NMR data (δ, ppm) for compounds **1**–**11**

Compound	Fc—H	N—H	N′—H	R
1	4.56 (s, 4H); 4.80 (s, 4H)	8.64 (s, 2H)	10.60 (s, 2H)	1.36 (t, 6H); 3.72 (q, 4H)
2	4.50 (s, 4H); 4.74 (s, 4H)	8.96 (s, 2H)	10.56 (s, 2H)	3.60 (d, 4H); 1.61 (m, 4H); 1.04 (t, 6H)
3	4.60 (s, 4H); 4.84 (s, 4H)	8.64 (s, 2H)	10.56 (s, 2H)	1.32 (d, 12H); 4.60 (m, 2H)
4	4.72 (s, 4H); 4.96 (s, 4H)	8.84 (s, 2H)	12.56 (s, 2H)	7.28-7.70 (m, 10H)
5	4.72 (s, 4H); 4.96 (s, 4H)	8.84 (s, 2H)	12.55 (s, 2H)	7.32-7.80 (m, 8H)
6	4.72 (s, 4H); 4.96 (s, 4H)	8.78 (s, 2H)	12.44 (s, 2H)	7.32-7.80 (m, 8H); 2.40 (s, 6H)
7[a]	4.78 (s, 4H); 5.44 (s, 4H)	10.90 (s, 2H)	13.30 (s, 2H)	7.92 (b, 8H); 3.52 (s, 6H)
8[a]	4.78 (s, 4H); 5.46 (s, 4H)	11.16 (s, 2H)	13.36 (s, 2H)	8.10 (b, 8H)
9[a]	4.00 (s, 4H); 4.08 (s, 10H) 4.48 (s, 4H); 4.56 (s, 4H) 4.92 (s, 4H)	9.72 s, 2H)	12.00 s, 2H)	
10	4.46–4.72 (m, 8H)	9.00 (s, 1H)	6.20 (s, 1H) 10.66 (s, 1H)	1.28 (m, 6H) 3.46 (q, 2H) 3.76 (q, 2H)
11	4.32–4.56 (m, 8H)	8.82 (s, 1H)	6.10 (s, 1H) 10.56 (s, 1H)	0.96 (t, 6H) 1.60 (m, 4H) 3.24 (t, 2H) 3.58 (t, 2H)

s: singlet; d: doublet: t: triplet; q: quartet; m: multiplet; b: broad.
[a] DMSO-d_6 as solvent.

$\delta_{N'-H}$ owing to the deshielding effect of intramolecular hydrogen bond formation. In compounds **7** and **8**, δ_{N-H} and $\delta_{N'-H}$ approach δ 11.00 and 13.00 owing to the electron-withdrawing groups on the phenyl ring. All of this evidence tallies with the structures drawn from their IR spectra.

Three amino protons were observed in the ^1H NMR spectra of compounds **10** and **11,** two of which are similar to those of the aforesaid compounds, while the other appears at δ 6.00, belonging to the amide proton. Besides, the cyclopentadienyl proton signals are too complicated to differentiate. With the aid of elemental analysis data, the structures of **10** and **11** are presumed to be (b). This further confirmed the conclusion derived from the IR spectra.

To demonstrate the existence of intramolecular hydrogen bond, ^1H NMR spectra of compounds **1** and **10** at different concentrations with $CDCl_3$ as solvent were recorded. It was found that the most downfield peak remains unchanged.

Electrochemistry

Cyclic voltammetric data of compounds **1**–**9** and ferrocene are listed in Table 4. The CV curves of compounds **2** and **9** are depicted in Figs 1 and 2.

One pair of reversible redox peaks was observed in compounds **1**–**8,** indicating that they undergo a one-electron redox reaction. Their $\bar{E}_p$ values at about 0.85

Table 4. Cyclic voltammetric data

Compound	r (mV s^{-1})	E_{Pa} (V)	E_{Pc} (V)	$\bar{E}_p$ (V)	$I_{Pa} \times 10^{-7}$ (A)	$I_{Pc} \times 10^{-7}$ (A)	I_{Pa}/I_{Pc}
Fc—H	100	0.431	0.092	0.262	11.135	10.238	1.0876
1	200	0.969	0.714	0.842	7.9757	5.0220	1.5882
2	200	0.992	0.702	0.847	9.6806	5.6394	1.7166
3	100	0.971	0.691	0.832	9.3665	6.4629	1.4493
	200	1.006	0.701	0.854	11.376	6.5971	1.7244
4	300	0.914	0.697	0.806	2.4778	1.7375	1.4261
5	200	1.018	0.738	0.878	7.8158	5.2249	1.4959
6	600	0.991	0.736	0.864	5.7196	3.0481	1.8764
	400	0.979	0.735	0.857	5.0934	2.6940	1.8906
7	600	0.984	0.719	0.852	3.8643	2.1636	1.7861
8	400	0.949	0.823	0.886	0.7469	0.2062	3.6229
9	300	0.302	0.171	0.237	2.0645	2.8886	0.7147
		0.698	0.650	0.674	1.1214	0.1803	6.2214

[a] $E_p = 1/2(E_{pa} - E_{pc})$.

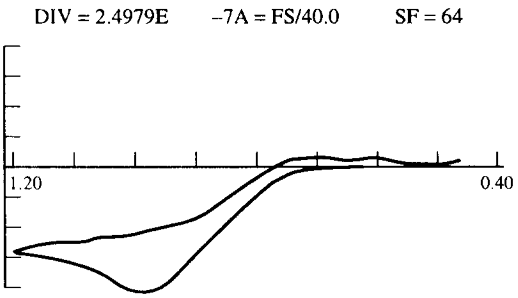


Fig. 1. Cyclic voltammogram of compound **2**.

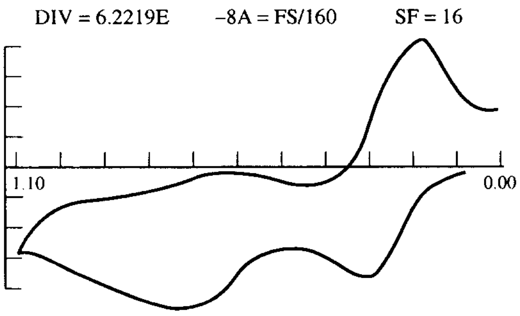


Fig. 2. Cyclic voltammogram of compound **9**.

V are higher than that of ferrocene (0.262 V), thus revealing that the acyl thiourea group is an electron-withdrawing group. In addition, at the same rate of scanning, their redox potentials are influenced by the properties of the substituents on the N′ atom. The more electron withdrawing the substituent is, the higher the $\bar{E}_p$ value becomes. For example, at the same scanning rate of 400 mV s^{-1}, $\bar{E}_p$ of compound **8** (p-NO$_2$) is 0.886 V, while that of compound **6** (p-CH$_3$) is 0.857 V. This is explained as follows: the strong electron-withdrawing property of p-NO$_2$ ($\sigma = 0.78$) and electron-donating property of p-CH$_3$ ($\sigma = -0.17$) can affect the electrochemical behaviour of the ferrocenyl group *via* the intramolecular hydrogen bonding planes.

There are two pairs of redox peaks in the CV curve of compound **9**, showing the characteristics of a multi-component redox system [6]. This is interpreted as resulting from two different kinds of ferrocenyl groups. The two monosubstituted ferrocenyls are electrochemically identical and are oxidized at the same potential, releasing two electrons at the same time. Their E_p (0.237 V) is lower than that of ferrocene, owing to the electron-donating properties of the amino group. Whereas the E_p value of the disubstituted ferrocenyl group (0.674 V) is higher than that of ferrocene, again confirming the electron-withdrawing properties of the acyl thiourea group.

Single crystal X-ray diffraction

To further confirm the existence of intramolecular hydrogen bonding the crystal structure of compound **5** was determined. X-ray analysis reveals that in each molecule there exist two independent intramolecular hydrogen bonds between the carbonyl oxygen and the hydrogen atom on N′ in either —C(O)—NH—C(S)—N′H— moiety, forming two parallel six-membered rings. The planar rings are approximately in the same plane as the cyclopentadienyl rings to which they are attached. The two phenyl rings are basically parallel as well. The molecular structure of compound **5** is depicted in Fig. 3. Table 5 lists the least squares planes of relevant groups and the dihedral angles

Table 5. Least-squares planes

Equation of plane 1 : $0.852(2)x-0.447(3)y-0.271(5)z+5.77(4) = 0$

Atoms	N(1)	C(17)	N(2)	C(18)	O(1)
Distances to Plane (Å)	0.02(1)	−0.01(1)	−0.02(1)	0.04(1)	−0.03(1)

Equation of plane 2 : $-0.680(3)x+0.668(3)y-0.300(4)z+0.29(4) = 0$

Atoms	C(11)	C(12)	C(13)	C(14)	C(15)	C(16)
Distances to plane (Å)	−0.00(8)	0.00(9)	0.00(6)	0.00(2)	0.00(1)	0.00(1)

Equation of plane 3 : $0.725(4)x-0.578(4)y-0.373(5)z+7.16(6) = 0$

Atoms	C(21)	C(22)	C(23)	C(24)	C(25)
Distances to plane (Å)	−0.00(1)	0.00(1)	−0.00(1)	0.00(6)	−0.00(1)

Equation of plane 4 : $0.874(2)x-0.341(3)y-0.343(5)z+3.09(4) = 0$

Atoms	N(3)	C(37)	N(4)	C(38)	O(2)
Distances to plane (Å)	−0.02(1)	0.05(1)	0.06(1)	0.04(1)	0.01(1)

Equation of plane 5 : $-0.739(3)x+0.606(4)y-0.290(4)z+3.32(3) = 0$

Atoms	C(31)	C(32)	C(33)	C(34)	C(35)	C(36)
Distances to plane (Å)	0.00(1)	0.00(1)	0.00(1)	0.00(1	0.00(1)	0.00(1)

Equation of plane 6 : $0.758(4)x-0.536(5)y-0.370(5)z+3.63(6) = 0$

Atoms	C(41)	C(42)	C(43)	C(44)	C(45)
Distances to plane (Å)	0.00(1)	0.00(1)	0.01(1)	0.00(1)	0.00(1)

Planes	1–2	1–3	1–4	1–5	1–6	2–3	2–4	2–5
Dihedral angle (°)	142.87	11.98	7.45	145.35	9.32	140.16	136.10	4.91
Planes	2–6	3–4	3–5	3–6	4–5	4–6	5–6	
Dihedral angle (°)	139.78	16.20	141.14	3.05	138.98	13.15	141.16	

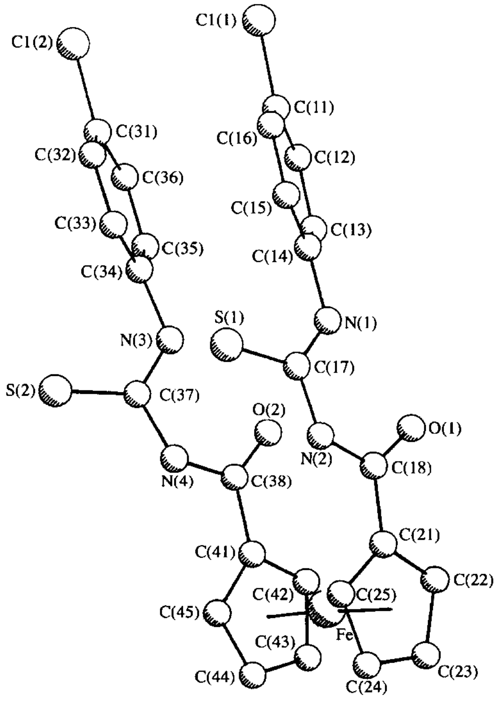


Fig. 3. X-ray diffraction single-crystal structure of compound **5**.

between them. This crystal consists of discrete molecules and the contact distances between the molecules are normal van de Waals' distances.

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