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Synthesis and intramolecular hydrogen bonding studies of 1-[*N*-formyl-*N*′,*N*′-disubstituted thiourea]-1′-[*N*′,*N*′-disubstituted amide]ferrocene derivatives

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Abstract—A contest between substitution and addition in the reaction of 1,1′-bis[formylisothiocyanate]ferrocene with aliphatic secondary amines was observed. All the compounds were characterized by IR, ^{1}H NMR, cyclic voltammetry and elemental analyses. Single crystal X-ray diffraction measurement revealed that there is a novel kind of intramolecular hydrogen bonding in the title compound (methyl substituents). The distance between N(1) and O(2) is 2.876 Å, and the angle N(1)–H(1)···O(2) is 177.7°. © 1997 Elsevier Science Ltd

Keywords: ferrocene; acyl thiourea; hydrogen bonding.

The synthesis and intramolecular hydrogen bonding behavior of some *N*-ferrocenoyl-*N*′-aryl(alkyl) thioureas and 1,1′-bis[*N*-formyl-*N*′-monosubstituted thiourea]ferrocene derivatives, which were obtained through the reaction of ferrocenoyl isothiocyanate or 1,1′-bis[formyl isothiocyanate]ferrocene with various primary amines, have been thoroughly investigated [1–3]. It was found that the intramolecular hydrogen bond between the carbonyl oxygen and the hydrogen atom on *N*′ is common in this kind of compound. A six-membered ring resulting from this hydrogen bonding was often observed in the single crystal X-ray diffraction structure of these compounds. The ^{1}H NMR signal for N′—H shifted downfield to about δ 12.00, while that of N—H appeared at about δ 8.00. In this paper, the reactions of 1,1′-bis[formylisothiocyanate]ferrocene with two secondary amines are reported. Not only the simultaneous substitution product b was separated, but product a was also isolated, in which substitution took place on one side chain, while the other chain underwent addition as shown in Scheme 1. The single crystal structure of compound 1 has been obtained. It was found that in the absence of a hydrogen atom on *N*′, an intramolecular hydrogen bond between the amide carbonyl on the substitution side chain and the N—H on the addition side chain was formed.

EXPERIMENTAL

All reagents and solvents were of analytical or chemical grade quality. Acetone and dichloromethane were dried by refluxing with P_2O_5 for 3–4 h after anhydrous potassium carbonate and calcium chloride treatment. KSCN was baked before use. Elemental analysis for C, H, N were performed on a CHN-CORDERM7-3 autoanalyser. Melting points were determined on a PHMK melting point apparatus (made in Germany) and are uncorrected. ^{1}H NMR spectra were recorded on a Jeol FX-90Q NMR, spectrometer using $CDCl_3$ as solvent and TMS as internal standard. IR spectra were obtained with a Nicolet FT-IR5 DX infrared spectrophotometer. The mass spectrum of compound 1 was recorded on a ZAB-HS mass spectrometer. Single crystal X-ray diffraction

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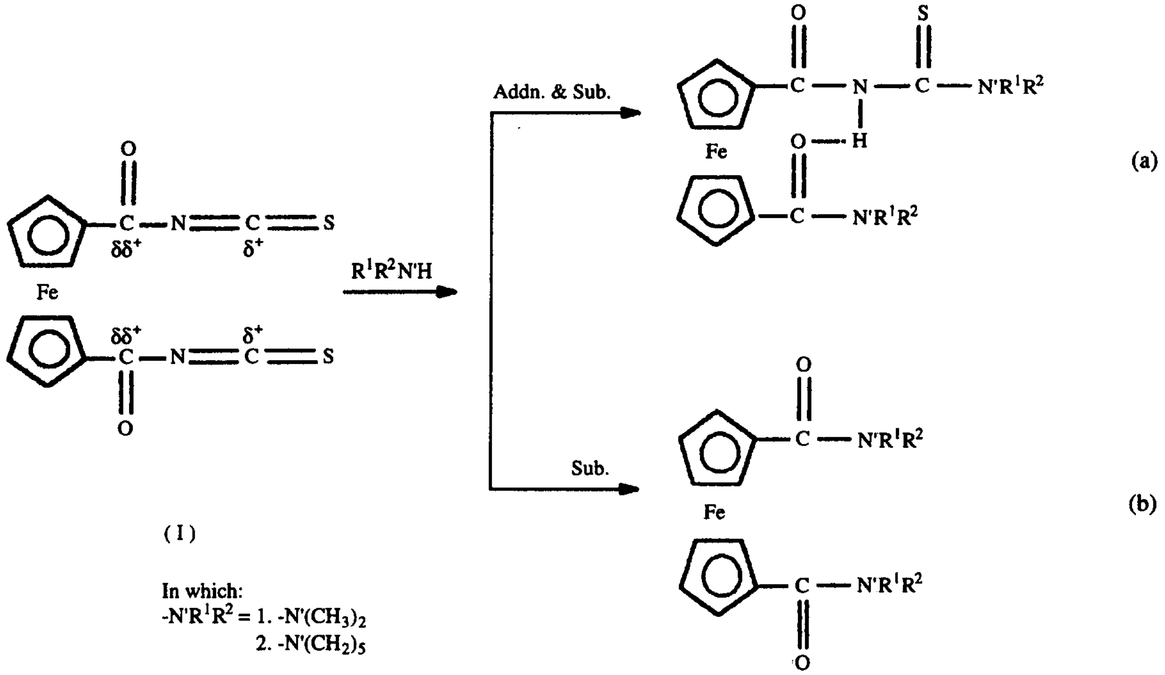

Scheme 1.

was obtained using an Enraf–Nonius CAD4 diffractometer. Cyclic voltammetric experiments were performed on a BAS-100B electrochemical analyser equipped with a three-electrode assembly with 0.1 mol L^{-1} TBAFB (Bu_4NBF_4) as supporting 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 reference electrode was 0.1 M $AgNO_3/Ag$ (in 0.1M Bu_4NBF_4–DMSO). A platinum filament was used as an auxiliary electrode.

Synthesis of 1,1′-*bis*[*formyl isothiocyanate*]*ferrocene* (I)

KSCN (0.533g, 5.5 mmol) was dissolved in acetone (15 cm^3) and added dropwise to the acetone solution (20 cm^3) of $Fc(COCl)_2$ (2.5 mmol) 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 reaction without further separation and purification.

Reaction of secondary amines with (**I**). Piperidine (0.55 cm^3 5 mmol) dissolved in acetone (20 cm^3) was added dropwise to the acetone solution of $Fc(CONCS)_2$ (2.5 mmol). The colour of the reaction mixture changed from dark red to brown. Then, the mixture was refluxed for 5 h and acetone was then distilled. The residue was dissolved in the minimum amount of $CHCl_3$. Yellow crystals (0.60g) were obtained using neutral Al_2O_3 (200–300 mesh) column chromatography, yield 55%. M.p. 168–169°C. Found: C, 59.0; H, 6.2; N, 9.0. Calc. for $C_{23}H_{29}FeN_3O_2S$: C, 59.3; H, 6.3; N, 8.8%. IR spectrum (KBr disk, cm^{-1}): 3164 w ($\nu_{N—H}$), 1540 m (δ_{CNH}), 1680 vs ($\nu_{C=O}$), 1614 s ($\nu_{C=O}$), 1368 w ($\nu_{C=S}$), 1245 s, ($\nu_{C—N}$), 1179 s ($\nu_{C—N'}$). ^1H NMR: δ 4.33 (s, 2H, C_5H_4), 4.44 (s, 2H, C_5H_4), 4.74 (s, 2H, C_5H_4), 4.80 (s, 2H, C_5H_4), 11.04 (s, 1H, NH), 4.24 (s, 2H), 3.56 (s, 6H), 1.68 (s, 12H). CV: scan rate: 200mV s^{-1}; E_{p_a}: 620 mV; E_{p_c}: 489 mV; $\bar{E}_p$: 554 mV; I_{p_a}: 1.4944×10^{-7}; I_{p_c}: 1.5585×10^{-7}; I_{p_a}/I_{p_c}: 0.95887.

Reaction of **I** with dimethylamine was carried out analogously to give Yellow crystals. Yield 50%. M.p. 157–159°C. Found: C, 50.6; H, 5.1; N, 10.3. Calc. for $C_{17}H_{21}FeN_3O_2S$: C, 50.9; H, 5.3; N, 10.5%. IR spectrum (KBr disk, cm^{-1}): 3164 w ($\nu_{N—H}$), 1557 m (δ_{CNH}), 1672 vs ($\nu_{C=O}$), 1598 s ($\nu_{C=O}$), 1384 w ($\nu_{C=S}$), 1261 s ($\nu_{C—N}$), 1138 m ($\nu_{C—N'}$). ^1H NMR spectrum: δ4.45 (s, 2H, C_5H_4), 4.50 (s, 2H, C_5H_4), 4.72 (s, 2H, C_5H_4), 4.90 (s, 2H, C_5H_4), 11.37 (s, 1H, NH), 3.52 (s, 3H, CH_3), 3.24 (s, 3H, CH_3), 3.14 (s, 6H, $2CH_3$). CV.: scan rate: 200 mV s^{-1}; E_{p_a}: 691 mV; E_{p_c}: 506 mV; $\bar{E}_p$: 598 mV; I_{p_a}: 4.6594×10^{-7}; I_{p_c}: 4.3638×10^{-7}; I_{p_a}/I_{p_c}: 1.0677. Mass spectrum (*m*/*z*, E.I.): 387, 342, 328, 284.

X-ray crystallography

Yellow crystals of compound **1** suitable for X-ray examination were obtained by the slow evaporation of an acetone/petroleum ether (60–90°C) solution. A single crystal with dimensions of *ca* 0.2 × 0.3 × 0.3 mm was mounted on an Enraf–Nonius CAD4 diffractometer with graphite-monochromated Mo-K_α

radiation ($\lambda = 0.071073$ nm). A total of 2189 independent reflections was collected within $\theta_{max} = 23°$ of $\omega/2\theta$ scans, at room temperature (299 ± 1K), of which 1527 were accepted as observable [$I \geqslant 3\sigma(I)$]. The intensities were fully corrected for Lp factors and empirical absorption [4]. The crystal belongs to the monoclinic space group $P2_1/c$, $a = 0.9034(2)$, $b = 1.4601(2)$, $c = 1.3888(3)$ nm, $\beta = 106.47(2)°$, $V = 1.757(1)$nm^3, $z = 4$, $D_x = 1.464$g cm^{-3}, $\mu = 9.844$ cm^{-1}.

The crystal structure was solved by the direct phase determination method (MULTAN82). One independent Fe atom was located on an E-map. The other non-hydrogen atoms were found in successive difference Fourier syntheses. The hydrogen atoms were not included in the refinement and the calculations of structure factors. The H(1) atom was located from the E-map. The remaining hydrogen atoms were added theoretically. All of them were refined isotropically. The coordinates and anisotropic thermal parameters of non-hydrogen atoms were refined by the full-matrix least-squares method and converged to $R = 0.053$ and $Rw = 0.061$ with unit weights. The highest electron density on the final difference Fourier map was found to be 0.77 eÅ^{-3}. All calculations were performed on a PDP11/44 computer using the SDP-PLUS program system.

RESULTS AND DISCUSSION

There are two active sites for R^{1}R^{2}N′H to attack in the intermediate **I**. If R^{1}R^{2}N′H attacks the carbon atom in the isothiocyanate group ($C^{\delta+}$), addition of R^{1}R^{2}N′H to the C=N double bond takes place, resulting in the thiourea product. The other site for R^{1}R^{2}N′H to attack is the carbonyl carbon atom ($C^{\delta\delta+}$). In this case, the isothiocyanate group is substituted by the amino group, and 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 secondary amines involved the contest between addition and substitution. Both products, mainly a, were isolated through column chromatography.

IR spectra

Two strong $\nu_{C=O}$ bands were observed in the IR spectra of compounds **1** and **2** at *ca* 1670 and 1600 cm^{-1} indicating that there are two kinds of carbonyl group. There is a weak absorption at 3164 cm^{-1} attributable to ν_{N-H}, but lower in wavenumber than ordinary ν_{N-H} absorptions (>3200 cm^{-1}). This is interpreted to be a sign of the formation of an intramolecular hydrogen bond. 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. IR spectra (Nujol mull) were also recorded and it was confirmed that there are no ν_{O-H} or ν_{S-H}. This indicates that compounds **1** and **2** exist in the keto–thione form.

^{1}H *NMR spectra*

In the ^{1}H NMR spectra of compounds **1** and **2**, there are four singlets of the cyclopentadienyl protons at δ 4.33–4.80, as the two Cp rings are in different chemical environments. δ_{N-H} appears at *ca* 11.00. It has shifted downfield compared with that of *N*-ferrocenoyl-*N′*-monosubstituted thioureas, which are often observed at about δ 8 [1–3]. This is owing to the formation of an intramolecular hydrogen bond between N—H and the carbonyl group on the other Cp ring. The alkyl protons split into three singlets with ratios of 3 : 3 : 6 and 2 : 6 : 12, respectively, in compounds **1** and **2**. This is in accordance with *N*,*N*-disubstituted-*N′*-benzoyl thioureas [5]. This is explained as follows: the lone pair electrons on *N′* may delocalize and conjugate with C=O and C=S, thus, the C—N′ bond becomes somewhat rigid. As can be seen from the single crystal structure of compound **1**, the protons on C(27) are in the deshielding areas of both Cp rings and amide carbonyl group. The protons on C(19) are in the deshieding area of the C=S group, whereas those on C(18) and C(28) are in the shielding areas of C=S and C=O double bonds. As a result, they absorb at 3.52, 3.24 and 3.14 ppm, respectively. The ^{1}H NMR spectra of compound **1** at 25, 60 and 70°C with CDCl$_3$ as solvent were recorded. It was found that the peak at δ 11.37 remains unchanged, indicating the existence of an intramolecular hydrogen bond.

Mass spectral studies of compound 1

The molecular ion peak was observed at 387. The peak at 342 is attributed to the fragment 1-[formyl isothiocyanate]-1′-[*N′*,*N′*-dimethylamide]ferrocene, which is derived from the parent molecule by losing a molecule of dimethyl amine. The peak at 328 is considered to be 1,1′-bis[*N′*,*N′*-dimethylamide] ferrocene, which is the McLafferty rearrangement product of the parent molecule.

Cyclic voltammetric studies

One pair of reversible redox peaks was observed in compounds **1** and **2**, indicating that they undergo one-electron redox reaction. Their $\bar{E}_p$ values occurred at *ca* 0.60 V and were higher than that of ferrocene (0.262 V) under the same conditions, thus revealing that the acyl thiourea group is electron withdrawing.

Single crystal X-ray diffraction analysis

To further confirm the existence of the intramolecular hydrogen bond, the single crystal structure of compound **1** was determined. X-ray analysis revealed that there is an intramolecular hydrogen bond between the N—H on the addition side chain and the carbonyl group on the other substituted side

Table 1. Selected bond distances (Å) and angles (°) between non-hydrogen atoms

Fe(1)—C(11)	1.980(5)	C(16)—N(1)	1.407(7)
Fe(1)—C(12)	2.0372(8)	N(1)—C(17)	1.401(8)
Fe(1)—C(13)	2.061(6)	C(17)—S(1)	1.659(6)
Fe(1)—C(14)	2.082(6)	C(17)—N(2)	1.361(7)
Fe(1)—C(15)	2.053(6)	N(2)—C(18)	1.459(7)
Fe(1)—C(21)	2.024(5)	N(2)—C(19)	1.460(7)
Fe(1)—C(22)	2.029(5)	C(21)—C(22)	1.422(8)
Fe(1)—C(23)	2.036(5)	C(21)—C(25)	1.444(7)
Fe(1)—C(24)	2.058(6)	C(21)—C(26)	1.479(7)
Fe(1)—C(25)	2.024(6)	C(22)—C(23)	1.413(8)
C(11)—C(12)	1.446(6)	C(23)—C(24)	1.407(8)
C(11)—C(15)	1.418(8)	C(24)—C(25)	1.422(8)
C(11)—C(16)	1.503(8)	C(26)—O(2)	1.252(7)
C(12)—C(13)	1.415(6)	C(26)—N(3)	1.332(8)
C(13)—C(14)	1.469(8)	N(3)—C(27)	1.474(7)
C(14)—C(15)	1.392(8)	N(3)—C(28)	1.479(7)
C(16)—O(1)	1.210(7)		

C(11)—C(12)—C(13)	105.2(3)	C(11)—C(15)—C(14)	107.5(5)
C(12)—C(13)—C(14)	108.8(5)	C(22)—C(21)—C(25)	107.3(6)
C(13)—C(14)—C(15)	108.0(6)	C(22)—C(21)—C(26)	130.0(5)
C(12)—C(11)—C(15)	110.6(5)	C(25)—C(21)—C(26)	122.6(5)
C(12)—C(11)—C(16)	127.2(4)	C(21)—C(22)—C(23)	108.1(5)
C(11)—C(16)—O(1)	123.0(5)	C(22)—C(23)—C(24)	109.0(5)
C(11)—C(16)—N(1)	114.0(5)	C(23)—C(24)—C(25)	108.1(5)
O(1)—C(16)—N(1)	123.0(5)	C(21)—C(25)—C(24)	107.5(5)
C(16)—N(1)—C(17)	120.7(5)	C(21)—C(26)—O(2)	120.5(5)
N(1)—C(17)—S(1)	120.3(5)	C(21)—C(26)—N(3)	118.7(5)
N(1)—C(17)—N(2)	115.8(5)	O(2)—C(26)—N(3)	120.8(6)
C(17)—N(2)—C(18)	120.4(5)	C(26)—N(3)—C(27)	125.1(5)
C(17)—N(2)—C(19)	124.1(5)	C(26)—N(3)—C(28)	118.5(5)
S(1)—C(17)—N(2)	123.8(5)	C(27)—N(3)—C(28)	116.3(5)
C(18)—N(2)—C(19)	115.4(6)		

Numbers in parentheses are estimated standard deviations to the least significant figure.

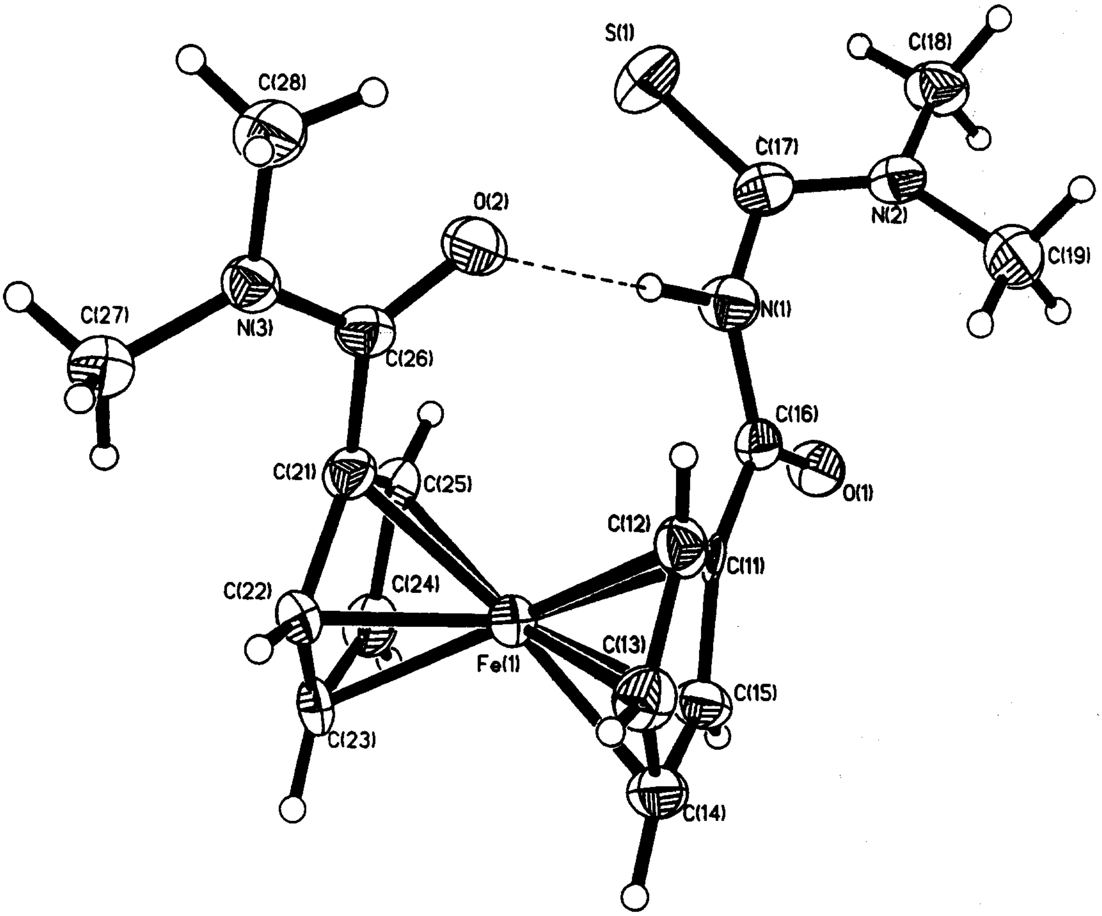

Fig. 1. The molecular structure of compound **1** showing the atomic labelling scheme.

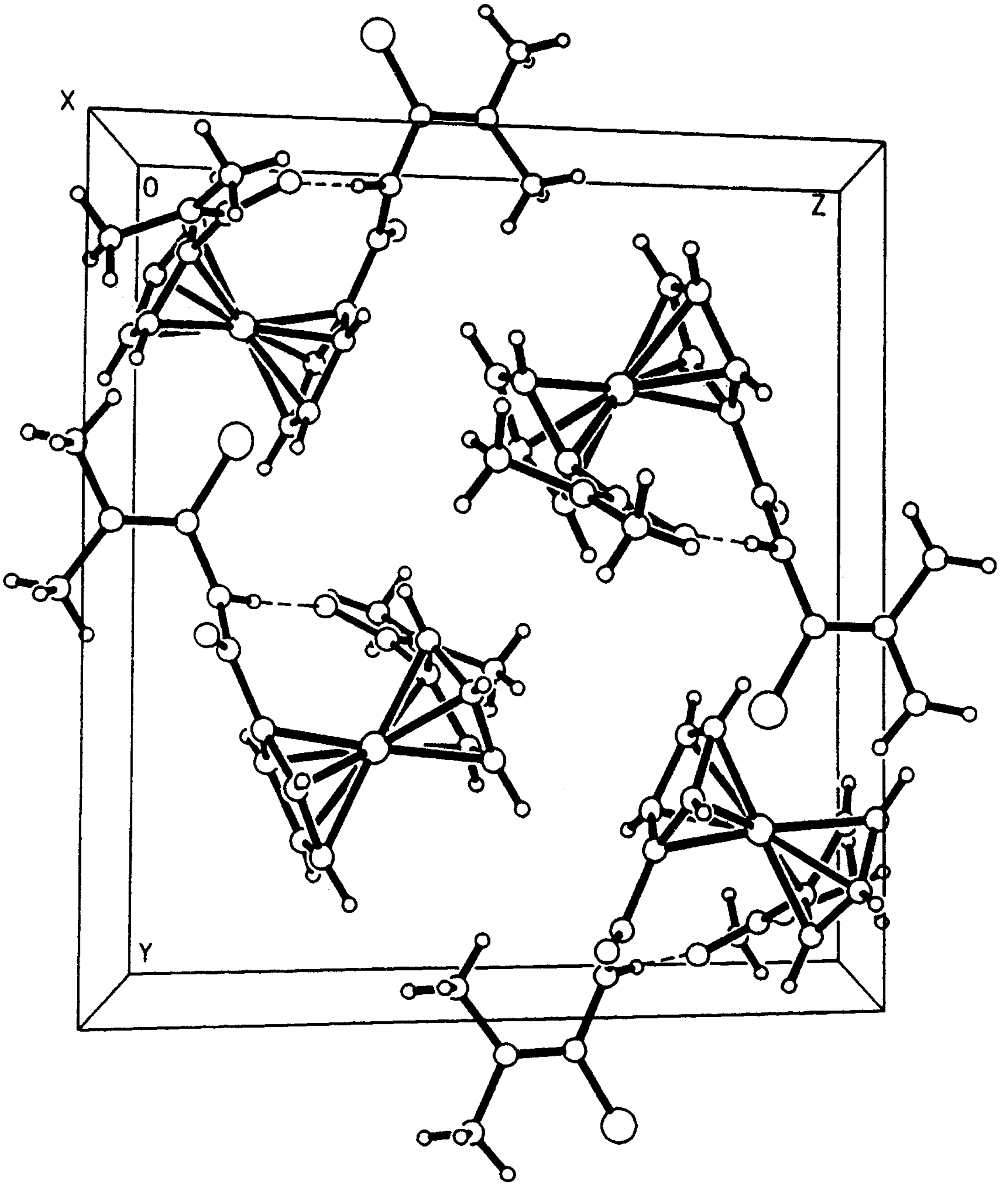

Fig. 2. Unit cell of compound 1.

chain. The distance between N_1 and O_2 is 2.876 Å, and the angle of $N_1—H_1\cdots O_2$ is 177.7°. Selected bond distances and angles are given in Table 1. The molecular structure is depicted in Fig. 1. and the packing in the unit cell is illustrated in Fig. 2.

Supplementary material available—Crystal data, full tables of bond distances and angles and anistropic parameters for compound **1**; calculated and observed structure factors for compound **1** have been deposited at the Cambridge Crystallographic Data Centre.

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