Determination of the Absolute Configuration of (−) -2,2,2-(Trifluoro-1-hydroxyethyl)ferrocene

Midori Goto,* Yoshimitsu Yamazaki,† and Masami Uebayasi†
National Institute of Materials and Chemical Research, 1-1, Higashi, Tsukuba, Ibaraki 305
†National Institute of Bioscience and Human Technology, 1-1, Higashi, Tsukuba, Ibaraki 305

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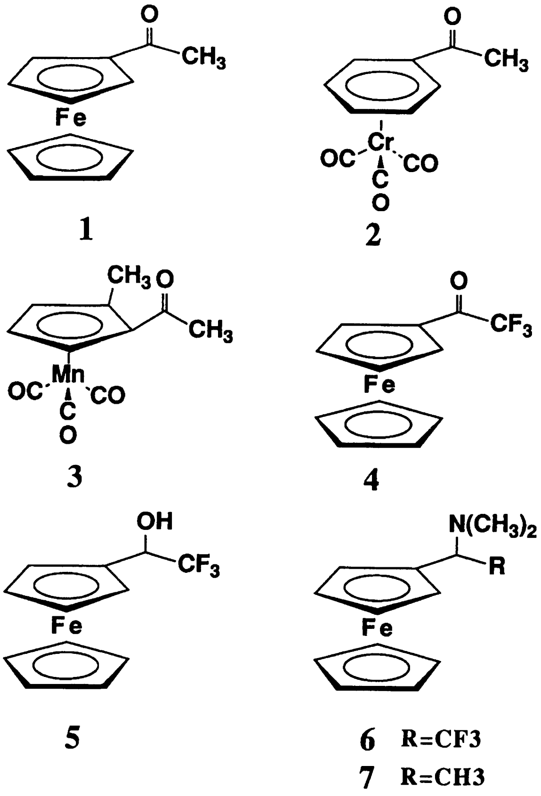
Synopsis. The absolute configuration of the title compound produced by the microbial reduction was determined through the anomalous dispersion effect of the iron atoms. The crystals are monoclinic, space group $P2_1$, with a=10.046(2), b=8.844(1), c=12.802(2) Å, β=95.61(1)°, V=1132(1) Å^3, Z=4, D_c=1.666 g cm^{-3}. There are two independent molecules in the asymmetric unit. Both of them have the same chirality of R configuration, though their molecular conformations are different.

The microbial reduction of prochiral ketones is one of the useful methods to prepare optically active secondary alcohols.[1] Its stereoselectivity is known to generally follow Prelog's rule, which predicts that the hydride is transfered onto the *re*-face of carbonyl group, resulting in an alcohol with a S configuration.[2] Acetylferrocene (**1**),[3] (η^6-acetophenone)tricarbonylchromium (**2**),[3] and (η^5-1-acetyl-2-methylcyclopentadienyl)tricarbonylmanganese (**3**)[4] are also reduced predominantly to the (S)-alcohols by many micrrorganisms, although these organometallic ketones have extraordinary structures as compared with naturally occurring ketones (Scheme 1). An important exception was recently found in the microbial reduction of 2,2,2-(trifluoroacetyl)ferrocene (**4**). Most of the screened microorganisms reduced (**4**) preferentially to the levorotatory alcohol (**5**).[5] This alcohol was prepared first by Sokolov et al.[6] and they assigned the R configuration to (−)-**5** by the circular dichroism (CD) spectroscopic data. Based on their assignment, we should conclude that Prelog's rule fails in the case of the reduction of the fluoro ketone (**4**). We were interested in this abnormality and to clarify

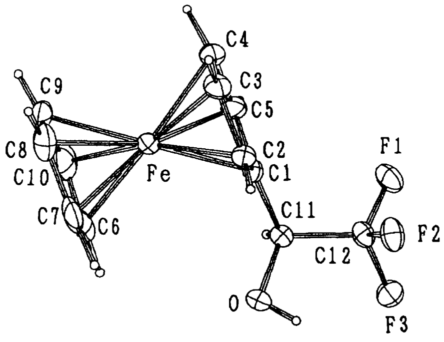


Scheme 1.

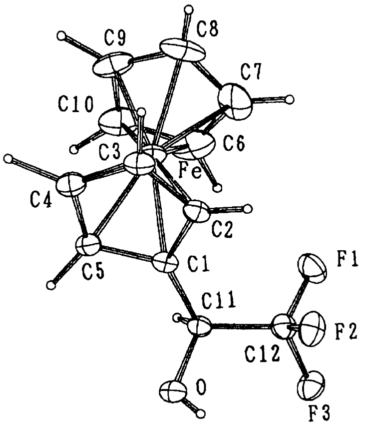
Table 1. Atomic Parameters[a)]

Atom	x	y	z	B$_{eq}$(Å^2)[b)]
FEA	10076 (1)	3562 (fix)	6809 (1)	3.79 (2)
F1A	6681 (3)	3347 (5)	9176 (4)	5.4 (1)
F2A	8473 (4)	3028 (5)	10204 (3)	5.4 (1)
F3A	7415 (4)	5134 (5)	10221 (3)	5.5 (1)
OA	9723 (4)	5414 (5)	9247 (3)	3.5 (1)
C1A	8967 (5)	3423 (8)	8039 (4)	3.2 (1)
C2A	10053 (6)	2389 (7)	8190 (5)	3.7 (2)
C3A	9976 (7)	1390 (8)	7326 (6)	4.7 (2)
C4A	8817 (7)	1750 (8)	6639 (5)	4.5 (2)
C5A	8198 (6)	3003 (8)	7086 (5)	4.0 (2)
C6A	10666 (19)	5773 (14)	6692 (13)	9.9 (5)
C7A	11802 (14)	4777 (22)	6885 (9)	10.2 (5)
C8A	11731 (9)	3746 (15)	5996 (8)	7.7 (3)
C9A	10571 (11)	4145 (11)	5359 (6)	6.6 (3)
C10A	9931 (15)	5342 (13)	5763 (9)	8.4 (4)
C11A	8586 (5)	4669 (6)	8743 (4)	3.0 (1)
C12A	7780 (6)	4031 (8)	9577 (6)	3.9 (2)
FEB	5300 (1)	−1396 (2)	6920 (1)	3.89 (2)
F1B	5376 (4)	61 (6)	9553 (4)	5.8 (1)
F2B	6267 (5)	−1882 (5)	10346 (3)	5.5 (1)
F3B	7157 (4)	310 (5)	10599 (3)	5.2 (1)
OB	8615 (3)	−1473 (6)	9343 (3)	3.8 (1)
C1B	6753 (5)	−1840 (6)	8107 (4)	2.9 (1)
C2B	5675 (6)	−2909 (7)	8124 (5)	3.7 (2)
C3B	5531 (7)	−3660 (8)	7156 (6)	4.7 (2)
C4B	6539 (7)	−3123 (8)	6524 (5)	4.4 (2)
C5B	7259 (6)	−1972 (7)	7116 (5)	3.7 (2)
C6B	4753 (14)	833 (13)	6986 (10)	8.5 (4)
C7B	3659 (12)	−126 (18)	7174 (9)	9.1 (4)
C8B	3404 (9)	−1073 (13)	6237 (11)	8.2 (4)
C9B	4324 (10)	−649 (11)	5546 (7)	6.7 (3)
C10B	5130 (10)	490 (10)	5998 (9)	7.1 (3)
C11B	7376 (5)	−845 (7)	8953 (4)	3.1 (1)
C12B	6537 (7)	−574 (8)	9850 (5)	4.1 (2)

a) Positional parameters are multiplied by 10^4. b) $B_{eq} = 4(a^2B_{11}+b^2B_{22}+c^2B_{33}+2abB_{12}\cos\gamma+2bcB_{23}\cos\alpha+2caB_{13}\cos\beta)/3$



Molecule A



Molecule B

	A	B		A	B
Fe–C1–C11–C12	−178.4	77.5	Fe–C1–C11–O	−58.1	−159.6
C2–C1–C11–C12	−82.8	−19.4	C2–C1–C11–O	37.5	103.6
C5–C1–C11–C12	92.7	166.7	C5–C1–C11–O	−146.9	−70.3

Fig. 1. A view of the two molecules of the asymmetric unit with the atomic numbering. Comparison of tortion angles

it we firstly determined the absolute configuration of (−)-**5** by X-ray crystallographic analysis, because the preceding assignment[6] was still ambiguous, as the CD spectrum was obtained for the dimethylamino derivative **6** after substitution on the asymmetric center atom and the conclusion was drawn only from a comparison of the spectrum with that for the reference (*R*)-(+)-[1-(dimethylamino) ethyl] ferrocene (**7**).

Experimental and Structure Determinations

(−)-2,2,2-(Trifluoro-1-hydroxyethyl)ferrocene (**5**) with an optical purity of more than 98% was prepared by the microbial reduction of **4** with *Xanthomonas campestris* as described previously.[5]

Yellow needle-shaped crystals elogated along *b*-axis were obtained from hexane. The crystals are unstable in air and therefore fairly good one (0.1×1.0×0.1 mm) was sealed in a glass capillary tube for analysis. The X-ray diffraction data were collected on an Enraf-Nonius four-circle diffractometer with graphite-monochromated Cu *K*α radiation (λ=1.5418 Å). The iron anomalous dispersion term for Cu *K*α (f''=3.204) is much larger than that for Mo *K*α (f''=0.845). Even considering the problem due to the higher

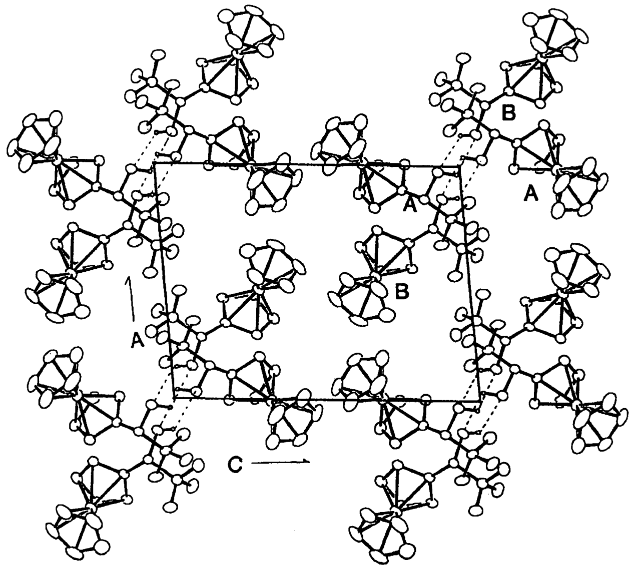


Fig. 2. Molecular packing as seen along the *b*-axis. Dashed lines indicate the hydrogen bonding. O(B)···O(A) distance 2.871(6) Å, O(B)···H–O(A) angle 116(9)°, O(A)···H–O(B) angle 107(10)°.

Table 2. Structure Factors

Comparison of the observed and calculated structure factors for reflections with significant anormalous dispersion effects

$h\|k\|l$	$\|F_{\mathrm{obsd}}\|$			$\|F_{\mathrm{calcd}}\|$		
	k=+	k=−	ΔF_{obsd}	k=+	k=−	ΔF_{cald}
420	39.74	22.94	16.60	40.16	23.05	17.11
−315	16.05	27.56	−11.51	15.30	27.65	−12.35
−139	20.91	31.00	−10.09	21.48	29.63	−7.15
−134	41.80	34.96	6.84	42.04	33.50	8.54
022	56.91	80.81	−23.90	57.83	74.15	−17.32
−734	17.07	9.12	7.94	16.97	9.14	7.83
−422	38.84	44.28	−5.44	39.43	44.02	−4.59
−821	12.82	17.99	−5.17	12.66	17.87	−5.21
113	47.34	57.13	−9.97	47.85	56.64	−8.79
423	39.32	30.55	8.77	40.17	29.96	10.21

Comparison of the observed and calculated structure factors for reflections with non−significant anormalous dispersion effects

$h\|k\|l$	$\|F_{\mathrm{obsd}}\|$			$\|F_{\mathrm{calcd}}\|$		
	k=+	k=−	ΔF_{obsd}	k=+	k=−	ΔF_{cald}
−212	34.05	34.52	−0.47	35.20	35.50	−0.30
222	32.28	31.64	0.64	33.83	33.05	0.78
−213	41.47	42.53	−1.06	41.78	42.79	−1.00
315	18.00	17.89	0.11	17.79	17.67	0.12
161	18.31	20.65	−2.34	18.02	19.69	−1.67
621	31.27	34.35	−2.08	31.68	33.34	−2.66
−452	15.20	15.19	0.01	14.56	14.23	0.33
−232	28.70	29.95	−1.25	27.41	28.19	−0.68
−512	59.38	57.99	1.39	62.09	61.04	1.05
−725	12.53	12.51	0.02	12.73	12.82	−0.09

Table 3. Selected Bond Distances and Bond Angels

a) Selected bond distances (Å)					
	A	B		A	B
Fe–C1	2.019 (5)	2.040 (5)	Fe–C2	2.052 (7)	2.049 (6)
Fe–C3	2.038 (7)	2.035 (7)	Fe–C4	2.040 (7)	2.065 (7)
Fe–C5	2.014 (6)	2.025 (6)	Fe–C6	2.053 (13)	2.050 (12)
O–C11	1.418 (7)	1.409 (7)	F1–C12	1.318 (7)	1.316 (8)
F2–C12	1.344 (8)	1.359 (8)	F3–C12	1.351 (8)	1.342 (8)
C1–C2	1.422 (8)	1.440 (8)	C1–C5	1.428 (8)	1.418 (9)
C1–C11	1.497 (8)	1.485 (8)	C2–C3	1.412 (10)	1.401 (10)
C3–C4	1.425 (10)	1.438 (11)	C4–C5	1.418 (10)	1.424 (9)
b) Selected bond angles (°)					
	A	B		A	B
C1–Fe–C2	40.8 (2)	41.2 (2)	C1–Fe–C3	69.0 (3)	68.7 (3)
C1–Fe–C4	69.6 (3)	68.6 (2)	C1–Fe–C5	41.5 (2)	40.8 (2)
C1–Fe–C6	107.5 (6)	109.2 (4)	C1–Fe–C7	121.9 (4)	121.1 (4)
C1–Fe–C8	159.4 (3)	156.6 (4)	C1–Fe–C9	158.4 (3)	162.6 (3)
C1–Fe–C10	123.0 (4)	127.0 (3)	C2–Fe–C3	40.4 (3)	40.1 (3)
C2–Fe–C4	68.6 (3)	68.3 (3)	C2–Fe–C5	68.6 (3)	68.7 (3)
C2–C1–C11	129.0 (5)	130.0 (5)	C5–C1–C11	123.9 (5)	122.6 (5)
O–C11–C1	111.9 (4)	108.6 (5)	O–C11–C12	108.4 (5)	109.4 (5)
C1–C2–C3	108.3 (5)	108.1 (6)	C2–C3–C4	108.8 (6)	108.9 (6)
C3–C4–C5	106.8 (6)	106.6 (6)	C4–C5–C1	109.1 (6)	109.1 (6)
C2–C1–C5	107.0 (5)	107.2 (5)	F1–C12–F2	107.2 (5)	106.7 (6)
F1–C12–F3	107.6 (5)	107.1 (6)	F3–C12–F3	105.6 (5)	105.2 (5)

crystal absorption when using Cu *Kα* radiation (in this case μ=111.3 cm^{-1}), the above effect has an advantage despite the crystal's poorer quality. 3300 reflection data were collected for $3° \le 2\theta \le 120.0°$, $-11 \le h \le 11$, $-9 \le k \le 9$, $0 \le l \le 14$, by using ω-θ scans, with scan width $(0.8+0.15\tan\theta)°$. The crystal decay was not found. An empirical correction for absorption based on Ψ scan was applied (minimum and maximum transmission factors 0.583 and 0.998). 2888 reflections with $|F_o| \ge 3\sigma|F_o|$ were used for refinement. The structure was solved by MULTAN 78.[7)] In the course of the refinement two refinements were performed. The refinement with the configuration shown in this article with anisotropic thermal parameters and without H atoms gave the *R* factor 0.065. In the model with the opposite enantiomorph it was 0.101, even though the calculation was repeated from the isotropic stage. This result is very significant for confirming the absolute configuration. The positions of 16 hydrogen atoms were located from the difference Fourier synthesis, while the remainder were added at the calculated position. The structure was refined by the full-matrix least-squares method with the hydrogen parameters being fixed in the refinement. The final *R* factor was 0.054 (R_w=0.073, $w=(0.0117|F_o|^2-0.3167|F_o|+2.607)^{-1}$). The final atomic parameters are shown in Table 1. To confirm the absolute configuration the Bijvoet pair were examined. The typical results are shown in Table 2. Thus the *R* conformation represents, without any doubt, the correct absolute configuration. The anomalous-dispersion terms for Cu *Kα* were taken from the International Tables for X-Ray Crystallography (1974).[8)] The calculations were carried out using UNICS3[9)] on a Facom M-380 computer.

Discussion of the Structure

There are two independent molecules (A,B) per asymmetric unit. The differences in their conformation are illustrated in Fig. 1 with the tortion angles. The molecular structure of the ferrocene moiety is almost similar to those of the isolated ferrocene[11)] and the ferrocene derivatives;[12)] Namely, the two five-membered rings have a nearly totally eclipsed conformation with the average Fe–C distance is equal to 2.041(12) Å, the average C–C distance is 1.42(1) Å and C–C–C angle 108.0(6)° in the cyclopentadienyl rings. The two cyclopentadienyl ring in a ferrocene molecule are planar and the dihedral angle between two rings is 0.8(5)° in A, and 1.5(4)° in B, respectively. The selected bond distances and angles are shown in Table 3. The packing of the molecules in the crystal is shown in Fig. 2. The molecules are linked together by OH···O hydrogen bridges.

Thus, the absolute configuration of (−)-**5** has been unambiguously determined to be *R*. This result indicates that Prelog's rule is not valid for the triflourinated substrate **4** in contrast to being valid for the corresponding non-fluorinated substrate **1**. The reason for the reversal in this stereoselectivity by the fluorine substitution is not clear. An abnormal interaction might occur between the very hydrophobic trifluoromethyl group and the enzyme binding site. Studies on the enzymes that reduce **4** in microorganisms are presently in progress.

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13) The lists of structure factors, the atomic parameters for hydrogen atoms and anisotropic thermal parameters for the non-hydrogen atoms are deposited as Document No. 66003 at the Office of the Editor of Bull. Chem. Soc. Jpn.