Absolute Configuration of a 1,2-Disubstituted Ferrocene Derivative with Planar and Central Elements of Chirality and the Mechanism of the Stereoselective Metalations of Optically Active α-Ferrocenyl Tertiary Amines[1]

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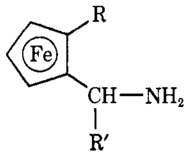
Abstract: Stereoselective metalation of optically active α-ferrocenyl tertiary amines produces lithioamines with a high degree of asymmetric induction. Lithiation of (*R*)-*N*,*N*-dimethyl-1-ferrocenylethylamine, for example, followed by treatment with anisaldehyde, produces (*S*,*R*,*S*)-2-(*p*-methoxyphenyl)hydroxymethyl-*N*,*N*-dimethyl-1-ferrocenylethylamine in high yield. The absolute configuration of the latter compound has been confirmed by a single-crystal X-ray structure determination. This represents the first absolute configurational determination of a 1,2-ferrocene derivative with chiral substituents, and enables unequivocal assignments for a large number of optically active ferrocene derivatives to be made. The high stereoselectivity of the sequence of reactions leading to the final product is an indication of the suitability of the ferrocenylamines as inductive reagents in four component peptide synthesis.

In connection with our interest in four component condensations[3] (4 CC) as an approach to peptide synthesis[4] it has become necessary to resolve certain questions pertaining to ferrocene stereochemistry.

Optically active ferrocene derivatives of the general formula **1**, or their antipodes, are particularly well-suited "steric templates" for asymmetrically induced syntheses, and have evolved as the most promising asymmetrically inducing amine components of stereoselective 4 CC, for the following reasons. (i) In the 4 CC products that are of interest, ferrocenylalkyl groups can be replaced by hydrogen under mild conditions.[4,5] (ii) Ferrocene derivatives with a plane of chirality[6] exhibit strong asymmetrical inducing power, without having large steric bulk close to the reactive site, in contrast to the asymmetrically inducing steric templates that contain only central elements of chirality,[4] where one extremely bulky group, a medium sized group, a small group, and the reactive site must be the four ligands of the inducing central chiroid.[7–9] (iii) Nucleophilic substitutions involving α-ferrocenylalkyl compounds proceed with retention of the configuration at the reacting center of chirality.[2,10,11] (iv) Compounds of type **1** are easy to synthesize from the readily available *N*,*N*-dimethyl-α-ferrocenylethylamine[12] by stereoselective lithiation,[13] reaction with a suitable electrophile, and replacement of the dimethylamino group by an amino group, making use of (iii).



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The unambiguous assignment of the absolute configurations of optically active ferrocene derivatives with a plane of chirality[6] and one or more centers of chirality is essential for the interpretation and further development of the stereoselective syntheses of the optically active ferrocene derivatives and their use as asymmetrically inducing amine components of four component peptide syntheses.

The absolute configurations of most optically active ferrocene derivatives, and in particular, the α-ferrocenylethyl compounds have not yet been assigned in an unambiguous manner. The *R* configuration had been assigned to (+)-α-ferrocenylethylamine by optical methods,[14] but the *S* configuration was obtained by the Horeau method,[15] and also from stereoselective 4 CC experiments,[5] and by nmr comparison.[5]

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(1) Stereoselective Syntheses. VIII.[2] This work has previously appeared as a communication in *Angew. Chem.*, **84**, 164 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 138 (1972).

(2) Preceding communication: G. W. Gokel, D. Marquarding, and I. Ugi, *J. Org. Chem.*, 37, 3052 (1972).

(3) G. Gokel, G. Ludke, and I. Ugi in "Isonitrile Chemistry," I. Ugi, Ed., Academic Press, New York, N. Y., 1971, p 145.

(4) (a) I. Ugi, *Rec. Chem. Progr.*, 30, 289 (1969); (b) G. Gokel, P. Hoffmann, H. Kleimann, H. Klusacek, G. Ludke, D. Marquarding, and I. Ugi, in ref 3, p 201; (c) I. Ugi, *Intra-Sci. Chem. Rep.*, 5, 229 (1971).

(5) D. Marquarding, P. Hoffmann, H. Heitzer, and I. Ugi, *J. Amer. Chem. Soc.*, **92**, 1969 (1970).

(6) K. Schlögl, *Top. Stereochem.*, **1**, 39 (1967).

(7) (a) I. Ugi, *Z. Naturforsch. B*, 20, 405 (1965); (b) E. Ruch and I. Ugi, *Top. Stereochem.*, **4**, 99 (1969).

(8) (a) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem Soc.*, **74**, 5828, 5851 (1951); (b) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).

(9) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971.

(10) (a) G. Gokel, P. Hoffmann, H. Klusacek, D. Marquarding, E. Ruch, and I. Ugi, *Angew. Chem.*, **82**, 77 (1970); *Angew. Chem., Int. Ed. Engl.*, **9**, 64 (1970); (b) G. Gokel and I. Ugi, *Angew. Chem.*, **83**, 178 (1971); *Angew. Chem., Int. Ed. Engl.*, **10**, 191 (1971).

(11) G. Gokel, P. Hoffmann, H. Kleimann, H. Klusacek, D. Marquarding, and I. Ugi, *Tetrahedron Lett.*, 1771 (1970).

(12) G. Gokel and I. Ugi, *J. Chem. Educ.*, **49**, 294 (1972).

(13) (a) D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, and I. Ugi, *J. Amer. Chem. Soc.*, **92**, 5389 (1970); (b) *Angew. Chem.*, **82**, 360 (1970); *Angew. Chem., Int. Ed. Engl.*, **9**, 371 (1970).

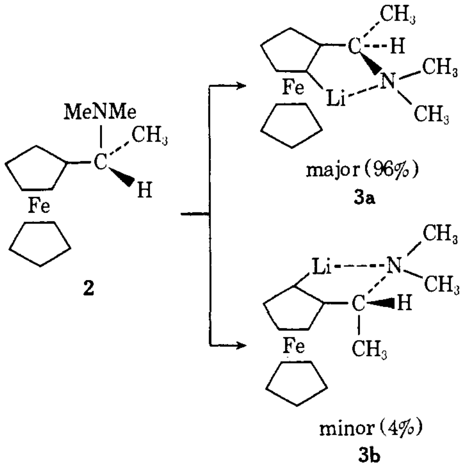
(14) (a) K. Schlögl and M. Fried, *Monatsh. Chem.*, **95**, 558 (1964); (b) H. Falk, C. Krasa, and K. Schlögl, *ibid.*, **100**, 254 (1969).

(15) (a) A. Horeau, *Tetrahedron Lett.*, 506, 965 (1962); (b) A. Horeau and H. B. Kagan, *Tetrahedron*, 2431 (1964); (c) A. Horeau, *Bull. Soc. Chim. Fr.*, 2673 (1964); (d) A. Horeau and A. Nouaille, *Tetrahedron Lett.*, 3953 (1966); (e) A. Horeau and J. K. Sutherland, *J. Chem. Soc. C*, 247 (1966); (f) R. Weidman and A. Horeau, *Bull. Soc. Chim. Fr.*, 117 (1967).

Results

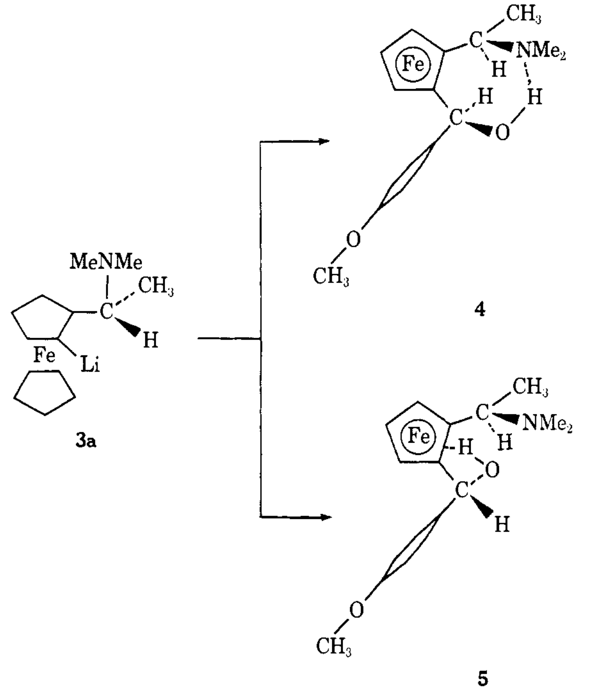
Lithiation of *N*,*N*-dimethyl-1-ferrocenylethylamine (**2**) with buyllithium in ether–hexane affords only ortho lithiation products.[13,16] We have previously shown that substantial asymmetric induction occurs in the lithiation of optically active **2**, Scheme I. In order to demonstrate conclusively that the predominant lithiation was taking place at the ortho position conformationally opposite to the terminal C-methyl group of the dimethylaminoethyl side chain, we condensed the lithioamine 3a with anisaldehyde to produce a solid derivative (**4**), whose crystal structure could be determined. Because the carbonyl carbon in anisaldehyde would become a saturated chiral center in the product we were also anxious to see if there would be high asymmetric induction at the incipient chiral center as well as the incipient chiral plane. This sequence is illustrated in Scheme II.

Scheme I



Two products were isolated from the sequence shown in Scheme II, by rapid work-up of the condensation phase, followed by chromatography of the crude reaction mixture over silica gel. Three bands appeared on the chromatography column when using 1:1 ligroin:acetone as eluent. The first two bands to elute were the isomeric amino alcohols **4** and **5**, respectively, and the third band was largely starting material. Compound **4** was found to exhibit an infrared absorption for the hydroxyl group which was broad and weak, indicating that the hydroxyl group was participating in a strong hydrogen bond with the nitrogen lone pair.[17] Compound **5** was found to exhibit a broad, strong hydroxyl absorption similar to that reported for other ferrocene compounds in which a hydroxyl is binding to the iron atom.[18] The nmr spectra of the two compounds were essentially similar except for a dramatic difference in the resonance assigned to the benzyl proton. In **4** this resonance appeared at δ 6.94 ppm (singlet, 1 H) and in **5**, δ 6.09 ppm (singlet, 1 H), Amino alcohol **4** is clearly the more stable of the two, as **5** converts to **4** on treatment with acid, base, or water.

Scheme II



Structure Determination

Optically active **4**, first recrystallized from *n*-heptane, was further recrystallized by the technique of vapor diffusion[19] using acetone or diethyl ether as the solvent and *n*-heptane as the counter-solvent. A needle-shaped specimen (dimensions 0.40 × 0.10 × 0.05 mm) mounted on its long axis was selected for data collection.

Crystal data: monoclinic, space group $P2_1$; a = 9.77 (1) Å, b = 11.15 (1) Å, c = 10.56 (1) Å; β = 120.6 (1)°; V = 603 Å^3;[20] calculated density (based on Z = 2) = 1.96 g/ml; observed density (measured by flotation in aqueous ZnI_2 solution) = 1.92 g/ml. Intensity data were collected on a Nonius CAD-3 automated diffractometer using Mo Kα radiation up to a θ limit of 25°. The crystal was aligned such that its rotation axis coincided with the b axis of the unit cell. The θ–2θ scanning technique was used in data collection, the scan ranging from -0.5 to $+0.5°$ in θ from the peak center. Attenuators were inserted automatically if the intensity of the diffracted beam exceeded 2500 counts per second. The take-off angle was set at 4°. The intensities of three check reflections, sampled at 20-reflection intervals, showed no variation greater than ±1.5% of the mean value. The standard deviation of each intensity $\sigma(I)$ was estimated using the formula[21] $\sigma(I)$ = (total count + $0.04I^2)^{1/2}$. After data reduction,[22] 1325 reflections

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[16] D. W. Slocum, T. R. Englemann, C. Ernst, C. A. Jennings, W. Jones, B. Koonsvitsky, J. Lewis, and P. Shenkin, *J. Chem. Educ.*, **46**, 144 (1969).

[17] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen, London, 1958, p 105.

[18] E. A. Hill and J. H. Richards, *J. Amer. Chem. Soc.*, **83**, 3840 (1961); D. S. Trifan, J. L. Weinmann, and L. P. Kuhn, *ibid.*, **79**, 6566 (1957); D. S. Trifan and R. Bacskai, *ibid.*, **82**, 5010 (1960).

[19] G. H. Stout and L. H. Jensen, "X-Ray Structure Determination," Macmillan, New York, N. Y., 1968, p 65.

[20] The unit cell parameters were obtained by accurately measuring the setting angles of ten strong reflections on the diffractometer using Mo K$\alpha_{(1)}$ radiation (λ 0.70926 Å).

[21] P. W. R. Corfield, R. J. Doedens, and J. A. Ibers, *Inorg. Chem.*, **6**, 197 (1967).

[22] Absorption corrections were not made. We justify this on the basis of the following: (i) the linear absorption coefficient of the compound was small (11.9 cm^{-1} for Mo Kα); (ii) the intensities of axial reflections (060 for the first crystal and $\bar{2}\bar{2}4$ for the second) showed essentially no systematic variation with ϕ; (iii) θ values used in data collection were confined to the relatively narrow range between 4 and 25°.

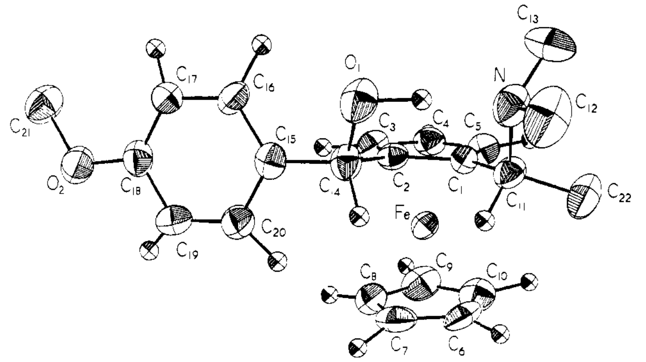

Figure 1. The absolute configuration of (*S*,*R*,*S*)-Fe(C_5H_5)(C_5H_3)-1-CH(OH)(*p*-$C_6H_4OCH_3$)-2-CH(CH_3)(N(CH_3)$_2$) (**4**). The cyclopentadiene rings are labeled $C_1C_2C_3C_4C_5$ and $C_6C_7C_8C_9C_{10}$. The hydrogen atoms (the nonlabeled spheres) were estimated from a final difference Fourier map.

(out of 1520) were found with intensities greater than 3σ and these were used in the structure analysis.

The *x* and *z* coordinates of the Fe atom were readily obtained from a Patterson map.[23] A difference Fourier map phased by the iron atom alone was complicated by the presence of a false mirror plane which made the interpretation of the map difficult. This problem was successfully handled by concentrating on the peaks found at bonding distance (~2 Å) from the iron atom. There were, as expected, 20 of these, corresponding to the ten cyclopentadiene carbons plus their mirror images. By a careful examination of the geometry described by these 20 "carbon atoms," it was possible to separate them into two mirror-related sets of ten atoms, both of which describe the ferrocene skeleton adequately. A structure factor calculation[24] phased by the iron atom and one of the sets of ten carbons then removed the false mirror plane quite satisfactorily and revealed the positions of many more atoms in the molecule. The rest of the nonhydrogen atoms were found *via* a succession of structure factor calculations and Fourier syntheses. Several cycles of full-matrix isotropic least-squares refinement, followed by anisotropic least-squares refinement,[25] resulted in a final *R* factor of 4.9%.[26] The positions of the hydrogen atoms not associated with the methyl groups were readily estimated from a final difference Fourier map.

The absolute configuration of a compound crystallizing in a monoclinic space group is best determined using data having both positive and negative *k* indices. Because the original set of data only contained reflections having positive *k* indices, data were recollected (following the method described earlier[22]) on another crystal (dimensions 0.30 × 0.08 × 0.07 mm), this time covering both *hkl* and $h\bar{k}l$ quadrants. This crystal was cut from a larger one and was mounted on the $\bar{1}\bar{1}2$ reciprocal axis, which corresponded roughly to the long dimension of the crystal. Least-squares refinement[27] resulted in *R* factors of 6.5 and 7.2% (1070 reflections) for the two configurations. This difference, according to Hamilton's significance test,[28] indicates that the configuration associated with the lower *R* factor has a better than 99.5% probability of being the right one.

The absolute configuration of **4** is shown in Figure 1. The final atomic positions are listed in Table I, the thermal parameters in Table II, the bond lengths in Table III and the bond angles in Table IV.[29] The two asymmetric carbon atoms are labelled C_{11} and C_{14}. As can be seen, the configuration about the amine-substituted carbon C_{11} is *R* and that about the hydroxyl-substituted carbon C_{14} is *S*. The configuration of the molecule as a whole, with respect to the plane of chirality, is *S*.[30] The conformations about the two asymmetric carbons are apparently determined by the hydrogen bond formed between the hydroxyl and amine groups (see Figure 1). This hydrogen bond is located above the doubly substituted cyclopentadiene ring (*i.e.*, on the opposite side of the ring from the iron atom). The angle of tilt between the cyclopentadiene

Table I. Final Atomic Positions for $FeC_{22}H_{27}NO_2$ (**4**)[a]

Atom	*x*	*y*	*z*
Fe	0.08856 (11)	0.00000 (0)	0.20803 (11)
N	−0.4191 (7)	−0.0854 (6)	−0.0428 (9)
O_1	−0.2543 (6)	−0.2698 (5)	0.1558 (7)
O_2	0.3586 (7)	−0.5402 (5)	0.6375 (7)
C_1	−0.1368 (8)	−0.0494 (6)	0.0610 (8)
C_2	−0.0540 (8)	−0.1454 (6)	0.1608 (8)
C_3	0.0861 (9)	−0.1732 (7)	0.1518 (9)
C_4	0.0851 (9)	−0.0908 (8)	0.0438 (8)
C_5	−0.0536 (8)	−0.0184 (7)	−0.0125 (8)
C_6	0.0751 (10)	0.1558 (7)	0.3062 (10)
C_7	0.1511 (11)	0.0696 (9)	0.4126 (10)
C_8	0.2919 (10)	0.0320 (7)	0.4104 (9)
C_9	0.2970 (10)	0.0975 (9)	0.2967 (11)
C_{10}	0.1649 (11)	0.1780 (8)	0.2327 (11)
C_{11}	−0.2906 (7)	0.0025 (8)	0.0397 (7)
C_{12}	−0.5652 (10)	−0.0530 (9)	−0.0381 (14)
C_{13}	−0.4577 (14)	−0.0996 (12)	−0.2026 (12)
C_{14}	−0.1051 (8*s*	−0.2087 (7)	0.2538 (8)
C_{15}	0.0118 (9)	−0.3007 (7)	0.3545 (8)
C_{16}	0.1333 (10)	−0.2682 (7)	0.4948 (9)
C_{17}	0.1204 (8)	−0.5034 (9)	0.4008 (7)
C_{18}	0.2410 (8)	−0.4692 (6)	0.5376 (8)
C_{19}	0.2458 (10)	−0.3500 (8)	0.5847 (9)
C_{20}	0.1333 (10)	0.2682 (7)	0.4948 (9)
C_{21}	0.3729 (11)	−0.6589 (8)	0.5885 (11)
C_{22}	−0.3264 (10)	0.1280 (8)	−0.0354 (11)

[a] Standard deviations in parentheses.

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(23) All the major computations in this paper were done using CRYM, an amalgamated set of crystallographic programs developed by Dr. R. E. Marsh's group at the California Institute of Technology.

(24) Throughout this work, scattering factors for iron corrected for anomalous dispersion effects (both real and imaginary) were used to compute the F_c's. The form factors for Fe, C, N, and O, and the $\Delta f'$ and $\Delta f''$ anomalous dispersion corrections for iron were all obtained from the "International Tables for X-ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1968.

(25) In the anisotropic least-squares refinement, the parameters were blocked such that the positional parameters were put in one matrix and the temperature factors and scale factor in the other.

(26) Listings of structure factors will appear following these pages in the microfilm edition of this volume of the Journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JACS-73-482. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(27) For economic reasons, the refinements associated with the second crystal were carried out isotropically (except for the iron atom). We feel that the differences between the *R* factors obtained here are so striking that extension of the refinement to include anisotropic temperature factors would be quite unnecessary.

(28) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(29) The results given in Tables I–IV, as well as the structure factor tables referred to in ref 25, are derived from the data collected from the first crystal (*i.e.*, corresponding to the data set with *R* = 4.9%).

(30) For an explanation of the *RS* nomenclature used here, see ref 13.

Table II. Final Anisotropic Temperature Factors[a] for $FeC_{22}H_{27}NO_2$ (**4**)[b]

Atom	$10^3\beta_{11}$	$10^3\beta_{22}$	$10^3\beta_{33}$	$10^3\beta_{12}$	$10^3\beta_{13}$	$10^3\beta_{23}$
Fe	12.3 (2)	6.0 (1)	12.6 (1)	−1.4 (3)	14.6 (2)	1.0 (3)
N	13.5 (11)	9.3 (7)	23.5 (14)	1.5 (15)	14.2 (21)	1.6 (17)
O_1	14.3 (9)	9.2 (6)	24.6 (11)	−4.3 (12)	15.5 (17)	4.4 (13)
O_2	14.5 (12)	8.6 (11)	14.4 (12)	1.8 (16)	11.8 (21)	4.7 (17)
C_1	12.6 (11)	6.2 (6)	10.8 (10)	0.5 (13)	10.1 (18)	0.3 (13)
C_2	14.9 (14)	7.0 (8)	15.8 (13)	−1.2 (17)	16.3 (23)	−2.1 (17)
C_3	12.7 (12)	6.4 (7)	11.8 (11)	−4.6 (15)	13.0 (20)	−2.5 (14)
C_4	21.0 (14)	9.3 (8)	12.6 (12)	−2.5 (2)	21.2 (23)	−2.5 (17)
C_5	16.0 (12)	8.7 (9)	14.1 (11)	−1.4 (18)	18.1 (20)	−0.2 (17)
C_6	21.6 (17)	5.8 (8)	23.4 (18)	−3.3 (18)	22.0 (31)	−9.1 (19)
C_7	25.1 (19)	10.3 (10)	15.9 (14)	−10.0 (23)	19.4 (28)	−11.5 (20)
C_8	22.1 (15)	8.8 (11)	17.1 (13)	2.4 (18)	12.0 (24)	−2.1 (18)
C_9	17.6 (16)	10.6 (10)	26.3 (19)	−11.8 (21)	22.4 (30)	−6.8 (24)
C_{10}	17.2 (16)	9.6 (9)	20.7 (17)	−9.4 (20)	14.9 (28)	−4.4 (20)
C_{11}	12.8 (9)	6.1 (5)	15.9 (10)	−1.8 (22)	11.2 (17)	−1.4 (24)
C_{12}	14.8 (14)	14.2 (11)	40.7 (27)	1.9 (20)	31.1 (36)	8.7 (28)
C_{13}	32.2 (23)	18.4 (15)	18.4 (18)	−6.4 (34)	6.4 (34)	−15.5 (29)
C_{14}	14.3 (13)	7.8 (7)	14.6 (12)	−2.0 (16)	15.0 (22)	3.6 (16)
C_{15}	15.7 (13)	8.6 (8)	14.4 (12)	9.3 (16)	21.0 (22)	3.5 (16)
C_{16}	21.2 (16)	5.4 (7)	16.1 (12)	0.4 (17)	22.8 (24)	0.1 (15)
C_{17}	18.2 (12)	7.5 (6)	12.5 (10)	−0.2 (23)	15.6 (19)	−0.1 (22)
C_{18}	14.5 (12)	8.6 (11)	14.4 (12)	1.8 (16)	11.8 (21)	4.7 (17)
C_{19}	22.2 (16)	8.3 (9)	15.2 (14)	−4.4 (20)	13.2 (26)	−4.6 (18)
C_{20}	18.1 (14)	8.3 (8)	14.9 (13)	−3.0 (18)	12.9 (24)	0.4 (18)
C_{21}	23.0 (19)	8.6 (9)	24.0 (18)	5.4 (21)	23.5 (32)	0.9 (21)
C_{22}	19.6 (16)	8.3 (9)	27.4 (19)	4.1 (20)	21.2 (32)	5.7 (22)

[a] The form of the anisotropic thermal ellipsoid is $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$. [b] Standard deviations in parentheses.

Table III. Bond Lengths (Å) in $FeC_{22}H_{27}NO_2$ (**4**)[a]

$Fe-C_1$	2.022 (8)	C_1-C_2	1.429 (10)
$Fe-C_2$	2.023 (8)	C_2-C_3	1.455 (13)
$Fe-C_3$	2.018 (8)	C_3-C_4	1.460 (12)
$Fe-C_4$	1.993 (8)	C_4-C_5	1.424 (12)
$Fe-C_5$	2.024 (7)	C_5-C_1	1.423 (12)
$Fe-C_6$	2.062 (9)	C_6-C_7	1.374 (13)
$Fe-C_7$	2.073 (9)	C_7-C_8	1.452 (16)
$Fe-C_8$	2.078 (9)	C_8-C_9	1.427 (14)
$Fe-C_9$	2.087 (11)	C_9-C_{10}	1.429 (15)
$Fe-C_{10}$	2.090 (9)	$C_{10}-C_6$	1.459 (16)
C_1-C_{11}	1.520 (12)	$C_{14}-C_{15}$	1.500 (11)
C_2-C_{14}	1.488 (11)	$C_{15}-C_{16}$	1.404 (11)
$C_{11}-N$	1.478 (11)	$C_{16}-C_{17}$	1.404 (12)
$C_{11}-C_{22}$	1.558 (13)	$C_{17}-C_{18}$	1.374 (10)
$C_{14}-O_1$	1.458 (10)	$C_{18}-C_{19}$	1.411 (11)
$C_{14}-C_{15}$	1.500 (11)	$C_{19}-C_{20}$	1.372 (13)
$N-C_{12}$	1.500 (15)	$C_{20}-C_{15}$	1.395 (12)
$N-C_{13}$	1.537 (14)	O_2-C_{18}	1.352 (10)
		O_2-C_{21}	1.455 (11)

[a] Standard deviations in parentheses.

Table IV. Bond Angles (deg) in $FeC_{22}H_{27}NO_2$ (**4**)[a]

$C_1-C_2-C_3$	108.1 (7)	$C_6-C_7-C_8$	108.1 (9)
$C_2-C_3-C_4$	106.5 (7)	$C_7-C_8-C_9$	107.8 (8)
$C_3-C_4-C_5$	107.9 (8)	$C_8-C_9-C_{10}$	108.0 (9)
$C_4-C_5-C_1$	108.9 (7)	$C_9-C_{10}-C_6$	106.6 (8)
$C_2-C_1-C_5$	108.5 (7)	$C_7-C_6-C_{10}$	109.4 (9)
$C_1-C_{11}-C_{22}$	111.5 (7)	$C_{15}-C_{16}-C_{17}$	120.7 (7)
$N-C_{11}-C_{22}$	113.1 (7)	$C_{16}-C_{17}-C_{18}$	120.0 (8)
$N-C_{11}-C_1$	108.4 (7)	$C_{17}-C_{18}-C_{19}$	119.3 (8)
		$C_{18}-C_{19}-C_{20}$	120.8 (8)
$O_1-C_{14}-C_2$	107.8 (6)	$C_{19}-C_{20}-C_{15}$	120.8 (8)
$O_1-C_{14}-C_{15}$	108.1 (6)	$C_{20}-C_{15}-C_{16}$	118.4 (7)
$C_2-C_{14}-C_{15}$	113.6 (8)		
		$C_{21}-O_2-C_{18}$	117.0 (7)
$C_{13}-N-C_{12}$	110.8 (9)	$O_2-C_{18}-C_{17}$	126.3 (7)
$C_{11}-N-C_{12}$	111.1 (7)	$O_2-C_{18}-C_{19}$	114.5 (7)
$C_{11}-N-C_{13}$	112.0 (8)	$C_{14}-C_{15}-C_{16}$	121.2 (7)
		$C_{15}-C_{15}-C_{20}$	120.3 (7)

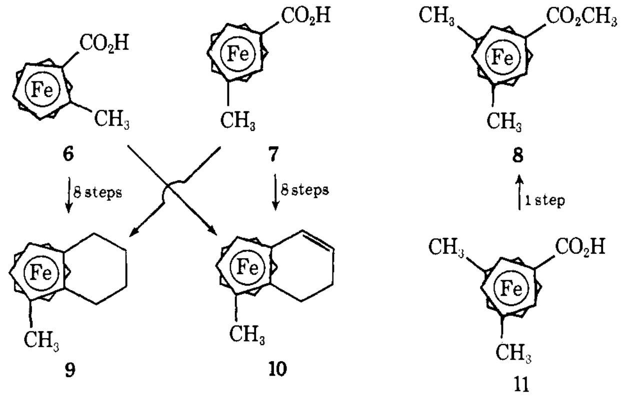
[a] Standard deviation in parentheses.

rings is 6°. A noteworthy feature of the structure is that, unlike ferrocene itself, the two cyclopentadiene rings are virtually eclipsed (the deviation from a totally eclipsed conformation is 6°). This phenomenon has been observed in quite a few ferrocene derivatives recently.[31,32] It is likely that the choice between the staggered and eclipsed conformations is determined by relatively subtle factors such as intermolecular packing.

Discussion

Considerable effort has been expended[6,33] on the determination of the absolute configurations of the optically active 1,2-disubstituted ferrocene derivatives with a plane of chirality; however, such an assignment (see Scheme III) was only achieved recently[33a]

Scheme III



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(31) (a) E. B. Fleischer and S. W. Hawkinson, *Acta Crystallogr.*, **22**, 376 (1967); (b) G. J. Palenik, *Inorg. Chem.*, **8**, 2744 (1969); (c) G. J. Palenik, *ibid.*, **9**, 2424 (1970); (d) L. H. Hall and G. M. Brown, *Acta Crystallogr., Sect. B*, **27**, 81 (1971).

(32) O. L. Carter, A. T. McPhail, and G. A. Sim, *J. Chem. Soc. A*, 365 (1967).

(33) (a) H. Falk and K. Schlögl, *Monatsh. Chem.*, **102**, 33 (1971); (b) see also G. Haller and K. Schlögl, *ibid.*, **98**, 2044 (1967).

by an unequivocal correlation of the configurations of optically active 1-methyl-2-carboxyferrocene[33] (**6**) and 1,1′-dimethyl-3-carboxyferrocene (**11**) whose absolute configurations had been previously determined by X-ray methods.[32]

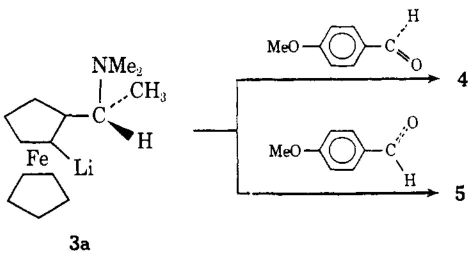
The preceding efforts[6,33b] to establish the absolute configuration of at least one chiral 1,2-disubstituted ferrocene led only to evidence that supported the tentative assignment. In particular, in reply to a recent statement,[33a] we wish to make clear that in the case of amines and of ferrocene derivatives, the configurational assignments of planar and central elements of chirality by product ratios of stereoselective reactions cannot be considered as unequivocal since they do not meet the criteria that have been defined for stereorelating syntheses.[13]

It is apparent that the stereoselective Friedel-Crafts reaction that had previously been used for configurational assignments of optically active ferrocene derivatives with a planar element of chirality is not a stereorelating synthesis, as has been claimed,[33a] but merely a stereoselective reaction, since one or the other of the diasteromeric products is formed preferentially, depending upon the reaction conditions.[34]

The determination of the absolute configuration of **4** not only confirms our previous mechanistic interpretations[13] of the stereoselective lithiations of *N*,*N*-dimethyl-1-ferrocenylethylamine (**2**) but provides some information with regard to the preferred orientation in which an aldehyde attacks a lithiated ferrocene derivative with a plane of chirality. The structure of **5** is clearly inferential, based on analytical data and reactivity.

If the reaction mixture is worked up immediately, substantial amounts of both amino alcohols are obtained. This indicates a rate of formation for the two products which is very nearly the same. If anything, **5** must be the kinetically favored product and not **4** because the former readily converts to the latter and not *vice versa*. That this should be so is reasonable if one examines the directions of attack which yield **4** and **5**, shown in Scheme IV.

Scheme IV



The condensation step which produces **5** involves steric interaction between a hydrogen and the dimethylaminoethyl side chain. In the corresponding reaction to produce **4**, the steric interaction is less between hydrogen and side chain but more with the carbonyl oxygen. Since **4** is the more stable compound, the strengths of the hydrogen bonds must be the determining factor. The strongly hydrogen-bonding nitrogen lone pair must contribute substantially to the energy of this species. It is also interesting to note that at room temperature, **4** is a solid whereas **5** is an oil.

Since the stereorelating lithiation,[13] in combination with the retentive nucleophilic substitution,[2,10] permits one to synthesize a wide variety of ferrocene derivatives with planar and central elements of chirality in a convenient manner, our X-ray result provides access to a large number of optically active ferrocene derivatives with known absolute configurations.

Experimental Section

(*S*,*R*,*S*)-2-(*p*-Methoxyphenyl)hydroxymethyl-*N*,*N*-dimethyl-1-ferrocenylethylamine (4). (*R*)-(+)-*N*,*N*-Dimethyl-1-ferrocenylethylamine (**2**) (12.8 g, 0.05 mol, $[\alpha]^{25}\text{D}$ +14.1° (*c* 1.5, ethanol)) was dissolved in 40 ml of anhydrous ether in a 300-ml, three-neck, round-bottom flask equipped with magnetic stirbar, reflux condenser, nitrogen inlet, and rubber serum cover. *n*-Butyllithium solution in hexane (Alfa Inorganics, 19.6 ml, 0.055 mol) was added by syringe through the serum cover in one portion. The resulting solution was stirred and refluxed for 1 hr, then allowed to stand briefly until it had reached ambient temperature. The serum cover was replaced by a pressure equalizing addition funnel charged with freshly distilled anisaldehyde (7.5 g, 0.055 mol) and 50 ml of anhydrous ether. The aldehyde solution was added dropwise to the metalated amine solution and spontaneous refluxing ensued. Ten minutes after the addition was complete, the mixture was hydrolyzed by addition of 75 ml of saturated ammonium chloride solution. The phases were separated and the aqueous phase was extracted twice with 100-ml portions of ether. The combined ether solutions were washed twice with 300-ml portions of distilled water, once with 300 ml of saturated salt solution, and dried over K_2CO_3 and the solvent removed *in vacuo*. The residue was a red-brown oil and weighed 25 g (*ca*. 100%). The entire crude mixture was then chromatographed over 700 g of silica gel (J. T. Baker, No. 3405, 60–200 mesh) using 1:1 (v/v) ligroin (bp 60–90°):acetone as eluent. The products eluted in three bands; compounds **4** and **5** were isomeric amino alcohols and compound **2** was starting amine. The yields were: **4**, 7 g, 28.4%; **5**, 4 g, 16.2%.

Compound 4. Recrystallization from *n*-heptane (10 ml/g) gave 5 g (20.2%) of a yellow powder, mp 110–111°, $[\alpha]^{22}\text{D}$ −20.8° (*c* 1.6, ethanol); nmr δ 1.33 (3 H, center of doublet, *J* = 6.9 Hz methyl), 2.19 (6 H, singlet, aminomethyl groups), 3.84 (3 H, singlet, methoxyl), 4.03 (9 H, singlet over small multiplet, ferrocene rings and methine proton), 6.94 (singlet, 1 H, benzyl), 6.95, 7.08, 7.50, 7.65 ppm (4 H, AB pattern, *J* = 9.0 Hz, aromatic protons); ir ($CHCl_3$) 3095, 2980, 2825, 1610, 1460, 1240, 1167, 1102, 1068, 1035, 999, 930, 820 cm^{-1}. *Anal.* Calcd for $C_{22}H_{27}O_2NFe$: C, 67.18; H, 6.92; N, 3.56. Found: C, 67.14; H, 7.09; N, 3.45.

Compound 5, a dark red-brown oil, was undistilled. The nmr spectrum is the same as above except that the substituted ring appears as a multiplet centered at δ 4.15 ppm and the unsubstituted ring is a singlet at 3.90 ppm. In addition, the benzyl proton is shifted from δ 6.09 to 5.45 ppm. The infrared (neat) data are: 3360 (broad), 2960, 2910, 2850, 1678, 1600, 1510, 1450, 1260, 1160, 1030 cm^{-1}.

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(34) (a) J. Tirouflet, R. Robard, and B. Gantheron, *C. R. Acad. Sci.*, **256**, 1315 (1963); *Bull. Soc. Chim. Fr.*, 96 (1965); (c) H. Falk and K. Schlögl, *Monatsh. Chem.*, **96**, 1065 (1965).