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Ferrocene derivatives, LXXI *; Stereochemistry of metallocenes, LVI * Synthesis and structure of optically active ferrocenylaminoalcohols

Hans Wally [a], Christoph Kratky [b], Walter Weissensteiner [a], Michael Widhalm [a] and Karl Schlögl [a]

[a] *Institut für Organische Chemie, Universität Wien (Austria)*
[b] *Institut für Physikalische Chemie, Universität Graz (Austria)*

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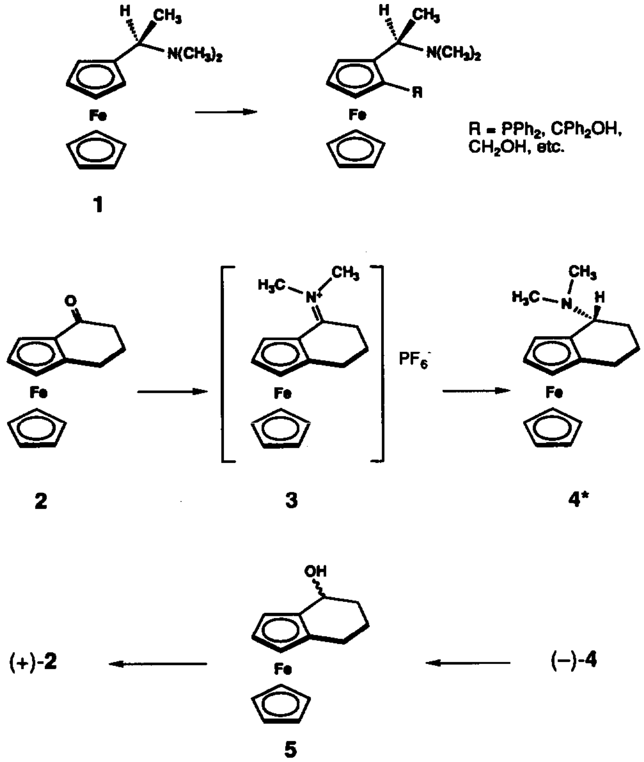
Abstract

The reaction of enantiomerically pure 1,2-(α-N,N-dimethylamino)-tetramethylene ferrocene (**4**) with butyllithium and subsequent treatment with either benzophenone or paraformaldehyde has yielded the aminoalcohols **6–11**. The absolute configurations of **4** and **6–11** were deduced from the X-ray structures of the (*R*,*R*)-tartrate of **4** (**4**-T) and the aminoalcohol **6**. In addition the optical purity of **4** was shown to be at least 95% by transformation into the ketone **2**. In solution the annelated six-membered ring in compounds **4** and **6–11** was found to adopt a preferred half-chair conformation very similar to that found in the solid state structures of **4**-T and **6**.

1. Introduction

Optically active ferrocene derivatives have been widely employed as chiral auxiliaries in asymmetric catalysis. In particular amino alcohols [1] and amino phosphines [2] are much used as precursors in the preparation of several types of transition metal complexes that have proved to be powerful catalysts in enantioselective alkylation, hydrogenation, hydrosilation, isomerization and cross coupling reactions [3]. The syntheses of such amino alcohols and amino phosphines or related compounds usually involve optically active amino ferrocenes. For several reasons (1′-N,N-dimethylaminoethyl)ferrocene (**1**) has become the key intermediate in almost all the synthetic procedures (Scheme 1); first, it is easy to resolve into its enantiomers [4] and secondly, regiospecific metallation reactions (in position 2) are highly stereoselective [5]. Hence, many derivatives of **1** have been prepared and tested for their efficiency as chiral modifiers in transition metal catalysts. Despite their unquestioned success, these compounds still show a rather high degree



Scheme 1. * Note: the configuration shown is that of (−)-**4**; this enantiomer forms the more soluble salt with (*R*,*R*)-tartaric acid.

Correspondence to: Professor K. Schlögl.

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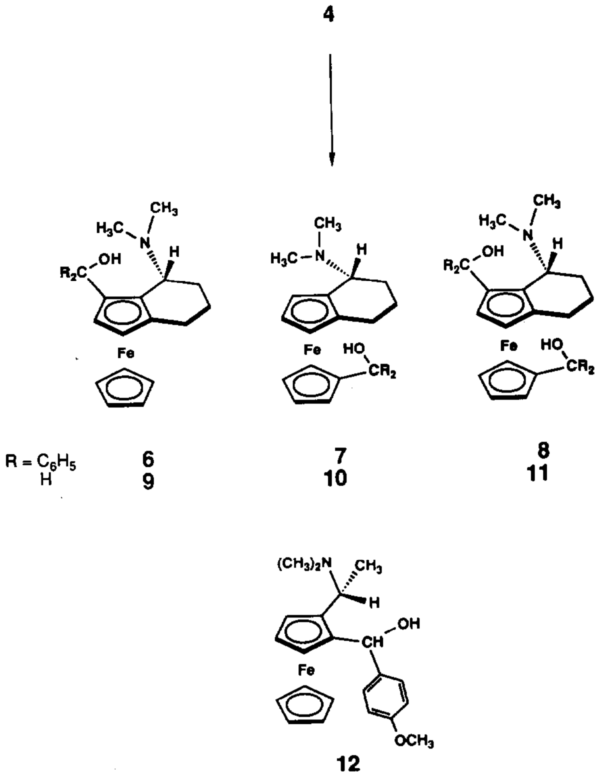
of conformational flexibility. The aminoalkyl side chain in particular may adopt several minimum energy conformations, a feature which is expected to increase the number of reactive conformers and thereby reduce the enantioselectivity of the catalysts.

It was thus a challenge to design optically active amino ferrocenes and derivatives with significantly less conformational flexibility in order to limit the number of feasible conformers, and so to change the geometry of the resulting transition metal complexes.

A *homo*annularly bridged amino ferrocene having the amino functionality on a "benzylic" carbon, such as **4**, seemed to be a promising species. We describe here the syntheses of the enantiomerically pure amino alcohols **6–11**, their absolute configurations, and their chiroptical properties. The molecular structures in the solid state are reported for the tartrate of **4** (**4**–T) and for the amino alcohol **6**. The conformational possibilities and minimum energy conformations are discussed in detail for compounds **4** and **6–11**.

2. Discussion

The amine **4** is accessible in good yield from α-keto-1,2-tetramethylene ferrocene (**2**), *via* the iminium salt **3** and subsequent reduction with KBH_4 [6]. A freshly prepared sample of **4** was resolved into its enantiomers *via* its tartrates. The enantiomers were characterized by their chiroptical properties, given in the Experimental section. The optical purity of the isolated antipods was shown by chemical correlation to be equal to or higher than 96%. For this purpose the amine **4** was converted *via* the alcohol **5** into the ketone **2**, which was then compared with an authentic optically pure sample of **2** [7].



Scheme 2.

In the course of the optical resolution we were able to isolate a suitable single crystal of the less soluble tartrate of **4**. An X-ray crystal structure analysis not only gave important structural information (see below) but also revealed the absolute configuration for the $(+)_{578}$-enantiomer of **4**: (1*R*,2*S*) [8] at the ferrocene unit and (*S*-*endo*) at the benzylic carbon. This *endo* configuration together with a *pseudo* equatorial conformation places the amino nitrogen slightly below the *homo*annularly substituted cyclopentadienyl (Cp) ring, a geometrical arrangement which is expected to fit the necessary condition for a highly stereoselective *ortho*-lithiation reaction.

Reaction of **4** with 2.5 equivalents of n-butyl lithium and subsequent treatment with benzophenone resulted in a mixture of mono- (*homo*- and *hetero*annularly) and di-substituted amino alcohols **6**, **7**, **8** in the ratio 62:19:19. Reaction of **4** with paraformaldehyde gave the products **9**, **10**, **11** in the ratio 59:18:23 (Scheme 2).

A comparison of the behaviour of **4** with that of **1** shows two significant differences: (i) the lithiation of **4** is less stereoselective than that of **1** but still pronounced, a consequence of the limited flexibility of the dimethylamino group; (ii) *ortho*-lithiation of **1** and **4** leads to products with reversed absolute configuration at the ferrocene unit. For example, lithiation of (*R*)-**1** and subsequent treatment with benzophenone gives an amino alcohol with a ferrocene configuration of $(1S, 2R)_m$ [*] whereas the same reaction sequence applied to $(1S, 2R)_m(R)_c$-**4*** (*R* configuration at the benzylic carbon as well!) gives the amino alcohol with the "opposite" ferrocene configuration $(1S, 2R, 3R)_m(R)_c$.

2.1. X-ray structures of the tartrate of 4 (4–T) and of the amino alcohol 6

4: The molecular structure of the less soluble (*R*,*R*)-tartrate of **4**(**4**–T) was determined by X-ray crystallography. Crystals of **4**–T belong to the monoclinic system, space group $P2_1$, with 2 molecules in the unit cell. The molecular conformation of **4**–T is shown in

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[*] The indices *m* and *c* refer to *metallocene* and *carbon* chirality, respectively.

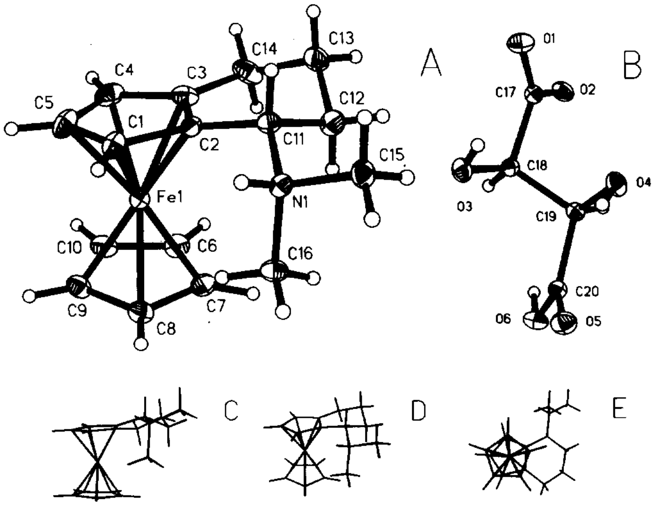

Fig. 1. Crystal structure analysis of the (*R*,*R*) tartrate of (+)(1*R*, 2*S*)$_m$(*S*)$_c$ − 4(4–T). A ORTEP-drawing (50% probability) of one formula unit $C_{16}H_{22}FeN$. B Drawing of the tartrate moiety $C_4H_5O_6$. Note that the two molecules have been drawn in arbitrary relative orientation, which is not the one observed in the crystal structure of 4–T. C, D Different views of the ferrocene moiety.

Fig. 1, final atomic coordinates are listed in Table 1. Since the absolute configuration of the tartrate moiety is known to be (*R*,*R*), a (1*R*,2*S*)-configuration at the ferrocene unit and (*S*) at the benzylic carbon (C11) can be assigned to the $(+)_{578}$-enantiomer of 4. In addition, refinement of the chirality – parameter η [9] yielded a value of $\eta = 0.99(7)$.

The cyclopentadienyl rings are essentially planar but deviate slightly (by 7°) from a parallel arrangement. They adopt a conformation which deviates by 15° from a perfectly staggered one. Bond lengths and bond angles in the ferrocene unit are quite normal; the average Fe–C_{ar} bond lengths are 2.067(18) Å, the average C_{ar}–C_{ar} bond lengths 1.432(8) Å.

The annelated six-membered ring adopts a half-chair conformation with the dimethylamino group in a *pseudo* equatorial position. When viewed along bond N1–C11 the dimethylamino group can be seen to be a staggered conformation with respect to the bond C11–C12 besecting the angle C15–N1–C16.

The ring carbon C14 lies essentially in the best plane of the substituted cyclopentadienyl ring, whereas C11 is 0.253 Å above that plane. The torsion angle C2–C11–C12–C13 opens up to 55.7° and the dimethylamino group is placed in an almost equatorial position, thus minimizing intramolecular steric interaction. The C–O bond lengths in the carboxylate anion are almost identical [1.261(4) and 1.269(4) Å] whereas in the hydroxycarbonyl group the C–O distances differ significantly [C–OH, 1.333(1) and C=O, 1.224(4) Å]. The crystal packing is dominated by the formation of three intermolecular H-bonds [O1 ··· H(O6): 1.54 Å; O2 ··· H(N1); 1.88 Å; O2 ··· H(O3); 2.15 Å].

A comparison of the structural data for 4–T with those for the tartrate of 1(1–T) [10] shows a very significant difference: in 1–T the dimethylamino group is located 1.461 and 1.533 Å (two molecules in the unit cell) above the substituted cyclopentadienyl ring whereas in 4–T the amine nitrogen is forced to lie 0.244 Å below that plane. However, despite that difference, in both cases, 1–T and 4–T, the (*R*,*R*)-tartrate crystallizes with the $(S)_c$-amine.

As mentioned above, the amino alcohol 6 was prepared by lithiation of 4 and subsequent treatment with benzophenone, followed by chromatographic separation (see Experimental section).

TABLE 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($Å^2 \times 10^4$) for the non-hydrogen atoms plus the crystallographically refined H-atoms in the crystal structure of 4–T. The equivalent isotropic displacement coefficient was obtained as one third of the trace of the orthogonalized U_{ij}-tensor. E.s.ds. are given in parentheses. The isotropic temperature factor has the form $T = \exp[-8\pi^2 U \sin^2\Theta/\lambda^2]$

	x	*y*	*z*	U_{eq}
Fe(1)	976(1)	5000	2172(1)	14(1)
N(1)	3634(2)	1588(3)	3120(2)	13(1)
H(N1)	3930(46)	1721(55)	2508(43)	36(11)
C(1)	1743(3)	3613(4)	1038(3)	19(1)
C(2)	1315(3)	2725(4)	1921(3)	14(1)
C(3)	−169(3)	3025(4)	1794(3)	19(1)
C(4)	−628(3)	4091(4)	818(3)	24(1)
C(5)	545(3)	4452(4)	361(3)	24(1)
C(6)	311(3)	6136(4)	3493(3)	20(1)
C(7)	1762(3)	5709(4)	3963(3)	19(1)
C(8)	2531(3)	6398(4)	3202(3)	19(1)
C(9)	1570(3)	7227(4)	2264(3)	20(1)
C(10)	184(3)	7060(4)	2446(3)	22(1)
C(11)	2032(3)	1450(3)	2703(3)	14(1)
C(12)	1359(3)	1140(4)	3752(3)	20(1)
C(13)	−234(3)	884(4)	3190(3)	22(1)
C(14)	−1007(3)	2290(4)	2566(3)	25(1)
C(15)	4314(3)	208(4)	3758(3)	18(1)
C(16)	4186(3)	2927(4)	3879(3)	17(1)
O(1)	5672(2)	3963(3)	11156(2)	20(1)
O(2)	4819(2)	1626(3)	11235(2)	19(1)
O(3)	5950(2)	3578(3)	8898(2)	17(1)
H(O3)	5696(56)	4313(64)	9103(48)	49(15)
O(4)	3009(2)	3747(3)	8710(2)	17(1)
H(O4)	3130(61)	4213(75)	8203(54)	69(20)
O(5)	3192(2)	3009(3)	6491(2)	20(1)
O(6)	3885(2)	659(3)	6975(2)	19(1)
H(O6)	4172(50)	−110(80)	7668(44)	55(14)
C(17)	5261(3)	2701(4)	10711(3)	14(1)
C(18)	5241(3)	2442(3)	9359(2)	12(1)
C(19)	3670(3)	2364(3)	8604(2)	13(1)
C(20)	3554(3)	2027(4)	7262(2)	15(1)

6: For the X-ray structure analysis a crystal prepared from the $(-)_{578}$ enantiometer of **4** was used. Crystals of **6** belong to the tetragonal system, space group $P4_12_12$, with 8 molecules in the unit cell. Figure 2 shows the molecular conformation of **6**, Table 2 lists final atomic parameters.

Since the absolute configuration of (−)-**4**, the precursor of **6**, is known to be (*R*) at the benzylic carbon, there must be an absolute configuration of (1*S*,2*R*,3*R*) at the ferrocene unit (and (*R*) at C11) for the $(+)_{578}$-enantiomer of **6**. This is corroborated by the result of the absolute structure refinement [$\eta = 0.74$ (16)]. The cyclopentadienyl rings are again essentially planar, but tilted by 5.8°. The arrangement of both rings is closer to a staggered than to an eclipsed conformation (12° away from being perfectly staggered). The average C_{ar}–C_{ar} bond length is 1.413(27) Å and the average C_{ar}–Fe distance is 2.049(12) Å. As in **4**, the ring carbon C11 shows a substantial out-of-plane deformation. It is located 0.348 Å above the best plane of the substituted Cp ring. Furthermore, carbon C14 also lies 0.238 Å above the Cp plane. This out-of-plane deformation of both benzylic carbons, C11 and C14, can be viewed as a tilt of the whole six-membered ring about an axis through carbons C2 and C3. The hydroxyl-substituted carbon C17 is also located slightly above the Cp plane (0.188 Å). There appears to be a strong intramolecular H-bond connecting the alcohol with the amine centres (N1 ··· O1: 2.72 Å). Since the proton lies closer to the nitrogen atom N1 than to O1 (O1 ··· H1: 1.45 Å; N1 ··· H1: 1.29 Å), the structure might alternatively be described as an ammonium alcoholate.

TABLE 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($Å^2 \times 10^4$) for the crystallographically refined atoms of **6**

	x	y	z	U_{eq}
Fe(1)	5345(2)	1912(2)	471(1)	24(1)
O(1)	6796(8)	−251(8)	1009(1)	22(3)
N(1)	8959(12)	915(11)	747(2)	27(3)
H(N1)	7877(144)	461(137)	866(23)	31(40)
C(1)	6065(12)	−46(12)	520(2)	19(5)
C(2)	7083(14)	782(13)	394(2)	22(3)
C(3)	6481(12)	1300(11)	141(2)	12(3)
C(4)	5164(12)	800(12)	116(2)	21(4)
C(5)	4902(14)	−47(12)	353(2)	22(3)
C(6)	3815(14)	2544(14)	730(3)	30(5)
C(7)	3686(15)	3160(15)	468(3)	43(4)
C(8)	4825(18)	3898(14)	410(3)	48(6)
C(9)	5721(15)	3792(13)	643(3)	33(5)
C(10)	5111(13)	2918(13)	838(2)	23(3)
C(11)	8601(12)	821(13)	453(2)	22(3)
C(12)	9324(14)	1862(13)	269(2)	28(5)
C(13)	8861(15)	1661(14)	−31(2)	43(6)
C(14)	7395(16)	2036(16)	−68(3)	40(6)
C(15)	9051(14)	2287(13)	865(2)	35(4)
C(16)	10228(14)	144(15)	813(3)	40(6)
C(17)	6242(12)	−1010(13)	780(2)	16(3)
C(18)	7259(12)	−2134(12)	698(2)	14(3)
C(19)	7899(14)	−2872(14)	911(3)	30(4)
C(20)	8809(13)	−3889(14)	857(2)	27(5)
C(21)	9123(13)	−4241(13)	577(2)	24(5)
C(22)	8474(13)	−3537(13)	370(2)	25(3)
C(23)	7524(14)	−2512(13)	426(3)	26(5)
C(24)	4885(12)	−1573(12)	868(2)	19(3)
C(25)	4378(13)	−2813(12)	764(2)	20(3)
C(26)	3127(14)	−3323(14)	851(2)	29(5)
C(27)	2386(15)	−2619(14)	1036(2)	31(4)
C(28)	2821(13)	−1393(12)	1146(2)	23(4)
C(29)	4090(12)	−875(13)	1059(2)	19(3)

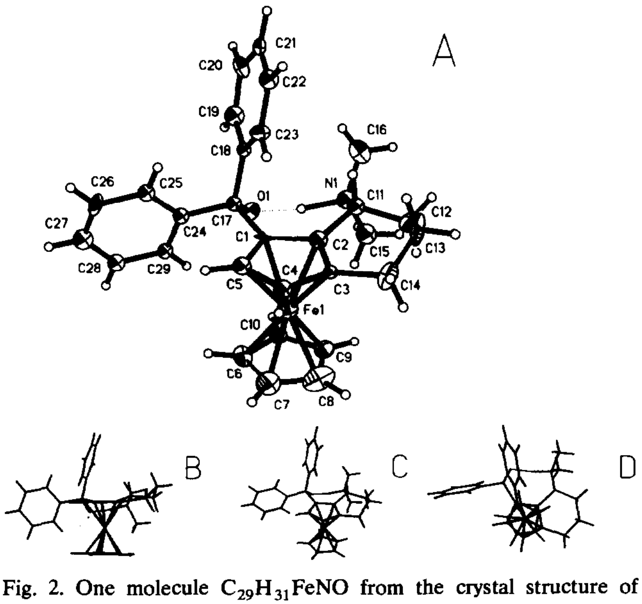

Fig. 2. One molecule $C_{29}H_{31}FeNO$ from the crystal structure of $(+)(1S,2R,3R)_m(R)_c$-**6**.

It is of interest to compare the structural data for **6** with those for a related alcohol derivative of **1**. The only available structure is that of the amino alcohol **12**, which was originally prepared by lithiation of optically active **1** and subsequent treatment with *p*-methoxybenzaldehyde [11]. The main structural difference between **6** and **12** is that in **6** both the amine nitrogen and the alcohol oxygen are located below the substituted Cp ring (O: 0.766 Å, N: 0.308 Å) whereas in **12** both groups are above that plane (O: 1.325 Å, N: 1.348 Å). In contrast to **6**, the benzylic carbon of **12** lies exactly in the plane of the Cp ring. However, in both cases the nitrogen is hydrogen-bonded to the oxygen (N–O distances are 2.716 Å in **6** and 2.789 Å in **12**). From these similar N–O distances it might be expected that, like **12** (and related compounds), **6** would be able to form complexes with dialkylzinc compounds, a necessary property for an enantioselective catalyst.

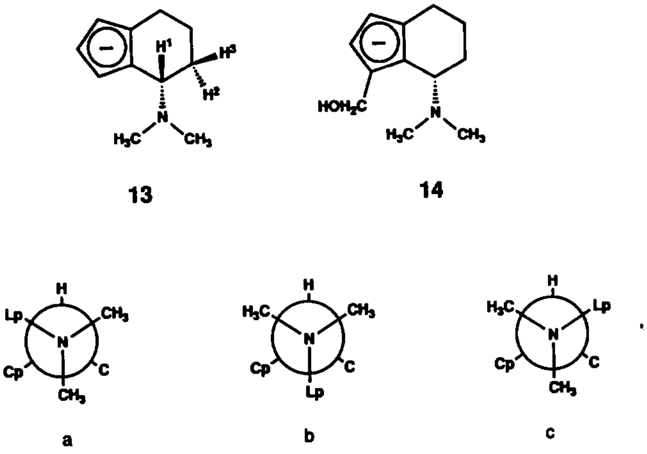

Fig. 3. Model Compounds **13** and **14** and possible minimum energy side chain conformations **a**–**c** viewed along the N–C single bond.

2.2. *Conformation of the amine 4 and the amino alcohols 6–11 in solution*

To check the conformational possibilities of the six-membered annelated ring, force field calculations were performed on the anions **13** and **14**, by use of the MM2 force field [12] implemented in the program MODEL [13]. The calculations show that the six-membered ring may adopt one of two low-energy half-chair conformations with the dimethylamino group either in a *pseudo* equatorial or a *pseudo* axial position. In addition, when viewed along bond N–C(benzylic), the dimethylamino group can be seen to adopt one of three possible staggered conformations (Fig. 3). For **13**, all 6 minimum energy conformations were found, and for **14** two conformers with reasonably low energy, both with a hydrogen bond between the amine nitrogen and the hydroxyl oxygen and the amine either in a *pseudo* equatorial or a *pseudo* axial position. Table 3 lists the relative steric energies for all conformers together with calculated vicinal coupling constants [14] between hydrogen H^1 and H^2 or H^3 (see Fig. 3). Inspection of Table 3 shows that in the minimum energy conformer the amino nitrogen adopts a *pseudo* equatorial position while the dimethyl amine unit prefers conformation **a** (Fig. 3).

Conformation **c** is only slightly higher in energy and must be expected to contribute significantly in a conformer equilibrium. All other conformers are higher in energy by at least 11.5 kJ/mol. The conformers of **14** also differ significantly in energy, with the *pseudo* equatorial amino arrangement more stable (8.4 kJ/mol) than the *pseudo* axial one.

Although **13** and **14** can be considered only as partial models for ferrocene derivatives, some conclusions can still be drawn for compounds **4**, **6**, **7**, **9** and **10**. First of all, a desymmetrization of the Cp ring in **13**, as in the ferrocene derivative **4**, will result in four possible diastereomeric arrangements: the amine can be either in an *endo* or *exo* configuration combined either with a *pseudo* equatorial or *pseudo* axial conformation (possible conformations **a**–**c** are not taken into account). Since for **4**–T the *endo* configuration was confirmed by the X-ray structure analysis, only the two remaining half-chair conformations of the six-membered ring need be considered. As is also clear from the X-ray structure, in the *pseudo* equatorial case the amine nitrogen is located below the substituted Cp-ring pointing towards the unsubstituted Cp-ring. In the *pseudo* axial case the dimethylamino group would lie even further below the Cp-ring but at the same time be closer to the iron atom and to the Cp′-ring, resulting in increased nonbonding interactions. Hence, it is to be expected that in the ferrocene **4** the *pseudo* axial conformation will be even more destabilized than in the anion **13**.

Additional evidence for a preferred *pseudo* equatorial conformation comes from the proton NMR spectra. As can be seen from Table 3, the calculated vicinal coupling constants (Fig. 3) are significantly different for *pseudo* axial and *pseudo* equatorial conformations. Table 4 lists the corresponding experimental coupling constants for compounds **4** and **6**–**11**. A comparison of

TABLE 3. Relative steric energies (kJ mol^{-1}) and estimated vicinal coupling constants (Hz) for model compounds **13** and **14**

	Conformation [a]		ΔE	$^3J(H^1\text{-}H^2)$	$^3J(H^1\text{-}H^3)$
13	ps-eq	a	0.0	11.5	4.6
		b	11.5	9.8	7.0
		c	0.8	11.2	5.0
	ps-ax	a	9.5	7.4	1.2
		b	4.4	3.8	2.7
		c	5.9	6.7	1.3
14	ps-eq		0.0	11.2	5.3
	ps-ax		8.4	7.3	1.2

[a] Conformational descriptors are defined in Fig. 3.

TABLE 4. Vicinal coupling constants $^3J(H^1\text{-}H^2)$ and $^3J(H^1\text{-}H^3)$(Hz) for compounds **4** and **6**–**11** [a]

	$^3J(H^1-H^2)$ [b]	$^3J(H^1-H^3)$ [b]
4 [c]	9.3	4.1
6 [c]	9.2	5.6
7 [c]	11.4	4.3
8 [c]	9.3	4.1
9 [c]	9.4	4.8
10 [d]	9.4	4.9
11 [c]	9.8	4.4

[a] The proton numbering scheme is shown in Fig. 3; [b] ±0.3 Hz; [c] $CDCl_3$; [d] C_6D_6.

the experimental and calculated values shows that the experimental coupling constants for **4** agree well with those calculated for a *pseudo* equatorial arrangement and a dimethylamine conformation **a** and **c**. Very similar coupling constants are also found for the amino alcohols **6–11**, strongly indicating a preferred *pseudo* equatorial arrangement of the amine also.

From the results of the calculations on **14** not only a *pseudo* equatorial amine conformation but also an N–H–O hydrogen bond can be expected. The effect of the hydrogen bond is best seen in the proton NMR spectrum of **6**. In contrast to compounds **7–11**, which give a single signal for the $N(CH_3)_2$ group, two well separated singlets are found in the spectra of **6**; moreover the signal of the hydroxyl proton is observed at 9.39 ppm. For **8–11** the chemical shifts of the hydroxyl proton are found in the range of 5.18–7.31 ppm. (The NMR spectra were recorded in $CDCl_3$, except for **10** where C_6D_6 was used; see Experimental section.)

From the results of the force field calculations and from the NMR data we conclude that the preferred conformation of the six-membered ring in **4** and **6–11** in solution is very similar to that found in the solid state for **4**–T and **6**.

3. Experimental details

The ^{1}H- and ^{13}C-NMR spectra in $CDCl_3$ (J modulated) were recorded on a Bruker AM-400 spectrometer at 400 MHz and 100 MHz. Chemical shifts, δ, are given relative to TMS as internal standard. Mass spectra were recorded on a Varian MAT-CH-7. Optical rotations were determined with a Perkin Elmer polarimeter 241 in EtOH (96%, $d = 1$ dm, 20°C), thermostated. CD-spectra were recorded on a dichrograph CD6 (Jobin Yvon) in EtOH (96%, c: $5 \cdot 10^{-3}$–$1 \cdot 10^{-4}$ mol l^{-1}, $d = 0.1$ or 1 cm). Elemental analyses were performed by the Mikroanalytisches Laboratorium der Universität Wien (Mag. J. Theiner). Melting points were determined on a Kofler melting point apparatus and are uncorrected.

3.1. *1,2-(α-Ketotetramethylene)-ferrocene (2)*

Prepared by published procedures [6a,b].

3.2. *1,2-(α-N,N-Dimethylaminotetramethylene)-ferrocene (4)*

Prepared as previously described [6c] from 9.52 g (37.4 mmol) of **2** to give 6.56 g (78%) of **4**, m.p.: 17–18°C; ^{1}H-NMR: δ 1.48 (1H, m), 1.94 (3H, m), 2.29 (1H, ddd, $J = 15.7$, 6.6, 3.5 Hz), 2.59 (6H, s), 2.68 (1H, m), 3.10 (1H, dd, $J = 9.3$, 4.1 Hz), 3.99 (1H, m), 4.05 (1H, t, $J = 2.4$ Hz), 4.07 (s, 5H), 4.14 (1H, m); ^{13}C-NMR: δ 22.75, 23.96, 24.50, 42.65 [$N(CH_3)_2$], 60.89, 64.07 (Fc), 65.13 (Fc), 65.68 (Fc), 69.89 (Fc), 84.42 (Fc), 90.04 (Fc); MS (30°C) m/e (rel.%): 205(11), 239(74), 240(26), 255(16), 283(100); Anal. Found: C 68.11, H 7.28, N 4.99. $C_{16}H_{21}FeN$ calc.: C 67.86, H 7.47, N 4.95%.

The optical resolution of **4** was achieved by fractional crystallization of the diastereomeric tartrates. Both antipodes were obtained optically pure and in good chemical yield. (−)(*R*) **4a**: $[\alpha]^{20}_{578}$−4.37°(c: 1.74), CD $\lambda(\Delta\epsilon)$ 251(−1.73), 272(+0.36), 290(−0.24), 337(+0.12), 453(−0.18); (+)(*S*) **4a**: $[\alpha]_{578}{}^{20}$ + 4.20° (c: 1.48).

3.3. *1-(Hydroxydiphenylmethyl)-2,3-(α-N,N-dimethylaminotetramethylene)-ferrocene (6), 1-(hydroxydiphenylmethyl)-1′,2′-(α-N,N-dimethylaminotetramethylene)-ferrocene (7) and 1,1′-bis(hydroxydiphenylmethyl)-2,3-(α-N,N-dimethylaminotetramethylene)-ferrocene (8)*

A magnetically stirred solution of 566 mg (2.0 mmol) of **4** in 5 ml of dry ether under argon was treated dropwise with 3.30 ml (5.0 mmol) of a 1.6 M solution of ^{n}BuLi in hexane. After 1 h stirring dry benzophenone (1.46 g, 8.0 mmol) was added in portions. Stirring was continued for 1 h after which the complex was destroyed with water. The organic layer was separated and the aqueous layer extracted with 3 × 20 ml portions of ether. The combined extracts were dried with magnesium sulphate and the solvent was removed *in vacuo* to give mixed products which were separated by sequential chromatographic steps; the crude mixture was chromatographed on silica gel (25–40 μm, column: 45 × 1.5 cm); petroleum ether/ethylacetate/triethylamine (85:10:5) eluted three fractions; the first was a mixture of **6** and **7**, followed by a small amount of a poorly characterized isomer of **8**, mp: 198–200°C, and the final fraction was pure **8**. Fraction 1 was again chromatographed on silica gel with petroleum ether/ethylacetate (80:20). After the complete elution of **6**, a small amount of triethylamine (5%) was added to the solvent to strip **7** from the column. An analytically pure sample of **6** was obtained by applying MPLC (silica gel, 25–40 μm, 40 × 4.3 cm) to crude **6** (from the preceding step) with petroleum ether/ethylacetate (80:20) as eluent.

6: yield: 570 mg (61%); m.p.: 164–165°C; ^{1}H-NMR: δ 1.36 (1H, m), 1.70 (3H, m), 1.80 (3H, bs), 2.22 (1H, dt, $J = -15.3$ Hz, 4.4 Hz), 2.56 (1H, m), 2.64 (3H, bs), 2.79 (1H, dd, $J = 9.2$ Hz, 5.6 Hz), 3.38 (1H, d, $J = 2.4$ Hz), 4.07 (1H, d, $J = 2.4$ Hz), 4.12 (5H, s), 7.20 (8H, m), 7.45 (2H, d, $J = 7.3$ Hz), 9.98 (1H, s); ^{13}C-NMR: δ 21.30, 23.35, 25.24, 36.41 [$N(CH_3)_2$], 43.83 [$N(CH_3)_2$], 58.58, 65.05 (Fc), 69.25 (Fc), 70.50 (Fc), 83.70 (Fc) 86.45 (Fc), 95.34 (Fc), 126.15 (Ph), 126.23 (Ph), 126.85 (Ph), 127.42 (Ph), 127.61 (Ph), 127.76 (Ph), 146.70 (Ph), 149.12 (Ph), a signal due to Ph_2C was not observed; MS (180°C) m/e (rel.%): 236(12), 283(100), 315(9), 343(11), 418(13), 420(25), 465(89). Anal. Found: C 74.56, H 7.00, N 2.91. $C_{29}H_{31}FeNO$ calc.: C 74.84, H 6.71, N 3.01%.

7: yield: 170 mg, (18%), m.p.: 137–139°C; ^{1}H-NMR: δ 1.40 (1H, m), 1.91 (2H, m), 2.10 (1H, m), 2.29 (1H, dd, J = 16, 1.5 Hz), 2.61 (6H, s), 2.67 (1H, m), 2.86 (1H, dd, J = 11.4, 4.3 Hz), 3.56 (1H, t, J = 2.4 Hz), 3.62 (1H, m), 3.84 (1H, m), 4.03 (1H, dd, 2.2, 1.1 Hz), 4.18 (1H, dd, J = 2.4, 1 Hz), 4.36 (1H, m), 4.43 (1H, m), 7.20 (8H, m), 7.52 (2H, m); ^{13}C-NMR: δ 23.33, 23.54, 28.43, 45.63 [$N(CH_3)_2$], 61.97, 65.45 (Fc), 65.58 (Fc), 65.67 (Fc), 67.69 (Fc), 68.45 (Fc), 69.21 (Fc), 75.14 (Fc), 77.08, 85.29 (Fc), 93.37 (Fc), 97.03 (Fc), 126.14 (Ph), 126.29 (Ph), 126.89 (Ph), 127.06 (Ph), 127.21 (Ph), 127.38 (Ph), 147.96 (Ph), 149.63 (Ph); MS (150°C) m/e (rel.%): 217(100), 229(39), 285(12), 303(22), 402(8), 420(11), 465(64).

8: yield: 206 mg, (16%), m.p.: 205–208°C; ^{1}H-NMR: δ 1.25 (2H, m), 1.63 (2H, m), 1.85 (2H, m), 2.32 (6H, bs), 2.73 (1H, dd, J = 9.3, 4.1 Hz), 3.61 (1H, bs), 3.67 (1H, m), 3.88 (1H, m), 4.13 (1H, bs), 4.27 (1H, t, J = 2.4 Hz), 4.42 (1H, t, J = 2.5 Hz), 5.58 (2H, bs), 6.84 (6H, m), 7.05 (4H, m), 7.25 (6H, m), 7.52 (2H, d, J = 7.5 Hz), 7.60 (2H, d, J = 7.5 Hz). ^{13}C-NMR: δ 22.48, 23.88, 26.96, 44.11 [$N(CH_3)_2$], 61.29, 67.55 (Fc), 68.13 (Fc), 68.61 (Fc), 68.77 (Fc), 76.02 (Fc), 76.30 (Fc), 78.24, 78.31, 85.90 (Fc), 90.99 (Fc), 94.36 (Fc), 94.42 (Fc), 126.46 (Ph), 126.60 (Ph), 126.63 (Ph), 126.75 (Ph), 126.82 (Ph), 126.85 (Ph), 127.27 (Ph), 127.31 (Ph), 127.43 (Ph), 127.62 (Ph), 146.26 (Ph), 146.85 (Ph), 146.92 (Ph), 146.99; MS (210°C) m/e (rel.%): 283(53), 301(19), 316(18), 394(66), 395(22), 465(25), 600(3), 628(5), 646(100).

When the reaction was carried out with (−)(R) **4**, the (+)(R) enantiomer of **6**, and the (−)(R) enantiomer of **7** were obtained; **6**: $[\alpha]_D^{20}$ + 136.7° (c: 1.195); CD λ ($\Delta\epsilon$): 244 (−0.70), 264(+2.66), 292(−0.31), 312(+0.04), 350(−0.10), 464(+0.35). **7**: $[\alpha]_D^{20}$ − 212.3° (c: 1.204); CD λ ($\Delta\epsilon$): 259(−3.60), 334(+0.27), 446(−0.52).

3.4. *1-Hydroxymethyl-2,3-(α-N,N-dimethylaminotetramethylene)-ferrocene (9), 1-hydroxymethyl-1′,2′-(α-N,N-dimethylaminotetramethylene)-ferrocene(10) and 1,1′-bis(hydroxymethyl)-2,3-(α-N,N-dimethylaminotetramethylene)-ferrocene (11)*

9, **10** and **11** were prepared in the same way as **6–8** from 500 mg (1.76 mmol) of **4**, 2.92 ml of ^{n}BuLi (1.6 molar) and 210 mg (7.04 mmol) of paraformaldehyde. The reaction was quenched after 1 h. Chromatography of the crude mixture on silica gel [column: 1.5 × 45 cm, 40–63 μm, petroleum ether/ethylacetate/triethylamine, (40/55/5)] afforded the aminoalcohols **9**, **10** and **11** in 210 mg (40%), 65 mg (12%) and 96 mg (16%) yield, respectively. **9**: oil, ^{1}H-NMR: δ 1.45 (1H, m), 1.92 (3H, m), 2.23 (1H, ddd, J = 15.6, 6.0, 3.2 Hz), 2.61 (1H, m), 2.61 (6H, s), 3.35 (1H, dd, J = 9.4, 4.8 Hz), 4.03 (1H, d, J = 2.4 Hz), 4.08 (1H, d, J = 2.4 Hz), 4.10 (5H, s), 4.17 (1H, d, J = 13.1 Hz), 4.30 (1H, d, J = 13.1 Hz). ^{13}C-NMR: δ 20.75, 23.29, 24.47, 45.08 [$N(CH_3)_2$], 59.82 (C–OH), 60.11, 64.64 (Fc), 66.11 (Fc), 70.27 (Fc), 84.76 (Fc), 85.23 (Fc), 86.76 (Fc). MS (120°C) m/e (rel.%): 131(100), 163(33), 239(39), 268(76), 283(38), 313(49). Anal. Found: C 64.98, H 7.51, N 4.56. $C_{17}H_{23}FeNO$ calc.: C 65.19, H 7.40, N 4.47%.

10: oil; ^{1}H-NMR: δ 1.46 (1H, m), 1.95 (3H, m), 2.32 (1H, ddd, J = 15.5, 6.1, 3.8 Hz), 2.53 (6H, s), 2.65(1H, m), 2.79 (1H, m), 3.91 (1H, m), 3.95 (1H, dd, J = 2.4, 1.0 Hz), 4.08 (3H, m), 4.13 (1H, m), 4.19 (1H, m), 4.30 (1H, d, J = 13.6 Hz), 4.34 (1H, d, J = 13.6 Hz). ^{13}C-NMR: δ 22.11, 24.40, 28.74, 45.13 [$N(CH_3)_2$], 59.25 (C–OH), 61.36, 65.68 (Fc), 65.73 (Fc), 66.00 (Fc), 66.64 (Fc), 67.51 (Fc), 68.38 (Fc), 70.13 (Fc), 85.62 (Fc), 90.56 (Fc), 92.16 (Fc); MS (60°C) m/e (rel.%): 134(56), 171(86), 191(34), 215(13), 237(27), 251(45), 269(100), 283(9), 313(76).

11: oil; ^{1}H-NMR: δ 1.37 (1H, m), 1.89 (3H, m), 2.22 (1H, ddd, J = 3, 6.3, −15.8Hz), 2.45 (6H, s), 2.56 (1H, m), 2.73 (1H, dd, J = 4.4, 9.8 Hz), 3.85 (1H, m), 4.01 (3H, m), 4.07 (1H, m), 4.18 (3H, m), 4.30 (2H, m), 5.18 (2H, bs); ^{13}C-NMR: δ 22.49, 23.72, 28.69, 45.04 [$N(CH_3)_2$], 58.41 (C–OH), 58.75 (C–OH), 61.49, 66.17 (Fc), 66.47 (Fc), 66.54 (Fc), 67.24 (Fc), 69.64 (Fc), 70.91 (Fc), 86.13 (Fc), 87.37 (Fc), 88.80 (Fc), 90.86 (Fc); MS (70°C) m/e (rel.%): 188(100), 215(8), 251(21), 280(42), 298(33), 325(7), 343(52).

When the reaction was carried out with (−)(R) **4**, the (−)(R) enantiomers of **9** and **10** were obtained; **9**: $[\alpha]_D^{20}$ −66.3° (c: 1.655); CD λ ($\Delta\epsilon$): 275(+0.10), 293(−0.33), 333(+0.08), 478(−0.12). **10**: $[\alpha]_D^{20}$ −24.1° (c: 0.815); CD λ ($\Delta\epsilon$): 273(+0.88), 299(−0.06), 334(+0.12), 460(−0.20).

3.5. *Crystal structure determination of 4-T*

Dark-yellow crystals were grown from methanol. A specimen of dimensions 0.5 × 0.3 × 0.3 mm was used. Diffraction data were collected at low temperature [89(1) K] on a modified STOE diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71069 Å). Unit cell parameters were obtained by least squares refinement against the setting angles of 55 reflections with $7° \le 2\delta \le 16°$. Crystals are monoclinic, space group $P2_1$, with 2 formula units ($C_{20}H_{27}FeNO_6$, formula weight 433.3) in the unit cell: a = 9.816(14) Å, b = 8.974(15) Å, c = 11.334(12) Å, β = 105.84(8)°, V = 959.4(0.9) Å^3, d_{calc} = 1.50 gcm^{-3} (calculated from the 89 K unit cell dimensions, $F(000)$ = 456 e.

Intensity data (ω-scan, $\Delta\omega = 1.5°$) were collected for two octants of reciprocal space ($-13 \leq h \leq 13$, $0 \leq k \leq 12$, $0 \leq l \leq 15$, $5.5° \leq 2\theta \leq 55°$), yielding 2756 observed, 2645 unique ($R_{int} = 0.023$) and 2554 significant [$F_{obs} > 4\sigma(F)$] structure factors. Lp correction and an empirical absorption correction ($\mu = 0.82$ mm^{-1}, and program DIFABS) were applied to the data. The structure was solved with direct methods and refined with least-squares, including anisotropic atomic displacement parameters (a.d.p) for all non-hydrogen atoms. H-atoms were included at calculated positions ('riding'), with fixed isotropic a.d.p., with the exception of H-atoms attached to N or O [H(N1), H(O3), H(O4), H(O6)], which were all observed in a ΔF-Fourier synthesis and refined with isotropic a.d.p. $R = 0.032$, $R_w = 0.044$ [$w_i = 1/\sigma^2(F)$] for 270 parameters and 2554 observations. A final difference electron density map showed features up to 0.4 e/Å^3 and down to -0.34 e/Å^3. Computer programs are listed [15].

3.6. Crystal structure determination of 6

Conditions analogous to the structure determination of **4**.T: Orange-red crystals grown from chloroform/ethanol, crystal size 0.4 × 0.3 × 0.3 mm, data collection temperature 88(1) K. Unit cell parameters from 57 reflections with $7° \leq 2\theta \leq 11°$. Crystals are tetragonal, space group $P4_12_12$, with 8 formula units ($C_{29}H_{31}FeNO$, formula weight 465.4) in the unit cell: $a = 9.819(7)$ Å, $c = 48.28(4)$ Å, $V = 4655(1)$ Å^3, $d_{calc} = 1.33$ gcm^{-3} (at 98 K), $F(000) = 1968$ e.

Owing to the large unit cell repeat along c, a very narrow aperture had to be placed in front of the detector during intensity data collection, resulting in a partial cutoff for some of the reflections. Intensity data (ω/θ-scan, $\Delta\omega = 1.2°$) collected for one octant of reciprocal space ($0 \leq h \leq 10$, $0 \leq k \leq 10$, $0 \leq l \leq 51$, $5.5° \leq 2\theta \leq 45°$), yielding 2671 observed, 1512 significant [$F_{obs} > 4\sigma(F)$] structure factors. Lp correction and an empirical absorption correction ($\mu = 0.67$ mm^{-1}, program DIFABS). All H-atoms riding at calculated positions except H(N1), which was observed and refined (isotropic a.d.p.).

$R = 0.067$, $R_w = 0.081$ [$w_i = 1/\sigma^2(F) + 0.0031\ F^2$] for 205 parameters and 1512 observations. Features up to 0.7 e/Å^3 and down to -0.6 e/Å^3 in a final ΔF-Fourier synthesis.

Lists of H-atom coordinates, thermal parameters and structure factors are available from the authors.

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