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Ring−Chain Tautomerism of the Novel 2-Ferrocenyl-2,4-dihydro-1*H*-3,1-benzoxazine

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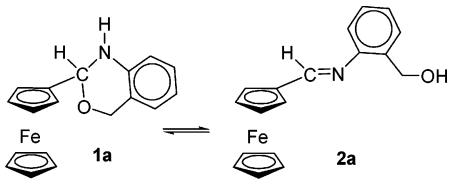
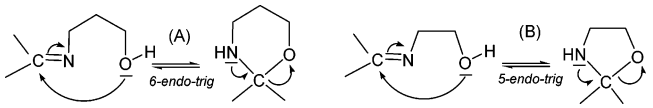


The synthesis and the study of the spectroscopic and electrochemical properties as well as the solution behavior of the novel 2-ferrocenyl-2,4-dihydro-1*H*-3,1-benzoxazine (**1a**) are described. NMR studies reveal the existence of a tautomeric equilibria between the cyclic (**1a**) and the open-chain form (**2a**). Electrochemical studies based on cyclic voltametry and ^{57}Fe Mössbauer spectroscopy as well as a comparative study of the ring-chain tautomerism of **1a** and that of 2-phenyl-2,4-dihydro-1*H*-3,1-benzoxazine (**3a**) are also reported.

The study of the ring−chain tautomerism[1] involving 1,3-O,N-heterocycles has attracted great interest in the past decade.[2] In this sort of process, an imino alcohol undergoes a reversible intramolecular C−H addition of the −OH group to the >C=N− moiety giving a 1,3-O,N-heterocycle.[1] For these systems, Baldwin[3] has established that the formation of 1,3-oxazines (via a 6-*endo-trig* process) is more favored than the 5-*endo-trig* reaction (Scheme 1), which would lead to oxazolidines. Besides that, it has been proven that this sort of tautomerism affects the reactivity of the two species involved in the process.[1,2] This property appears to be specially important from the point of view of their potential utility in organic synthesis as well as in medical or physical chemistry.[1,2]

SCHEME 1. *Six-Endo* and *Five-Endo-Trig* Processes



On the other hand and despite (a) the wide variety of examples of ring−chain tautomerism of 1,3-oxazines reported so far,[1−2,4] (b) the increasing effort devoted to the study of the effects induced by the substituents upon this equilibria,[2] and (c) the potential utility of the incorporation of a ferrocenyl group in the backbone of the oxazines, as far as we know, oxazines holding ferrocenyl units have not been reported so far. In the view of this, and as a part of a project directed toward the synthesis of ferrocene derivatives containing two different heteroatoms with good donor abilities (i.e., N and S, O, or N′),[5] in this work we present the first example of a 3,1-benzoxazine holding a ferrocenyl group at position-2, as well as the study of the tautomeric equilibrium between the cyclic and the open-chain (Schiff base) forms.

The reaction between equimolar amounts of ferrocenecarboxaldehyde (hereinafter referred to as FcCHO) and aminobenzyl alcohol in refluxing benzene produced 2-ferrocenyl-2,4-dihydro-1*H*-3,1-benzoxazine (**1a**) (Scheme 2). These results are in sharp contrast with those obtained when FcCHO was treated with $H_2NCH(R^1)CH_2OH$ (R^1 = H, Me, or CHMe), which gave $[(\eta^5\text{-}C_5H_5)Fe\{(\eta^5\text{-}C_5H_4)CH{=}N\{CH(R^1)CH_2OH\}]$,[5b−e] in agreement with Baldwin's rules.[3]

Compound **1a** was characterized in the solid state by elemental analyses, FAB$^+$ mass spectra, infrared, visible−ultraviolet, $^{13}C\{^1H\}$ NMR, and Mössbauer spectroscopy. The elemental analyses of **1a** were consistent with the proposed formula, and its infrared spectrum showed

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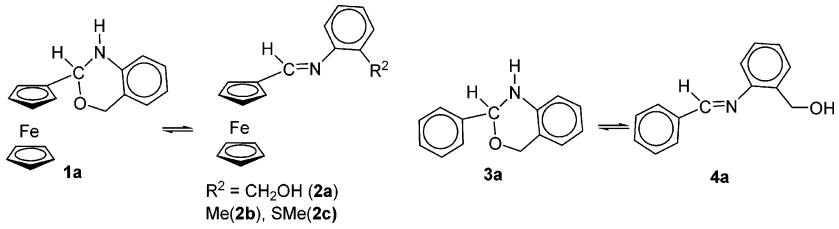
SCHEME 2. Ring−Chain Tautomeric Processes for Compounds under Study



a sharp and intense band at 3348 cm^{-1} due to the stretching of the >N−H functional group of the oxazine. The solid state $^{13}C\{^1H\}$ NMR spectrum of **1a** showed five signals in the range 60−95 ppm, of which the most intense was assigned to the carbon nuclei of the C_5H_5 ring. The resonances at $\delta = 88.4$ and 82.7 ppm were due to the *ipso*-carbon of the C_5H_4 ring and that of the −CHN< fragment of the oxazine ring, respectively, while the remaining two signals were assigned to the C^3 and C^4 nuclei of the C_5H_4 moiety. In the lower field regions the signals due to the aromatic carbon nuclei were also observed.

It is well-known that the ^{57}Fe Mössbauer spectroscopic study of ferrocene derivatives is a very useful tool to elucidate the effects induced by the substituents upon the electronic environment of the iron(II) nuclei.[6] In general, it is widely accepted that electron-donating substituents cause an increase in the quadrupole splittings (ΔE_q) relative to ferrocene, whereas electron-withdrawing groups produce a decrease in the ΔE_q parameter.[6c] Since as far as we know, **1a** is the first example of a 2-substituted [3,1]-benzoxazine bearing a ferrocenyl group, it seemed interesting to characterize it by Mössbauer spectroscopy. The ^{57}Fe Mössbauer spectrum of **1a** (Figure 1) consists of a single quadrupole

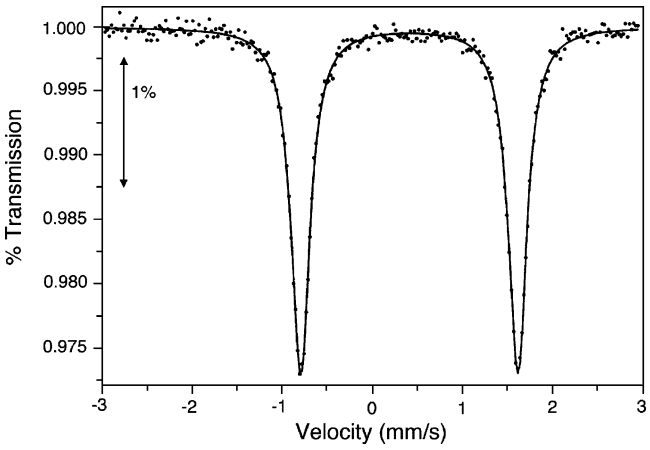


FIGURE 1. ^{57}Fe Mossbauer spectrum of **1a** at 80 K.

doublet indicating a unique iron site. For **1a**, the ΔE_q parameter is greater than those of the Schiff bases: $[(\eta^5\text{-}C_5H_5)Fe\{(\eta^5\text{-}C_5H_4)CH{=}N(C_6H_4\text{-}2\text{-}R^2)\}]$ [R^2 = Me (**2b**) or SMe (**2c**)[5f]] (Table 1), thus indicating that the oxazine

TABLE 1. ^{57}Fe Mössbauer Hyperfine Parameters (at 80 K)[a]

	1a	2b	2c
i.s.	0.489(2)	0.525(2)	0.502(2)
ΔE_q	2.408(2)	2.255(4)	2.251(4)
Γ	0.254(4)	0.237(4)	0.361(6)
E_{pa}	102	232	250
E_{pc}	23	157	191
$E_{1/2}$	62	194	184
ΔE	79	75	132

[a] Isomer shift (i.s.); quadrupole splitting (ΔE_q); full-width at half-heigth (Γ) (in mm/s) and electrochemical data (in mV) [anodic (E_{pa}), cathodic (E_{pc}), and half-wave potentials ($E_{1/2}$) (referred to the ferrocene/ferricinium couple)]; and separation of the peaks (ΔE) for **1a** and $[(\eta^5\text{-}C_5H_5)Fe\{(\eta^5\text{-}C_5H_4)\text{-}CH{=}N\text{-}(C_6H_4\text{-}2R^2)\}]$ [R^2 = Me (**2b**) or SMe (**2c**)]

moiety has a weaker electron-withdrawing ability than the >C=N− group but it is greater than that of hydrogen in ferrocene itself (ΔE_q = 2.41 mm/s at 80 K). These findings suggest that the electron-withdrawing ability of the substituents in the three cases increases according to the sequence H ≤ 3,1-benzoxazine < $CH{=}N(C_6H_4\text{-}2\text{-}R^2)$.

Proton and $^{13}C\{^1H\}$ NMR spectra of **1a** in acetone-d_6 at 300 K showed two sets of superimposed signals. One of them agreed with those expected for the 2-substituted [3,1]-benzoxazine, while the remaining group of resonances was consistent, according to the literature,[5] with the presence of the Schiff base: $[(\eta^5\text{-}C_5H_5)Fe\{(\eta^5\text{-}C_5H_4)\text{-}CH{=}N(C_6H_4\text{-}2\text{-}CH_2OH)\}]$ (**2a**), thus suggesting the coexistence of the ring (**1a**) and open-chain (**2a**) tautomers in solution. The relative proportions **1a/2a** were determined by integration of the well-separated signals due to the protons of the "N−CH(ring)-O" (for **1a**) and that of the imine group (in **2a**). In all cases, the samples were dissolved in the appropiate deuterated solvent and the solutions were allowed to stand for some time to be sure that the equilibria were reached. To elucidate whether the extent of the tautomeric equilibria would be tuned by the solvent, the ^{1}H NMR spectra were also registered at 300 K in methanol-d_4 and benzene-d_6. The results obtained[7] revealed that the equilibrium is solvent dependent and the percentage of the open-chain form (**2a**) increased according to the sequence benzene-d_6 < acetone-d_6 < methanol-d_4, thus suggesting that the ring form is less favored in solvents with greater dielectric constants.[8] This finding is consistent with the results obtained for related organic oxazines. The spectrum of a freshly

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(7) Molar ratios **1a/2a** in benzene-d_6 = 13.7, acetone-d_6 = 2.50, methanol-d_4 = 0.5, and DMSO-d_6 = 1.1 at 300 K.

(8) *Handbook of Chemistry and Physics*, 84th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, 2004.

(9) Molar ratios **3a/4a** = 14.1 (benzene-d_6), 7.4 (acetone-d_6), and 2.2 (methanol-d_4).

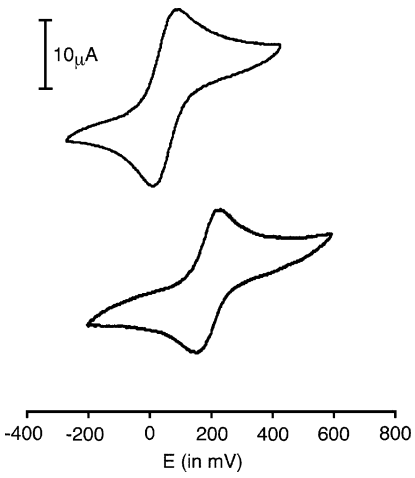

FIGURE 2. Cyclic voltammograms of 10^{-3} M solutions of **1a** (top) and [(η^5-C_5H_5)Fe{(η^5-C_5H_4)-CH=N-(C_6H_4-2SMe)}] (bottom) in CH_3CN at 20 °C and a scan speed = 100 mV/s.

prepared solution of **1a** in $CDCl_3$ showed a **1a/2a** molar ratio = 3.0, but after 5 h of storage at 300 K the ^{1}H NMR spectrum revealed the presence of **1a**, **2a**, and FcCHO in a 27.7:10.2:1.0 ratio, thus indicating that partial hydrolysis of the imine form occurred in solution.

Previous studies on ring−chain tautomeric equilibria of 2-aryl-substituted benzoxazines have shown that the ratio between the ring and open-chain forms are strongly dependent on the electronic character of the substituents.[2,4] To compare the effects induced by the substituents on position-2 of the oxazine ring on the tautomeric equilibria we performed a parallel study with 2-phenyl-2,4-dihydro-1*H*-3,1-benzoxazine (**3a**). The results obtained showed that the proportion **3a/4a** decreased according to the sequence benzene-d_6 > acetone-d_6 > methanol-d_4.[9] This trend is similar to that found for the system **1a** ↔ **2a**, but the comparison of the ratios [ring form/open-chain form] obtained in the polar solvents revealed that the replacement of the phenyl group by a ferrocenyl moiety produces a significant displacement of the equilibria to the Schiff base form. Some authors have reported that for 2-phenyloxazolidines and -perhydro-1,3-oxazines the influence of the substituents on the aryl ring upon the relative stability of the tautomers is controlled by several electronic effects, among which the intramolecular hydrogen bonding between the OH group and the imine nitrogen together with the polarization of the >C=N− link appear to be particularly important.[2e,f] The replacement of the phenyl group in **3a** and **4a** by the ferrocenyl unit, which has a stronger electron-donor ability,[10] introduces significant variations on the electronic density on the imine nitrogen, which would affect the strength of the intramolecular N···OH bond. The variations observed in the chemical shifts of the ^{13}C nuclei of the $-CH_2-$ moiety for the two imine forms (**2a** and **4a**) also support this hypothesis.

Electrochemical data for **1a** were obtained from cyclic voltammetric studies of freshly prepared solutions (10^{-3} M) in CH_3CN using $(Bu_4N)[PF_6]$ at different scan rates, ν {from 0.05 to 1.0 V s^{-1}}. The cyclic voltammogram of **1a** (Figure 2) exhibited an anodic peak with a directly associated reduction in the reverse scan and the I_{pa}/I_{pc} molar ratios were close to 1.

All these findings are consistent with those expected for a simple reversible one-electron-transfer process. For **1a**, the ΔE value departs from the constant value of 59 mV (theoretically expected for an electrochemically reversible one-electron step oxidation−reduction process[11]), suggesting that a structural reorganization takes place on oxidation and the half-wave potential $E_{1/2}$ is smaller than the values reported for [(η^5-C_5H_5)Fe{(η^5-C_5H_4)CH=N(C_6H_4-2-R^2)}] [R^2 = Me (**2b**) or SMe (**2c**)[5f]] (Table 1).

Since the ^{1}H NMR spectrum of **1a** in acetonitrile-d_3 revealed that in this solvent the tautomeric equilibria is strongly displaced toward the cyclic form, the results obtained from the electrochemical studies are consistent with the better donor ability of the oxazine ring, when compared with that of the imine moiety in good agreement with the results obtained from the Mössbauer studies.

In summary, the studies presented have allowed (a) the preparation and characterization of the first example of a new type of 3,1-benzoxazines holding a ferrocenyl group and (b) the elucidation of the effect induced by the binding of the oxazine moiety upon the environment of the iron(II) as well as the relative importance of the presence of a ferrocenyl (in **1a**) or a phenyl (in **3a**) substituent in position 2 on the extent of the tautomeric equilibria. In particular, for a given solvent, the higher electron-donor ability of the ferrocenyl moiety produces a greater displacement of the tautomeric equilibria to the Schiff base form (**2a**) than its analogue holding a phenyl group. Besides that, ^{1}H NMR studies of **1a** in $CDCl_3$ revealed that the imine form (**2a**) degraded slowly, thus suggesting that **2a** is more prone to hydrolyze and consequently less stable than **4a** (which arises from **2a** by replacement of the "(η^5-C_5H_4)Fe(η^5-C_5H_4)" moiety by a phenyl ring) in $CDCl_3$.

Experimental Section

2-Ferrocenyl-2,4-dihydro-1*H*-3,1-benzoxazine (1a). A suspension formed by FcCHO (2.70 g, 12.6×10^{-3} mol) and 50 mL of benzene was stirred at 20 °C for 20 min and filtered out. Then aminobenzyl alcohol (1.55 g, 12.6×10^{-3} mol) was added to the filtrate. The reaction flask was connected to a condenser equipped with a Dean−Stark apparatus, and the mixture was refluxed until ca. 15 mL of the benzene−water azeotrope had condensed on the Dean−Stark apparatus. The hot solution was then filtered out and concentrated to dryness on a rotary evaporator. The gummy residue was treated with diethyl ether and stirred at 20 °C for ca. 30 min. The yellow solid formed was collected by filtration, air-dried, and then dried in a vacuum for 2 days (yield: 3.62 g, 85%). Anal. Calcd for $C_{18}H_{17}NOFe$: C, 67.73; H, 5.37; N, 4.39. Found: C, 67.7; H, 5.6; N, 4.4. MS (FAB^+) m/z = 319 $[M]^+$. IR: 3348 cm^{-1}, ν (>NH). Solid-state $^{13}C\{^1H\}$ NMR data: δ = 66.2 (C^4), 67.8 (C^3), 70.3 (C_5H_5), 82.8 (>CHN−), 88.1 (C^1), 119.4 ($C^{4'}$and $C^{6'}$), 122.8 ($C^{2'}$), 124.3 ($C^{3'}$), 127.1 ($C^{5'}$), 141.5 ($C^{1'}$), in this case the signals due to the carbon-13 nuclei of the $-CH_2-$ moiety and of the pair (C^2 and C^5) were masked by the signal due to the C_5H_5 fragment. UV−vis data of a solid sample: λ_{max} (in nm) = 455 and 277 and of a 1×10^{-4} M solution of **1a** in CH_3OH: λ_{max} (in nm) = 462 (log ϵ = 2.8), 334 (sh, log ϵ ~ 3.4), and 290 (log ϵ = 3.9).

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Supporting Information Available: $^{13}C\{^1H\}$ NMR spectrum of a solid sample of **1a** (Figure S1), $\{^1H-^1H\}$ NOESY spectra of the solutions obtained after disssolution of **1a** (in benzene-d_6) (Figure S2) and **3a** (in $CDCl_3$) (Figure S3); tables containing ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data for **1a**−**4a**, (at 300 K) in several deuterated solvents (Tables S1−S4); characterization data for **2b** and **2c** (Table S5), and a detailed description of the materials and methods used. This material is available free of charge via the Internet at http://pubs.acs.org.

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