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**Research Article**

# Efficient synthesis of deuterium-labelled ferrocenes

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## Summary

An efficient method for the synthesis of perdeuterated ferrocene (ferrocene-$d_{10}$), 1,1′-dimethyloctadeuteroferrocene, 1-ethylnonadeuteroferrocene, 1,1′-diethyloctadeuteroferrocene, 1-deuteroacetylferrocene, 1,1′-deuterodiacetylferrocene, 1-acetylnonadeuteroferrocene and 1,1′-diacetyloctadeuteroferrocene is described, using acid-catalysed exchange reactions, where the deutero reagent can be generated *in situ* from trifluoroacetic anhydride (TFAA) and $D_2O$. Copyright © 2005 John Wiley & Sons, Ltd.

**Key Words:** ferrocene; perdeuterated ferrocene; deuterium exchange

## Introduction

Ferrocenes have in recent years gained increasing interest as building blocks for molecular magnets,[1] biosensors,[2] catalysts[3,4] and as diagnostic agents.[5] Ferrocene **1** (Figure 1) is attractive as a possible electron donor building block and shows a high molecular mobility at ambient temperatures.[6,7]

It has been found that in complexes with other mobile molecules, ferrocene shows interesting mobility properties.[8] Hence the use of perdeuterated ferrocene **2** (ferrocene-$d_{10}$, Figure 1) and comparing with the parent ferrocene **1** (ferrocene-$h_{10}$) can help to separate various contributions to molecular interactions and therefore, more clearly explain properties of materials.

Forty years ago Fritz and Schafer[9] reported on the synthesis of perdeuterated ferrocene **2** using repeated acid-catalysed exchange (six exchanges) by $D_3PO_4$. Base-catalysed[10] exchange with $Ca(OD)_2$ at elevated temperature led to high ferrocene loss and poor yields. A recent study[11] in our laboratory reported on an apparently promising acid-catalysed deuterium exchange of ferrocene with $D_2O$–trifluoroacetic anhydride (TFAA) at moderate temperature to obtain the perdeuterated compound **2** after four

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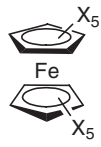
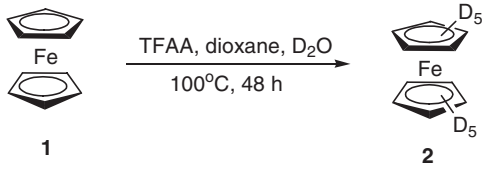



X = H = Ferrocene-$h_{10}$
X = D = Ferrocene-$d_{10}$

**Figure 1.**




**Scheme 1.**

exchanges with a yield of 90% per exchange. We now report here the result of an improved and efficient synthetic strategy based on the acid-catalysed deuterium exchange of ferrocene, which allows for near complete exchange in only two cycles. The application of the method in the deuterium exchange of ferrocene derivatives bearing electron donating substituents or electron withdrawing substituents is also discussed.

## Results and discussion

In the preceding study[11] the deuteration was conducted in a sealed thick-walled glass tube, but experience has shown that the reaction can be successfully carried out in a two-necked flask under an atmosphere of nitrogen. In the present paper we address this technique by conducting several acid-catalysed deuterium exchange reactions of ferrocenes under homogenous conditions (Scheme 1).

In the previous report[11] the concentration of the reagents used, required four exchanges to achieve a deuterium enrichment of 95%, with a chemical yield of 90% observed for each step. We investigated the effect of reagent concentration and have found that at higher concentrations than previously used, the deuterium exchange is enhanced significantly.

Furthermore, additional experiments have shown that a mere twofold increase in the deutero reagent concentration allows for a smooth and fast exchange, with the result that only two successive exchanges are required to prepare perdeuterated ferrocene **2** in good yield (Table 1).

**Table 1. Concentration effect on the deuterium exchange of ferrocene in TFAA–$D_2O$ system**

| Ferrocene (equiv.) | $D_2O$ (equiv.) | TFAA (equiv.) | 1,4-dioxane (equiv.) | First exchange | | Second exchange | |
|---|---|---|---|---|---|---|---|
| | | | | Yield (%) | D-content (%) | Yield (%) | D-content (%) |
| 1 | 10.50 | 13.38 | 30.03 | 87 | 74 | 95 | 95 |
| 1 | 10.50 | 6.69 | 16.92 | 98 | 78 | 98 | 96 |

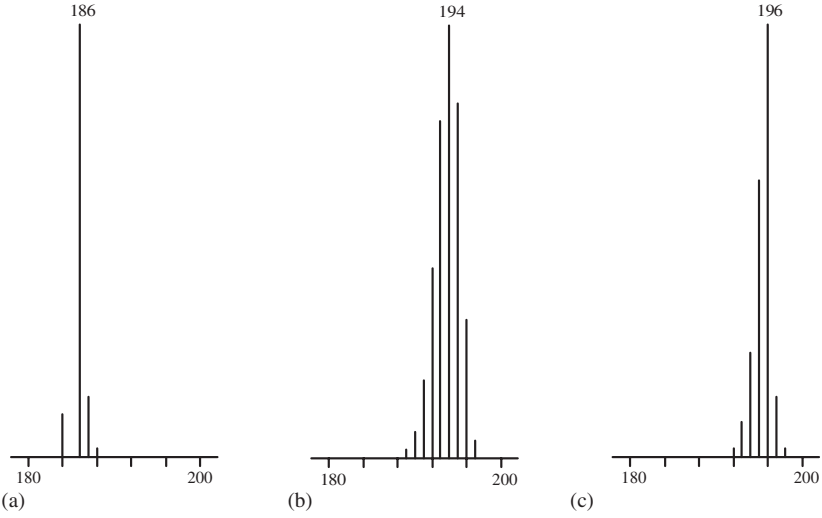


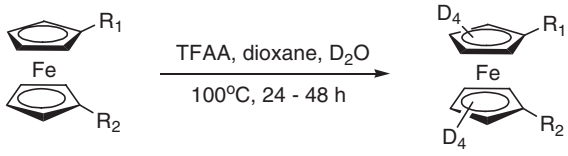

**Figure 2. High-mass part of GC-mass spectra of (a) ferrocene-$h_{10}$, (b) the first deuterium exchange and (c) the second deuterium exchange. The intensities are in arbitrary units**

The mass spectrum of **2** exhibits a molecular peak at *m*/*e* 196 and a second peak at *m*/*e* 126 corresponding to the $C_5D_5Fe^+$ fragment. Comparison of this mass spectrum with that of ferrocene-$h_{10}$ (Figure 2(a)) reveals that the former decadeuteroferrocene **2** is statistically composed of 56–57% ferrocene-$d_{10}$, 31–33% ferrocene-$d_9$ and 11–13% ferrocene-$d_8$ plus other isotopomers present in negligible amounts.

Examination of the mass spectra of deuterated ferrocene after each stage, one can conclude that 74–78% of the protons were exchanged in the first reaction (Figure 2(b)) and 95–96% after the second treatment with TFAA–$D_2O$ (Figure 2(c)).

Literature[12] indicated no proton signals were observed for compound **2** by $^1H$ NMR ($CDCl_3$) and the $^{13}C$ NMR ($CDCl_3$) showed only one signal at




**3**, $R_1 = R_2 = CH_3$
**5**, $R_1 = CH_2CH_3$, $R_2 = H$
**7**, $R_1 = R_2 = CH_2CH_3$

**4**, $R_1 = R_2 = CH_3$
**6**, $R_1 = CH_2CH_3$, $R_2 = D$
**8**, $R_1 = R_2 = CH_2CH_3$

**Scheme 2.**

**Table 2. Effect of donor substituents on deuterium exchange of ferrocene**

| Substituent | Duration of heating at 100°C (h) | Deuteriun content (%) |
|---|---|---|
| Ferrocene | $2 \times 48$ | 96 |
| 1,1′-dimethyl- | $2 \times 24$ | 96.5 |
| 1,1′-diethyl- | $1 \times 48$ | 92.0 |
| Ethyl- | $1 \times 48$ | 88.0 |

76.90 ppm. In the present study, the $^1$H NMR ($CDCl_3$) spectrum shows a small signal for the remaining undeuterated protons at 4.2 ppm while the $^{13}$C NMR ($CDCl_3$) for compound **2** have a multiplet dominated by a triplet at 67.32 ppm.

The utility of this method was next further evaluated in substituted ferrocenes, with electon donating groups (Scheme 2).

The results as shown in Table 2, showed a high degree of exchange was achieved in ferrocenes containing electron donating groups.

Thus 1,1′-dimethyloctadeuteroferrocene **4** was obtained from 1,1′-dimethylferrocene **3** by two exchange steps ($2 \times 24$ h) with a yield of 90–93% per exchange. This was confirmed by mass spectrometry, which showed a molecular ion at *m/e* 222 and additional peaks at *m/e* 139 and 83 corresponding to $C_5D_4CH_3Fe^+$ and $C_5D_4CH_3^+$ fragments, respectively. The $^1$H NMR spectrum of **4** showed a high intensity singlet at 1.98 ppm due to the undeuterated $CH_3$-groups. The presence of a very small resonance at 4.05 ppm is due to the presence of about 3.5% residual undeuterated protons of the cyclopentadienyl rings, which is in good agreement with GC/MS data, which indicates that 96.5% exchange is achieved.

In a similar manner, as shown in Scheme 2, acid-catalysed deuterium exchange of 1-ethylferrocene **5** and 1,1′-diethylferrocene **7** at 100°C for 48 h gave the deuterated compounds **6** and **8** with 88 and 92% deuterium contents, respectively.

Attempts to promote exchange under mildly basic conditions (refluxing in pyridine–$D_2O$ solution) were unsuccessful as no deuterium exchange was observed for the cyclopentadienyl protons in methylsubstituted ferrocene.[13]

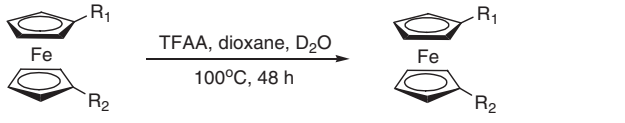
It is known[14] that the effect of electron-donor and electron-acceptor substituents on the electron density distribution in a molecule of ferrocene type is governed by the ratio of contributions of inductive, conjugative and hyperconjugative effects to the total electronic effect of the substituents. The electron-donor inductive effect increases from methyl to ethyl, while the hyperconjugation effect operates in the opposite direction. This agrees with our results of the electrophilic deuterium substitution of ferrocene, where the high (96.5%) deuterium exchange was achieved for dimethyl-substituted ferrocene **4**, slightly lower for diethyl (92%) **8** and lower still (88%) for monoethyl-substituted ferrocene **6**.

Slocum *et al.*[13] examined the base-promoted deuterium exchange of several ferrocene systems and reported that some of the electron-withdrawing substituents, particularly acetyl- and 1,1′-diacetyl- are capable of activating the ferrocene ring toward the electrophilic deuterium exchange and only the cyclopentadienyl ring bearing the substituent were exchanged in mono-substituted ferrocene. Hence in order to ascertain the influence of electron-withdrawing substituents on the acid-catalysed electrophilic deuterium exchange and to compare with that of electron-donating groups, acetylferrocene **9** and 1,1′-diacetylferrocene **11** (Scheme 3) were subjected to acid-catalysed deuterium exchange reactions in a one pot reaction at 100°C for 46 h.

No exchange for the cyclopentadienyl ring protons of acetylferrocene **10** and 1,1′-diacetylferrocene **12** was observed, however incorporation of deuterium into the acetyl group was seen as evidenced by signals at *m*/*e* 231 for **10** and *m*/*e* 276 for **12** in the GC/MS. This conclusion was supported by $^{1}H$ and $^{13}C$ NMR spectrometry.

Furthermore, we found that Friedel–Crafts acetylation of ferrocene is applicable to synthesize deuterated ferrocene derivatives, which one would normally consider difficult to synthesize by direct exchange on ferrocene (Scheme 4).

Thus, acetyldeuteroferrocene **13** and 1,1′-diacetyldeuteroferrocene **14** were obtained successfully by the Friedel–Crafts acetylation of perdeuterated ferrocene **2** in good yields.

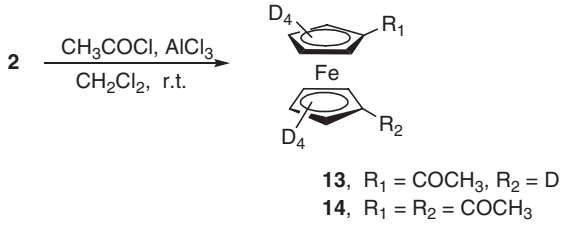



**9**, $R_1 = COCH_3$, $R_2 = H$
**11**, $R_1 = R_2 = COCH_3$

**10**, $R_1 = COCD_3$, $R_2 = H$
**12**, $R_1 = R_2 = COCD_3$

**Scheme 3.**




**Scheme 4.**

## Conclusion

We have found that acid-catalysed deuterium exchange using the TFAA–$D_2O$ system is an attractive, mild and widely applicable deuteration method for several ferrocenes. The deutero reagent can be generated *in situ* by simple mixing of TFAA and $D_2O$ in an open vessel under inert atmosphere at a high deuterium reagent concentration which results in fewer exchange steps and higher yields. The nature of substituents plays an important role in directing the site of deuteration. Electron donating substituents, such as alkyl groups promote selective deuteration in the cyclopentadienyl ring. In contrast, in ferrocenes containing electron-withdrawing groups, such as acetyl, incorporation of deuterium is confined to the acetyl group. However acetyl perdeuterated ferrocene can be synthesized indirectly by the Friedel–Crafts acetylations of perdeuterated ferrocene.

## Experimental

### *Materials*

Ferrocene, TFAA, $D_2O$ and 1,1′-dimethylferrocene were commercial samples and used as received. HPLC 1,4-dioxane was predried prior to use. Acetylferrocene **9** and 1,1′-diacetylferrocene **11** were prepared by Friedel–Crafts acetylations of ferrocene.[15] 1-Ethylferrocene **5** and 1,1′-diethylferrocene **7** were obtained as described in the literature.[16,17] Column chromatography was carried out using silica gel Kieselgel 60 type Merk (0.015–0.040 mm). Mass-spectra analyses were performed on VG MassLab 12-250 GC-mass spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded on a 400 MHz NMR (Bruker) spectrometer (400 MHz for $^1H$ NMR and 100 MHz for $^{13}C$ NMR) in deuterochloroform, using TMS as internal standard.

### *Perdeuterated ferrocene (**2**) (general procedure)*

A solution of ferrocene (8 g, 43.01 mmol) in dry 1,4-dioxane (62 ml) was treated with TFAA (40 ml). Subsequently, $D_2O$ (9.0 g, 450 mmol) was added dropwise with stirring at 10°C under an argon atmosphere. The brown mixture

was heated at 100°C for 48 h, cooled to ambient temperature, poured into ice-water (400 ml) and extracted with diethyl ether ($4 \times 200$ ml). The organic portions were separated and carefully washed with an aqueous solution of $K_2CO_3$, water and finally dried over anhydrous $MgSO_4$. The organic solvent was evaporated to dryness under reduced pressure and the dark brown solid residue was purified by column chromatography on silica gel with *n*-hexane–ethyl acetate (10:1) to yield the partially deuterated ferrocene (78% deuterium content). The dark-orange crystals of perdeuterated compound **2** with deuterium content of 96% were obtained after a second exchange in 98% yield. It is important to note that the material should be thoroughly dried before commencing the second exchange. All exchange products were identified by GC-MS. The GC-MS of the partially deuterated ferrocene after the first exchange shows signals at *m*/*e* 197 (3%), 196 (33%), 195 (81%), 194 (molecular ion, 100%), 193 (78%), 192 (44%), 191 (18%), 190 (6%), 189 (1%), 186 (0%), 127 (2%), 126 (36%), 125 (48%) and 56 (58%), while the GC-MS of **2** after the second exchange shows *m*/*e* 198 (2%), 197 (14%), 196 (molecular ion, 100%), 195 (64%), 194 (25%), 193 (8%), 192 (2%), 191 (<1%), 186 (0%), 128 (0.5%), 127 (5%), 126 (55%), 125 (18%), 124 (6%), 123 (1%), 122 (1%) and 56 (58%). GC-MS of ferrocene-$h_{10}$: *m*/*e* 188 (1%), 187 (14%), 186 (molecular ion, 100%), 184 (10%), 121 (48%) and 56 (31%).

### *1,1′-Dimethyloctadeuteroferrocene (**4**)*

This compound was synthesized by the deutero-exchange of 1,1′-dimethylferrocene **3**, as described for **2** at 100°C for 24 h. The first exchange gave 1,1′-dimethyldeuteroferrocene in 93% yield with 84% deuterium content. The second exchange gave the perdeuterated compound **4** in 90% yield with 96.5% deuterium content. $^1$H NMR ($CDCl_3$) δ: 1.98 (s, 6H, $CH_3$). $^{13}$C NMR ($CDCl_3$) δ: 14.23, 67.31, 69.34, 83.58. GC-MS: *m*/*e* 224 (1%), 223 (16%), 222 (molecular ion, 100%), 221 (37%), 220 (15%), 219 (4%), 218 (0.8%), 217 (<1%), 214 (0%), 140 (2%), 139 (10%), 138 (18%), 137 (15%), 136 (5.8%), 135 (1.7%), 134 (<1%), 83 (10%) and 56 (28%).

### *1-Ethylnonadeuteroferrocene (**6**)*

The same general procedure described above was followed for deuteration of ethylferrocene **5**. One exchange was enough to produce the desired 1-ethylnonadeuteroferrocene **6** in 89% yield with 88% deuterium content. The pure product was obtained after column chromatography on silica gel, eluting with *n*-hexane–diethyl ether (9:1) as an orange crystals. GC-MS: *m*/*e* 225 (1.2%), 224 (15%), 223 (molecular ion, 100%), 222 (76%), 221 (42%), 220 (26%), 219 (15%), 218 (5%), 217 (2%), 216 (<1%), 214 (<1%), 208 (44%), 207 (47%), 206 (30%), 126 (57%) and 56 (69%). $^1$H NMR ($CDCl_3$) δ: 1.26 (m,

3H, $CH_3$); 2.45 (m, 2H, $CH_2$). $^{13}C$ NMR ($CDCl_3$) δ: 14.46, 21.97, 66.83, 67.29, 68.15, 90.62.

*1,1′-Diethyloctadeuteroferrocene (**8**)*

This compound was synthesized by the deuterium exchange of 1,1′-diethylferrocene **7** as described for **6**. The yield of **8** after one exchange was 93% with a deuterium content of 92%. GC-MS: *m/e* 252 (2%), 251 (17%), 250 (molecular ion, 100%), 249 (50%), 248 (23%), 247 (10%), 246 (4%), 245 (1%), 244 (<1%), 243 (<1%), 242 (<0.5%), 235 (22%), 220 (20%), 125 (23%) and 56 (48%). $^1H$ NMR ($CDCl_3$) δ: 1.26 (m, 6H, $2CH_3$); 2.42 (m, 4H, $2CH_2$). $^{13}C$ NMR ($CDCl_3$) δ: 14.72, 21.83, 67.12, 67.63, 90.51.

*1-Deuteroacetylferrocene (**10**)*

This compound was synthesized in two exchanges from acetylferrocene **9** as described for **2**. The pure compound obtained by column chromatography on silica gel, eluting with *n*-hexane–ethyl acetate (10:3). The partially deuterated ferrocene from the first exchange was obtained in 97% yield with 95% deuterium content. This after the second exchange gave compound **10** in 91% yield and 99.5% deuterium content. GC-MS: *m/e* 233 (3.8%), 232 (25%), 231 (molecular ion, 100%), 230 (11%), 229 (8%), 228 (0%), 213 (14%), 185 (73%), 129 (47%) and 56 (39%). $^1H$ NMR ($CDCl_3$) δ: 4.50 (t, 9H, $C_5H_4$ and $C_5H_5$). $^{13}C$ NMR ($CDCl_3$) δ: 69.47, 69.73, 72.20, 79.21, 202.01.

*1.1′-Deuterodiacetylferrocene (**12**)*

This compound was synthesized by one exchange from **11** as described for **10** and purified by column chromatography on silica gel, eluting with ethyl acetate–petroleum ether (1:1). Compound **12** was formed in 53% yield and having 90% deuterium content. GC-MS: *m/e* 278 (2%), 277 (17%), 276 (molecular ion, 100%), 275 (73%), 274 (32%), 273 (10.5%), 272 (3%), 271 (<1%), 270 (0%), 258 (14%), 230 (24%), 202 (69%), 184 (12%), 120 (31%) and 56 (52%). $^1H$ NMR ($CDCl_3$) δ: 4.50 (s, 4H, $C_5H_4$), 4.76 (s, 4H, $C_5H_4$); the presence a small signal at 2.31 shows that ~10% of protons from $CH_3$ are not deuterated. $^{13}C$ NMR ($CDCl_3$) δ: 70.82, 73.46, 80.59, 201.13.

*1-Acetylnonadeuteroferrocene (**13**)*

A solution of anhydrous aluminium chloride (190 mg, 1.4 mmol) in dry dichloromethane (2 ml) was treated with acetyl chloride (110 mg, 1.4 mmol) and the mixture was stirred under nitrogen at 20°C for 30 min. To this a solution of perdeuterated ferrocene **2** (200 mg, 1.02 mmol) in dry dichloromethane (4 ml) was added dropwise (10 min) and the mixture was stirred under nitrogen at 20°C for 48 h. The mixture was poured into ice and extracted

with dichloromethane ($3 \times 20$ ml), washed with water, brine and finally dried over anhydrous $MgSO_4$. Evaporation of solvent in vacuum affords an orange solid residue. The pure product **13** was isolated as orange crystals in 63% yield after column chromatography on silica gel using petroleum ether–ethyl acetate (3:2) as eluent. Latter fractions from the column affords the dideuteroacetyl compound **14** as orange crystals in 21% yield. GC-MS of **13**: *m/e* 238 (14%), 237 (molecular ion, 100%), 236 (67%), 235 (20%), 234 (3%), 219 (37%), 194 (82%), 138 (72%), 131 (52%), 96 (32%), 71 (16%), 69 (89%), 56 (111%). $^1$H NMR of **13**: ($CDCl_3$) δ: 2.39 (s, 3H, $CH_3$). $^{13}$C NMR of **13**: ($CDCl_3$) δ: 27.41, 69.43, 69.61, 72.09, 79.12, 202.13.

*1,1′-Diacetyloctadeuteroferrocene (**14**)*

This compound was synthesized by acetylation of **2** (200 mg, 1.02 mmol) by acetyl chloride (220 mg, 2.8 mmol) in the presence of anhydrous aluminium chloride (370 mg, 2.8 mmol) in dry dichloromethane as described for compound **13**. The pure product was isolated as orange crystals in 71% yield by column chromatography as for compound **13**. GC-MS of **14**: *m/e* 279 (10%), 278 (molecular ion, 100%), 277 (45%), 276 (2%), 264 (15%), 219 (45%), 207 (72%), 131 (67%), 124 (34%), 96 (33%), 71 (34%), 69 (116%), 56 (62%). $^1$H NMR of **14**: ($CDCl_3$) δ: 2.35 (s, 6H, $2CH_3$). $^{13}$C NMR of **14**: ($CDCl_3$) δ: 27.48, 70.66, 73.31, 80.41, 200.90.

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