



Ferrocene-based Redox Enantioselective Sensors for Chiral Carboxylates

Yasmine Willener,^a Kevin Joly,^b Christopher J. Moody,^b Sarah L. Horswell,^b James H. R. Tucker^a
^a School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK
^b School of Chemistry, University of Nottingham, University Park, Nottingham, NG6 2RD, UK
 Email: yxw514@bham.ac.uk



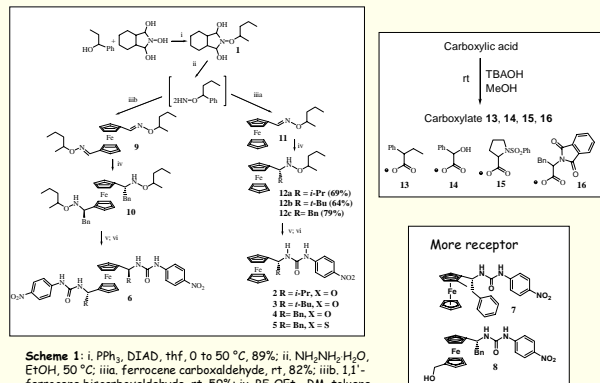
Introduction

The aim is to design redox active enantioselective sensors for a selection of chiral carboxylates. Our aspiration is to develop an electrochemical method for chiral sensing that could develop into a novel method for quantifying the enantiomeric excess (*ee*) from asymmetric reactions.

Aims & Methodology

1. Design and synthesise ferrocene-based receptors
2. Determine the binding constants of these receptors towards chiral carboxylates
3. Establish the effectiveness of these receptors as enantioselective sensors
4. Develop self-assembled monolayers of ferrocene-based sensors on gold electrodes

Synthesis of Receptor and Host Compounds



Scheme 1: i. PPh_3 , DIAD, thf , 0 to 50 °C, 89%; ii. $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH, 50 °C; iii. ferrocene dicarbonyl chloride, rt, 82%; iii.b. 1,1'-ferrocene dicarbonyl chloride, rt, 59%; iv. BF_3OEt_2 , RM, toluene, -78 °C; v. Zn dust, AcOH / H_2O , 3:2, thf traces, ultrasound, 6 h, 40 °C; vi. ArNcX, dry CH_2Cl_2 , rt.

Possible Receptor/Guest Complexes

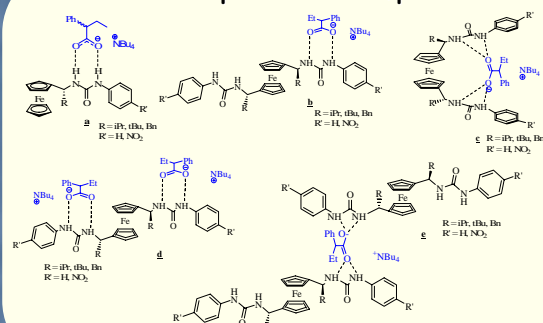


Figure 1: a-c. 1:1 complex of host/guest; d. 1:2 complex of host/guest; e. 2:1 complex of host/guest.

Binding Studies by ¹H NMR

Change in the ¹H NMR spectrum upon addition of guest carboxylates confirms binding through H-bonding interactions.



Figure 2: ¹H NMR in CD_3CN of (a) **4** (5 mM) and (b) **4** in the presence of one equivalent of (*S*)-**11** (5 mM total concentration).

¹H NMR Job Plot in CH_3CN establishing the stoichiometry as 1:1

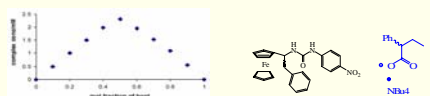


Figure 3: ¹H NMR Job plot in CD_3CN of host with (*S*)-2-phenylbutyrate guest (5 mM total concentration).

Binding Studies by Electrochemistry

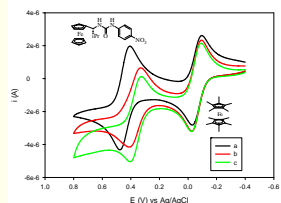


Figure 5: Cyclic voltammograms of **2** (0.55 mM) and decamethylferrocene (dmfc) (0.34 mM), in (a) the absence (b) the presence of 1 eq and (c) the presence of five equivalents of (*S*)-**11** in CH_3CN .

Although generally no significant differences in $\Delta E_0'$ was observed upon addition of an excess of either enantiomer of guest to the receptors, a difference in ΔE_{obs} (= $E_{\text{obs}} - E_0'$) host) was found for receptor **4** and guest **15** at around equimolar amounts of host and guest (see fig 6), as well as for receptor **8** and guest **16**.

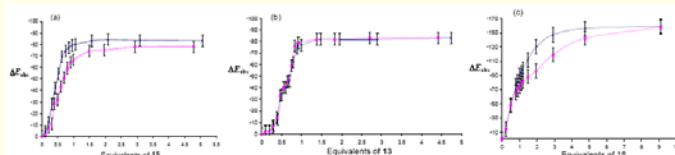


Figure 6: Titration of the ΔE_{obs} value in CH_3CN of the redox wave of (a) receptor **4** against equivalents of (*S*)-**13** (blue diamonds) and (*R*)-**15** (pink squares) (b) receptor **4** against equivalents of (*S*)-**13** (blue diamonds) and (*R*)-**13** (pink squares), (c) receptor **8** against equivalents of (*S*)-**15** (blue diamonds) and (*R*)-**16** (pink squares).

Table 2. $\Delta E_0'$ values (vs. dmfc) recorded upon complexation of various chiral carboxylates by receptors **2-8** (ca. 0.5 mM) in CH_3CN .

| Compound | $\Delta E_0'$ (vs dmfc) mV ($n = 5$ mV) | | | | | | | |
|----------|--|------------------|-----------------|-----------------|-----------------|-----------------|-------------------|-------------------|
| | (<i>S</i>)-13 | (<i>R</i>)-13 | (<i>S</i>)-14 | (<i>R</i>)-14 | (<i>S</i>)-15 | (<i>R</i>)-15 | (<i>S</i>)-16 | (<i>R</i>)-16 |
| 2 | -84 | -83 | -57 | -57 | -84 | -81 | a | a |
| 3 | -81 | -82 | -73 | -76 | -96 | -92 | a | a |
| 4 | -81 | -82 | -59 | -63 | -83 | -78 | -75 | -74 |
| 5 | -92 ^a | -93 ^a | a | a | a | a | a | a |
| 6 | -141 | -146 | -103 | -112 | -127 | -136 | a | a |
| 7 | -88 | -90 | -70 | -66 | -91 | -82 | a | a |
| 8 | -90 ^a | -88 ^a | -74 | -75 | -94 | -94 | -150 ^b | -151 ^b |

a: not determined
 b: redox wave displayed irreversible behavior upon complexation
 c: redox wave displayed irreversible behavior upon excess of guest

Binding Studies by UV-vis

Band at 337 nm decreases and band at 368 nm emerge as the 1:1 complex forms.

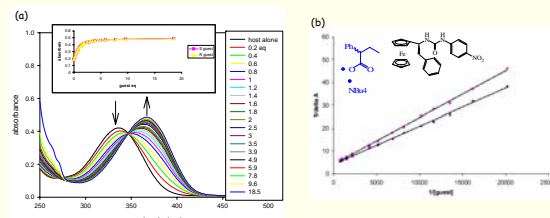


Figure 4: (a) UV-vis titration of **3** (0.025 mM) in CH_3CN against molar equivalents of (*R*)-**11**. The inset shows the increase of absorbance at 368 nm upon the addition of (*R*)- & (*S*)-**11**; (b) Benesi-Hildebrand plots for **4** with (*R*)-**11** (pink squares) and (*S*)-**11** (blue diamonds) in DMSO at 380 nm.

The Benesi-Hildebrand equation was used to obtain the binding constants. To ensure that a significant amount of complexation was only achieved in the presence of a large excess of guest (as required by this method), the solvent was changed from CH_3CN to DMSO.

Table 1. Binding constant values, $\log K$ (± 0.04) at 293 K in DMSO, obtained by UV-vis spectroscopy using the Benesi-Hildebrand method.

| Compound | $\log K$ at 293 K in DMSO (± 0.05) | | | | | | | |
|----------|--|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | (<i>S</i>)-13 | (<i>R</i>)-13 | (<i>S</i>)-14 | (<i>R</i>)-14 | (<i>S</i>)-15 | (<i>R</i>)-15 | (<i>S</i>)-16 | (<i>R</i>)-16 |
| 2 | 3.38 | 3.31 | 3.22 | 3.12 | 3.15 | 3.11 | a | a |
| 3 | 3.34 | 3.31 | 2.95 | 3.10 | 3.02 | 3.03 | a | a |
| 4 | 3.42 | 3.33 | 2.98 | 2.93 | 3.25 | 3.03 | b | b |
| 5 | 3.72 | 3.64 | a | a | a | a | a | a |
| 6 | 3.87 | a | a | a | a | a | a | a |
| 7 | 3.38 | 3.39 | a | a | 3.06 | 2.82 | a | a |
| 8 | 3.24 | 3.16 | b | b | 2.86 | 2.84 | 2.43 | 2.06 |

a: not determined
 b: no straight line

Self-Assembled Monolayers (SAMs) on Gold

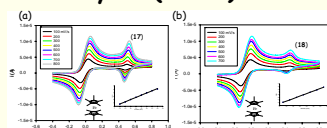
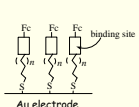


Figure 7: Cyclic voltammogram of (a) receptor **17** + dmfc (0.56 mM), and (b) receptor **18** + dmfc (0.61 mM), at different scan rates in DCM. The inset shows a linear relationship between $\log v$ and the scan rate, which confirms reversibility of the SAMs.

Studies of these SAMs on gold electrodes in the presence of guests are in progress. Better enantioselectivity could be achieved due to the forced ordering at the surface.

Conclusion

A series of chiral ferrocenylalkylureas hosts have been tuned to bind a range of chiral carboxylates guests through H-bonding interactions. Furthermore it has been shown that opposite enantiomers of guest **15** and **16** can be distinguished by electrochemical means if a suitable host is designed. These results can be largely explained through differences in binding constant values extracted from the UV-vis titrations.

References

For synthesis and electrochemistry studies, see:
 P. Laurent, H. Miyaji, S.R. Collinson, I. Prokes, C.J. Moody, J.H.R. Tucker, A.M.Z. Slawin, *Org. Lett.* **2002**, *4*, 4037 and Willener Y.; Joly K.; Moody C. J.; Tucker J. H. R. *J. Org. Chem.* **2008**, *73*, 1225.

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