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Electrochemical Method for the Determination of Enantiomeric Excess of Binol Using Redox-Active Boronic Acids as Chiral Sensors

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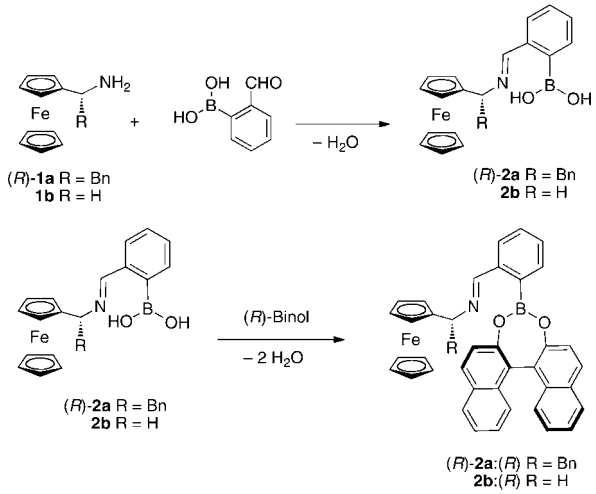
The development of convenient methods for separating and/or differentiating enantiomers has long been a challenge for chemists. Given the move toward developing single-enantiomer pharmaceuticals over racemates,[1] there is increasing interest in analytical techniques that allow the rapid determination of enantiomeric excess (ee), for example in the screening of asymmetric reactions.[2] NMR spectroscopy is an established method for determining the composition of a mixture of enantiomers through the use of chiral shift reagents.[3] However, potential drawbacks include the requirement of distinguishable NMR signals for the resulting pair of diastereomers and a high-enough concentration of the sample to allow accurate integration of these signals, particularly at high ee values. An alternative approach would be to use a reagent containing a redox-active or photoactive subunit, so that the enantiomeric composition of the mixture can be read-out at a lower concentration using, for example, electrochemistry or fluorescence spectroscopy. The electrochemical sensing of guest species by redox-active receptors is an established area of supramolecular chemistry.[4] However, there are only a handful of accounts of attempts at chiral sensing using this approach.[5] This contrasts with the many examples of chiral sensing using conceptually similar photoactive receptors that function through a colorimetric or fluorescent response.[6] As far as electrochemical approaches to chiral sensing are concerned, there has been some work involving other methodologies;[7] however, as evidenced by a recent review,[7a] until now no electrochemical system has been developed which can determine ee values in a practically useful range of 90−100%.

Boronic acids and esters have a rich pedigree in supramolecular chemistry through their ability to bind various diols and anions.[8] Furthermore, it has previously been demonstrated that substrates can be sensed electrochemically by boron-based receptors containing ferrocene groups.[4e,5d,e] Given these precedents and recent reports that chiral boronic acids can be used as NMR shift reagents for the determination of ee in enantiomeric mixtures of diols[3c] and amines,[3d] we decided to investigate the extent to which ferrocene-based chiral boronic acids can be used for chiral sensing using electrochemistry. The results of this study are presented herein where we demonstrate the determination of ee using an electrochemical method that rivals the concentrations and sensitivities found in other spectroscopy-based methods.

Scheme 1[a]



[a] Each reaction: 5 min in $CDCl_3$ (NMR experiments) and 5 min in DCM and 0.1 M TBA·PF_6 (electrochemical experiments) in the presence of 3 Å molecular sieves.

The receptor system we used was based on the chiral ferrocene amine (*R*)-**1a**, which is readily accessible in high enantiopurity.[5a] It was reacted with 2-formylphenylboronic acid to form the Schiff base adduct (*R*)-**2a**, which was then treated with each enantiomer of Binol to form the diasteromeric boronate esters (*R*)-**2a**:(*R*) and (*R*)-**2a**:(*S*) respectively (see Scheme 1 for reaction with (*R*)-Binol).

It was immediately clear by ^{1}H NMR spectroscopy in $CDCl_3$ that the geometries of each complex were different. In particular, signals corresponding to the benzyl protons and the underivatized cyclopentadienyl (Cp) protons were markedly more upfield for the (*R*)-**2a**:(*R*) complex. It was also apparent that (*R*)-Binol was more tightly bound by (*R*)-**2a** than its enantiomer, with a competition study revealing the ratio of binding strengths, K_R/K_S, to be ca. 19.

The X-ray structure of the (*R*)-**2a**:(*R*) complex shows a pseudo-tetrahedral geometry at the boron atom, it being bonded to the imine nitrogen in addition to one carbon and the two oxygen atoms (Figure 1). A similar geometry in solution was indicated by ^{11}B NMR spectroscopy in $CDCl_3$,[9] which revealed a significant upfield shift in the ^{11}B signal upon formation of the (*R*)-**2a**:(*R*) complex.

Such a geometry gives the structure a degree of rigidity, which is no doubt a factor both in governing the enantioselectivity of the system and in communicating any binding events to the ferrocene unit (vide infra). The structure also suggests that the

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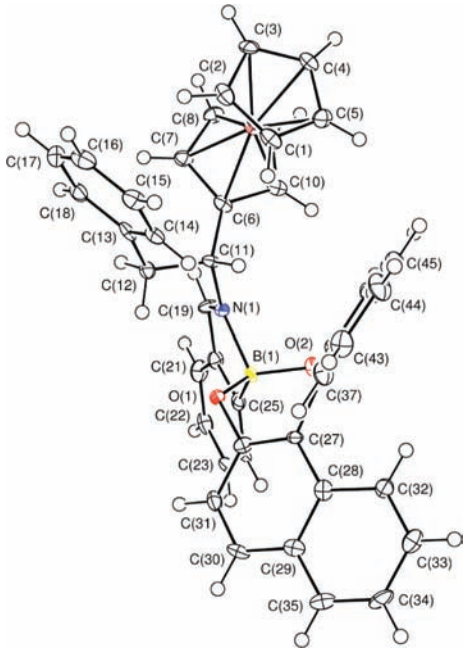

Figure 1. Crystal structure of the complex (*R*)-**2a**:(*R*) with ellipsoids drawn at 50% probability level (toluene solvent molecule omitted).

upfield shifts of the benzyl and underivatized Cp ring protons in the NMR spectrum are likely to arise from anisotropic shielding effects due to their close proximity (e.g., distance from benzyl centroid to H attached to C(2) = 2.8 Å), and models suggest that rotation of this benzyl group in solution would also allow a stacking interaction with one aromatic face of the (*R*)-Binol unit. These models also indicate that, for the (*S*)-Binol enantiomer, a similar three-way geometry, where the bulky aromatic units (benzyl, ferrocene, and Binol) are held in close proximity to one another, would not be possible for steric reasons, which is consistent with weaker binding in (*R*)-**2a**:(*S*) and the absence of upfield shifts in its NMR spectrum.

Control studies with the achiral boronic acid **2b** gave identical NMR spectra with (*R*)- and (*S*)-Binol. Furthermore, studies with the opposite enantiomer of the ferrocene amine, (*S*)**-1a**, revealed that the (*S*)-Binol bound the respective imine adduct more strongly than its enantiomer, with the two diasteromeric complexes giving NMR spectra identical to those of their opposite enantiomers. These studies confirm that differences in binding strengths and spectral signals are solely due to the intrinsic stereochemistries of the host and guest.

The ability of the ferrocene group to electrochemically detect the binding of either enantiomer of Binol was then investigated by square wave voltammetry (SWV) and cyclic voltammetry (CV). Compounds (*R*)-**1a** and (*R*)-**2a** (ca. 3 mM in dry DCM) gave reversible ferrocene-based redox couples at $E^{\circ\prime} = 542$ and 570 mV, respectively (by SWV vs decamethylferrocene, dmfc, as internal reference). Upon addition of an excess amount (to ensure full complexation) of (*R*)- and (*S*)-Binol to solutions of the adduct (*R*)-**2a**, potentials of 665 mV ($\Delta E^{\circ\prime} = +95$ mV) and 614 mV ($\Delta E^{\circ\prime} = +44$ mV), respectively, were observed,[10] which indicated not only the sensing of Binol in solution but, more importantly, electrochemical discrimination between each of its enantiomers (Figure 2).

Control studies on the complexes formed between the achiral ferrocene **2b** and (*R*)- and (*S*)-Binol revealed no differences (outside of experimental error) in potential values ($E^{\circ\prime} = 647$ and 642 mV, respectively, by CV vs dmfc). Furthermore, the complexes formed with the opposite enantiomer (*S*)**-2a** gave, within experimental error, the same shifts as their respective enantiomeric adducts. These studies indicate that the difference in the formal potentials $\Delta E^{\circ\prime}$ (51 mV) of the diastereomeric complexes (*R*)-**2a**:(*R*) and (*R*)-**2a**:(*S*) is consistent with the electrochemical sensing of chirality, and this value compares favorably with other known attempts at distinguishing between enantiomers using related methods.[5,7b]

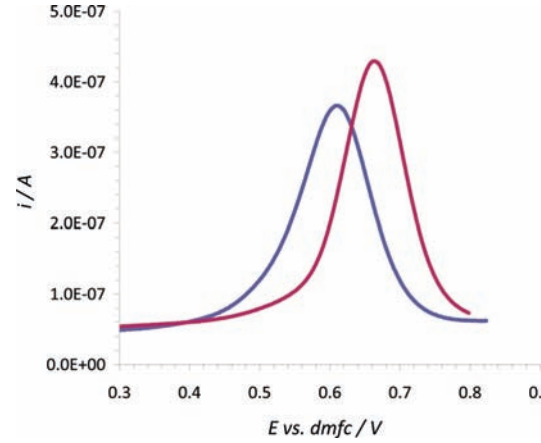

Figure 2. Square wave voltammograms in DCM of (*R*)-**2a**:(*S*) in blue and (*R*)-**2a**:(*R*) in red (0.1 M TBA·PF_6).

The chiral sensing observed with this system must originate from the complex (*R*)-**2a**:(*R*) undergoing a larger drop in stability upon oxidation than (*R*)-**2a**:(*S*), since complex formation with (*R*)-Binol produces the larger positive shift in electrode potential.[11] The binding constant ratio for the two complexes in their oxidized forms, K_R^+/K_S^+, was estimated as ca. 2.5. Therefore, the greater stability of the (*R*)-Binol complex over its (*S*)-Binol counterpart decreases by approximately 1 order of magnitude upon their oxidation. A plausible explanation for this decrease is that the effects of steric interactions present in the reduced forms of these complexes, which in the case of (*R*)-**2a**:(*S*) significantly hinder its stability, are lessened upon their oxidation. This situation could arise if the N−B coordinative bond is considerably weakened by the presence of the proximate positively charged ferrocenium unit.

With the chiral sensing established, it was then decided to examine the extent to which the differences in binding strength and electrode potential for complexes (*R*)-**2a**:(*R*) and (*R*)-**2a**:(*S*) would allow the enantiomeric composition of various mixtures of Binol to be determined. Solutions were prepared using a 10-fold excess of Binol, in order to minimize the presence of uncomplexed (*R*)-**2a**. One-wave behavior[4b] was exhibited, with the observed electrode potential (E_{obs}, the potential of the maximum current) gradually shifting to more positive values as the % of (*R*)-Binol increased (Figure 3). Significantly, a plot of E_{obs} against ee revealed a linear dependence for mixtures where % ee (*S*)-Binol ≥ 60% (Figure 4).

The dependence allows discrimination between mixtures containing 98% and 90% ee of (*S*)-Binol (the estimated error in ee from the plot is ca. ±3%),[12] enabling small (<5%) amounts of (*R*)-Binol to be detected at a concentration of ca. 10^{-5} M.

To conclude, these studies provide a clear proof of principle for the accurate determination of ee using an electrochemical method. Furthermore, the sensitivities observed at relatively low analyte concentrations could make this a promising alternative

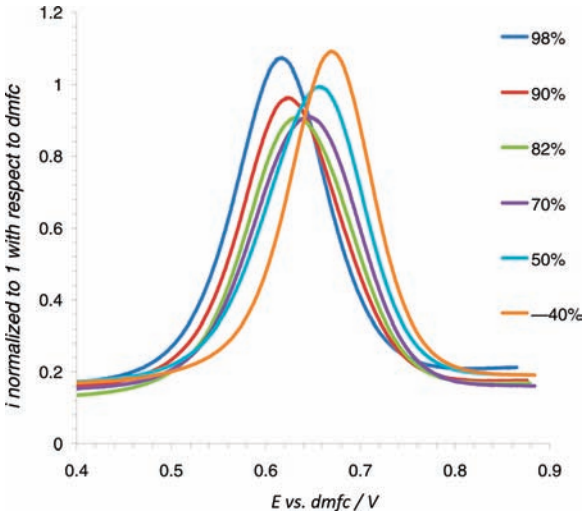

Figure 3. Square wave voltammograms of (*R*)-**2a** (DCM, 3.14×10^{-5} M, 0.1 M TBA·PF_6), each in the presence of a 10-fold excess of Binol with varying enantiomeric composition, as expressed by % ee of (*S*)-Binol in the legend (−40% equates to 40% ee of (*R*)-Binol).

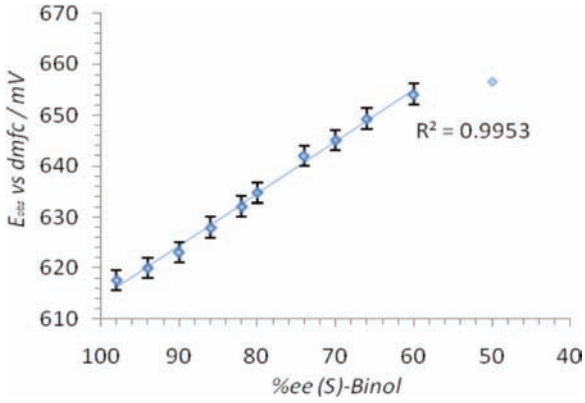

Figure 4. Plot of E_{obs} against % ee of (*S*)-Binol showing the linear dependence between 60% and 98% ee.

to more established methods for ee determination. Given the known chiral target versatility (amines and diols) of three-component boron-based assemblies,[3c,d] we are now planning further studies on a range of chiral analytes using related redox-active systems to fully explore the scope of this new electrochemical approach to chiral sensing.[13]

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Supporting Information Available: Synthesis, NMR binding and competition studies, electrochemical measurements, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) In the 90−99% ee range, a reasonable error for an NMR chiral shift reagent would be ca. ±2−3%.
(13) Preliminary studies indicate that enantiomers of diols with central chirality (e.g., 1,2-diphenylethane-1,2-diol) can also be distinguished electrochemically using (*R*)-**2a**.

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