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# Nuclear Magnetic Resonance Signaling of Molecular Chiral Information Using an Achiral Reagent

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Molecular chirality is key information in various biological events. Thus, chirality which is induced, detected, controlled, or applied using biomimetic or supramolecular concepts is attracting attention.[1] Also, chiral parameters of asymmetric compounds, including their absolute configurations and enantiomeric purity, are important in pharmaceutical applications. Great effort has been made to develop artificial host molecules to enable detection of chiral information by using UV/vis,[2] fluorescence,[3] CD,[4] and NMR spectroscopies.[5] Of these, chiral analyses using an achiral host have been achieved,[6,7] although these methods were limited to detection of ICD signals due to complexation with chiral guest(s).[6] Until now NMR spectroscopic detection of guest chirality using an achiral host has not been possible in the absence of a chiral medium[7a] or chiral auxiliary[7b] because this method is principally based on chiral discrimination by the host and/or diastereomeric host−guest complex.[8] Therefore, NMR spectroscopic detection using an achiral host remains challenging, although NMR spectroscopy gives more information than does CD spectroscopy and might lead to molecular spin quantum computers.[9] In this paper, we report the first instance of chiral guest information detection by signaling from an achiral host in $^1$H NMR spectroscopy. We used oxoporphyrinogen **1** as an achiral host (see Figure 1a,b) since it can bind guests through hydrogen-bonding at pyrrolic NH groups.[10] **1** also offers tautomeric variation of its structure since di-*tert*-butylated oxohexadienylidene groups at *meso*-positions can reversibly interconvert to di-*tert*-butylated phenol groups in concert with a change in the conjugated form of its tetrapyrrolic macrocycle.[10b,11]

Mandelic acid **2** was selected as a guest because of the importance of chiral sensing of its enantiomers and since it plays a critical role in biological systems.[12] Addition of 9.3 equiv of *rac*-**2** into a $CD_2Cl_2$ solution of **1** resulted in downfield shifts of the peaks due to quinonoid alkenic protons, *tert*-butylic protons, and pyrrolic $\beta$-proton and disappearance of the peak due to pyrrolic NH in the $^1$H NMR spectrum (Figure 1c). For pure *R*-enantiomer, peaks due to quinonoid protons and pyrrolic $\beta$-protons in **1** also split into two peaks ($\Delta\delta$ = 0.132 ppm (39.62 Hz) and $\Delta\delta$ = 0.156 ppm (46.77 Hz), respectively) although there is no difference in the positions and shape of the peaks due to *tert*-butylic protons (Figure 1d). Splitting persisted even after addition of a large excess (~30 equiv.) of mandelic acid[13] indicating that the two peaks do not correspond to those of *R*-**2**-complexed and noncomplexed **1**. **1** behaves similarly in the presence of the pure *S*-enantiomer (4.8−28 equiv).[13] Thus, guest chirality causes the unusual peak splitting, which was also observed for guest **3**.[13]

When racemic and nonracemic mixtures of **2** were applied in this system, we found that peak separations depended on the respective % enantiomeric excesses (ee) ($\Delta\delta$: 0−0.14 ppm for quinonoid peaks; 0−0.15 ppm for $\beta$-pyrrolic peaks, Figure 1e). Surprisingly, plotting differences in chemical shifts of split peaks against the % ee values resulted in a linear correlation with a coefficient of $r^2$ = 0.996 (Figure 1f). This clearly indicates that chiral information of the guest is transferred to the host and can be detected as splitting of the NMR

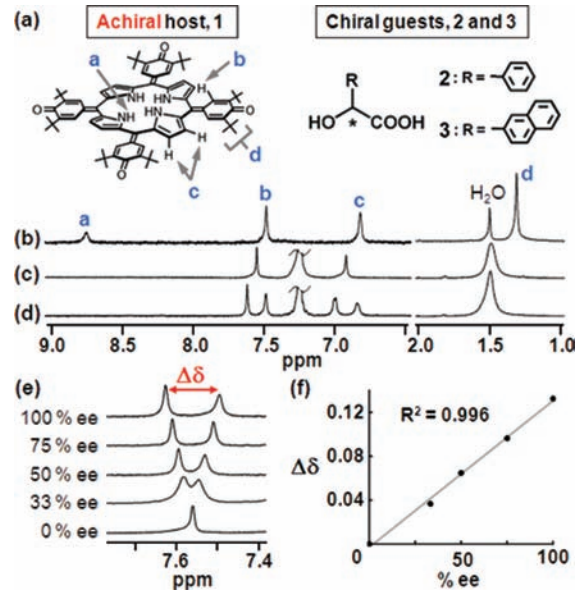


***Figure 1.*** (a) Structures of achiral host **1** and chiral guests **2** and **3** used in this study. (b, c, and d) $^1$H NMR spectra (~1.4 mM in $CD_2Cl_2$ at 25 °C), respectively, of **1** alone, **1** in the presence of 9.3 equiv of *rac*-**2** and **1** in the presence of 8.8 equiv of *R*-**2**. (e) Partial $^1$H NMR spectra of **1** (quinonoid protons) in the presence of **2** having various enantiomeric excess values, % ee. (f) Correlation between differences in chemical shifts of split peaks and the % ee values.

signals of the achiral host. This is the first demonstration of the utilization of an achiral host for determination of enantiomeric purity by observing the magnitude of peak splitting. This differs from the case of chiral hosts (shift reagents): the % ee is generally determined from the ratio of peak areas due to diastereomeric host−guest complexes.[8]

The origin of the peak splitting was investigated by UV/vis and CD spectroscopies. When excesses of *R*- or *rac*-**2** were added into a solution of **1** in $CH_2Cl_2$, the solutions changed color from purple to red (Figure 2a). UV/vis spectra of these solutions were identical (Figure 2a, red-lined spectrum).[13,14] The CD spectra of $CH_2Cl_2$ solutions of **1** in the presence of excesses of *R*-, *S*-, or *rac*-**2** showed substantial ICD signals depending on the chirality of **2** (Figure 2b). This strongly suggests complexation of **1** with **2** and was confirmed by $^1$H NMR spin−lattice ($T_1$) relaxation measurements.[13] UV/vis titration studies using *R*-**2** at room temperature revealed a gradual intensification of the new absorption band at 789 nm with accompanying intensity decrease and splitting of the Soret-type band originally due to free **1**, with isosbestic points at 357 and 643 nm (Figure 2a). Plots of the absorbance change at 789 nm against *R*-**2** concentrations could not be curve-fitted well ($r^2$ = 0.982) using a nonlinear least-squares analysis based on a 1:1 stoichiometry. On the other hand, curve fitting based on a 1:2 stoichiometry provided an excellent correlation coefficient



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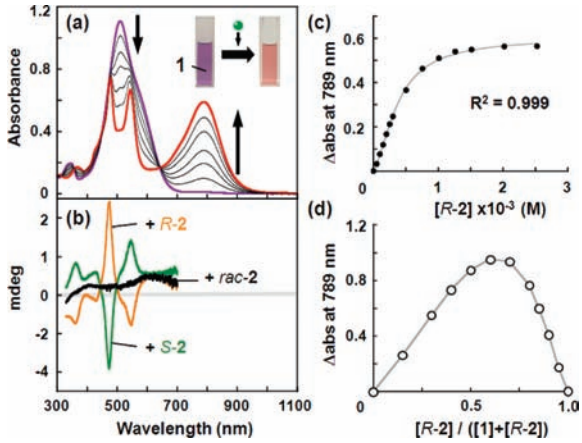


***Figure 2.*** (a) UV/vis spectral changes observed during titration of **1** ($10^{-5}$ M in $CH_2Cl_2$) with *R*-**2** and (b) CD spectra of $10^{-5}$ M $CH_2Cl_2$ solutions of **1** in the presence of excess *R*-, *S*-, or *rac*-**2**. (c) Profile of absorbance change at 789 nm against concentration of *R*-**2**. (d) Job's plot for the complexation of **1** and *R*-**2** at constant total concentration ($10^{-3}$ M).

($r^2 > 0.999$; Figure 2c), and the first and second apparent binding constants were calculated to be $1.3 \times 10^3$ and $5.3 \times 10^3$ $M^{-1}$, respectively,[13] indicating a substantial cooperative effect, $K_2 > K_1$. Job's plot for **1** and *R*-**2** gave a maximum at 0.67 mol fraction (Figure 2d) also consistent with formation of a complex of 1:2 stoichiometry (**1**:**2**). Importantly, the UV/vis titration and Job's plot analysis for **1** and *rac*-**2** suggest the formation of a 1:2 complex of similar stability ($K_1 = 1.6 \times 10^3$ $M^{-1}$; $K_2 = 4.9 \times 10^3$ $M^{-1}$) to that of the **1**/*R*-**2** complex.[13] By $^1$H NMR, for a 1:2 complex with chiral guest *R*-**2**, appearance of two peaks for proton "b" (Figure 1) is due to formation of two stable diastereomers of roughly equal populations.[4a] Conversely, **1**/*rac*-**2** exhibits a single peak representing the average chemical shift of "b" of all the **1**/**2** complexes (because of fast guest exchange). If ee is reduced from 100%-*R* by adding a portion of *S*-**2**, then the population of **1**/*R*-**2**/*S*-**2** must increase although a peak due to this complex was not observed due to rapid exchange between either diastereomer. The latter effect yields peaks at average chemical shifts for **1**/*R*-**2**/*S*-**2** and each diastereomer and effectively shifts the peaks from their 100%-ee positions toward the average chemical shift of the **1**/*rac*-**2** mixture to a degree determined by the % ee. We believe that this implies a low stability for the **1**/*R*-**2**/*S*-**2** complex relative to the homochiral diastereomers.

It should be noted that the UV/vis spectrum of the **1**/*R*-**2** complex (Figure 2a) differs from that of the hydrogen-bonding based **1**/anion complex, which gives a blue-colored solution.[10b] Therefore, complex formation involves another binding mechanism, which must be related to guest acidity since we obtain identical spectra by adding other organic acids such as methanesulfonic acid into a $CH_2Cl_2$ solution of **1**.[13] The split Soret band in the UV/vis spectrum of acid complexed **1** is strongly indicative of its lower symmetry. Variable temperature $^1$H NMR studies (VT-NMR, −85−25 °C) on a $CD_2Cl_2$ solution containing **1** and 4.3 equiv of *R*-**2** indicate the following: (1) the *tert*-butyl peak of **1** gradually split into two peaks as the temperature decreased, and (2) a new peak appeared at 6.49 ppm.[13] Since both spectral changes were also observed in the case of *rac*-**2**,[13] these changes should be due to a protonation-driven tautomerization of host **1** to its porphodimethene form, which contains two phenol *meso*-substituents. The peak at 6.49 ppm is exchangeable as expected,[13] and solution-state FT-IR spectroscopy (in $CH_2Cl_2$ at 0 °C) supports the protonation: the di-*tert*-butylphenol OH band at 3602 $cm^{-1}$ with carboxyl anionic C═O band at 1590 $cm^{-1}$ were found in the **1**/**2** complex but not in solutions of **1** and **2** alone.[13] Therefore, **2** induces the protonation/tautomerization from **1** to the protonated porphodimethene (Figure 3a). Complex formation must be based on electrostatic interaction between the carboxylic anions in **2** and the cationic groups in the protonated tautomer of **1** similar to that observed in other anion complexes of porphyrin dications.[4a]

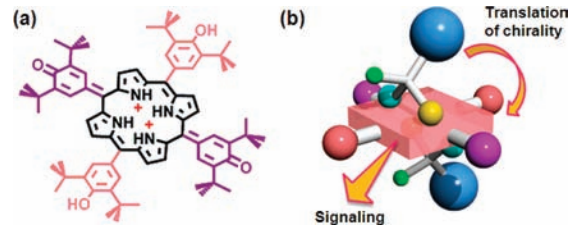


***Figure 3.*** (a) Structure of one of the protonated tautomers of **1** and (b) schematic illustration of the concept of this work: translation of chiral information from guest into NMR signals through an achiral host.

In summary, we have demonstrated that achiral **1** works as a host for signaling chiral information of α-hydroxycarboxylic acids in $^1$H NMR spectroscopy. In particular, enantiomeric excess can be determined by the split proton resonances of the achiral host. The present results provide a breakthrough concept (Figure 3b) in the field of supramolecular chemistry dealing with chirality in host−guest systems.

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**Supporting Information Available:** Experimental details and additional characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) See Supporting Information.
(14) Removal of **2** by water washing restores the UV/vis spectrum of **1**, indicating that no serious changes to the tetrapyrrole framework occur.

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