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Induced Chirality Sensing through Formation and Aggregation of the Chiral Imines Double Winged with Pyrenes or Perylenes

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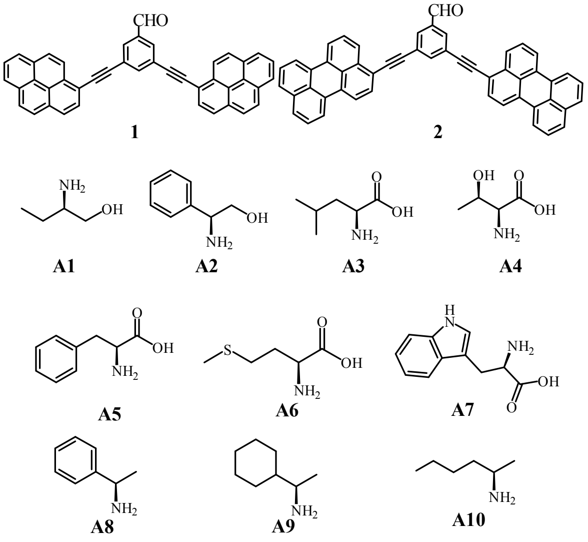
Reaction of chiral amines with benzaldehydes 3,5-disubstituted by two pyrenes or perylenes afforded corresponding double winged chiral imines, which aggregated to show significantly enhanced circular dichroism spectra at the transition bands of the chromophores in the mixture solutions of DMF and H_2O.

The rapid emergence of chiral compounds produced by asymmetric synthesis or from natural origin put forward the requirement for high throughput detection of the absolute configuration and optical purity of chiral products.[1] Circular dichroism (CD) is regarded as one of the most versatile and widely-utilized chiroptical techniques,[2] possessing the advantage of directly differentiating molecular/supramolecular chirality without the assistance of other chiral substances. However, weak CD signals were often encountered with chiral organic compounds.[3] Moreover, most chiral molecules contain no chromophore and have absorption only in the far or deep UV region, which makes CD detection susceptible to absorption interference from solvents or non-target compounds. Supramolecular chirogenesis represents a viable and promising approach for chiral differentiation,[4] and we have demonstrated that supramolecular self-assembly could cause significant chiral recognition and photochirogenesis.[5] Through supramolecular complexation, the chiral properties of analytes could be efficiently transferred to a reporter to allow for CD detection at the transition bands of the reporter. Further, chiral supramolecular assembly often leads to highly responsive exciton coupling CD (ECCD)[6] due to the electronic coupling amongst proximal, asymmetrically oriented chromophores.[7]

Imine formation has recently been developed as an attractive strategy for sensing of chiral amines.[8] Sophisticated designed aromatic aldehydes, such as dialdehyde chromophores[9] or aldehydes bearing coordination-sites,[10] have been used for sensing chiral amines by inducing ECCD of the chromophores. On the other hand, chiral aggregation of chromophores often leads to strong ECCD signals.[6,7] We envision that proper combination of the imine formation and chiral aggregation could lead to a convenient and highly responsive ECCD-based chirality sensing. Herein, we report the successful application of the strategy for chirality sensing of amines.



Scheme 1. Double winged sensors **1** and **2** and chiral amines **A1-A10**.

We designed aromatic aldehydes **1** and **2** (Scheme 1), in which two pyrenes or perylenes were substituted to the central benzaldehyde for the purpose to facilitate the chromophore aggregation. Ten chiral reagents, including chiral

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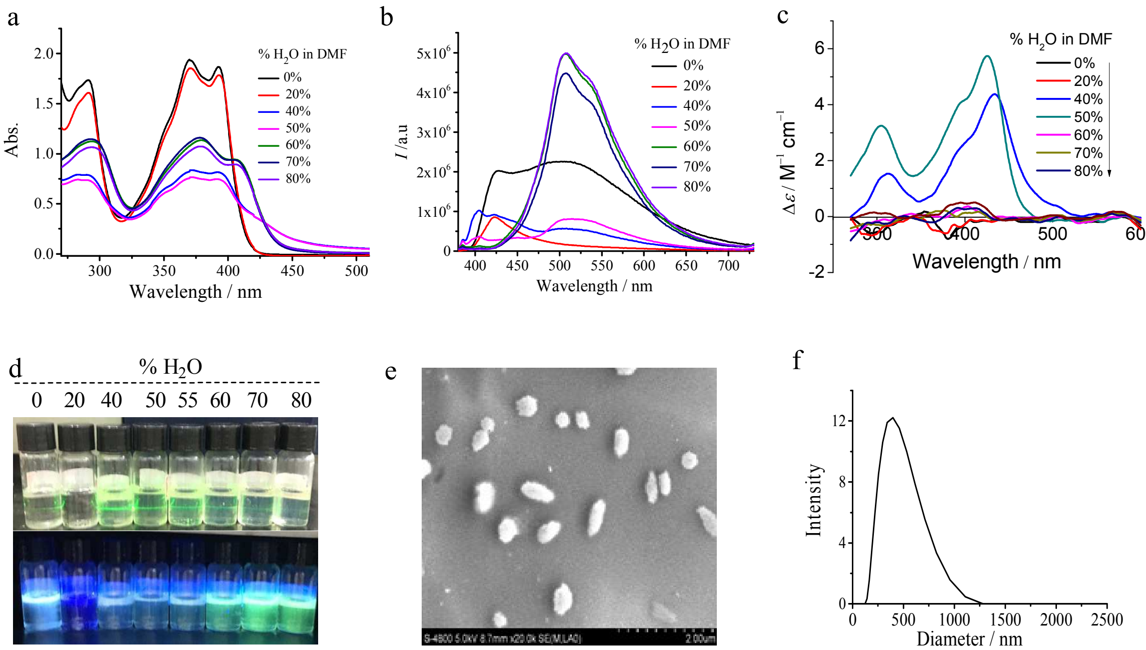

Fig 1. Water content-dependent (a) UV–vis, (b) fluorescence and (c) CD spectra of the chiral imine (40 μM) formed by reacting **1** with (*S*)-**A6**. (d) Light scattering (upper) and emission (lower) of the chiral imine in DMF solution having various water contents. (e) SEM and (f) DLS measurements of the aggregated imine obtained from the mixture of DMF/H$_2$O (1:1 v/v).

amines with (**A1-A7**) or without (**A8-A10**) an additional functional group, were selected as the analytes. The double winged benzaldehydes were synthesized by the Pd-catalyzed Sonogashira cross-coupling reaction by reacting 3,5-bisethynylbenzaldehyde with 1-bromopyrene or 1-bromoperylene, respectively, and were characterized by NMR and HRMS.[11] The UV-vis spectra of **1** and **2** were apparently bathochromic shifted comparing with pyrene and perylene (Fig. S8 and S10)[11] to show strong absorption in the visible range. Both **1** and **2** readily formed imines by reacting with chiral amines, and the ^{1}H NMR tracing experiment indicated that the aldehyde hydrogen proton completely disappeared within 30 min after the addition of an amine (Fig. S12).[11] However, all imines thus formed in DMF showed negligible CD signals in the S$_0$-S$_1$ transition of both **1** and **2**. The CD silence is presumably due to two reasons: There is no driving force to fix the chromophore groups in a chiral fashion. Also, the chiral groups are far from the pyrene or perylene units and cannot strongly disturb the transition of chromophores.

In order to verify the hypothesis of aggregation-induced chirality sensing, we examined the solvent-induced aggregation behaviour of the chiral imines by adding water into the DMF solution of chiral imines. It turned out that the aggregation was highly water content-dependent. As illustrated in the Fig. 1a, the UV-vis spectra of chiral imine, formed by reacting **1** with (*S*)-**A6**, were only slightly changed in 20% water relative to that in pure DMF, but significantly deceased and broadened when the water content was increased to 40%. This suggested an aggregation of the chiral imine which should be driven mainly by the hydrophobic interaction and the π–π stacking. The UV-vis baseline apparently raised in 40% water, indicative of an aggregation that caused scattering of light. Similar UV-vis spectrum was seen in 50% water.

Slightly unexpected, further increasing the water contents led to less broad absorption spectra with dropped baseline, implying a decline of aggregation sizes. Such a water content-dependent aggregation was confirmed by Tyndall scattering experiments (Figure 1d), as strong scattering was observed in solutions containing 40% and 50% water, which however reduced in solutions containing more water. In pure DMF, a broad fluorescence spectrum (Fig. 1b, black line) was observed, which could be assigned as a mixture of the monomer and excimer fluorescence. Adding water led to a fluorescence quenching firstly, but then an increase of the fluorescence at the longer wavelength when further increasing water content (Fig. 1b, 1d). Interestingly, the chiral imine showed strong CD signal in 40% and 50% water, but only weak or negligible CD spectra in the solutions with other water contents (Fig. 1c).

All above results demonstrated that the aggregating sizes and models of the chiral imine changed with the solvent

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compositions. The strong scattering observed in 40-50% water suggested relatively large aggregation sizes. Indeed, scanning electron microscopy (SEM) study revealed that the aggregation formed in 50% water led to nanoparticles with an average diameter about 400 nm (Fig. 1e), which is consistent with the dynamic light scattering (DLS) analyses (Fig. 1f). It is not yet clear the mechanism for the solvent composition-dependent aggregation changing but seems plausible due to a switching of the solvent structure with the water contents. This is partially supported by the fact that very similar solvent composition-dependent aggregations were seen with the imine formed by **2** and (*S*)-**A6**, which showed unique spectral response in the water content range of 40% to 60% (Fig. S13-S19).[11]

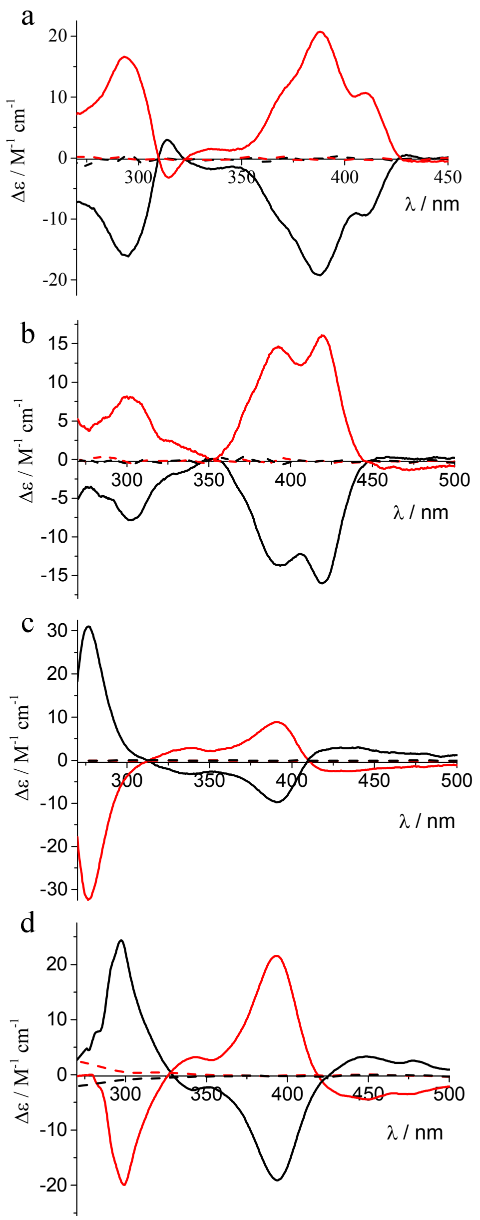
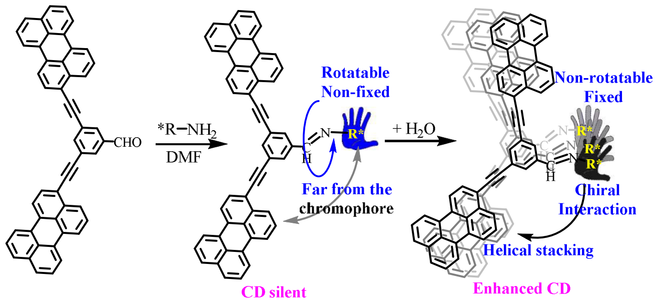


Fig. 2 CD spectra of 50 μM chiral imines formed by (a) **1** with **A1**, (b) **1** with **A5**, (c) **2** with **A6** and (d) **2** with **A7**, measured at 25 °C. Red and black lines represent the CD spectra of chiral imines formed with (*R*)- and (*S*)- amines, respectively. Dotted and solid lines represent the CD spectra measured in DMF and in DMF / H_2O (1:1, v/v), respectively.

We therefore selected DMF/H_2O (1:1, v/v) as the solvent for the CD sensing of chiral amines. CD measurements demonstrated strong signal responses for all chiral amines examined, which is in opposite to the CD-silence in pure DMF (Fig. 2 and Fig. S20-S35). As shown in Fig. 2a, positive CD signals peaked at 421 nm, 393 nm and 302 nm were seen for the (*R*)-**A1**, while (*S*)-**A1** showed completely opposite CD spectrum, suggesting an efficient enantiodifferentiating sensing. Very strong CD spectra were also observed with the perylene-based sensor **2**. As exemplified in Fig. 2c and 2d, almost no CD signal could be seen from the chiral imines in the homogenous phase of DMF. However, significantly enhanced CD signals were observed at the perylene's ^1L_a band, with CD spectra of the (*R*)- and (*S*)-amines exhibiting totally mirror image, and the deviation from the perfect reflection is mainly due to the deviation in controlling the imine formation and aggregation condition. Such a strong and enantiodifferentiating CD response clearly demonstrated the feasibility of the present system for sensing of chiral amines. Moreover, the fine CD spectral properties were chiral guest-dependent. For the sensing with **1** as an example, **A1** gave a CD maximum at the wavelength of 393 nm with a shoulder at 421 nm (Fig 2a), while **A5** offered a maximum at 423 nm (Fig 2b). Very different relative peak intensities were also observed with other chiral amines and with the sensor **2** (Fig. 2c, 2d). We attribute the strong CD induced by aggregation to the exciton coupling effect, which usually occur with chirally arranged chromophores. The sensor **1** did not show typical bisignate ECCD signals (Fig 2a,2b), which is presumably due to the multiple coupling from different transitions among the closely oriented chromophores that may lead to mutual cancellation of opposite CD signals. The ECCD spectra are highly sensitive to the stacking geometry of chromophores, the difference on the shape and intensity implies a non-identical stacking structure caused by different chiral amines. Adding achiral amine lead to the decrease of the CD intensity (Fig.S36), suggesting the chirality sensing is sensitive to amino impurity.



Scheme 2. The mechanism for the aggregation-induced chirality sensing.

We propose that the chiral stacking of the pyrene and perylene groups should be responsible for the significant CD response upon forming aggregations. As shown in scheme 2, for non-aggregated chiral imines, the chiral moieties are non-fixed and far from the chromophores, and therefore cannot essentially disturb the optical properties of the chromophores. However, when aggregation is formed by adding water, the rotation of the chiral imine moiety is prohibited. Since simple chiral amines **A8-A10** exhibited strong CD response, the steric interaction should play a main role in chirality transfer.

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However, we do not rule out the possible effect from the hydroxyl and carboxyl groups of **A1-A7** in assisting the aggregation formation and chirality transfer. The chiral steric interaction will lead to staggered stacking of the chromophores to induce helical structure. In this way, the chirality of the imine substituents was efficiently transferred to the helical stacking of chromophores to cause significantly improved ECCD response. The detailed analyses as for the correlation between the aggregated structure of the chiral imines and CD responses through theoretical calculation[12] are in progress.

The excellent enantiomeric differentiation observed with the present system encouraged us to explore its possible application for measuring enantiomeric composition of chiral amines. The CD spectra of solutions spanning the enantiomeric composition between 100% S configuration and 100% R configuration were measured at 25 °C. As shown in Fig. 3, the CD intensity of imine formed by **A5** was strongly dependent on enantiomeric compositions. A calibration curve was built from the CD amplitudes at 420 nm vs the enantiomeric excess (Fig. 3, inset), which revealed a perfect linear relationship ($R^2 = 0.997$), Good linear relationships were also observed for **A1**, **A3** and **A4** (Fig. S37-39). The CD signals of 5 unknown samples of varying ee for each chiral amine were recorded to investigate the sensing accuracy towards unknown samples, and the corresponding calibration curves were used to calculate the ee's (Table S1). The average absolute errors of sensors towards the analytes were determined to be below 3%, demonstrating a potential for using the aggregation system for sensing the enantiomeric composition. For practical chirality sensing with the present system, precisely controlling the solvent composition and reducing the interference from impurity should be important.

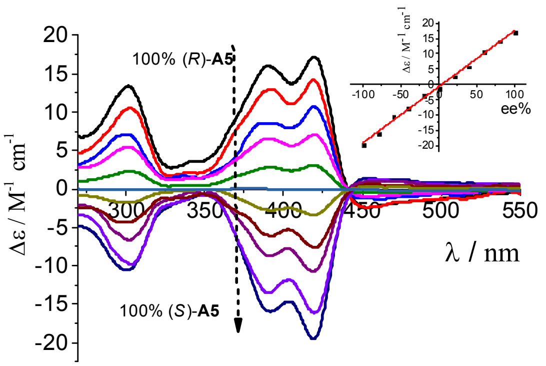

Fig. 3 CD spectra of the imine (30 μM) formed by reaction of **1** and **A5** of different ee's, measured in DMF/H_2O (1:1, v/v) 25 °C. Inset: Plot of the ellipticity at 420 nm as a function of %ee.

In summary, we established a convenient and highly efficient supramolecular chirality sensing strategy through a two-step chirality transition process: The double-winged benzaldehydes were reacted with chiral amines to give corresponding chiral imines, which formed chiral supramolecular assemblies through a solvent-induced aggregation. The non-aggregated chiral imines were CD-silent, while aggregated chiral imines showed highly strong CD responses due to the chiral steric interaction amongst chiral substituents in the aggregation. This work represents the first implementation of induced chiroptical sensing by combining the chiral imine formation and solvent-induced aggregation and opens a new and promising avenue for sensing the absolute configuration and enantiomeric composition of chiral amines.

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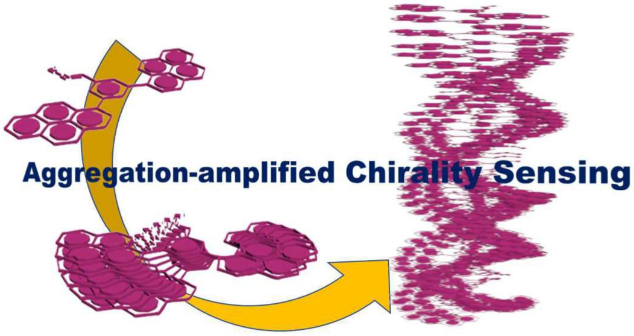

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