Optical chirality sensing using macrocycles, synthetic and supramolecular oligomers/polymers, and nanoparticle based sensors

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Optical sensors that respond to enantiomeric excess of chiral analytes are highly demanded in chirality related research fields and demonstrate their potential in many applications, for example, screening of asymmetric reaction products. Most sensors developed so far are small molecules. This Tutorial Review covers recent advances in chirality sensing systems that are different from the traditional small molecule-based sensors, by using macrocycles, synthetic oligomers/polymers, supramolecular polymers and nanoparticles as the sensors, in which supramolecular interactions operate.

Key learning points

Two major approaches to chirality sensing, i.e., using chiral sensors that form diastereomeric complexes with chiral analytes and using achiral or dynamically racemic sensors that exhibit induced chirality upon analyte binding.

Versatile sensing ensembles based on macrocyclic hosts that have a cavity for chiral auxiliary, chiral analytes or reporting dye.

Synthetic or supramolecular polymers that show chiral analyte induced helical chirality.

Chirality sensing based on chiral analyte-dependent nanoparticle assembly.

Introduction

Within the area of chemical sensing, there has been considerable interest in designing synthetic optical sensors that effectively discriminate between enantiomers of a certain class of chiral compounds. Those sensors, here referred to as chirality sensors, are designed to interact with chiral analytes via covalent or noncovalent interactions, giving spectroscopic responses that depend on the enantiomeric excess (ee) of the tested chiral analytes. These sensors have shown their potential in many fields where chirality is an important parameter, for instance, they have dramatically facilitated the development of asymmetric syntheses by offering an effective means of determining ee of the reaction products. In the case of optical sensors, given that the sensor–analyte interactions take place fast enough, which is usually not a problem for supramolecular sensors, the rapidness and relatively low cost of spectroscopic assays will confer great advantages over prevailing methods such as chromatographic techniques, especially when hundreds of reaction products need to be quickly analyzed to optimize the reaction conditions.

Chirality sensing is to distinguish right-handed and left-handed chirality and/or to determine the optical purity of chiral samples. There are two major approaches to discriminate between enantiomers by (i) using chiral sensors that form diastereomeric sensor–analyte complexes giving different UV-Vis absorption, fluorescence or NMR responses, and (ii) using achiral sensors that show induced chirality upon sensor–analyte interactions that give responses detectable by chiral discriminating spectroscopy such as CD (circular dichroism) or circularly polarized luminescence (CPL). A third, less common approach also exists, which does not involve the use of any chiral auxiliary or chiral discriminating spectroscopy, but is based on a specific interaction of the sensor with (R)- and (S)-analytes by forming molecular complexes or assemblies that generate an ee-dependent response in a spectroscopic instrument that possesses no intrinsic chiral discriminating capacity.

Most of the chirality sensors so far designed, by any of the three approaches described above, are based on small molecules, which have already been covered by several excellent comprehensive reviews, therefore they are not discussed here. In spite of the great success achieved with those small-molecule based sensors, often, an elaborately designed sensor...
structure is required. In the case of chiral sensors, (i) the differences in association constants of the diastereomeric sensor–analyte complexes should be sufficiently large, if the resulting diastereomeric complexes possess identical UV-Vis absorption or fluorescence spectra; or (ii) alternatively, the spectroscopic properties of the diastereomeric complexes should be different to allow discrimination by UV-Vis absorption, fluorescence or NMR methods. In the case of achiral sensors, they may be flexible in their conformation or exist as a racemic mixture of rapidly inter-converting enantiomeric conformers. Upon chiral analyte binding, the conformation of the sensor molecule should be effectively restricted that results in chirality induction, or the energy difference between the diastereomeric conformers should be sufficiently large to bias the formation of either conformer, leading to nonracemic composition of the conformers that might be probed by spectral responses.

Recently, new concepts have been introduced to the area of optical chirality sensing. Instead of using small molecules, supermolecules are designed as sensors for chirality sensing. Macrocyclic hosts that have a cavity, either achiral or chiral, may provide sensing properties that cannot be achieved by small molecules. For example, the large cavity of cucurbiturils and cyclodextrins may allow inclusion of multiple guest molecules, while the interactions among the entrapped guest molecules can be exploited to design simple chirality sensing ensembles, without

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the need of covalently conjugating an analyte binding site to the sensor molecule.

Certain synthetic oligomers and polymers are known to exist in helical structures. For example, synthetic oligomers in suitable solvents can undergo folding in a helical fashion, driven by intramolecular hydrogen bonding and/or solvophobic interactions. Macromolecular helicity can also result from synthetic polymers possessing bulky side chains that create higher rotation energy barriers. These helical oligomers or polymers are dynamically racemic in the absence of any external influence, while simple sensor design can allow single-helicity induction by analyte binding. Alternatively, those helical oligomers or polymers bearing chiral substituents selectively form a cavity with single helicity, which thereby binds chiral guest molecules in an enantioselective manner.

A seemingly promising, yet not fully exploited, platform for chirality sensing is one that employs supramolecular polymers formed by self-assembly of small building blocks, such as aggregates of π-conjugated dye molecules, Langmuir–Blodgett films, supramolecular gels, and coordination polymers. Similar to synthetic oligomers or polymers, supramolecular polymers can easily possess helical structures, exhibiting “supramolecular chirality” as distinct from the “molecular chirality”. Yet the supramolecular polymers are formed via noncovalent interactions among the building blocks, the latter is hence much easier to design and synthesize than synthetic oligomers/polymers. This may facilitate sensor design and optimization for example to achieve spectral responses in a long wavelength window to minimize interference from impurities or chiral catalysts from asymmetric syntheses. Besides the structural diversity of the building blocks, the higher local concentration of the binding sites and the relative orientation between them that can be tuned good for analyte binding are the additional advantageous characters that the supramolecular polymer based sensors can offer. In both synthetic and supramolecular polymer based sensors the possible cooperative interactions occurring between the sensor and analyte molecules may afford chiral amplification that could be employed to design chirality sensing systems with higher sensitivity and accuracy as well.

Finally, the unique self-assembling capabilities and spectral properties of nanoparticles can be utilized in the design of highly sensitive chirality sensors, as they have proved potent in bio-sensing and imaging. The nanoparticles themselves can also be the signal reporter and the structural framework to load ligand molecules on the surfaces in the manner that could in principle be made good for chirality sensing.

Compared to the small-molecule based sensors, chirality sensing in these four supramolecular systems exhibits unique characteristics. In general, sensors established on the basis of various cooperative interactions provide more chances for mirror-symmetry-break. In fact, “sergeant and soldiers” and “majority rule” effects often are observed in these systems because of the efficient chiral amplification. Small ee could therefore be determined more sensitively than in the small-molecule sensory systems. In addition, the establishment of hierarchical chiral systems may further enhance the sensitivity for detecting and quantifying chirality. On the other hand, drawbacks exist as well. The S-shaped chiroptical response to ee due to chiral amplification is powerless for sensing ee above 95% or below 5%. In the cases of polymeric systems and nanomaterials, the sample preparation might be lengthy in order to obtain a stable and reproducible optical response. Also those oligomer or polymer sensors might be sensitive to environmental conditions such as temperature, ionic strength, and the presence of impurities, which could limit the practical applications.

In this Tutorial Review, we will describe those four classes of chirality sensors and discuss the mechanisms on which they operate to afford interesting chirality sensing performances that are different from the traditional small-molecule based chirality sensors.

Macrocycles

Macrocyclic sensors are here referred to as barrel-shaped compounds with a cavity. It is because of this cavity, its size and hydrophobicity or hydrophilicity, that these macrocyclic sensors are able to accommodate multiple guest molecules within the cavity, which is intriguing for chirality sensing in several ways. These guest molecules may include a chiral analyte, chiral molecule responsible for enantioselective binding with the chiral analyte, and/or chromophore responsible for generating spectroscopic outputs. By assembling those species within a macrocyclic host, synthetic efforts to covalently conjugate them are not needed, while more flexible and versatile sensing schemes can be designed.

The macrocyclic sensors can be themselves chiral or achiral. Achiral cucurbituril sensors represent a kind of active current interest. Inoue et al. examined the enantioselective guest recognition of cucurbituril hosts. The enantioselectivity relies on the inclusion of a chiral auxiliary to form ternary diastereomeric complexes of the analyte. Cucurbit[6]uril (CB[6]) and the chiral auxiliary 2-methylpiperazine (MP) forms a 1 : 2 inclusion complex in aqueous solution (Fig. 1). Guest molecule 2-methylbutylamine (MB) replaces one of the MPs from the CB[6] cavity, forming a ternary [CB[6][MP][MB]] complex with enantioselectivities. This ensemble exhibits a remarkable 19-fold selectivity for the formation of the [CB[6][R]-MP][S]-MB complex over its diastereomer [CB[6][S]-MP][S]-MB, evaluated from the isothermal titration calorimetry (ITC) measurements. The enantioselectivity was explained in terms of a larger enthalpy loss in the case of formation of the [CB[6][S]-MP][S]-MB complex due to more severe

![Fig. 1 Enantioselective recognition of guest molecules (G) by cucurbit[6]uril (CB[6]) and a chiral auxiliary 2-methylpiperazine (MP). (Reprinted with permission from J. Am. Chem. Soc., 2006, 128, 14871–14880. Copyright 2006 ACS.)](image-url)
distortion of MP positioning within the CB cavity from its original optimal location. Although the system does not show any spectroscopic output and the scope of the analytes is limited, it demonstrates a promising strategy on which more practically useful sensing schemes can be bared, by for example, using an indicator displacement assay. It also suggests the role of geometric factors of the included molecules within the cavity.

Nau and coworkers have recently developed two different chirality sensing assays based on the inclusion complexes of cucurbituril hosts and dye molecules, that act as spectroscopic reporters. One of them employed the stereospecific enzymatic reactions (Fig. 2). Enzymes able to convert specifically the L-enantiomers of amino acids to amines were chosen, following the fact that the amines show significantly higher affinities towards the CB[7] host than the amino acid substrates. Therefore, at suitable substrate concentrations, the amine produced by the enzymatic reactions, but not the amino acid substrate, displaces the fluorescent dye Dapoxyl previously included within the CB[7] cavity, leading to quenching of Dapoxyl fluorescence. When a mixture of enantiomers was subject to the analysis, the extent of fluorescence quenching depends on ee of the analytes. Because of the stereospecificity of enzymatic reactions and the sensitivity of the fluorescent assay, an accurate measurement of ee higher than 99% is made possible by using a high analyte concentration. Such assays for the high end of ee are not achieved with traditional small-molecule based sensors.

Another one from the Nau group is a CD-based chirality sensing assay that relies on the formation of a ternary complex among achiral CB[8], achiral dye and the chiral analyte (Fig. 3). The CB[8]-dye complex remains achiral and thus is CD silent, while the co-inclusion of a chiral aromatic analyte inside the CB[8] cavity effectively induces a strong CD signal in the dye absorption region. The CD signal depends linearly on the ee of chiral analyte. This assay applied for a broad scope of analytes since it relies on non-covalent interaction between the CB host and the aromatic moieties of the guest molecules. This is a significant breakthrough compared to that based on small-molecule based sensors that require certain reactive functional groups to be present in the analyte. The assay is operable for micromolar concentrations of analytes and can be used for real time monitoring of chemical reactions, for example, the racemization of (S)-1-phenylethanol catalyzed by an amberlyst.

It is quite surprising that other macrocycles have not been paid much attention, in particular the cyclodextrins that have a chiral cavity, despite the facts that multi-point interactions between guest molecules included within the chiral cavity of cyclodextrin have been shown to induce supramolecular chirality from the achiral guest. This actually results from tight packaging within the chiral space of cyclodextrin cavity by more than one guest molecules. In this case at least one guest molecule acts as a spacer that helps to fill the cavity, a mechanism that has been popular since the 1990’s for creating cyclodextrin-based room-temperature phosphorescence (RTP) systems, using for example a third component to enhance the RTP of bromonaphthalenes in aqueous cyclodextrin solutions. This actually opens up a new entry to chirality sensing by using cyclodextrin if the third component is the chiral analyte, as shown in this example.

Regarding the macrocycle-based chirality sensing systems here we emphasize those where the cavity includes more than one guest molecules (including the chiral analyte) and the sensor affords additional advantages benefiting from the cavity size and its hydrophobicity or hydrophilicity, while the ensemble is formed by the coupled supramolecular interactions among the guest molecules and the cavity.

**Synthetic oligomers/polymers**

Some of the polymers exist in helical conformation with the same amount of left- and right-handed conformers, equilibrium of which can be biased by the presence of a chiral analyte that interacts with the polymer. Quite often the so-called “majority-rules” effect was observed, in which a small ee produces a non-proportionally large CD signal, and thus the CD-ee curve shows a steeper slope around 0% ee. This phenomenon has been proposed by...
Yashima et al.\textsuperscript{16} to be applicable to the determination of a small enantiomeric imbalance. The working system is a stereoregular cis-transoidal poly(phenylacetylene) \textbf{1} consisting of a polyacetylene backbone as the chromophore and bulky crown ether as the pendant binding unit for amino acid (Fig. 4). Upon binding to \textit{l}- and \textit{d}-alanine (Ala), \textbf{1} exhibits strong chiral amplification, which was apparent even with 0.01 equiv of \textit{l}-Ala. An extremely strong “majority-rules” effect was observed and 5\% ee of Ala was able to generate a full ICD signal. Detection of extremely small enantiomeric excess of 0.005\% of Ala is possible. This system has been successfully applied to 19 \textit{I}-amino acids as well as 5 chiral amino alcohols.

Using the same concept of design, a stereoregular cis-transoidal poly(phenylacetylene) bearing a phosphoric acid monoethyl ester pendant was shown to form preferred helicity upon complexation with a series of optically active pyrrolines and piperazines in DMSO and in water.\textsuperscript{17} Strong chiral amplification was observed for \textbf{2} upon binding to (S)-3. The “majority-rules” effect is not as strong as that observed with \textbf{1}, 40–60\% ee of (S)-3 is needed to generate a full ICD signal. Lyotropic nematic and cholesteric liquid crystalline phases were observed for \textbf{2} in the presence of chiral amines. It shall be pointed out that the nematic and cholesteric liquid crystalline phases showed almost the same X-ray diffraction patterns, which indicates that the dynamically racemic and one-handed helices have the same helical structure, a hint that may help understand the operation mechanism. An issue that remains uncertain is the prediction of the occurrence or not of chiral amplification in the polymer based chirality sensors. This also exists with oligomer and supramolecular polymer based sensors, which will be discussed later in this Review, since the mechanism of chiral amplification remains unclarified.

Detection of high ee close to 100\% is however more important in asymmetric syntheses. Anslyn et al.\textsuperscript{18} recently developed a new concept of measuring ee higher than 95\% with lower errors, using the “majority-rules” active polymer \textbf{1} previously reported from the group of Yashima.\textsuperscript{16} By adding an equivalent amount of the opposite enantiomer, the high ee value of the sample was converted into low ee, thus cleverly employing the sensitive high slope of the low ee region (refer to Fig. 4C). The calibration curve exhibited a slope of 6.2 mdeg/(\% ee), which is higher than the slope of linear response (1.3 mdeg/(\% ee)) obtained in the same range of Yashima's system. For sample, with ee values from 95\% to 100\%, remarkably low errors were found, lower than commonly reported chiral HPLC error values of 0.5 to 1%. This system could well detect ee's over 95\%, at lower ee values larger errors however were observed. Meanwhile, the instability of the polymers necessitates the development of a more robust system for further practical applications.

Shinkai et al.\textsuperscript{19} observed an unexpected chirality induction from cationic polythiophene \textbf{4} by monosaccharides. Achiral polymer \textbf{4} in a good solvent (methanol) showed a peculiar CD signal when diluted with a poor solvent (chloroform) in the presence of galactose (pre-dissolved in DMSO). A colour change was observed, together with the appearance of new absorptions at 510 nm, 542 nm and 588 nm, respectively, indicating possible π-π* transitions in the formed aggregates of polymer \textbf{4}. Enantiomers of galactose, glucose and fructose generated symmetric ICD signals. The observed CD signal correlated linearly with the enantiometric ratio of galactose, which means no chiral amplification occurs in this case in which the chiral analyte seems to induce helical stacking of the polymers. More interestingly, the number of hydroxyl groups in the tested saccharides appears crucial to the ICD signals from the aggregates of \textbf{4}, since four-OH saccharides such as fucose and 2-deoxygalactose barely induce any CD signal. Thus, a multi-point hydrogen bonding mechanism was proposed for the chiral induction in \textbf{4} by saccharides. An approximately linear relationship was also observed between the optical rotation [\textgreek{x}]) as the polarizability indicator and the ICD signal at 598 nm. It was hence proposed that saccharides with larger dipole moment possibly induced stronger chiral mode of \textbf{4}. This phenomenon suggested that the dipole moment difference of the saccharides could be the reason that causes diverse ICD signals upon association with \textbf{4}. The system was applied for pattern recognition of saccharides.
Achiral polymers bearing chiral pendants were also developed for chirality sensing. Polythiophene conjugated with permethyl-\(\alpha\)-cyclodextrin via flexible hexamethylene chain, 5,20 was found to exhibit a weak positive Cotton effect on the main absorption band of the polythiophene backbone, suggesting that the appending cyclodextrin via a long flexible chain was ineffective in inducing a homochiral structure in the polymer backbone. Yet amino acids and dipeptides indeed enable induction of chirality-dependent hypochromic changes in the absorption spectra. Enantiomeric DD/LD-dipeptide pairs were better differentiated than the D/L-amino acid pairs, with the highest DD/LD selectivity of ca. 14 observed with Phe–Phe dipeptides. Chirality responsive behavior of poly(phenylacetylene)s bearing \(\beta\)-cyclodextrin pendants via ester, ether, and amide linkages21 was found to be linkage dependent. The amide linked polymers 6 exhibited a unique enantioselective gelation in response to the chirality of chiral amines. It appears that the relatively rigid linkage is more effective in communicating the chirality message of the pendants into the polymer backbones. In the latter case, the co-inclusion of more than one guest species within the chiral cavity of cyclodextrin may afford peculiar performance in chirality sensing, given the advantage of the poly(phenylacetylene) backbone that is known to afford chiral amplification (refer to Fig. 4C).

Given the difficulty in obtaining reproducible polymers, synthetic oligomers appear advantageous. Those with foldable conformations, termed foldamers, are the major structures that have been employed to build sensors that either show induced helicity upon chiral guest binding or enantioselectively recognize chiral guests. Hydrogen bonding driven achiral hydrazide foldamers,22 containing 1, 2, 4, 6 or 12 repeating dibenzozyldihydrazide residues (oligomers 7, 8–13), were designed as candidates of saccharide receptors.23 Chirality induction by alkyl-substituted mono- and di-saccharides was observed in chloroform. NMR, X-ray and IR spectroscopy reveal that, while short oligomers 7, 8 and 10 exists in rigid and planar conformation, longer oligomers 11–13 exhibit helical conformation with a rigid cavity of diameter 10.6 to 11.1 Å. Half of the carbonyl groups orientate inwardly that bind saccharides efficiently via hydrogen bonding. Moderate ICD signals were observed from oligomers 11–13 upon binding to saccharides (\(\alpha\)-D-glucose, \(\alpha\)-D-glucose, \(\beta\)-D-ribose and \(\beta\)-maltose), which was shown by a Job plot in 1:1 stoichiometry. This report highlights the importance of the helical conformation of the oligomers in the possible induction of chirality by a chiral analyte.

While saccharide binding induces chirality in helical foldamers 11–13 that have an achiral framework and originally exist as dynamic racemic mixtures, analogous helical foldamers that contain stereogenic centers could exist in a preferred handed helicity and therefore recognize chiral saccharides diastereoselectively. Wang et al.24 synthesized three chiral aromatic hydrazide foldamers with two \(R\) or \(S\)-proline residues incorporated at the backbone termini, which, due to their helical cavity structure, were shown to form 1:1 complexes with substituted glucose enantiomers 16 and 17 with good enantioselectivity. For example, the binding constant of 14/17 complex is 144 times higher than that of the 14/16 complex. The CPK model suggests...
that 14, 15a and 15b all exist in a helical conformation facilitated by intramolecular hydrogen bonding, as also indicated by the downfield shifts of the amide proton resonances. While 15a and 15b show mirror-imaged CD signals, non-mirror-imaged ICD signals were observed when 16 or 17 was allowed to interact with 18 in chloroform since diasteromers were formed. Mirror-imaged ICD signals were observed for enantiomeric complexes 15a/17 and 15b/16, 15a/16 and 15b/17. These observations suggest the potentials in chiral sensing, for example for ee measurements.

Abe and co-workers reported that synthetic poly- and oligo(meta-ethynylpyridine)s took a well-ordered helical structure upon binding to saccharides. The chirality of saccharides was transferred to the helical sense of the oligomers/polymer. Oligomers poly(m-ethynylpyridine)s 18 of 1, 2, 3, 4, 5, 6, 12, 18 and 24-mers (Fig. 5) were synthesized using Sonogashira acetylene coupling chemistry. 12, 18, and 24-mers were synthesized using 6-mer as the start “monomer” to generate relatively “clean” polymers. The polymers in CH₂Cl₂ exhibited two absorption maxima at 275 nm and 323 nm, respectively. The molar extinction coefficient at 275 nm depends linearly on the oligomer length up to 12-mer, whereas derivation starts to occur from 18-mer, suggesting the presence of intramolecular hydrogen bonding interaction of the saccharide-OH groups

Fig. 5 Conformation change of synthetic polymer 18 driven by saccharide complexation. (Reprinted with permission from J. Am. Chem. Soc, 2004, 126, 2022–2027. Copyright 2004 ACS.)

with the pyridine N-atoms in a polymer occurs to drive the helical conformation. Native saccharides were found to induce CD signals as well.

The same group also reported modification of an ethynylpyridine polymer into co-oligomers which undergo dynamic transformation from self-dimers in to helical complexes with saccharides (Fig. 6). Oligomers 19–23 consist of (1H)-4-pyridone and 4-alkoxy pyridine rings connected through an acetylene bond at their 2,6-position. Vapor pressure osmometry (VPO) of oligomer 19 and its methyloxymethyl protected derivative, 19-MOM, revealed that 19 favoured the dimer form while 19-MOM existed in its monomer form. 1H NMR confirmed that the oligomers self-associated via hydrogen bonding between N atoms of the 4-alkoxy pyridine rings and protons of (1H)-4-pyridone. Addition of octyl β-D-glucopyranoside to the solutions of oligomers 20–23 induced remarkable CD signals around 335 nm from the 1:1 interaction complex. Although the self-association of the oligomer itself obscured the quantitative characterization of the exact CD-active complex and the remaining dimers, the dynamic transformation between the CD-silent dimer and CD-active helical oligomer–saccharide complex was observed in saccharide recognition. This mechanism is of interest in that a structural change occurs upon saccharide binding, which may have resulted in an amplified signal output or better chirality sensing if allosterism would operate.

Jeong et al. reported an indolocarbazole foldamer 24 with larger aromatic components. It binds chiral organic ions, camphorsulfonates and cyclic monophosphate (cAMP), in the formed one-handed helical conformation. The ICD signal was found switchable through acid–base chemistry. When foldamer 24 binds (R)- or (S)-10-camphorsulfonate, intense mirror-imaged ICD signals were observed at 362 nm, suggesting biased formation of the diastereometric helical complexes. The helical structure was further verified from the specific rotation value of (R)-10-camphorsulfonate, which changes from $-32^\circ$ to $+224^\circ$ upon addition of foldamer 24. Hydrogen bonding interaction was identified from the large downfield shifts of the pyrrole–NH protons by 1.29, 1.73 and 2.57 ppm. The fact that the resonance signal of the aromatic CH in the central indolocarbazole

Fig. 6 Saccharide recognition by oligomers 19–23.
was hardly shifted suggests that the two indolocarbazole rings stack to afford the helical conformation. Modelling, together with exciton chirality analysis, showed that (R)-10-camphorsulfonate induced $\beta$-helix formation in 24. Low temperature $^1$H NMR suggested that in the presence of (S)-10-camphorsulfonate, over 90% of 24 existed in a one-handed helix, while the minor component was hardly detected even at $-80$ °C. TFA was able to quench the ICD signals generated from foldamer 24 and cAMP, which can be recovered by DABCO base, indicating a CD switching behaviour. This is insightful for understanding the mechanism of chiral induction in 24. It remains not straightforward to compare the chirality sensing performance of foldamer 24 with that of the above-mentioned other foldamers, yet structurally it differs in that it contains a larger aromatic component and less repeating units, which may afford not a complete turn structure with a seemingly larger cavity.

Helically folded aromatic oligoamide 25$^{28}$ represents a hetero-foldamer that consists of more than one kind of repeating units. Its hollow cavity was assumed to encapsulate tartaric acid. A long pyr-pyz-pyr linear segment was introduced to enlarge the diameter of the cavity, while the naphthyridine amide residue was incorporated to bind chiral tartaric acids. Upon addition of 1 equiv. D- or L-tartaric acid, the NMR signal of the free oligoamide 25 disappeared completely, indicative of a very high binding affinity. CD titration by pure D- or L-tartaric acid revealed an intense ICD signal, showing that the balance between the $M$- and $P$-forms of 25 is biased to one direction upon tartaric acid binding. The crystal structure validated that tartaric acid was completely encapsulated and surrounded by the oligomer. Other structurally related guest molecules such as meso-tartaric acid that differs from D- or L-tartaric acid only in the orientation of two OH groups and D- or L-malic acid with one less OH group were also tested. The binding was found to be weaker, which demonstrates the high sensitivity of oligomer 25 towards a subtle difference in the chirality information of the analytes. The multiple components in the oligomer seem to contribute to this character.

Given the fact that most biomacromolecules function in aqueous environments, developing water-soluble chirality sensors based on synthetic oligomers/polymers has also been targeted. Water-soluble synthetic oligoresorcinols (26–28)$^{29}$ were reported to self-assemble into single helical conformations in alkaline aqueous solutions and were applied as a chirality sensor for chiral guests (Fig. 7). 28 adopted double helices at low pH, which dissociated into single strands with increasing pH due to deprotonation of the phenolic protons as confirmed by $^1$H NMR. However, 8, 5 and 2 OH-protons remained bound to 28, 27 and 26 even in the presence of excess NaOH because of their high $pK_a$ of > 12. The oligoresorcinols adopted all cisoid-conformations through intramolecular hydrogen bonds between the phenoxide anions and the neighboring hydroxyl groups of the contiguous 2,2'-biphenol units. Addition of optically active ammonium (S)-29 induced a bias in the helical sense of 28, verified by the red-shift of the absorption at 331 nm as well as by the ROESY spectra. Binding of (R)-29 and (S)-29 induced mirror-imaged CD signals between 250–400 nm, which increases upon cooling from 25 to 0 °C. Short oligomer 26 generated almost no CD signal, implying that a minimum number of units in the oligomer is needed for the effective binding and the helical bias induction by the chiral guest molecules.

In terms of the chiral induction it can be either intermolecular or intramolecular or both. This was shown from the work of Huc et al.$^{31}$ Octamer 30 containing a chiral (R)- or (S)-phenethylamine group and achiral heptamer 31 were designed to verify the intramolecular and intermolecular chiral induction, respectively. Intramolecular chiral induction was confirmed to occur in octamer (R)-30 and (S)-30 by their CD spectra that featured two mirror-imaged CD signals at 270 nm and 322 nm, respectively, relating to the electronic transitions of a pyridine chromophore. The preference of $M$- or $P$-helix led by the chirality induction was further characterized by $^1$H NMR. The ratio of the right- and left-handed helical diastereomers of octamer (R)-30 was ca. 70:30 with a diastereometric excess of 40% at 10 °C. When achiral heptamer 31 was titrated by (S)-phenylpropionic acid 32, $^1$H NMR signals of two amide protons shifted downfield by 0.4 ppm and 0.15 ppm, respectively, which was attributed to two hydrogen bonds between peripheral acylaminopyridine units of heptamer 31 and carboxylic acid. Two positive CD bands were observed at 270 and 322 nm when (S)-phenylpropionic acid was titrated towards heptamer 31. Excessive acid however slowly...
decreased the CD intensity, suggesting partial unfolding of heptamer 31. The fact that the same CD bands were observed in the cases of intra- and inter-molecular chirality induction indicates the identical handedness induced in the synthetic oligomers. (R)-Mandelic acid 33 led to similarly induced CD bands in 31, implying that the same chirality induction mechanism operates. Titrations by (R)-camphorsulfonic acid 35 generated a more intense ICD signal at 1 eq., while the signal at 322 nm vanished and a new CD band was observed quantitatively at 290 nm. This was explained in terms of strong protonation of the diacylaminopyridines by (R)-camphorsulfonic acid that causes conformation rearrangement in the oligomer. As chiral octamer (S)-30 also contains “free” diacylaminopyridines for binding external chiral acids, besides the chiral phenylethylamine group, intermolecular handedness may also be induced. Titration by chiral acids 32–34 towards octamer (S)-30 showed no significant further effect on the CD signal from the “free” diacylaminopyridines region, showing that the intramolecular induction is more efficient than the intermolecular one. This may relate to the fact of less chance of observing chiral amplification in cases of achiral foldamers upon binding to chiral analytes, probably because the bias energy barrier between the P- and M-helices of the foldamers is not too high. With limited examples available, it is still too early to conclude if with these foldamer based sensors there would be a minimum number of repeating units and an optimal rigidity of the backbone that would be needed to ensure good performance.

Another interesting chirality sensing ensemble utilizing oligomeric structures (Fig. 8) was developed by Tanaka and Matile, where the oligomeric structure was not responsible for chiral recognition but forming the transmembrane pores. The sensing ensemble consists of egg yolk phosphatidylcholine (EYPC) vesicles entrapping self-quenched carboxyfluorescein (CF) dye, pore-forming molecule 36 and enzyme Subtilisin Carlsberg, for ee assays of polyglutamate. Rigid rod-like oligophenyl compound 36 with β-strand side chains is driven by intermolecular hydrogen bonding between the β-strands rolls into an oligomeric barrel-shaped pore in the lipid bilayer. The inner barrel surface contains cationic histidine and lysine residues that create pore blockage by poly-anionic guests such as polyglutamates. Stereospecific enzymatic reaction breaks down poly-L-glutamate, but not poly-N-glutamate, into monomeric glutamate now as a poor pore blocker, pore blockage therefore occurs only significantly for poly-N-glutamate. Without pore blockage, the self-quenched CF dye would be released from inside the vesicles through the pore, resulting in recovery of its fluorescence due to dye dilution. The rate of CF fluorescence enhancement of vesicle solutions treated with 36 following an enzymatic reaction thus reports ee of the polyglutamate analyte. Similar to the above-mentioned CB[7] assay that also relies on enzymatic reactions (Fig. 2), an ee value up to 99.9% can be accurately determined, again partly owing to the stereospecificity of the enzymatic reaction. Although this assay is limited for polyglutamate ee sensing, it provides an attractive approach of combining enzymatic reaction with a synthetic membrane transport system constructed by a synthetic oligomer, for sensing high ee close to 100%. This may be regarded as a dynamic macrocyce sensor.

It shall be pointed out that, although none of the foldamers discussed in this Review has yet been applied for chirality sensing, possibly due to the limited scope of chiral guest molecules that can interact with the foldamers, the structural framework and the design methodology demonstrated in those systems should provide useful guidance for developing foldamer-based chirality sensors, if a suitable analyte binding site, for example, an aldehyde group, and/or a chromophore could be attached.

**Supramolecular polymers**

Differing from synthetic oligomers/polymers, the building blocks of supramolecular polymers are held together by non-covalent interactions such as hydrogen bonding, aromatic π-stacking, and metal coordination. The ease of rationally designed building blocks to self-assemble into highly ordered helical superstructures in the presence of a chiral species in principle allows simple sensor design that the chiral
analyte induces the sensor molecule to undergo a helical aggregation. The monomer–polymer equilibrium due to reversibility of the noncovalent interactions endows supramolecular polymers with stimuli-responsive properties,34 which has been exploited for designing chemical sensors based on analyte-modulated aggregation.34

Fenniri group reported in 2002 an elegant example of chiral guest induced supramolecular chirality – helical rosette nanotubes formed by 37 with amino acid inducible chirality, although the system has not been exploited for ee sensing.15 The bicyclic base (GC base, fused by guanine and cytosine) motif in 37 forms a six-membered supermacrocycle in water stabilized by 18 hydrogen bonds, which further aggregates into a tubular architecture driven by the strong hydrophobic interaction. Attaching to GC base by the 18-crown-6-ether moiety provides a binding site for amino acids and the possibility of noncovalent interactions endows supramolecular aggregates to be influenced by the amino acids. This offers an efficient approach for chirality sensing of amino acids.

The enantiomer of higher concentration, supporting the enantiomer of higher concentration, totally generated by the enantiomer of higher concentration, supporting the proposed autocatalytic mechanism of this process, whereas a lower concentration enantiomer cannot express its chirality at the nanotubular level. The hydrophobic effect of the crown ether group allows small, aromatic, and hydrophobic amino acids to bind more easily to the GC base derivative compared to the other larger and hydrophilic amino acids. This offers an efficient approach for chirality sensing of amino acids.

He et al.36 established a chirality-sensing system based on pseudoisocyanine (PIC, 38) aggregates. Achiral PIC 38 is known to form J-type aggregates, with its critical aggregation concentration in water tuneable by salt concentration. In the presence of L-/D-phenylalanine, the ICD signal of PIC J-aggregates was observed in aqueous NaCl solution, the intensity of the Cotton effect being remarkably enhanced with increasing concentration of L-/D-phenylalanine. The ICD signal as a function of ee of phenylalanine exhibits the “majority-rules” effect, i.e. the chiral amplification. In addition, the chiral J-aggregates induced by D-tryptophan show opposite ICD signals to those led by L-phenylalanine, suggesting that the helicity of the chiral J-aggregates depends on the side group of aromatic amino acids.

Columnar porphyrin aggregates are also employed for chirality sensing. In the work of Watarai and co-workers,37 tetracationic porphyrin, the protonated form of 5,10,15,20-tetra(4-pyridyl)-21H,23H-porphine 39, is dissolved in an organic phase. Tetracationic porphyrin, the deprotonated form of Cu(n)-meso-tetrakis-(4-sulfophenyl)prophine 40, is facilely dispersed in an acidic aqueous phase of pH 2.3. Their mixing occurs at the toluene/water interface, leading to the formation of heteroaggregates consisting of 39 and the same amount of 40. When phenylalanine is introduced to the aqueous phase, centrifugal liquid membrane-circular dichroism (CLM-CD) spectra of the heteroaggregates reflect the absolute configuration of the amino acid. The sign of the CD signal of the heteroaggregates formed at the liquid–liquid interface is determined by the chirality of phenylalanine, while it is almost not detected from the organic or aqueous phase, which means that chiral heteroaggregates are only formed at the interface. The linear correlation between the CD signal at 410 nm and ee of phenylalanine, which means the absence of chiral amplification, allows the measurement of the chiral purity of a phenylalanine sample. Chirality of tyrosine and tryptophan can also be analyzed by the same interfacial chirality induction strategy, although the sensitivity is lower than that for phenylalanine.

Combining porphyrin aggregation with reversible covalent bonding between boronic acid and cis-diol, new systems were developed for cooperative molecular recognition of saccharides. Shinkai et al.38 developed a saccharide sensing scheme using porphyrin 41 aggregates. The boronic acid groups in 41 allow reversible interactions with saccharides. Helical porphyrin aggregates formed in aqueous solutions reflect the chirality of the added saccharide. By carefully comparing the absolute configuration of the tested monosaccharides and the sign of the exciton coupling CD signals, it was deduced that the helical orientation in the porphyrin-based aggregates is totally controlled by the direction of the 1,2-diol group in the furanose or pyranose form of the saccharide molecule. The system in principle should be applicable to ee sensing for saccharides, despite being not examined.
Employing aggregation of perylenebisimide (PBI) dyes in aqueous solutions and the interaction of boronic acids with diols, a new system for assays of ee, identity, and concentration of \( \alpha \)-hydroxy carboxylates was explored by Jiang et al.\(^{19} \) Achiral PBI dyes 42 and 43 bearing \( \text{para-} \) and \( \text{ortho-} \)-phenylboronic acid groups exist in small dimers or oligomers in the absence of an analyte, yet it forms large aggregates upon binding with \( \alpha \)-hydroxy carboxylate guests, leading to a decrease in perylene absorption around 500 nm. Meanwhile, the formed aggregates were optically active as shown by the strong bisignate ICD signal from the achiral perylene chromophore, which affords the capacity of ee determination by CD for seven \( \alpha \)-hydroxy carboxylates that bear no chromophore. The profile of the ICD spectrum is characteristic of the configuration of \( \alpha \)-hydroxy carboxylates, which was successfully used for analyte chirality differentiation by following a linear discriminant analysis (LDA). With most of the tested \( \alpha \)-hydroxy carboxylates a linear CD-ee relationship was found. In two cases, however, nonlinear dependence of CD intensity on analyte ee was observed, where a so-called opposite “majority-rules” was seen in that the slope is steeper at high ee. By combining the CD–ee dependence and the analyte-induced absorption quenching, the concentrations and ee’s of “unknown” samples were calculated simultaneously with the average absolute error within ±2.1%. Note that the boronic acid group that interacts with the chiral analyte locates away from the chromophore by a long distance, yet an effective chirality induction was shown by the observation of coupled exciton CD signals. This example therefore highlights the potential of using induced helical aggregation of achiral dyes for CD measurement of ee of those chiral analytes that bear no chromophore or bear a chromophore but it is far away from the chiral center. This expands the scope of application in chirality sensing of the classic CD spectroscopy that normally requires the presence of a chromophore next to the chiral center for direct measurements.

An interesting variation of the chirality induction approach in supramolecular polymers is not by using an achiral monomer but by a racemic mixture of enantiomers.\(^{40} \) \( N \)-Fmoc-\( L- \) and \( D- \)-alanes, \( L-\text{-}D-44 \), can gelate in a variety of organic solvents, while the fibrous or flat nanostructures observed in SEM show no apparent chiral structure. SEM images of the gels formed from the racemic mixtures with a slight enantiomeric excess show however obvious chiral twist. The highest CD signal was observed in the gel formed by \( L-\text{-}D-44 \) mixture of ee 2%, whereas the signal started to drop beyond ee 2%. This is different from the normal “majority-rules” active systems, despite the fact that the slope of CD signal versus ee is still steepest at 0% ee. This distinctive character of the racemic assemblies offers a new strategy for chirality sensing. Upon introduction of a small amount of amino acid derivatives to the racemate, a strong CD signal was observed since the perturbation of the added species leads to diastereoselective aggregation. This affords an extremely sensitive supramolecular chirality sensing system for protected amino acids of ee close to 0.

A macrocycle sensor has been shown to selectively recognize a guest enantiomer as described in the previous section, and its aggregates also hold potential for chirality sensing at the supramolecular level. Tsukube’s group\(^{41} \) designed a cholesterol-armed cyclen 45 for chiral recognition. The Na\(^+\)-45 complex is amphiphilic and thus pertains to aggregate in aqueous solution with a critical aggregation concentration of \( 4.0 \times 10^{-4} \) M in 80/20 H\(_2\)O/EtOH (pH 7.2), forming a chiral hydrophobic cavity that allows chiral species to be extremely sensitively sensed even by the naked eye to view the fluorescence of dansyl-L- and D-amino acid anions at the \( 10^{-7} \) M level, with a \( L-\text{-}D-\) enantioselectivity of maximum 2.2. ICD signals of Na\(^+\)-45 complex aggregates upon binding to dansyl-L- and D-amino acid anions exhibited opposite signs, correlating thereby the sign of the ICD signal to the absolute configuration of the amino acids. It is probably because of the too strong binding of both enantiomers, the enantioselectivity remains moderate.

Oligo(\( p \)-phenylenevinylene)s (OPVs), which possess an extended \( \pi \)-conjugation, are known for their optical and electronic properties. Molecular recognition driven self-assembly has been
applied to organize dimers of 46 into helical OPV stack aggregates.\textsuperscript{42} Saturation of the CD signal was observed at a (−)-phenylyphos concentration well below stoichiometry, indicating the operation of an nonlinear effect, known as the “sergeant and solders principle”.\textsuperscript{43} Moderate “majority-rules” effects were found, again showing chiral amplification. The resolution and detection of ee values apply well to other phencyphos derivatives (chlocyphos and anicyphos) and mandelic acid.

Apart from absorption, fluorescence, NMR and CD, the dynamic light scattering technique (DLS) can be used for chirality sensing when employing supramolecular polymers. Li and coworkers\textsuperscript{44} reported that chiral R-1,1,2-naphthol-derived calix[4]arene 47 undergoes analyte-dependent aggregation. The calixarene framework in the aggregates and appending chiral binaphthyl groups provide a chiral space for binding of the chiral analyte. Fluorescence of 47 is quenched effectively by Cu(II) and it recovers when mandelic acid (MA) is introduced, depending on the identity of the MA enantiomers. The limit of detection for chiral discrimination of MA is 2 \times 10^{-8} \text{M} by using fluorescence assay. The absolute configuration of MA is also reflected in the nanostructure of the self-assembly of the Cu(n)-47 complex. Mixture of the Cu(n)-47 complex and (R)-MA are organized to larger aggregates than that of Cu(n)-47(S)-MA. The difference in size distribution of the enantiomeric aggregates allows sensitive detection by DLS. The detection limit (2 \times 10^{-7} \text{M}) is improved by 100-fold compared to that of the fluorescence assay.

Coordination polymers were also exploited for chirality sensing. By mixing Ag(0) and cysteine (Cys) in aqueous solutions, coordinate polymers 48\textsuperscript{45} with a repeating unit of the Ag(0)-Cys form were obtained. The self-assembly occurs immediately in aqueous solution at pH 5, thanks to the argentophilic\textsuperscript{46} and electrostatic interactions. The limit of detection for Cys is at the micromolar level using absorption and CD signalling, while the molecular chirality of Cys is reflected by the sign of the induced CD signal, thus assuming a zero-background sensing system. Similar metalophilic interaction also occurs with other d\textsuperscript{10}/d\textsuperscript{8} transition metal ions such as Au(I), Cu(I), Pt(II) and Pd(II),\textsuperscript{46} chirality sensing using this concept shall be applicable to a broad scope of chiral analytes when the chiral analyte is equipped with a thiol (−SH) or pyridine group. Using luminescent rare-earth metal ion directed chiral assembly in solutions or in Langmuir–Blodgett films were also shown.\textsuperscript{47} This forms another basis of chirality sensing using metal complexes that would find applications in chirality sensing.

Chirality sensing in supramolecular systems are not limited to the solution phase, supramolecular gel is also a potential medium for discrimination of chiral species. A supramolecular chirality sensing system for phenylalanine (Phe) has been designed by Zhang et al.\textsuperscript{48} By simply mixing two equivalents of Phe and one equivalent of Cu(II), supramolecular hydrogel of the Cu(II)-Phe complex is formed (Fig. 9). Judging from the CD signals of the ν-ν transition of Cu(n), absolute configuration of Phe can be identified in the CD spectra of the corresponding xerogels. The gelation ability of the 2Phe–Cu metallogelator critically depends on ee of Phe. A full hydrogel state can be obtained when the ee value is higher than 80%, while the hydrogel collapses if the ee value is lower than 30%. This supramolecular system is stabilized by intermolecular hydrogen bonding, coordination of carboxylic/amine groups toward Cu(n), hydrophobic and/or π–π stacking interactions. In accordance with this assumption, no gelation was observed by replacing aromatic Phe with other amino acids. This establishes a new platform using supramolecular hydrogel for chiral sensing and recognition.

Nanoparticles

Nanoparticles in general act as both a signal reporter and the framework to immobilize chiral ligands. Size and shape of the nanoparticles therefore represent important parameters for their performance since they not only define the optical properties, but also the density and relative orientations of the ligands on the particle surface that are critical for their interactions with chiral analytes.

Uridine 5’-triphosphate (UTP) capped silver nanoparticles (Ag NPs, Fig. 10) have been prepared for chirality sensing of Cys.\textsuperscript{49} Difference in the interactions of ν- and υ-Cys with modified Ag NPs is displayed in the UV-Vis absorption. Upon
introduction of D-Cys, the yellow solution of Ag NPs rapidly turns red with a remarkable change in the absorption spectra, because of the D-Cys induced aggregation of Ag NPs. The same phenomenon does not occur when L-Cys is applied, implying that L-Cys is unable to induce the aggregation. The striking difference in the absorption spectra of the Ag NPs solution containing D- and L-Cys therefore enables enantiodiscrimination of Cys. Furthermore, enantioselective separation and enantiomeric purification were made possible by centrifuging the solution of Ag NPs with racemic Cys. The precipitates consist of UTP-capped Ag NPs and D-Cys that can be collected while L-Cys remains in the solution. With no need of CD measurement, chirality sensing can be easily monitored even by the naked eye.

Another colorimetric sensor for chiral discrimination of histidine (His) using Ag NPs was reported by Li’s group. The Ag NPs clusters, L-Arg–ZnTPPS–Ag NPs (Fig. 11), were obtained by simply mixing the sulfonated zinc tetraphenylporphyrin (ZnTPPS) modified Ag NPs and L-arginine (L-Arg). L-Arg not only provides a chiral recognition site, but assembles ZnTPPS–Ag NPs into clusters, via its coordination to ZnTPPS. The Ag NPs clusters exhibit stronger recognition ability to His and methionine (Met) than to other amino acids. However, only L-His can induce assembly of L-Arg–ZnTPPS–Ag NPs. An obvious colour change occurs during L-His induced aggregation, while D-His hardly leads to any colour change. The induced aggregation was assumed to result from the interaction of the carboxylate, amine and imidazole groups of His with the L-Arg–ZnTPPS–Ag NPs. The induced CD signal at 200 nm can be used for empirical assignment of the absolute configuration of His.

A fluorescent nanoparticle-based sensor was similarly developed for resolution of L/D-enantiomers. Aggregation of L-/D-Cys decorated CdTe quantum dots (L-/D-QDs) and gold nanorods (GNRs) was investigated by Xia et al. When D-Cys is introduced into the mixture of L-QDs and GNRs, a dynamic nanoparticle–nanorod assembly is formed, leading to quenching of the fluorescence of the QDs by 74%. In contrast, adding L-Cys to the mixture of L-QDs and GNRs only results in a slight or negligible change in the fluorescence. This implies that heterochiral interaction results in more notable fluorescence quenching than the homochiral interaction, which is further confirmed by the likewise assembly of L-/D-Cys in the presence of the L-QDs and GNRs. Not only can L-/D-Cys be directly quantified by fluorescence responses, the ee of the racemic Cys can be detected by the intensity of fluorescence as well.

Plasmonic chirality from the plasmonic nanoparticle dimers was also chosen as a candidate for chirality sensing. Through covalent binding between Au and S atoms, Au NP dimers are assembled in the presence of Cys (Fig. 12). The Au NP dimers prepared by L-Cys and D-Cys, respectively, exhibit distinguished induced plasmon-chirality as shown by their CD signals, allowing therefore a selective chirality sensing of Cys, since only a slight change in the CD signal is observed when other amino acids are introduced. It appears that the nanoparticles based chirality sensing is more straightforward as the difference in the changes of color or luminescence may be visible to the naked eye when an individual enantiomer is introduced. Despite the possible difficulty in obtaining reproducible nanoparticles as in the case of polymers, developments of nanoparticle based chirality sensors are promising, considering the
fact that robust methodologies are available for the synthesis and fabrication of nanoparticles of varying sizes and shapes.

Conclusions and remarks

We summarized four classes of chirality sensing systems that operate considerably differently from the traditional way of using small molecule-based sensors in terms of the design strategy and/or the sensing mechanism. These four chirality sensing systems are employing macrocycles, synthetic oligomers/polymer supramolecular polymers and nanoparticles based sensors. It should be emphasized that the developments of these supramolecular chirality sensing systems benefit very much from the accumulation of knowledge of small-molecule based chirality sensing. A major advantage of the supramolecular chirality sensor is the possibility of signal amplification because multivalent interactions may occur between these sensors and the chiral analytes. The diversity of structural frameworks that can be employed and readily made offers more chances for creating such sensors.

In order to render these supramolecular optical chirality sensing systems readily applicable for real analysis, for example for high throughput screening (HTS), three challenges need to be addressed. First, the scope of chiral analytes is typically limited to certain classes of compounds with reactive groups to form metal complexes or dynamic covalent bonds, such as amines, aldehydes, carboxylic acids, and alcohols, while a large portion of the synthetic reaction products do not contain those functional groups. In this regard, Nau’s cucurbituril-dye ensemble strategy (Fig. 3) stands out as it only requires an aromatic moiety for the analyte to interact within the macrocyclic cavity, and thus expands the scope of the chiral analyte. Given the availability of many other macrocyclic sensory frameworks such as calixarene, calixpyrrole, calixresorcinarenes, and even the recently actively investigated cycloparaphenylenes, this strategy could have more extension in designing chirality sensors for a broader scope of analytes. Similarly more chirality sensing systems can be designed utilizing noncovalent interactions, in particular the recently actively investigated halogen bonding. In these cases the dynamic characters of the noncovalent interactions may raise an issue of reproducibility of the formed supramolecular ensembles such as supramolecular polymers and ligand protected/stabilized nanoparticles, that deserves further efforts. Second, precisely measuring ee close to 100% is of greater interest in asymmetric syntheses, yet this has been scarcely realized using optical sensors. Two examples with a capacity of sensing high ee are described in this Review, albeit based on stereospecific enzymatic reactions that would have a severely limited analyte scope and require careful optimization of the reaction conditions. A strategically straightforward but challenging-to-achieve approach is to enhance the absolute CD intensity in the chirality induction approach using an achiral sensor or the enantioselectivity of a chiral sensor. Alternatively, the strategy of exploiting “majority-rules” active polymers by adding an equal equivalent of an opposite enantiomer seems promising, while the limitation of needing the knowledge of the analyte concentration could probably be removed by chemometric methods. Finally, synthetic difficulty should be taken into account to render the chirality sensor readily available for real applications. Easily synthesizable sensors can be designed, taking the supramolecular polymer approach as an example, by simply attaching an analyte binding site to a chromophore capable of aggregation, without the need for more prudent consideration in the position of the analyte binding site, which is often the case with small molecule based sensors.

It shall be noted that the investigation into these four classes of chirality sensors remains quite young, and detailed systematic explorations are needed to optimize structural and medium parameters that define the chirality sensing performance. For example, for oligomer/polymer based sensors, whether there are minimum sizes of sensors and optimal rigidity of the backbone that, together with the choice of suitable solvent(s), could ensure a good performance. We believe that with the huge basis of knowledge we have at hands of the small molecular based chirality sensors, chirality sensing strategies discussed here would grow mature and help to produce highly sensitive and facile chirality sensors eligible for real applications.

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Notes and references
