### 1

# Introduction

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Chirality is a widespread phenomenon in nature and plays an important role in chemistry, pharmacology, biology, and medicine. If a molecule cannot be superimposed on its mirror image, it is called a chiral molecule. The structure is mirrored into symmetrical molecules and chiral enantiomers. As a ubiquitous phenomenon in nature, chirality has been extensively studied at the molecule level. Most biomolecules are chiral and exhibit single structure, such as DNA, amino acids, peptides, and sugars. Moreover, lots of important biological reactions involve chiral interactions [1, 2]. Since Louis Pasteur firstly separated the tartaric acid enantiomers in 1848, chirality has fascinated the chemistry world [3, 4]. In the pharmaceutical industry, the left-handed or right-handed isomers of some molecules show completely opposite pharmacological effects and toxicity. To avoid the adverse effects of chiral drugs, the selective synthesis of chiral drugs has been a research hot spot in the field of pharmacy. Therefore, it is of great scientific and practical significance to explore the role of material chirality in the origin of life, chemical reactions, and disease treatments. Until now, molecular-scale research is relatively mature, and chiral research and exploration promotes the progress of science and technology in different fields, especially in nanoscience.

## 1.1 Chirality and Asymmetry

Chirality is a geometric property that implies that a mirror image of an object cannot overlap with the original object [5, 6]. Notably, this attribute is related to the scale or the state of matter; thus, it can exist in any object, real or imaginary. The term "chirality" refers to unique geometric shapes of atoms, molecules, particles, etc., other than the resulting optical or chemical effects. In chemistry, two nonsuperimposable objects that have a mirror-symmetry relationship are called enantiomers. The simple physical properties of pure enantiomers of organic materials, such as melting temperature, evaporation temperature, and color, exhibit identical features.

Chiral molecules with the same chemical composition and have no mirror symmetry are diastereomers. Diastereomers have different physical properties. Because of many choices for the geometric positions of atoms in nanoparticles (NPs), diastereomers with small differences are the most common in NPs, such as phase transition temperatures or color. Furthermore, the secondary properties of chiral assemblies (including optical, chemical and biological performances) are the derivatives of the geometry of a particular chemical object at one or all the scales mentioned above. Of course, these properties are the main reasons for formation of chiral molecular and nanoscale structures in most cases and determine the functionality and practicality of chiral nanomaterials.

Moreover, the difference between individual objects and a collection of a mass of these objects also require the secondary effects of chiral nanostructures. The collection of chiral objects is usually in the solution of chiral molecules or dispersions of individual chiral NPs. The relative number of respective enantiomers determines the possibility of observing the secondary properties of chiral chemical structures. Notably, individual objects, such as molecules, nanoparticles (NPs), or higher order structures, can be chiral. However, positive and negative polarization rotations of different enantiomers may cancel out each other. Thus, the spectral detection of dispersions or solutions may display no rotatory optical activity. Moreover, ensembles of chiral molecules, NPs, and their nanostructures can usually exhibit equivalent enantiomers. Thus, these ensembles are called racemic mixtures. When the amount of one enantiomer is higher than that of the other one, the mixture is called non-racemic. Typically, when the molar preference of one enantiomer is relative to the other one, it is usually expressed as an enantiomeric excess. The enantiomeric excess is measured as a percentage (%), and typically abbreviated as ee. When a solution or dispersion is made up of a single enantiomer, it is called homochiral with an ee of 100%. As pointed out by Kelvin [7], Pasteur [8], and Piutti [9], homochiral compounds are common in bioorganic materials. However, they are not applicable in many inorganic nanostructures, as discussed in this book. Through chiral separation [10], e-beam lithography, and NP self-organization [11], nearly all homochiral chemical systems have been obtained from inorganic nanostructures.

## 1.2 Chiral Origin of Nanomaterials

### 1.2.1 Chiral Geometries of Nanoparticles

The typical pictorial representation of NPs as perfect spheres, cubes, ellipsoids, etc. may not be the best way to keep in mind when it comes to understand their chirality. Asymmetric NP cores, ridges, apexes, adatoms, vacancies, dislocations, etc. conduce to chiral geometric forms of these chemical species [12]. In addition, edges, apexes, and faces of an inorganic material cannot be coated with surface ligands uniformly or in a widely accepted radial manner. Therefore, the surface layer contains asymmetry, except for core defects, and causes the chiral geometric elements. The latter can happen, as exemplified by the epitaxial lattice-to-lattice coalescence of NPs, also



**Figure 1.1** (a) Type 1 chirality: the inorganic core with chiral shape. (b) Type 2 chirality: chiral surface of the inorganic core. (c) Type 3 chirality: chiral pattern of the surface ligands. (d) Type 4 chirality: polarization effects [1]. Source: Ma et al. 2017, Reproduced with permission of American Chemical Society.

known as oriented connection [13]. Even if the overall shape of the NP is spherical, or the inorganic core crystallinity is perfect, or the stabilizers evenly modify, the NP may still be chiral. Under the external bias conditions of a given electric or magnetic field, the high polarizability of the inorganic core makes the electron density asymmetrical, resulting in chirality. Therefore, there may be multiple sources of chirality in NPs, and it may be difficult as well as interesting to know which of them is/are responsible for specific secondary effects.

The first type of chirality is related to the asymmetry of the nanostructure's inorganic core. The object here is a continuous part of an inorganic substance, which defines the nanostructure's inorganic properties (Figure 1.1a). NPs with different shapes have been included in this group, such as tetrahedrons with variable truncations [8], twisted gold clusters [14, 15], and twisted nanorods (NRs) [16]. Apart from the NPs, nanohelices [17], twisted ribbons [18], and asymmetric objects with less traditional shapes (such as nanopillar caps [19]) are also included to this part.

In most situations, instead of packing a collection of atoms in a specific crystal lattice, the geometry of the NP core can be taken into account as a whole, especially for nanocolloids via bottom-up techniques. Overall shape of NPs should be given for the materials with chiral lattices, exemplified by macroscale crystals of tartaric acid separated by Pasteur. Assuming that an inorganic material was fabricated with a chiral crystal lattice by the top-bottom method, such as lithography, a mirror-symmetric cube is realistic. However, a non-racemic ensemble of such NPs and a chiral bias at the atomic scale during the growth will be required to explore chirality in such materials.

From the synthetic point of view, though the organization of the inorganic core is often strongly affected by the surface ligands, Type 1 chirality does not consider surface ligands. In fact, it is difficult to distinguish whether the surface layer chirality is resulted from the chiral packing of atoms in the small cores (0.5–1.5 nm) or vice versa. Thus, from this perspective, one may consider it as a controversial issue to distinguish the ligand shell chirality and core chirality; however, this is not the case. Actually, it is possible to decouple the chirality of the NP cores and the organic shells. Chiral geometries of inorganic cores with several nanometers have been reserved in the case of altered composition of the surface layer, such as twisted rods and helices [20–22].

Moreover, from the thermodynamic view, geometrically distorted structures will be more stable than perfectly packed symmetric crystal lattices. Therefore, organic ligands are not essential for the occurrence of the NP cores chirality. For example, as observed in gold nanoclusters, the energy preferred to the chiral structure instead of the symmetric structure, which resulted in the transition from the symmetric cubic to the twisted lattice [23]. As a point to illustrate the importance of understanding the chirality of ligand-free NPs, chiral inorganic NPs with a limited amount of stabilizers might be characteristics of interstellar matter.

The driving force of the chiral configurations of NP cores is different from that of surface ligands, including the thermodynamically favorable distortion of the nanoscale inorganic substance lattice. For example, a perfect tetrahedron can be prepared merely by one atomic packing; however, a tetrahedron with four different apexes possesses degenerate ways to arrange these apexes. Compared with an achiral perfect tetrahedron, such degeneracy makes the defects stable with an entropy of c. 8 kJ mol<sup>-1</sup>. Therefore, according to the enthalpy contributions of each defect, a clear distribution of chiral NPs can be obtained. Nevertheless, not all NPs can be explained by such a purely geometric illustration. It is essential to explore the amount of entropy and enthalpy caused from the defects of chirality.

Other types of chiral NP geometries are associated with the existence of surface ligands. These surface ligands make adequate for experimental observations under certain conditions. Type 2 chirality of NPs is related to asymmetries of the NP core surface. When the chiral surface ligands result in such asymmetries, it can be called chiral footprint [24]. More generally, it is inorganic surface chirality. In the presence of stabilizers or other factors, the NP core atoms exhibit distortions and displacements, such as addition of atoms, erosion of atoms, or atomic reconstruction responding to chiral media (Figure 1.1b). Different from Type 1 chirality, in this case, the shape of the inorganic core may be achiral. The surface ligands display intense interactions with the core of inorganic materials. Usually, two anchoring groups are carried along with the inorganic core, and the two oxygen atoms are from two carboxylates, or carboxylate groups and thiolates. Particularly, the anchoring groups may lead to the distortions easier than the weak ligands with single-point attachment. For example, the L-cysteine methylester, N-isobutyryl-cysteine, and D/L-penicillamine ligands possess carboxylates and thiol groups, which may result in chiral distortions [25-27].

In most cases, Type 2 chirality is related to surface ligands. Note that surface ligands can be chiral, racemic, or achiral. Type 2 chirality exhibits a significant difference from Type 1 and Type 3 (discussed later). Type 2 chirality is affected and related to the specific surface states of inorganic matter, while the electronic states related to the inorganic core (plasmonic, excitonic, etc.) are not affected [24]. To further illustrate the importance and universality of Type 2 chirality of individual NPs, it will be discussed in the context of classical researches of surface chirality, such as inorganic surfaces associated with the origins of life [28]. This type of chirality may happen in a lot of cases, as exemplified by surface reconstruction. For a detailed example, when all mirror symmetry planes are destroyed, the surface atoms shift in unusual configurations can appear after the adsorption of tartaric acid on Cu [29, 30] or Ni surfaces [24] (Figure 1.1b). It seems that the double or higher coordination of the ligands is essential; otherwise, the ligands might easily rotate freely around their unique NP bonds, and such thermal agitation may result in full racemization (*ee* = 0%).

Type 3 chirality in individual NPs is related to chirality of the stabilizer shell, as exemplified by the molecules with chiral organic shell and achiral for their core and surface [10, 31]. Importantly, achiral surface ligands may also result in chirality. Here, the stabilizer molecules packing on their surface are related to the symmetry breaking (Figure 1.1c). In other words, the geometry of the object considered here is a collection of the surface-bound organic constituents. Type 3 chirality of chiral NPs shows obvious different biological and chemical properties, since it is the main determinant factor for NP–protein interactions, NP assembly into the superlattices, as well as chiral separations.

The bonding mode of stabilizer molecules might not follow the underlying inorganic crystal lattice symmetry and may lack the necessary symmetry elements. This chirality can be produced by the chiral arrangement of Au-thiolate ligands, such as a staggered arrangement. Taking Au<sub>38</sub>(SCH<sub>2</sub>CH<sub>2</sub>Ph)<sub>24</sub> NP as an example, it displays a prolate shape and has a face-fused biicosahedral Au23 core protected by three short Au(SR)<sub>2</sub> and six long Au<sub>2</sub>(SR)<sub>3</sub> staples. The Au<sub>23</sub> core is a perfect  $D_{3h}$  symmetry [10]. In particular, the long staples are organized in a chiral staggered configuration, which consists of two triblade fans with three staples. They can rotate either in a clockwise or anticlockwise. In the case of short staples, they are slightly tilted, to follow the handedness of the long staples. Similarly, Au<sub>40</sub>(2-PET)<sub>24</sub>, Au<sub>38</sub>(2-PET)<sub>24</sub>, and Au<sub>38</sub>(SCH<sub>3</sub>)<sub>24</sub> clusters were reported to show chirality analogous to Type 3 chirality, which are arranged around the achiral metal core by the chirality of the Au-thiolate ligand [32, 33]. Some of the organic shells may show a patchy-like geometry, which may cause a nonsuperimposable mirror image, particularly for the three-dimensional (3D) surface layer [34]. It is worth to mention that when the temperature rises to the activation energy threshold for the translation of molecules, as exemplified by thiols along the underlying inorganic surface, mobility of the organic molecules on the surface of NPs may give rise to the transformation of one NP enantiomer into another one.

Type 4 chirality in individual NPs can be described as chiral field effect (Figure 1.1d) [35]. This type of chirality, unique to NPs, is related to high polarizability of some inorganic nanomaterials. Similar to Type 3 chirality, the atoms

are achiral distributed in the NP core; however, the electrical field of the surface ligands or other source may affect the distribution of electrons. In achiral ligands with chiral adsorption patterns, it may produce asymmetric polarization patterns. The asymmetric polarization patterns can also occur in chiral ligands with achiral adsorption patterns, as well as in the conditions for chiral ligands with chiral adsorption patterns. Chirality can be produced near enantiomers by high polarizability of the inorganic core typical for plasmonic NPs. It is normal for chiral ligands with achiral adsorption patterns to show Type 4 chirality. The modified NPs often show a chiroptical activity in the ultraviolet (UV) range (200–400 nm). Because of the polarizability of the NPs, the circular dichroism (CD) spectrum during the UV part may change in comparison to their original chiral ligands. Moreover, chiral bands can also be produced in the plasmonic region, such as ~405 nm for Ag NPs, 520 nm for Au NPs. These NP systems can include peptides [36], peptide nanotubes [37], or proteins [38], which are physically or chemically adsorbed on surfaces.

Under the incident electromagnetic radiation, the high polarizability of metal NPs can give rise to localized areas high electrical field around them, which are usually called "hot spots." And then, it can lead to intense electronic transition enhancement for organic ligands. In addition to Raman scattering enhancement, these hot spots can also enhance chiral activities [39]. This strong effect derives from the polarization of electron density in NPs, which reflects the existence of the organic matter chirality in the hot spots. Therefore, it has been classified as Type 4. Notably, because of the resonance between the adjacent plasmon polarization oscillations, chiral band is enhanced by the hot spots in NP assemblies. Due to their popularity in the academic literatures, it can be attractive to attribute the chiral activities of the NP assemblies to the plasmonic enhancement effects. As a matter of fact, the diverse contributions to the CD activity requires to be evaluated [22].

In general, it is essential to understand the atomic and molecular structures to distinguish the different types of chirality (Type 1, Type 2, Type 3, and Type 4) for NPs. In fact, it is still quite difficult to decouple the chiral effects from all those asymmetric geometric features based merely on the results of CD or optical ration dispersion (ORD). Nevertheless, this is feasible to illustrate the molecular dynamics of NPs and their interactions with the incident photons based on multiscale computational methods. It can be simply assumed that there is Type 4 chirality in plasmonic NPs with a chiral surface layer.

### 1.2.2 Structural Origins of Chirality

Type 1 chirality in NPs was distinguished in experiments [40] and simulations for Au nanoclusters [41]. Taking advantage of genetic algorithms and many-body potentials, the density functional theory (DFT) calculations method serves as a powerful tool for simulations of chiral nanostructures among the computational tools. Only relatively small atomic systems of the above-mentioned chiral nanoclusters can be studied at present. DFT studies have shown that methyl thiol ligands on a truncated cuboctahedron with a face-centered cubic structure can result in chiral atomic packing of the inorganic core, such as  $Au_{38}$  cluster coated with 24 HSCH<sub>3</sub> molecules

resulting in chiral distortions on the Au<sub>38</sub>(SCH<sub>3</sub>)<sub>24</sub> cluster [42]. The Hausdorff chirality measure (HCM) shows a quantitative measure of asymmetry for any geometric figure [43], the HCM value increases with the number of thiol molecules. HCM is equal to 0.160 and 0.121 for methyl thiol-stabilized Au<sub>28</sub>(SCH<sub>3</sub>)<sub>16</sub> and Au<sub>38</sub>(SCH<sub>3</sub>)<sub>24</sub> clusters, respectively [44]. Similarly, some theoretical studies have shown that many of the asymmetric or asymmetric topological structures have energy close to or lower than the lowest energy ordered isomers for bare Au nanoclusters in the range of 10–75 atoms [45].

Type 2 chirality was distinguished in NPs capped by *N*-isobutyrylcysteine [25]. These molecules were attached to the Au surface in the form of two points and distorted the underlying inorganic core, resulting in intense CD activity (Figure 1.2A,B) [26]. Another representative research was about  $Au_{102}(p-MBA)_{44}$  clusters. A chiral stabilizer shell appeared due to the hydrogen bonding between carboxylic acids; the achiral *p*-MBA gave rise to a chiral displacement of atoms on the Au surface [47]. The ligand exchange following the synthesis experiments demonstrated the chiral memory of NPs. Taking CdTe NPs as an example, the surface memory was also found for NPs with Type 2 chirality [27]. The surface of thiol-coated CdTe NPs was distorted with the addition of a chiral ligand. The achiral thiol-coated CdTe still showed a symmetrical mirror chiroptical band, which was similar to the original chiral L-cysteine methyl ester hydrochloride-coated CdTe, after the ligand exchange reaction in the presence of the achiral thiol. Such effects were related to the "stored" chirality on the NPs surface instead of that in the NP core.

Type 3 chirality was distinguished in NPs with a symmetric Au core. The ligand stabilizers were attached to the "staples" motif and created chiral patterns on the surface of NPs. In the case of Au<sub>38</sub>(SR)<sub>24</sub> protected by three RS(AuSR) and six RS(AuSR)<sub>2</sub> units, both of the crystallographic nanostructures and the optimally simulated nanostructures exhibited an achiral gold core with 23 atoms (Figure 1.2C) [46]. However, the geometric arrangement of the nine Au-S units indicated chiral  $D_3$  symmetry. Such nanoclusters demonstrated intense chiral optical activity corresponding to the metal-metal or ligand-metal charge transfer (Figure 1.2D). Similarly, Au<sub>40</sub>(2-PET)<sub>24</sub> generated enantiomers with opposite CD signals following the separation on a chiral cellulose-mediated high performance liquid chromatography (HPLC) column, in spite of the achiral molecule of the thiolate stabilizer. The 2-positron emission tomography (PET) staples on the Au<sub>40</sub> cluster surface were believed to cause the enantiomeric preference in NP adsorption to cellulose [32]. Notably, other types of chirality also existed in the above-discussed NPs. It may be worth to point out that rarely NPs only displayed one type of chirality. Due to the involvement of different scales and different matter (organic or inorganic), the secondary effects of all types were obvious different.

Type 4 chirality in NPs is suitable for an achiral metal core placed in a chiral environment. Charge-perturbed particle-in-a-box calculations demonstrated that chiral stabilizers placed in achiral adsorption patterns on a metal NP surface resulted in chiral image charges in inorganic crystal lattices. The asymmetry of the adsorption mode and the influence of the ligand on the electrostatic perturbation have a significant inducing effect on the chirality of the symmetrically polarizable core



**Figure 1.2** (A) Calculated conformers of deprotonated *N*-isobutyryl-L-cysteine on Au<sub>8</sub> nanocluster. (B) Comparison between simulated and experimental VCD spectra of *N*-isobutyryl-L-cysteine on Au nanoclusters [26]. (C) Chiral  $D_3$  arrangement of the Au-S atoms (a). Optimal SCH<sub>3</sub> arrangement on structures (b). (D) Simulated rotatory strength and chiral spectra [46]. (E) Au<sub>28</sub>(R-methylthiirane)<sub>6</sub> (a) and Au<sub>28</sub>(glutathione)<sub>6</sub> (b) using partial charges for the molecules and their image charges. (F) The simulated CD spectra [35]. Source: (A–C) Reproduced with permission from Refs [26, 46], respectively. Copyright 2006 and 2010, respectively, American Chemical Society; (E, F) Reproduced with permission from Ref [35]. Copyright 2006 Royal Society of Chemistry.

(Figure 1.2E,F) [35]. Some researches ascribed the observed optical and chemical effects to this type of chirality. Typically, their dispersions show chiral optical activity of the stabilizers (such as L-glutathione) and inorganic core (such as Au) in the spectral window. This observation indicated that the chirality of surface ligands was transferred to the plasmonic oscillation structure of the metal core through a variety of possible mechanisms.

The near-field effect often includes the description of various plasmonic NPs and has been extensively treated theoretically [48] and experimentally [49]. As a matter



**Figure 1.3** (a) CD spectra of Au NPs with or without E5 peptide. (b) The calculated CD spectra for a dipole of chiral molecule and for a dipole – nanoparticle complex with two separations [51]. (c) Salt-dependent CD spectrum evolution of ssDNA-modified Ag NPs with ionic strength. (d) The design of "individual plasmonic chiral NPs" using Au/Ag core-shell nanocube. The UV-vis absorption and CD spectra of ssDNA-coated Ag nanocubes [52]. Source: (a-c) Reproduced with permission from Refs [51, 52], respectively. Copyright 2011 and 2013 American Chemical Society.

of fact, an explanation of the CD activity of the plasmonic NPs typically involves the effect of the NP field on chiral stabilizers and/or the field of stabilizers on the NP core, such as Au NPs with chiral 1,3-disubstituted diaminocalix arene ligands [50], peptide-coated Au NPs (Figure 1.3a,b) [51], and photo-synthetic proteins [38]. High enhanced rotatory optical activity is ascribed to the field effects (Figure 1.3c,d) [52], which displayed substantial practical value.

The far-field electromagnetic coupling between a localized plasmon of an achiral structure and the surrounding chiral molecular layer may also give rise to CD activity. Far-field electromagnetic coupling effect caused the unexpected chiral distortions of the electron gas. It has been confirmed by comparing experimental results with a simple electromagnetic model, which included a plasmonic object coupled with a chiral medium [49]. So far, even a chiral NP may be considered a complex chiral system with multiple chiral geometric structures simultaneously. In addition, due to other chirality triggered by the chiral arrangements of the stabilizer shell, it is quite difficult to point out the thermodynamic origin of chirality in NPs. Noted that the secondary properties-optical, chemical, biological properties could be derived from one configuration rather than the other enantiomer configuration, resulting in the understanding of different contributions to chirality in NPs. Therefore, it is still challenging to determine the origin of secondary effects of chirality in many nanomaterials.

Therefore, the ligand exchange of chiral ligands on the NP surface, such as thiolate to phosphine, often gives rise to the chiral band modification. However, it remained unclear as to the NP structure alterations in this process and remaining chiral/achiral structure of the metal core [53]. The chiral ligand (*N*-isobutyrylcysteine) was exchanged and caused the chiral inversion by stabilizers, but the atomic structure of the NPs remained unchanged. Even if the ligand was exchanged with achiral ligands, the induced surface chiral distortion could be retained, especially for multiply anchored ligands, such as carboxylate groups and thiolate ligands. Importantly, both the stabilizer shell and the metal core may change by the ligand exchange, including the average size. The ligand exchange can give rise to smaller or larger size clusters. For example, if the ligands are exchanged with hexanethiol,  $Au_{75}$  clusters can be obtained [54]; however,  $Au_{13}$  icosahedron can be formed from  $Au_{25}$  by etching the core [55]. The ligand exchange chirality causes alterations in the metal core, which requires further studies.

## 1.3 Relationship with Known Chiral Materials

#### 1.3.1 Similarity to Chiral Inorganic and Organic Molecules

Considering the diversity of chiral structure origins of NPs, it should be emphasized that these geometric shapes also exist in many other chiral materials based on the traditional chemistries and compounds. The structural design of different scales and multifunctional "building blocks" may be extended from various branches of classical chemistry to nanomaterials of "nano"chemistry [56]. For example, the NP assemblies resemble the well-known supramolecular assemblies of organic molecules [57]. Besides, as the similar in the scales and geometries between the NPs and the liquid crystal (LC) phases [58], the similarity has led to the emergence of hybrid nanoparticle–liquid crystal (NP–LC) materials, which is a promising direction in the field [59]. The cholesteric LCs may be a preferentially selected system for future study. It may be an attractive research direction to study the chiral induction of achiral LCs in the nematic phase.

The twisted NR pairs from Au or tellurium (Te) exhibit obvious similarities to the well-known binaphthyl compound (BINAP) with the geometry analogous to that of open scissors [60]. Chiral compounds assembled through metal center coordination bonds also have many similarities, although their scale usually is smaller than individual NPs or their assemblies [61]. Moreover, propeller-like coordination complexes, as one of the earliest chiral inorganic compounds, have been achieved in inorganic NP assemblies with a DNA-bridged NR assembly around an NP [62]. Large-scale coordination compounds, such as metal–organic frameworks (MOFs) and polyoxometalates (POMs) [63], have also been extended to the nanoscale. Importantly, the chiral geometries and chirality transfer mechanisms of chiroptical POMs

resemble those of individual NPs. Therefore, it has paved a flexible and feasible way for the construction of chiral POM–NP hybrid nanostructures [64].

### 1.3.2 Similarity to Biological Nano- and Mesoscale Compounds

As in biology, a great majority of biological molecular and supramolecular compounds are chiral, which can be attributed to homochirality of life on Earth. There are multiple considerations for the similarities between the chirality of NPs and biomacromolecules. One common phenomenon is that chiral biomolecules are generally used as ligands at the surfaces of NPs, which partly contributes to chirality of individual NPs. Moreover, the size of the NPs is similar to the observed biological macromolecules. The characteristic size of numerous proteins is a few nanometers, while that of amino acids and nucleotides is usually smaller than 1 nm. Some proteins are even larger, with a size of tens of nanometers. Furthermore, some anisotropic protein molecules reach mesoscale dimensions. Therefore, a 300-nm-long triple helix of collagen molecule assembles in over 20 µm fibrils. Almost all soluble globular proteins, their oligomers, and complexes display intricate molecular shapes. These nanoshapes show obvious chiral activity and belong to a number of chiral point groups. In this case, the analogy to NPs with Type I chirality is very clear. To further expand this idea, the surface chemistry of water-soluble NPs shows an obvious similarity to the chemistry at the interface of protein molecules and aqueous media due to the dependence on the same chemical groups: -OH, -COOH, -NH<sub>2</sub>, etc. Therefore, the stabilizer shell chirality can be compared with the atomic-scale packing of similar chemical groups and segments on the outer surface of protein or DNA globules. Similar parallel processing can also be carried out between the "staples" of the surface ligands on NPs and packaging of peptides, such as chaperonin molecular units [65].

### 1.3.3 Hierarchical Chirality

The chiral geometric structures of inorganic and biological nanostructures show obvious similarities. New insights may be brought into NPs and other nanostructures by the juxtaposition of biological and inorganic nanostructures, one of which is hierarchical chirality. For example, in proteins, cooperative behavior of hydrogen bonds and other intermolecular interactions can give rise to secondary nanostructure patterns from amino acid chirality at the atomic scale, as exemplified by  $\alpha$ -helices and  $\beta$ -sheets. The secondary chiral structures may further generate the tertiary and quaternary structures of proteins. As common in protein complexes and rodlike viruses, helicoids can be produced with the self-assembly and aggregation of proteins [66]. Due to the complementarity of the chiral motifs and cooperativity of the interactions, atomic-scale chirality of NP stabilizers and NP cores can result in a similar hierarchy of chiral inorganic NPs structures. In the arrangements of stabilizers on the NP surface, cooperativity interactions are evident [67]. Hierarchical chirality can be observed in NP assemblies, such as the chiral supraparticles from Au NRs with a twisted rod arrangement originated from the CdTe NPs shell with amino-acid

surface ligands. More complex hierarchical assemblies can also be prepared. The assembly of chiral NPs is similar to that of tobacco mosaic virus [68].

Other research fields associated with chiral NPs may also be inspired by the relationship between the chirality of individual NPs and biological molecules, which are based on the difference in biological activity of different enantiomers. The interactions between chiral graphene quantum dots and mammalian cell membranes show the difference, which have been observed experimentally and computationally. Different enantiomers of NPs may selectively interact with chiral biomolecules, such as enzymes, membranes, and even DNA. Therefore, they may bring distinct environmental and health hazards. These chiral NPs have not been observed in experiments and will be resolved in the future.

## 1.4 Characterization Methods

### 1.4.1 Optical Spectra of Chiral Nanostructures

Optical characterizations are the core secondary properties of chiral molecules and nanostructures in the field of physical phenomena. Therefore, it may be useful to study the origin of chiral NPs, their relationship with geometric structures, and chiroptical information from different types of NPs. Most of the chiroptical activity of individual NPs is associated with two quantum mechanical phenomena at the nanoscale, which are plasmons in metallic NPs and excitons in semiconducting NPs. The delocalization of charge carriers over the NPs can be characterized by these electronic states and therefore mainly depend on the crystal lattice of the NP core. In addition, metal-to-ligand charge transfer (MLCT) transitions may occur at the interface of the stabilizers and metal core [69]. All these excited states are influenced by shapes, sizes, surface ligands, and the surrounding dielectric environment of the NPs. When nanostructures exhibit a chiral shape, their plasmons and excitons may display chirality. Moreover, any other optoelectronic properties may also show chirality, which depend on the symmetry of the inorganic core and the overall electronic structure related to the excited states of the NP core. Certainly, the MLCT transitions depend on the chirality of ligands. They also depend on the symmetry of the NP core because of Type 2 chirality in the NPs and the contribution of other chirality.

In general, CD spectra and optical rotation dispersion (OR or ORD) spectra are the most commonly used spectroscopy tools in this field. They are generally used to describe the electronic transitions of chiral NPs from the visible (vis) to the near ultraviolet (UV) photons, including electronic and plasmonic transitions. The circular polarization of the incident photons can determine their vibrational components and can be measured by vibrational circular dichroism (VCD) and the Raman optical activity (ROA) methods [70]. Similarly, in the case of inorganic structures, CD and ORD spectroscopy are the most commonly used tools, and other spectroscopies can be applicable as well [26].

The ORD spectrum describes that optical rotation of a substance changes with the wavelength of light that passes through it. In this case, smaller wavelengths lead to greater optical rotation with the same path traveled by the light. The ORD spectrum can describe polarization plane rotation when a linearly polarized light beam passes through a material. Equation (1.1) describes the plane rotation per unit length, which expresses the circular birefringence of the chiral media. When the left circular polarization and right circular polarization components of linearly polarized light propagate in the chiral media, the difference between the refractive indices  $n^{\rm L}$  and  $n^{\rm R}$  can be positive or negative, related to the common chemical names of right- and left-handed media, respectively.

$$\alpha = \frac{\pi}{\lambda} (n^{\rm L} - n^{\rm R}) \tag{1.1}$$

ORD spectrum can offer responsible experimental signals for chiral NPs, which can also be calculated by theory. However, these spectra are inconvenient for answering the fundamental question on the chiral activities of electronic states in NPs due to their intense effect by scattering. In the meanwhile, ORD spectroscopy can also illustrate the practicality of chiral nanomaterials in polarized optoelectronics and other fields. As in the case of CD spectroscopy, it can detect the differential absorption of left- and right-handed circularly polarized light (electromagnetic radiation) and gives rise to their ellipticity alteration when the radiation beam passes through the sample. The chiral CD bands appear in the same spectral windows as the standard absorption bands of non-polarized light. Either positive or negative CD bands can occur, depending on the relative absorption of each circularly polarized component of the incident radiation. As a differential method, complex CD spectra may occur.

It is essential to clearly understand the interaction between light and matter in asymmetric nanostructures for the determination of the chiral geometric elements and the sign and intensity rationalization of multiple CD "waves." It may seem too complicated and convoluted. However, in fact, it can be quite simple to display commercial software packages (such as Lumerical, Gaussian, COMSOL) when one can identify the chirality type of the individual NPs, as exampled by Type 1, Type 2, Type 3, Type 4 or their combination thereof. It can also be applied to NP assemblies. Usually, the chemical characterization and separation of the nanoscale enantiomer mixtures determine the complexity of CD or ORD spectrum calculations [1]. As expected with improved computational power, it can be a standard part of the NP researches.

From the perspective of computational aspects, the ORD and CD spectra can be calculated based on semiclassical electrodynamic models with quantum mechanical perturbation theory. And special equations can be derived, which can address polarized light scattering caused by the oscillating electric dipole moment (linear oscillation) and magnetic dipole moment (circular oscillation). Both linear oscillation and circular oscillation are caused by the incident electromagnetic radiation. In the case of CD, the transition moment of the electric dipole interferes with the transition moment of the magnetic dipole, and the rotatory strength  $R_j$  for the  $j^{\text{th}}$  transition is obtained according to Eq. (1.2) [71].

$$R_{j} = Im(\langle \psi_{0} | \hat{d} | \psi_{j} \rangle \cdot \langle \psi_{j} | \hat{m} | \psi_{0} \rangle)$$
(1.2)

From Eq. (1.2), basic physical insights about the origin of quantum mechanics of CD activity can be obtained. Notably, only the symmetry requires to be considered when one predicts the intensity and algebraic sign of any transition. If the transition is to be observed, the two integrals of the ground state wave function  $\psi_0$ , the  $j^{\text{th}}$  excited state wave function  $\psi_j$ , the electric dipole moment operator  $\hat{d}$ , and the magnetic dipole moment operator  $\hat{m}$  cannot disappear at the same time. In other words, the electric and magnetic dipole moments must allow this transition at the same time. This strict selection rule limits the point groups where two transition moments do not disappear at the same time. The only possible groups for the CD spectrum are  $C_n$ ,  $D_n$ , O, T, and I. In fact, for these point groups, chirality is usually possible not only the CD spectrum of chiral media. Notably, there are many chiral biological, organic, and nanoscale systems that contain the point groups of  $C_n$  and  $D_n$ . However, in the case of chiral point groups O, T, and I, they are usually less observed.

As shown in Eq. (1.2), transition moments are vectors, and they are combined into a dot product to produce the scalar rotatory strength of each  $j^{\text{th}}$  state. The rotatory intensity is defined as a dot product, which also means its null magnitude in the case of two transition moments perpendicular to each other. The greater contribution may origin from the parallel transition moments (positive rotatory strength) or antiparallel transition moments (negative rotatory strength). Interestingly, for any CD transition, the ground state wave function  $\psi_0$  is the same (Eq. (1.2)). It means that the amplitude differences and the algebraic sign differences of various transitions mainly come from the alteration in the excited state wave functions  $\psi_i$ .

It is also easy to see the abnormally high intensity of CD spectra and high anisotropy g-factor value of the inorganic chiral nanoscale structures from Eq. (1.2). The electrical and magnetic susceptibility of metals and semiconductors are higher than that of organics, which typically represents the inorganic materials. Therefore, the instantaneous dipole moment and dot product of the interaction between the incident photon and the nanoscale inorganic matter are larger than those of organic objects of similar sizes. The CD spectrum calculation may depend on some different methods in Eq. (1.2) to calculate the wave function of the excited state. Generally speaking, time-dependent density functional theory (TD-DFT) is the selected method for calculating the CD spectrum of individual NPs [1].

### 1.4.2 Methodological Aspects for Computational Studies

The evaluation of the chiral properties of the individual NPs and their higher order structures can be done through by computer simulations. As shown in Eq. (1.2), the CD spectrum calculation can depend on some various methods to achieve ground wave functions and excited state wave functions. In addition, the classical models use the polarizability of individual atoms as input information. It can calculate the CD spectra from local dipole moment polarization as a static response to the electric field of other dipoles to generate a dipole vector system and the incoming electromagnetic radiation. Taking into account the development of high-performance computing

facilities and efficient computer codes in the past 20 years, the DFT method can handle small NPs at the atomistic scale, while classical electrodynamic calculations, such as finite difference time-domain method and finite element integration, may continue to be used in larger assemblies containing many coarse-grained NPs [72].

Accurate knowledge of their shape is required for the simulation of CD bands of the individual NPs and their assemblies. An atomic-level detail for individual NPs can be offered from high-resolution imaging techniques [73]. It is essential to confirm the inherent asymmetry (Type 1 chirality) of inorganic cores. However, it can only describe NPs with sufficient high stability and a high-temperature phase transition at the atomic level for the electron tomography. In addition, chirality of NPs is determined by the average geometric shapes in a large ensemble. When realizing tomographic geometric shapes in simulation, the variability of their geometric shapes should be carefully considered. The organic molecules on the surface of NPs are transparent to the electron beam, and their geometric positions require to be determined by various techniques; for example, it may be firstly purified by electrophoresis or solvent extraction, and then characterized by nuclear magnetic resonance (NMR), infrared (IR), and VCD spectra, finally simulated the chirality activity (VCD, CD) based on the geometrically placed ligand on the surface of the NPs [26]. The orientation of the ligand on the surface of the NPs can be determined by the transition dipole moment orientation under different vibrations. X-ray diffraction (XRD) may indicate the lowest energy conformation pattern, which can be used as candidate methods to characterize the geometric ligand placement on the surface of the NPs [46].

In the case of sole computation, one should ideally start with a high-level and ab initio quantum chemistry model, which is composed of inorganic cores, organic shells, and solvents. However, currently most of the NPs of interest cannot afford the computational cost, and these restrictions will most likely be relaxed in the next two to five years. In practice, the choice of the theoretical level largely depends on the NP sizes, which range from classical molecular modeling and coarse-grained models to large nanostructures with dozens or hundreds of NPs, as well as the most advanced quantum chemical modeling for small clusters with tens of atoms. It is notable to mention that the trend of using DFT should be pointed out instead of wave-function-based methods, because the former provides a better compromise between accuracy and efficiency in systems with transition metal atoms than the latter [74].

Models based on DFT and wave functions need to choose a basis set to describe the electronic density. These basis sets are composed of more mathematical functions for better description of the electron density and other properties that depend on them. However, in practice, the individual NPs and their assemblies are too large to fully describe all the electrons. To overcome this inherent computational limitation, most of the DFT calculations depend on the effective core potential (ECP), which is a simplified empirical expression for the average electrostatic potential generated by the closed shell of the heavier atoms and core electrons, which are usually starting from the third row on the periodic table. In fact, the calculated electrostatic

shielding internal electrons are in the atomic nucleus of an atom, which requires complete quantum chemical processing of the electrons. We add an empirical function to correctly parameterize the element and get the same shielding effect. This approximation is usually feasible because most molecular structures, bonding patterns, and electronic properties rely entirely on valence electrons, not core electrons. Finally, the description of valence electrons may also require some approximation. The most commonly used basis set describes the single-electron atomic orbit as the empirical sum of Gaussian functions. Each function has an exponent  $\zeta$  defining the distance between the decay rate of the function and the nucleus. Generally, the larger the number of Gaussian functions describing valence electrons, the better the result, but when we move from a single- $\zeta$  basis (one Gaussian function per valence electron) to a double- $\zeta$  basis (two Gaussian functions), the performance will rapidly decline. In practice, recent DFT calculations depend on a double- $\zeta$  basis, with ECP as a compromise between efficiency and accuracy. Obviously, with the improvement of the computing power, larger and better basis sets may become feasible.

It is a difficult task to carry out the quantum chemical computation even used with described methodological trade-offs. Most computational implementations use some form of linear response theory to deal with the TD-DFT problem and achieve a description of the excitation energy and excited state orbit. We assume that it is equivalent to the excited state wave functions in Eq. (1.2). The TD-DFT formalism is accurate in principle, but the approximate form of the exchange correlation function may introduce errors. In practice, it is necessary to verify the calculation results with experimental data. Another inaccuracy source is the requirement of the narrow orbital range around the bandgap, which can be included in the TD-DFT modeling of electronic transitions. In a precise theory, all Kohn-Sham one-electron orbitals have entered an iterative process of mixing them, resulting in multi-electron orbitals for the holes and charges associated with each transition. In practice, an NP with hundreds of atoms may generate thousands of orbitals, even if small ECP basis set is used to reduce the electron number in the model; this is a prohibitively large number of one-electron Kohn-Sham orbitals. In the description of the hole and charge pairs for the electronic transition, the choice of the number of occupied orbitals and virtual/unoccupied orbitals to be mixed is a matter of trial and error, and a compromise is sought between the computational cost and the accuracy of results.

The root number in the iterative process also affects the calculation performance and the quality of results. Each root corresponds to an electronic transition, starting from the energy band transition to a higher energy transition. There is no rule of thumb to define how many root calculations are required to describe the energy in the NP's UV–vis spectrum range. It is usually best to gradually increase the root number until the spectrum matches the energy range of interest. In this incremental search, two problems are required to be solved before obtaining reliable results. First, as increasing the number of the excited state, it needed to evaluate the range of orbits entering into the iterative mixing, as low-lying occupied orbitals and highly unoccupied orbitals might become important, that is, their weight in describing the average orbit of the excited state can no longer be ignored. Secondly, the model calculation needs to go deeper than the last band of interest in the high-energy region of the spectrum, because the last band is usually not clearly defined, and this additional number of excited states significantly increases the computational cost of the modeling. Autschbach discussed in detail the trade-off between accuracy and cost in a review of similar tutorials [1, 71].

#### 1.4.3 Selected Computer Modeling Study

Researchers investigated CdS NPs stabilized with penicillamine via DFT calculations with the BP86 functional and a double- $\zeta$  ECP basis set for the Cd atoms. Although a detailed optimized structure was calculated by means of a series of angles and the distances between atoms to evaluate the chirality of the structure, we must consider this method as qualitative, because of these raw data do not offer a chirality measure of NP, which requires calculation of CD spectrum or chirality index. The electronic structure is also qualitatively analyzed by the method of Kohn–Sham orbitals (sometimes referred to as molecular orbitals), but these orbitals are single-electron properties, while CD and other electronic excitation phenomena are essentially multi-electron processes, requiring the actual evaluation of the state of the excited state orbitals. A very attractive qualitative finding from their work is the discovery of multiple binding ligand molecules NP. The key observation is that a single self-coordinating ligand may have a free rotating surface, and this degree of freedom will result in thermal breakdown of the arrangement of chiral ligands.

For L-cysteine- and D-cysteine-stabilized CdS NPs, there is a quantitative match between the CD spectra in dispersions and TD-DFT calculations (Figure 1.4A,B) [75]. Although the NP in the simulation is much smaller than that in the experiment, all the main spectral characteristics and the sign of polarization rotation are almost consistent with the experimental spectrum. The calculation is based on 16 representative transitions of an electromagnetic frequency characteristic window of a nuclear reactor. Interestingly, the TD-DFT model shows that the chiroptical band around 390 nm may not only come from the bandgap transition but also from the  $p \rightarrow s$  type excitation of sulfur atoms. Based on the quantum state of semiconductor nanowires with screw dislocations, a chiral semiconductor nanowire or nanorod model is calculated. Two-dimensional or three-dimensional periodic lattices can produce optically active quantum supercrystals. Due to the quantization of the size of the nanowire energy spectrum, its activity can change in many ways. The model shows that optical chirality is caused by screw dislocations in cylindrical nanowires that are much longer than the diameter (Figure 1.4C-E) [12]. The model proposes that inherent chirality of CdSe/ZnS nanocrystals is caused by naturally occurring chiral distortions (Figure 1.4F) [76]. For large-scale semiconductor nanomaterials, the finite-difference time-domain Maxwell solver based on the interaction of circularly polarized photons with the model structure can calculate a medium-scale semiconductor spiral [11].

A ring was formed from such double coordination between the ligand and the metal cluster, which contains the stereogenic center, the  $\alpha$ -carbon atom. Here, the cluster is composed of only eight atoms, and the two types of chirality (Type 1 and



**Figure 1.4** (A) TD-DFT CD spectra for D-CdS [75]. (B) UV-vis and corresponding CD spectra of CdS-D and CdS-L NPs from experimental results. (C, D) Theoretically simulated CD spectra upon intraband transitions  $(1, \pm 2) \rightarrow (1, \pm 3)$  in ZnS nanowires with (a) right- and left-handed screw dislocations [12]. (E) The right-handed screw dislocation and the general calculated CD spectra [12]. (F) The intrinsic CD of the L- and D-CdSe/ZnS semiconductor NRs [76]. Source: (A,B) Reproduced with permission from Refs [75]. Copyright 2016 Royal Society of Chemistry; (C-F) Reproduced with permission from Refs [12, 76]. Copyright 2015 American Chemical Society.

Type 2) are actually the same. The ligand in the cluster induces a twisted structure (Type 2), but the cluster is too small, and then affects the whole. The structure of the cluster changes, not only its surface atoms (Type 1). The degree of chirality depends on the degree of the asymmetry of the stereocenter and, therefore, on the local conformation around it. The authors calculated six different conformations of VCD and found that the intensity, position, and algebraic sign of the vibration band are related to the conformation around the chiral carbon atom, but not to the side chain conformation. One thing to pay attention is the sampling of the conformational space of the ligand, because the flexible chain always has a large number of local minima related to the rotation of the dihedron. These degrees of freedom are not properly sampled by standard geometric optimization techniques, which are usually based on the energy gradient, which is not enough to bring the molecule from one local

minimum to another, due to the energy gradient close to zero at the minimum. This is a problem for this small model with only one ligand, while for a larger and more realistic system, there are dozens of ligands on the surface of a large NP, which may become a serious flaw.

To sample the conformation of Au NPs from Au<sub>28</sub> to Au<sub>75</sub>, a genetic-symbiotic algorithm was used [44]. This optimization technique is not based on the potential energy gradient, so in principle, it can effectively sample the local minimum in the construction space. For efficiency reasons, this initial optimization was performed using classical potentials. Only the representative local minimums were further optimized at the quantum chemical level, using local density approximation (LDA) and generalized gradient approximation (GGA) using pseudo potential (a form of ECP) and double- $\zeta$  basis functions. If there are high-quality classical parameters available for the conformation search, this method should be considered as an acceptable choice, because a large number of independent structures need to be considered, and the quantum chemical potential requires a too high thorough sampling. The authors discovered two populations of Au<sub>28</sub> NP, one is formed by nearly degenerate amorphous clusters and the other formed by ordered NPs belonging to the T point group, in which the T isomers lying c. 60 kJ mol<sup>-1</sup> above the disordered nanostructure. Based on the HCM, the degree of chirality of each population was evaluated. Both the disordered and the T isomers presented values larger than zero, with a slightly larger value for the T isomer. They also evaluated the effect of adding SCH<sub>2</sub> thiol groups on the surface of NPs. The general trend was either the induction of chirality in the achiral NPs or the increase in the chirality degree of the chiral NPs. The analysis of the optimized structures showed that thiol passivation tends to induce a disordered structure in the NP core, leading to the elimination of the symmetry plane, otherwise it will make the NP achiral. The Au<sub>28</sub> NPs were subsequently used to test a semi-analytical model and used the dipole moment approximation to calculate the CD spectra, which was first proposed by DeVoe and Applequist. Unfortunately, the authors did not use quantum chemistry methods to calculate the CD spectra of NPs, nor did they compare the calculated spectra with the experimental results. Therefore, we are unable to assess the quality of the results.

The TD-DFT calculations used the same theoretical level, sampling the first excited states of each NP. In the case of determining the excited states number, the calculated energy range of the UV-vis and CD spectra varied according to the NP size, from 1.5–3.5 eV for the smallest NP to 2.2–3.3 eV for the largest NP. The spectra included a Gaussian broadening of 0.1 eV to produce the line shapes of the rotation intensity calculated by TD-DFT. The result is a more complex spectrum compared to the UV-vis line shape of the same broadening in most research systems. For the CD spectra of these calculated capped NPs, the most important and common observation is that there is a single transition with a negative or positive rotatory strength for any broadened band, because the overall sign of any CD band comes from the sum of many individual transitions. This is important for the experimental data analysis of the changes in either the intensity or the algebraic sign of CD bands. It cannot be attributed to a single transition but must be regarded as the collective result of many changes in individual transitions. It may be shifted, damped, or

even suppressed. In any case, multiple transitions must be evaluated to describe a single-frequency band [1].

An important problem is the effect of solvation on chirality of NPs. Most calculations were performed on a single NP in a vacuum, whereas most experimental data were carried out in suspensions. Although we do not have specific literatures on the influence of solvents on the chiral properties of individual NPs, there is general literature dedicated to this topic. We can point out that two main contributions are expected to play an important role in the evaluation of general chiral properties. First, because the relative population of different minimum energy conformations will change significantly under different solvation conditions, the solvent effect should be considered from the beginning of the geometric optimization step. Second, the phase transition is also affected by solvation. These two effects can be observed even with simplified continuum models [77].

In summary, a review of the theoretical research on chirality of NPs proposes quantum chemistry and electrodynamic calculations as natural choices for understanding the chiral activity origin of inorganic nanostructures and calculation methods suitable for different chirality type. It is worth noting that single NPs have greater correlation with quantum mechanical methods, and electrodynamic calculations are more suitable for larger nanostructures. There is still room for improvement in these two methods, and the widespread use of high-performance computing equipment and software will be conducive to the increasing research on rival computers in the next few years. Prospectively, the combination of experimental and computational research will provide a basis for the design and fine-tuning of materials based on chiral NPs [2, 78, 79].

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