Design and Applications of Liquid Crystal Biophotonic Sensors for Ion Detection

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1. Introduction

Liquid crystals (LCs) have been the star materials in the past decades due to the subtle integration of the molecular ordering and fluidity. Since the first observation of liquid crystalline behavior by Reinitzer in 1888, the research on these strange and fascinating materials has gathered wide attention. Based on the phase-transition condition, the LCs are classified into two types including thermotropic LCs and lyotropic LCs. The thermotropic LCs can realize phase transition driven by temperature, widely used in optical devices. However, the lyotropic LCs can realize phase transition under various solvent concentrations, usually studied in the field of biology. In this review, we focus on discussing the thermotropic LCs because of their application potential in sensors. Up to now, a variety of mesophases of the LCs have been explored, among which the smectic phase, nematic phase, chiral nematic phase, and blue phase are the most common. The smectic phase possesses a positional order besides the orientational order and is the most orderly mesophase. The nematic phase is the simplest and most widely studied LC phase, within which the LC molecules show only orientational order of their long molecular axis without the positional order. In addition, the chiral nematic LCs (CLCs) are composed of either inherently chiral molecules or the achiral molecules accompanied by chiral agents. The blue phase LCs, which appear in a narrow temperature range, hold platelet texture with short coherent length, typically showing fast responsive time in the submilliseconds range. Based on the diverse molecule alignments of the LCs, some unique performance including the stimuli-responsive property and optical property have been investigated in depth, laying solid foundation for the practical applications in the fields of LC displays, adaptive lenses, gratings, color filters, and sensors.

The LC sensors, born in the interface of the material science and sensing technology, have become the feasible and widely used tools to detect analytes such as biomolecules, gases, dyes, and temperature. As LC molecules can be tailored to respond to targeted chemical species, their optical signals can be tuned by the analytes displayed at the interface. The detection principle of the LC sensors is typically based on the competitive binding of an LC and a targeted analyte to a common molecular receptor, which results in the reorientation of the LC molecules and the variation of the optical images. Compared with traditional sensing techniques such as the metal–oxide–semiconductor sensors, light-addressable potentiometric sensors and electrochemical sensors, the LC sensors hold the advantages of portability and low cost and show visualized output signals that can be directly observed by the naked eyes using some optical techniques. Up to now, a variety of LC sensors have been designed and fabricated, such as the large-birefringence nematic LCs (NLCs) for cancer biomarker detection, the label-free LC biosensor for cecropin B detection, and the LC fiber temperature sensor with high sensitivity. In this review, the exploitation of LCs in ion detection is summarized, which has not been reviewed by other authors in recent years. Ions are widely distributed in nature and bionts and are important for human physiological processes and natural
ecological environment.[40–42] With the development of industry and technology, ion-polluted water has been a non-negligible problem that is threatening the water ecotope and reducing the living quality of human beings.[43,44] Most of the ions are not biodegradable and can accumulate in the organisms to cause diseases. For example, Pb²⁺, known as a common heavy metal ion, is widely used in the industry and can lead to anemia and hepatitis.[45] It is declared by the World Health Organization (WHO) that Pb²⁺ with the concentration of 50 ppb is enough to bring irreversible damage to the mental health of children.[46] In addition, some metal ions play important roles in living organisms. For example, in hemoglobins and myohemoglobins, Fe²⁺ is essential for capturing oxygen.[47] During the transportation of adenosine triphosphate (ATP), the transmembrane diffusions of Ca²⁺ and Na⁺ are critical.[48] Considering the significance of detecting ion concentrations both in the nature and in bionts, various efforts have been devoted to investigating LC ion sensors. As a result, it is necessary to summarize the current work and outlook the development directions of this field, laying the foundation for future research.

To take advantage of the LC ion sensors, various strategies have been used to fabricate the sensors with different device structures and detection targets. The geometries of sensors, including the flat geometry, spherical/hemispherical geometries, and irregular geometry, can decide the performance of the sensors directly and should be considered according to the actual demands. The initial alignments of the LC molecules can greatly influence the sensitivity of the sensors and are also closely related to the sensing mechanisms. In addition, the optical signals of the LCs can help to estimate the ion signals. These basic theory for designing sensors will be discussed in Section 2 in detail. In Section 3, two types of LC ion sensors, aiming at detecting metal ions and nonmetallic ions, respectively, are illustrated to show the research status of this field. For the detection of metal ions, the structure is organized based on different receptors and their corresponding detection mechanisms. For the detection of the nonmetallic ions, we focus on different detection targets including the hydrogen ions, halogen ions, and arsenic ions. Furthermore, the current challenges and potential development directions of the LC ion sensors are introduced briefly in Section 4 to provide guidance for future research. The overall outline of this review is shown in Figure 1.

Figure 1. Schematics showing the overall outline of this review, including the design and application of the LC ion sensors.

2. Design Principles

LC phase is the intermediate phase between the crystalline and the liquid states, arising from the noncovalent and orientation-dependent interactions between the molecules. It typically consists of one or more kinds of organic compounds with rod-shaped, disc-shaped, or bent core-shaped geometries.[49,50] Generally speaking, organic molecules used to achieve the LC phases usually have three characteristics.[51] First, the molecules must have anisotropic shapes with their length–diameter ratio greater than 4. Second, the long axes of the molecules should be significantly rigid. Furthermore, polar groups are essential at the end of the molecules. Those characteristics allow the self-assembly and ordered arrangement of the molecules, providing the LCs with anisotropy on the refractive index, conductivity, and magnetic moment.[52–57]

The self-assembly of the LCs is driven by the elastic force between the molecules, which is relatively weak and makes it feasible to tune the LC orientation by external stimuli such as electric field,[58] magnetic field,[59] and surface alignment.[60,61] In addition, the optical properties of the LCs, such as the birefringence and photonic stopband, provide a visual approach for observing the LC alignments.[62–65] Integrating the stimulus-responsive property and optical property endows the LCs with efficient approaches to apperceive external ion signals and express the signals visually, laying foundation for the design and fabrication of the LC ion sensors. In the following, we will introduce the design principles of the LC ion sensors from three aspects, including the geometries, alignments, and optical signals. The sensitivity of the sensors, which can be measured by the responsive time and the limit of detection (LOD), is determined by three factors of the LC phase including the thickness, specific surface area, and elastic potential energy. These factors are highly relevant to the geometries of the sensors and the alignments of the LCs. The optical signals of the sensors, which are derived from the birefringence and photonic stop-band of the LCs, can help to estimate the type and concentration of the ions.

2.1. Geometries

For designing an LC ion sensor, the geometry of the sensor should be considered according to the actual demands. Up to now, four different geometries, including the flat geometry,[66] the spherical/hemispherical geometries,[67] and the irregular geometry,[68] have been widely studied. For the flat geometry, the LCs are filled in the cells by capillary perfusion in their
isotropic phases. The alignment of the LCs can be easily controlled by the surface pretreatment of the cell, providing a convenient way for fabricating sensors.\([69,70]\) The upper surface of the flat geometry can be switched among solid surface, aqueous surface, and air surface. For the detection of ions, the aqueous surface is the most commonly used, in which the LC cell is in the form of a copper grid immobilized on a glass substrate. The sensitivity of the LC–aqueous interface is relevant to the thickness of the copper grid.\([71–73]\) With the decrease in the grid thickness, the sensitivity of the sensor increases due to a thinner LC layer. However, when the thickness is smaller than the threshold, the orientation of the LC molecules will be immobilized by the alignment layer on the substrate, therefore hindering the LC reorientation. As a result, the thickness of the copper grid should be regulated properly during fabrication. Such a flat geometry is also suitable for detecting gas samples and aqueous samples, showing satisfactory universality.\([74,75]\) However, the LOD of this geometry is limited by its low specific surface area, making it incapable of detecting trace quantities of ions. In addition, due to the rigidity of the LC cell, it is unfeasible for the flat geometry to realize the in vivo detection and flexible devices.

To improve the sensitivity, the spherical/hemispherical geometries have been proposed to increase the specific surface area of the LC phase. The spherical geometry is generally fabricated by emulsifying techniques such as membrane emulsification, stirring emulsification, and microfluidic encapsulation, with the LCs acting as the dispersed phase and the aqueous phase acting as the continuous phase.\([76–78]\) Stirring emulsification is the simplest and the most convenient method to prepare emulsions in bulk, while the obtained LC droplets hold broad size distribution. The membrane emulsification is a promising technique for producing LC droplets with uniform size. Microfluidic encapsulation is utilized to obtain the droplets with precisely controlled size while showing low yield. The LC droplets can be uniformly distributed in the aqueous phase and therefore possess large specific surface area and low LOD.\([80]\) However, the stabilities of the LC droplets in the aqueous phase and therefore possess large specificity to realize the in vivo detection and flexible devices.

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In addition to aiming at achieving LC ion sensors with irregular geometry, LC polymers have been developed. The LC polymers are usually prepared by the polymerization reaction of the LC monomers, initiators, chiral dopants (for the CLC polymers), and receptors, showing diverse compositions and controllable shapes.\([83,84]\) Considering the orientation transition where the NLCs will be impeded by the polymer network, the CLCs, which can express optical signals by Bragg reflection, are supposed to be the ideal candidates for fabricating LC polymers. In the absence of ions, the CLCs in the polymer can selectively reflect the light with the central wavelength, consistent with the helical pitch. With the existence of ions, the combination of the ions and receptors leads to the swelling or shrinkage of the polymer, therefore resulting in the variation of the helical pitch. As a result, a wavelength shift of the reflected light can be observed by naked eyes. Such LC ion sensors with irregular geometry show excellent potential in wearable devices, which can be used for personal protection in the special environments such as sewers, laboratories, and oceans.

In general, for most of the analytes, the flat geometry is an alternative option with easy fabrication process and simple structure, while it is incapable of detecting trace quantities of ions or achieving flexible devices. In addition, the spherical/hemispherical geometries hold low LOD due to the high specific surface area, while their stability remains to be improved. Moreover, the irregular geometry has potential in achieving wearable devices while the fluidity of the LC molecules is reduced by the polymer network. It is of great significance to subtly choose the geometry according to the actual demands.

### 2.2. Alignments

The stimuli–responsive reorientation has been proved to be the key factor for realizing the ion detection. Up to now, various reorientation models have been studied. For the flat/irregular geometries, the orientation transition between planar and homeotropic is the most common.\([85]\) For the spherical/hemispherical geometries, the transition between bipolar and radial is widely used.\([86]\) In addition, the reorientation from anisotropy to isotropy driven by the phase transition of the LCs is also an alternative.\([81,87]\) The LC reorientation can directly affect the optical signals of the sensors. Considering the close relationship between the LC reorientation and the LC alignment, it is of great significance to subtly design the LC alignment in the initial state and therefore obtain the expected optical signals.

Typically speaking, the initial alignments of the LC molecules are related to the orientation force provided by the alignment layer at the phase interface. At the LC–solid interface, the alignment layers such as siloxane, aliphatic chain, and oligonucleotides favor the perpendicular alignment of the molecules,\([90,91]\) while the parallel raviné prepared by etching techniques and polyimide (PI) treated by directed rubbing can lead to parallel alignment.\([90,91]\) In addition, at the LC–aqueous interface, the LC alignment can be tuned by varying the components of the aqueous phase. For example, common surfactants such as octadecy trimethyl ammonium bromide (OTAB) and sodium dodecyl sulfate (SDS) favor the perpendicular alignment due to the hydrophobic interaction between the surfactants and the LC molecules. The hydrophobic interaction can trigger the self-assembly of the surfactants at the LC–aqueous interface with their hydrophobic parts combining with the LCs and their hydrophilic parts combining with water.\([92–94]\) Other amphiphatic molecule such as aliphatic acids, phospholipids, and lipopolysaccharides can also play the similar role.\([95–97]\) In addition, for saline solutions, the LC alignment at the interface can be decided by the solutes.\([98]\) For example, solutes such as iodide, perchlorate, and thiocyanate have large ionic radius and weak hydration and therefore favor the perpendicular alignment. Chloride and bromide, which possess small radius and strong hydration, can lead to the parallel alignment. Such phenomena are induced by the dipole-induced dipole interaction between the LC molecules and the solutes. Take notice that the ions mostly exist in the aqueous phase, the LC–aqueous interface is widely used in fabricating the LC ion sensors, and the initial alignments
of the LC molecules at the LC–aqueous interface have been deeply investigated for controlling the LC reorientation.

In addition, the initial alignment of the LC ion sensors is relevant to the sensing mechanisms. For example, for the LC Hg$^{2+}$ sensors based on the Hg$^{2+}$ receptors, OTAB is an alternative alignment layer due to its electrostatic interaction with the receptors. The parallel alignment of the LC molecules is obtained in the initial state because of the chaotic distribution of OTAB under the influence of the electrostatic interaction.\cite{105} While for the H$^+$ sensors based on the protonation/deprotonation of the aliphatic acid, the deprotonated aliphatic acids self-assemble at the LC–aqueous interface as the alignment layer, leading to the initial perpendicular alignment.\cite{99} Moreover, for the sensors based on the CLCs, the parallel alignment is usually required for achieving satisfactory Bragg reflection.\cite{100,101} Worth mentioning is that the sensitivity of the LC sensors can be improved using twisted LC alignment.\cite{102} Nayani et al developed an LC sensor with twisted interfacial ordering.\cite{103} The sensor shows homeotropic orientation at the LC–solid interface due to the interaction between the nitrile group and metal ions, yet, adopts a planar orientation at the LC–air interface. Such a twisted orientation provides an initially strained state of the LCs, enhancing the elastic potential energy and allowing the release of the energy during the responsive process. As a result, the LC sensor with faster responsive rate and greater responsive sensitivity is realized. In general, subtly designing the initial alignment of the LC molecules can improve the optical signals and plays an important role in fabricating the LC ion sensors for expected performance.

2.3. Optical Signals

The optical signals of the LC ion sensors are derived from the birefringence and photonic stopband of the LCs, varying with the external ion signals. By analyzing the optical signals under polarizing microscope (POM) digitally or directly by naked eyes, the type and concentration of the ions can be determined. In general, the LC ion sensors with different geometries display different optical signals. For the flat geometries confined in the LC cells, the dark field can be observed when the LC molecules are in homeotropic orientation. The bright field may appear when the LC molecules are in planar orientation, hybrid orientation, or disordered orientation, indicating phase change of the incident light.\cite{104} Theoretically speaking, the phase retardation ($\tau$) can be calculated by the equation below.

$$\tau = \int_{0}^{l} 2\pi \Delta n_{\text{eff}}(z) / \lambda dz$$

(1)

where $l$ is the thickness of the LC cell, $\lambda$ is the wavelength of the incident light, and $\Delta n_{\text{eff}}$ is the effective refractive index of the LCs. The value of $\Delta n_{\text{eff}}$ can be calculated by the equation

$$\Delta n_{\text{eff}} = \frac{n_0 n_e}{\sqrt{n_e^2 \cos^2 \alpha + n_o^2 \sin^2 \alpha}} - n_o$$

(2)

In this equation, $n_e$ and $n_o$ are the extraordinary and ordinary refractive index of the LCs, and $\alpha$ represents the angle between the director and the substrate normal. The above equations allow us to calculate the average tilt angle of the LC molecules based on the phase retardation and to further estimate the ion concentration.\cite{105} For the spherical geometry, the fan-shaped optical texture can be observed when the LC molecules are in the radial orientation, while the uniform bright image appears when the LC molecules are bipolar. For hemispherical geometry, the bright-fan image under the POM corresponds to the parallel alignment and the dark-cross image corresponds to the perpendicular alignment.

The ion sensors based on the CLCs can show photonic bandgap along the axis, selectively reflecting light when the stopband is in the visible range. The central wavelength of the reflected light depends on the incidence angle and the helical pitch of the CLCs and can be estimated by Bragg law.

$$\lambda = nP \cos \theta$$

(3)

in which $P$ is the helical pitch, $n$ is the average refractive index, and $\theta$ is the incident angle.\cite{106} When the incident light is parallel to the helical pitch, the bandwidth of the reflected light depends on the refractive indices and the helical pitch and can be calculated according to the equation\cite{107}

$$\Delta \lambda = P(n_o - n_e)$$

(4)

As the helical pitch is closely related to the analytes, the wavelength of the reflected light can be used to estimate the concentration and type of the ions. In general, the unique optical properties of the LCs provide us with efficient approaches to observing ions by the optical signals, which are invisible in other sensing techniques.

3. Applications of LC Ion Sensors

3.1. LC Sensors for Metal Ion Detection

Metal ions are widely distributed in the nature, biont, and laboratory, and they play critical roles in many natural and physiological activities. In the human body, the metal ions are the essential components for maintaining osmotic equilibrium, as well as indispensable parts for a wide range of enzymatic reactions.\cite{108,109} In tap water, a moderate amount of silver ion is utilized for sterilization.\cite{110} In cropland, fertilizers containing metal ions are beneficial for the growth of the crops.\cite{111} However, when the concentration of the metal ions exceeds a certain amount, they will become harmful to the ecological environment and human organs, finally leading to serious public security issues. As a result, it is of great necessity to adopt effective measures to monitor the concentration of the metal ions. Up to now, LC sensors have been proved to be the alternative candidates for detecting the metal ions due to impressive signal amplification property and stimuli–responsive reorientation property of the LC molecules. A variety of LC sensors based on different receptors, including biomolecules, ligands, fluorogens, and crown ethers, have been proposed using various detection mechanisms. Shown in Table 1 is a summary of the LC sensors for metal ion detection.
Table 1. LC sensors for metal ion detection.

| Liquid crystal | Geometry  | Receptor          | Target         | LOD   | Detection principle                                           | References |
|----------------|-----------|-------------------|----------------|-------|---------------------------------------------------------------|------------|
| SCB            | Flat      | Oligonucleotide   | Hg$^{2+}$      | 0.1 nM| Hg$^{2+}$ binds with DNA by T–Hg$^{2+}$–T bond                | [112]      |
|                | Hemisphere|                   |                |       |                                                               |            |
|                | Flat      | Pb$^{2+}$         | 3 nM           |       | Pb$^{2+}$ binds with DNA and from G-quadruplexes              | [113]      |
| Photochemically degraded SCB |           |                   |                |       |                                                               |            |
| SCB            | Flat      | DNAzyme           | Pb$^{2+}$      | 36.8 nM| Pb$^{2+}$ activates DNAzyme to disassemble dsDNA              | [66]       |
|                | Hemisphere|                   |                | 0.7 nM| Pb$^{2+}$ binds with DNAzyme to release OTAB                  | [22]       |
|                | Flat      |                   |                | 16.7 pM| Pb$^{2+}$ activates DNAzyme, followed by the RCA reaction     | [115]      |
|                |           |                   |                | 0.65 nM| Pb$^{2+}$ activates DNAzyme and disturbs the AIE molecules    | [116]      |
| CLCs           | Irregular | Poly(acrylic acid)| Ca$^{2+}$      | 0.35 mM| Ca$^{2+}$ coordinates with –COO⁻ and leads to the shrinkage of the polymer | [117]      |
|                |           |                   |                |       |                                                               |            |
|                |           | Benzoic acid LC monomers |        | 0.1 mM| Ca$^{2+}$ coordinates with –COO⁻ and leads to the shrinkage of the polymer | [84]       |
| SCB            | Flat      | PAA-b-LCP         | Ca$^{2+}$      | 2.5 mM| Ca$^{2+}$ coordinates with –COO⁻ and leads to the shrinkage of PAA | [118]      |
|                |           |                   |               |       |                                                               |            |
| Agarose-dispersed LCs | Irregular |                   | ZT            | 10 μM | Hg$^{2+}$ forms complex with ZT specifically                  | [119]      |
|                |           |                   |                |       |                                                               |            |
| SCB            | Flat      | Hydroxyl groups   | Pb$^{2+}$      | 100 ppb| The coordination between Pb$^{2+}$ and NiFe$_2$O$_4$          | [121]      |
|                |           |                   |                |       |                                                               |            |
|                |           | Cyano groups      | Cu$^{2+}$      | 0.16 ng mm$^{-2}$ | The coordination between Cu$^{2+}$ and SCB | [122]      |
|                |           |                   |                |       |                                                               |            |
|                |           | Oligonucleotide   | Cu$^{2+}$      | 100 nM| The coordination between Cu$^{2+}$ and oligonucleotide        | [123]      |
|                |           |                   |                |       |                                                               |            |
|                |           | Bovine serum albumin |           | 1 nM  | The coordination between Cu$^{2+}$ and bovine serum albumin   | [124]      |
|                |           |                   |                |       |                                                               |            |
|                |           | MeDTC             | Hg$^{2+}$      | 0.5 μM| The chelating between Hg$^{2+}$ and MeDTC                     | [125]      |
| CLCs           | Sphere    | H$_2$O$_2$        | Fe$^{3+}$      |        | The luminol reaction participated by Fe$^{3+}$                | [126]      |
| NaDC/RhB/NaOH  |           |                   |                | 4.4 μM| The fluorescence quenching caused by Fe$^{3+}$                | [127]      |
| SCB            |           | Deprotonated stearic acid |       | 40 pm | The shift of the laser wavelength caused by Cu$^{2+}$        | [128]      |
| SCB            | Flat      | Cl$_2$            | Mn$^{2+}$      | 3.7 μm mm$^{-2}$| The redox reaction between Cl$_2$ and Mn$^{2+}$             | [129]      |
|                |           |                   |                |       |                                                               |            |
|                |           | Deprotonated stearic acid |        | 50 μM/30 μM| The electrostatic interaction between metals and deprotonated stearic acid | [130]      |
| CLCs           | Irregular | Crown ether       | Ba$^{2+}$/K$^+$|         | The combination of crown ether and ions                       | [131]      |
|                |           |                   |                |       |                                                               |            |
|                |           | Crown ether       | K$^+$         | 120 nm m$^{-1}$ | The combination of crown ether and K$^+$                   | [132]      |
3.1.1. Metal Ion Detection Based on Biomolecules

Nucleic Acids: Among all of the biomolecules, nucleic acids have been considered as crucial molecules for understanding biological phenomena in living organisms since DNA was confirmed as the genetic material in 1952. They have gained increasing attention as specific sensor receptors because of their abundant functional groups such as –NH₃, –COOH, and heterocyclic nitrogen, as well as their tunable electric charge, which depends on the pH value. Over the past decade, the development of ion sensors based on nucleic acids has increased tremendously. Two common strategies have been used to bind the nucleic acids and ions together with high specificity, including the coordination between Hg²⁺ and thymine and the stabilization of G-quadruplexes using Pb²⁺. In addition, Yang et al. demonstrated that the double-stranded nucleic acids can obviously disrupt the LC orientation and produce an obvious response in the optical textures, laying a foundation for a highly sensitive sensing platform composed of the LCs and nucleic acids. As a result, a lot of efforts have been devoted to investigating the LC ion sensors using the nucleic acids as receptors.

The interaction between Hg²⁺ and the nucleic acids can form T–Hg²⁺–T bridged bonds and therefore affect the alignment layer at the interfaces to change the LC alignment. This mechanism has been utilized to construct the LC ion sensors for Hg²⁺ detection. For example, a label-free LC biosensor has been proposed by Yang et al. The LC sensor is composed of the capture probes (an 18-mer oligonucleotide with an amino at its 5′ end, which can be bound to the glass substrate via simple nucleophilic addition reaction), the hairpin oligonucleotide probes with loop sequence, the appropriate probes (an oligonucleotide that is partially complementary with the hairpin probe), and the LCs as the signal amplifier. In the absence of Hg²⁺, the hairpin probes are uncombined and evenly distributed in the LC phase. The LC molecules align vertically under the influence of the alignment layer. In contrast, with the existence of Hg²⁺, the hairpin probes hybridize with the appropriate probes via the T–Hg²⁺–T interaction and lead to the open loop of the hairpin probes. Subsequently, the 3′-terminals of the opened hairpin probes hybridize with the capture probes. The DNA duplexes holding large steric hindrance are finally obtained, which can greatly change the surface topology and induce a homeotropic-to-tiled transition of the LCs. With the help of POM, a change of the optical image from dark to bright can be observed. While this LC Hg²⁺ sensor involves multiple components, the impressive specificity and low LOD (0.1 nM) make it suitable for the primary screening assay of Hg²⁺.

To further reduce the LOD of the sensors based on the T–Hg²⁺–T interaction, recently, Hong et al. achieved an LC droplet sensor for detecting Hg²⁺. The sensor is composed of the cationic surfactants and the oligonucleotide aptamers with Hg²⁺ binding property. In the absence of Hg²⁺, the electrostatic interaction between the negatively charged oligonucleotide and the positively charged surfactant can disturb the organization of the surfactant at the LC–aqueous interface, causing the LCs to adopt a planar orientation. However, in the presence of Hg²⁺, the hairpin structure forms via the T–Hg²⁺–T interaction, decreasing the electrostatic interaction and leading to the self-reassembly of the surfactant. Therefore, the homeotropic orientation of the LCs is achieved, which can be determined by the change of the optical response from the bright-fan image to dark-cross image under POM. The LOD of this sensor is 100 pm, indicating its outstanding sensitivity.

Apart from T–Hg²⁺–T interaction, G-quadruplexes derived from the self-assembly of Pb²⁺ and guanine-rich nucleic acids have also been widely explored, possessing highly stable structures with a common four Hoogsteen H-bonded structural motif. Typical G-quadruplexes exhibit the coordination pockets occupied by a variety of physiological cations such as

![Figure 2](https://example.com/image2.png)

**Figure 2.** The LC ion sensors based on nucleic acids. a–c) Liquid crystal Hg²⁺ sensor showing the optical responses resulting from transition of the LC orientation induced by the Hg²⁺–T interaction and lead to the open loop of the hairpin probes. Reproduced with permission. d–g) Liquid crystal Pb²⁺ sensor showing the optical responses deriving from transition of the LC orientation induced by the interactions among CTAB, the aptamer, and Pb²⁺. Reproduced with permission.
K⁺, Na⁺, NH₄⁺, and Pb²⁺. Among all of the cations, Pb²⁺-stabilized G-quadruplex adopt a more compact structure due to its small ionic radius and high charge density. As a result, the specific identification of Pb²⁺ using G-quadruplexes, which can further influence the alignment layer, is supposed to be useful for Pb²⁺ detection.

Based on the earlier mechanism, Verma et al. proposed a label-free Pb²⁺ sensor with high sensitivity using spinach RNA as the aptamer, CTAB as the surfactant, and the LC as the signal amplifier (Figure 2d–g).[113] The LCs in the sensor align in parallel in the presence of the spinach RNA aptamer due to the electrostatic interactions between CTAB and RNA, which can change to homeotropic alignment in the presence of Pb²⁺, which is caused by the formation of the stable G-quadruplexes. Solution-phase measurement of circular dichroism (CD) is utilized to investigate the structural change of the RNA aptamer. An increment in ellipticity at the 270 nm peak is observed in the CD spectra with the existence of Pb²⁺, indicating the stabilization of the parallel quadruplex structure of RNA. Worth mentioning is that those LC sensors based on the specific recognition of ions and nucleic acids can also be utilized for oligonucleotide detection using different ions as the receptors and thus exhibit satisfactory flexibility and promising application potential.

Enzymatic Reactions: Apart from the specific interactions between the nucleic acids and ions, enzymatic reactions are also ideal candidates for detecting ions. Some enzymatic reactions can change the pH value of the solution to protonate or deprotonate the surfactants, thus inactivating the LCs in the initial state. In the presence of Pb²⁺, the catalytic strand is activated, leading to a dark-to-bright optical image transition under the POM. In contrast, other metal ions such as Ca²⁺, Cu²⁺, Zn²⁺, and Ag⁺ are still able to cleave the DNA strands and disturb the LC orientation, indicating the remarkable high selectivity.

To reduce the LOD, various efforts have been devoted to improving the LC Pb²⁺ sensors based on DNAzymes. An LC droplet-based Pb²⁺ sensor with an LOD of 0.7 nm, which is 52 times lower than that of the aforementioned sensor, has been proposed by Duong et al.[23] The low LOD is due to the large specific surface area brought by spherical geometry. In addition, the rolling circle amplification, a rapid isothermal nucleic acid amplification method that can produce an extremely long single-stranded DNA, is also used to realize the LOD of 16.7 pm, further reducing the LOD by 40 times (Figure 3a,b).[115] However, although these studies have realized extremely low LOD, they are still suffer from the problem of time consumption, which is a hindrance to their broad use for real-time detection.

Aiming at solving the problem of time consumption, a new LC Pb²⁺ sensor composed of the LCs and an aggregation-induced emission (AIE) lumogen has been developed recently (Figure 3c–e).[116] The sensor shows fluorescence property as the aggregated AIE fluorogens are highly emissive due to the restricted molecule rotation. TPE–PPE is utilized as the AIE material, in which the emission dipole moment along the short-axis direction is greater than that along the long-axis direction. The molecular orientation of TPE–PPE is consistent with that of the LC molecules under the influence of the elastic force. As a result, with the addition of Pb²⁺, the DNA molecules in the sensor are catalytically cleaved, disturbing the orientation of the LCs and TPE–PPE and resulting in a darker fluorescence. Due to the high sensitivity of the AIE lumogen, the response time of the LC Pb²⁺ sensor is less than 20 s, which enables its application in the real-time detection.

3.1.2. Metal Ion Detection Based on Coordination

Apart from the biomolecules mentioned earlier, some other organic or inorganic molecules, which can bind with the metal ions via coordination bonds, also show potential in ion detection. The coordination bonds, as the typical covalent interactions between metals and ligands, have been demonstrated to be effective in many fields such as self-healing polymers, smart responsive surfaces, and sensors.[114] A variety of metal–ligand coordination compounds holding unique properties have been
realized, laying foundation for the detection of a vast range of metal ions including Cu$^{2+}$, Hg$^{2+}$, Ca$^{2+}$, and Pb$^{2+}$. The metal ions in the coordination compound can provide empty electron orbitals, and the ligands usually provide lone pair electrons, which occupy the empty orbitals and stabilize the coordination system. Up to now, various LC ion sensors based on the coordination have been achieved.

**Carboxy Group:** The coordination between Ca$^{2+}$ and the carboxy group (–COOH) has been proved to be a promising candidate for Ca$^{2+}$ detection with high specificity. A bridged structure of –COO–Ca–OOC– can be obtained after coordination, which can lead to the movement of the LC molecules and therefore change the optical signals. Myung et al. studied the affinity of different bivalent ions to –COOH and found that Ca$^{2+}$ showed the highest binding affinity. This is because Ca$^{2+}$ has a larger ionic radius compared with other ions. Based on this phenomenon, an interpenetrating polymeric network (IPN) of the CLCs intertwined with the network-structured poly(acrylic acid) (PAA) has been proposed to quantitatively measure the CaCl$_2$ concentration. When detecting Ca$^{2+}$, the formation of –COO–Ca–OOC– can lead to the shrinkage of the network, resulting in the blueshift of the helical pitch. The photonic bandgap wavelength is inversely proportional to Ca$^{2+}$ concentration. LOD of 0.35 mM is successfully achieved. In addition, as the detection range of the sensor (0.35–3.4 mM) is consistent with the normal level of total calcium for healthy human serum and saliva, the sensor is further applied as a biosensor for detecting other physiological indexes in the human body.

**Other Ligands:** Apart from the –COO–Ca–OOC– system, many other ligands have also been explored to fabricate the LC ion sensors. 5-(pyridine-4-yl)-2-(5-(pyridin-4-yl)thiophen-2-yl)thiazole (ZT) is a sulfur- and nitrogen-containing ligand that is soluble in water. As shown in Figure 4a–c, in the presence of Ca$^{2+}$, the –COO–Ca–OOC– complex can lead to the shrinkage of the PAA chains, and an orientation change of the LC molecules, which to some extent hinder the LC reorientation and extend the responsive time. As a result, how to accelerate the responsive rate to achieve the real-time detection still remains a challenge for the –COO–Ca–OOC– system.
Moreover, other common ligands such as –CN, –OH, and –NH₃ are also alternative options for fabricating LC ion sensors. Each of these ligands has unique detection mechanism. For example, based on the theory that metals possessing high electrophilicity (Cu, Al, Fe) are easier to coordinate with –CN than those possessing low electrophilicity (Ag, Na, Mn), CuClO₄₂⁻ is directly spin coated on the glass substrate to achieve a homeotropic orientation of the LCs, which can be used for Cu²⁺ detection. In addition, surfactant-stabilized NiFe₂O₄ nanoparticles have been synthesized using chemical coprecipitation method and are incubated in the LC sensor to detect Pb²⁺. The abundant Fe–OH on the nanoparticles can interact with Pb²⁺ and disrupt the LC orientation. Biomolecules such as bovine serum albumin and oligopeptide possess a large amount of –COOH and –NH₃, and thus can chelate Cu²⁺ as the multidentate ligands, which have also been widely used for fabricating LC Cu²⁺ sensors. Furthermore, the amphiphilic potassium N-methyl-N-dodecylthiocarbamate (MeDTC) with its polar hydrophilic head group acting as the Hg²⁺ ligand has been doped into the LCs for Hg²⁺ detection with LOD of 0.5 μM (Figure 4d–f). While the LODs of the LC sensors based on coordinated bonds are higher than those based on the biomolecules in the previous section, the diversity of metal–ligand coordination compounds is still an advantage with excellent application prospects. In the future research, more efforts need to be devoted to improving the sensitivity of these sensors.

### 3.1.3. Metal Ion Detection Based on Fluorescence

The aforementioned LC ion sensors are able to display optical texture transition under the POM or show color change caused by the helical pitch variation. Those conventional observation methods rely on the naked eyes for rough image recognition, which may lead to false-positive judgments. Therefore, strategies that allow more accurate and quantitative detection while maintaining the sensitivity of the LC ion sensors are merited. Considering that it has been feasible to introduce fluorogens into the LCs through either electrostatic interactions or chemical modifications, measuring the analytes by fluorescence signal seems to be an alternative strategy. As a result, a variety of work has focused on the fabrication and characterization of the fluorescent LC sensors with ion detection property.

The feasibility of detecting ions with fluorogens was verified by the work reported in 2004, in which the oligonucleotides were functionalized with a fluorophore and a quencher moiety at the 3’- and the 5’-termini, respectively. In the presence of Hg²⁺, the T–Hg²⁺–T bridged bonds are formed to give rise to a hairpin structure, leading to the combination of the fluorophore and quencher moiety and resulting in significant fluorescent quenching. The fluorescence intensity is negatively correlated with the concentration of Hg²⁺. LOD of 20 nM has been successfully realized. Based on the pioneering work above, Iwai et al. integrated the fluorogens and CLC droplets together and realized a CLC droplet sensor with Fe³⁺ detection property. The detection relies on the fluorescent behavior of the luminol reaction participated by Fe³⁺. The photonic bandgap of the CLC is controlled to be near the emission peak to enhance the chemiluminescence emission maximum. However, the fluorescence effect is too weak for the quantitative and stable measurement, which is supposed to be solved by countermeasures such as using both right- and left-handed CLCs and introducing dyes with narrow emission.

Considering the urgent need for enhancing the fluorescence intensity of the fluorogens-based LC ion sensors, two different strategies including AIE and whispering gallery mode (WGM) have been proposed. To take advantage of the AIE, the uminophore molecule rhodamine B is assembled with sodium deoxycholate in NaOH solution, and the 3D spherical microcrystals possessing both highly ordered thermotropic LC behavior and AIE property are obtained (Figure 5a–c). With the existence of Fe³⁺, the electrons in the fluorogens can be easily transferred to Fe³⁺ containing unoccupied d orbitals, leading to the quick fluorescent quenching of the AIE LCs. The fluorescence intensity is negatively correlated with the concentration of Fe³⁺. LOD of

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**Figure 4.** The LC ion sensors based on coordination. a–c) The molecule alignment and optical signal of the LC Ca²⁺ sensor based on PAA-b-LCP with and without Ca²⁺. Reproduced with permission. Copyright 2019, Elsevier. d–f) The molecule alignment and optical signal of the LC Hg²⁺ sensor based on MeDTC with and without Hg²⁺. Reproduced with permission. Copyright 2016, Elsevier.
the sensor is 4.4 μM. In the later work reported by Duan et al.,\cite{128} WGM lasing was utilized to reduce the LOD of the fluorescent LC sensor (Figure 5d). The LC sensor is processed into the spherical geometry, which can act as the optical microcavity. Fluorescence is trapped in the optical microcavity by the total internal reflection to generate a high-intensity laser. Due to the double-amplification effect of the LC molecules and WGMs, LOD of 40 pm for Cu\(^{2+}\) has been successfully achieved, which is six orders of magnitude lower than the threshold defined by the WHO (31.5 μM), promising an outstanding application potential of this sensor in the detection of trace quantities of Cu\(^{2+}\).

3.1.4. Other Detection Methods

Redox: Apart from the strategies mentioned earlier, other alternative candidates such as redox, crown ether and electrostatic bonding also show splendid prospects in fabricating LC ion sensors. Redox changes the chemical composition of the sensors, leading to variation of the alignment layer and affecting the LC orientation. For example, a redox-based LC Mn\(^{2+}\) sensor has been fabricated by directly adding the LCs on Mn\(^{2+}\)-decorated surfaces.\cite{129} Upon exposure to Cl\(_2\) gas, Mn\(^{2+}\) on the surfaces is oxidized into MnO\(_2\), leading to an orientation transition from perpendicular to planar due to the reduction of the binding energy between the LC molecules and Mn atoms. Such a sensor can be utilized for monitoring Mn\(^{2+}\) concentration on the surface. The LOD of the sensor is related to the functional groups on the LC molecules. By replacing the nitrile-containing LCs with the pyridine-containing LCs, the LOD can be decreased from 7.0 ± 0.3 to 3.7 ± 0.2 pm mm\(^{-2}\). This is because the binding energy variation of the pyridine before and after redox is far larger than that of the nitrile, as calculated by the theoretical simulation. This work establishes a design principle based on the computation and envisages an opportunity to design the LCs that respond selectively to oxidizing or reducing ions.

Electrostatic Interaction: The electrostatic interaction between negatively charged surfactants and positively charged metal ions can block the self-assembly of the surfactants at the LC-aqueous interface, therefore realizing the ion detection. Han et al. developed an LC droplet sensor for heavy metal ion detection based on the electrostatic interaction.\cite{130} In the absence of the ions, the LC molecules in the droplets show radial alignment under the influence of the surfactant stearic acid, displaying dark-crossed appearance under the POM. However, a bright, fan-shaped appearance is observed when the LC droplets are incubated with ion solution, indicating a bipolar alignment of the LCs. Further research reveals that the LC droplet sensor has different LOD for different ions. The LOD for Co\(^{3+}\) is 50 pm while that for Cu\(^{2+}\) is 30 pm. Such a difference in the LOD originates from the different adsorption affinity of each ion. This LC droplet sensor based on the direct combination of the surfactant and heavy metal ions is convenient and simple, but lacks stability and specificity. The optical signal of the sensor will change with the volatilization of the solution, which shows an adverse effect on the judgment.

Crown Ethers: Crown ethers, as the typical cyclic compounds, show extraordinary performance in selective binding with metal ions based on the size matching between the ions and the internal cavity of crown ether moiety, which modulates the pitch of the CLCs. Relying on this mechanism, Stroganov et al.\cite{131} came up with a novel type of crown ether-containing LC sensor for Ba\(^{2+}\) and K\(^{+}\) detection. A polymer-stabilized CLC film is synthesized by the photopolymerization of the nematic diacylate, chiral dopant, and crown ether-containing acrylate. By immersing the film in a salt solution, the crown ether fragments specifically bind with the metal ions, forming a separated microphase that leads to the increase in the chiral dopant concentration in the CL phase. As a result, the central wavelength of the Bragg reflection blue-shifts by 68 nm, indicating the decrease in the helix pitch. By directly using the crown ether as the chiral dopant, Kado et al. achieved the selective sensing of K\(^{+}\) based on a CLC membrane.\cite{132} The combination of K\(^{+}\) with the crown ether leads to the formation of a sandwich structure and thus reduces the helical twisting power (HTP) of the chiral dopant. Therefore, a redshift of the central wavelength is observed with the existence of K\(^{+}\). In future studies, it is necessary to explore more crown...
ether-based LC sensors to realize detection of other alkali ions such as Na\(^+\) and Li\(^+\), which is hard to achieve by the existing LC sensors.

### 3.2. LC Sensors for Nonmetallic Ion Detection

Among all of the nonmetallic ions, H\(^+\), arsenic ions, and halogen ions have attracted great attention due to their crucial roles in the industrial production and daily life. H\(^+\) is usually produced by ionization of acids and determines the acidiety of the solution. A moderate amount of H\(^+\) can promote human physiological activities\([149]\), while the excess of H\(^+\) may cause physiological disorders of human body\([150]\). In addition, As\(^{3+}\) is a common metalloid ion that possesses biological activity and shows acute poisoning when its concentration exceeds the threshold value\([151,152]\). Moreover, the excess of halogen ions such as I\(^-\) and Cl\(^-\) can also cause adverse effects such as hypothyroidism and hyperchloraeemia\([153,154]\). As a result, it is important to adopt effective measures to monitor the concentration of those nonmetallic ions (Table 2).

#### 3.2.1. Hydrogen Ion Detection

Based on the protonation and deprotonation of the aliphatic acids, various LC H\(^+\) sensors have been achieved. Different pH values can lead to different protonation states of the aliphatic acids, therefore altering the LC alignment. Specifically speaking, when the pH value is low, the aliphatic acids are protonated and dissolved in the LC phase, disrupting the arrangement of the LCs. When the pH value is high, the aliphatic acids become deprotonated and amphiphilic and thus can orderly arrange at the LC–water interface to achieve a homeotropic orientation. Based on this mechanism, an LC droplet sensor composed of hexanoic acid (HA) and 5CB has been proposed\([99]\). The sensor can show an optical image transition from a dark-cross shape to a bright-fan shape under a minimal change of the pH value with fast and intensive response (Figure 6a,b). The LOD of the sensor can be adjusted via changing the concentration of HA. By varying the doping ratio of HA, the critical pH value could be fine tuned according to the demand in the practical application. In addition, to realize the quantitative monitoring of a large pH range, several individual LC H\(^+\) sensors with gradient critical points were arranged in a microfluidic device with inlet and out channels by Chen et al.\([155]\). The critical pH points of the sensors are adjusted by varying the type of the pH-sensitive dopants, changing the concentration of the dopants, as well as tuning the ionic strength in the solution. In this work, the pH value of the sample solution can be determined by the number of the bright LC sensors in the device. Such a microfluidic system based on the LC sensors can be utilized as the pH tag for continuous and on-site water analysis.

Apart from the aliphatic acids, block copolymerization composed of PAA and liquid crystalline fragment, the so-called poly(acrylic acid)-b-poly(4-cyanobiphenyl-4′-oxyundecyl acrylate) (PAA-b-LCP), also exhibits the protonation and deprotonation property and can achieve the LC H\(^+\) sensor via the same mechanism. Lee et al.\([80]\) coated CLC droplets with PAA-b-LCP, in which the PAA fragment contacted with water while the LCP fragment dissolved in the CLC phase (Figure 6c,d). At the low pH value, the PAA is protonated and favors the radial orientation of the CLC. In contrast, at the high pH value, the deprotonated PAA leads to the swelling of the block polymer, which favors the homeotropic orientation. The H\(^+\) signal can be observed by the transition of the optical image from randomly distributed small spots to bright central spots.

Moreover, utilizing the chiral dopants with pH-responsive property, the CLC H\(^+\) sensors can also be achieved, in which H\(^+\) can directly change the HTP of the chiral dopants, therefore varying the helical pitch of the CLCs. Based on this mechanism, a temperature and pH double-sensitive CLC film has been
proposed by Chen et al.\textsuperscript{[156]} Such a film is achieved by the UV polymerization of the CLC monomers and the chiral H-bonded assembly. The reflection band showed an obvious redshift with the increase in the pH value. The pH sensitivity of the sensor can be explained by the –OH -induced breaking of the hydrogen bonds in the polymer, which results in the decrease in the HTP. Fourier transform infrared (FTIR) spectra are collected to prove the important role of the hydrogen bonds in the sensor. It is found that the small peaks corresponding to the hydrogen bonds disappeared after the film is treated with the alkaline solution. While this preliminary work realizes the detection of H\textsuperscript{+}, the detection efficiency is extremely low that it takes 5 days to achieve the complete color change. The low efficiency is attributed to the lack of deformability in the CLC film, which impedes the change of the helical pitch. To solve this problem, Stumpel et al. fabricated an interpenetrating polymer LC hydrogel with H\textsuperscript{+} detection property.\textsuperscript{[68]} By introducing an interwoven PAA hydrogel into the CLC network, the polymer becomes deformable that can realize dimensional alteration under different pH values. As a result, the sensor turns red in the alkaline solution while turns green in the acid solution. The detection is reversible and sensitive, providing a referable idea for designing LC sensors using the IPNs of hydrogels and LCs.

With the development of the LC H\textsuperscript{+} sensors, the detections of biomolecules including enzymes, substrates, and proteins, which embody the broad application prospects of H\textsuperscript{+} sensors, can be realized by integrating the ion sensors and biological receptors together.\textsuperscript{[165,166]} As many of the physiological processes involving enzymatic reaction and protein adsorption are closely related to H\textsuperscript{+} concentration in the body fluid, a variety of studies have been devoted to investigating the modified LC H\textsuperscript{+} sensor for biomolecule detection. By combining the PAA-b-LCP-coated CLC sensor with glucose oxidase and cholesterol oxidase, the detection of glucose and cholesterol with low LOD (0.5 \(\mu\)M for glucose and 2.5 \(\mu\)M for cholesterol) has been realized based on the generation of H\textsuperscript{+} during the oxidizing reactions.\textsuperscript{[80]} In addition, other enzymatic reactions, such as the hydrolysis reaction of urea driven by urease,\textsuperscript{[157,158]} the degradation of penicillin under the catalysis of penicillinase,\textsuperscript{[159]} and the interaction between paraoxon and paraoxonase,\textsuperscript{[160]} have also been utilized for fabricating biosensors based on the concentration variation of H\textsuperscript{+}. Furthermore, the PNIPAM-b-LCP-coated LC droplet H\textsuperscript{+} sensors have been utilized for protein detection (PNIPAM: poly(N-isopropylacrylamide) and LCP: poly(4-cyanobiphenyl-40-oxyundecylylacrylate)).\textsuperscript{[161]} The initial configuration of the LC droplets without proteins is radial, which turns...
bipolar with the existence of proteins. Such a protein adsorption process could only occur at pHs below the isoelectric points of the proteins. These biomolecule detection strategies based on H\(^+\) reveal the versatility of the LC H\(^+\) sensors and greatly expand the application prospect of the LC materials. Using other receptors such as aptamers, antibodies, and peptides, the detection range of those sensors can be further extended.

### 3.2.2. Halogen Ion Detection

The detections of other nonmetallic ions including halogen ions and arsenic ions are also of great necessity due to their wide distributions and non-negligible toxicity. Up to now, the detection of halogen ions still remains a challenge due to the lack of suitable receptors. The dipole-induced dipole interaction, which can influence the LC alignment, has been proved to be an alternative candidate for fabricating LC sensors with halogen ion detection property. Hallett et al. investigated the ionic structure at the LC–aqueous interface by X-ray reflectivity for determining I\(^-\)/C\(_0\) and Br\(^-\)/C\(_0\) in the solution.\[^98^]\) I\(^-\)/C\(_0\), as a typical chaotropic ion, holds large ion radius and weak hydration and can lead to the orientation transition from planar to homeotropic LCs. In contrast, Br\(^-\), as a kosmotropic ion, shows small ion radius and strong hydration and is not able to perturb the orientation of the LCs. The underlying driving force of the I\(^-\)/C\(_0\)-induced LC reorientation is the dipole interaction between the LC cyano groups and polarizable I\(^-\). As a result, it is feasible to distinguish I\(^-\) and Br\(^-\) by investigating the LC orientation at the LC–aqueous interface using X-ray reflectivity. It is found that the areal density of I\(^-\) determined from the X-ray reflectivity is close to the LC areal density, indicating the one-to-one binding between I\(^-\) and LC molecules. However, for Br\(^-\), X-ray reflectivity reveals that there is no localization of ions at the interface. This work highlights the interactions between the LC molecules and halogen ions and can help guide the design of the LC-based lab-on-a-chip devices. In addition, Carlton et al. found that the LC reorientation triggered by the halogen ions was closely related to the pH value of the solution (Figure 7a,d).\[^162^]\) The tilt angle of the LCs at the NaCl (1 M) solution interface is nearly 90° when the pH value is below 9 and continuously decreases to 0° with the increase in the pH value. This conclusion can also guide the fabrication of the LC sensors for halogen ion detection.

### 3.2.3. Arsenic Ion Detection

As\(^{3+}\) is one of the most common metalloid ions with high solubility and toxicity. It can bind with erythrocyte and cause irreversible damage to the cytomembrane. Recently, a label-free LC-based As\(^{3+}\) detection strategy utilizing ssDNA as the receptor was proposed by Nguyen et al.\[^163^]\) (Figure 7e). In the absence of As\(^{3+}\), the ssDNA receptor binds with the surfactant by electrostatic interaction and disturbs the self-assembly of the surfactant, leading to the planar orientation of the LC molecules. While in the presence of As\(^{3+}\), the specific binding of the receptor and

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**Figure 7.** The LC ion sensors for halogen ion and arsenic ion detection: a,b) The POM images and LC alignments of the LC Cl\(^-\) sensor using C16/Au as the alignment layer in contact with 1 M NaCl at different pH values. c,d) The POM images and LC alignments of the LC Cl\(^-\) sensor using octadecyltrichlorosilane (OTS) as the alignment layer in contact with 1 M NaCl at different pH values; Reproduced with permission.\[^162^]\) Copyright 2012, American Chemical Society. e) The sensing mechanism and optical signals of the LC As\(^{3+}\) sensor. Reproduced with permission.\[^163^]\) Copyright 2020, Elsevier.
As$^{3+}$ results in the reorientation of the LCs from planar to homeotropic. The LOD (50 nM) is well below the maximum permissible level of As$^{3+}$ in drinking water (133 nM) set by the USA Environmental Protection Agency and the WHO, indicating the remarkable application prospects of the sensor.

In addition, AsO$_4^{3-}$ also has toxicity to human beings. Majeed et al.\textsuperscript{[164]} elucidated the photocatalytic effect of TiO$_2$ on the LC sensor for AsO$_4^{3-}$ detection. Upon exposure to UV light, the TiO$_2$ in the sensor can generate electron–hole pairs, which can absorb AsO$_4^{3-}$ to form coordination compounds, leading to the disturbance of the LCs. This sensor is expected to realize the detection of As$^{3+}$ by introducing the redox reaction involving As$^{3+}$ and AsO$_4^{3-}$. However, the LOD of such an AsO$_4^{3-}$ sensor still remains to be improved.

4. Conclusion

An LC phase, as a mesophase between the liquid and the solid, shows satisfactory stimuli–responsive properties and optical properties and has been widely applied in the field of sensors. The LC molecules in the sensors can be tailored to respond to targeted chemical species and realize the transition of optical signals. In addition, ions are widely distributed in the nature and bions and have been proved to be critical for human physiological processes and natural ecological environment. Appropriate amount of ions is beneficial, while excessive ions can cause irreversible damages. As a result, it is of great significance to realize the on-demand detection of ions in both body fluids and water samples accurately and instantly. In consideration of the superiority of the LC sensors such as portability and low cost, various efforts have been devoted to the design and application of the LC ion sensors, which are reviewed by this article elaborately.

The flat geometry, spherical/hemispherical geometries, and irregular geometry are four of the most common geometries of the LC ion sensors, among which the flat geometry is simple but holds high LOD, the spherical/hemispherical geometries show low LOD but poor stability, and the irregular geometry is promising in wearable devices. During the design of the sensors, the geometry should be considered according to the actual demands. In addition, the initial alignments of the LCs can greatly influence the sensitivity of the sensors and are closely related to the sensing mechanisms. Moreover, the optical signals of the sensors are derived from the birefringence and photocromatic stopband of the LCs, varying under the external stimuli and providing a valid approach for estimating the type and concentration of the ions. By taking into account the geometry, initial alignment, and optical signal simultaneously, the design of the LC ion sensors with high specificity, excellent sensitivity, and satisfactory stability is supposed to be realized.

To fabricate the LC ion sensors with satisfactory metal ion detection property, various detection receptors including the biomolecules, ligands, fluorogens, and crown ethers have been utilized, either by doping in the LC phase or by modifying at the interface. Each of the receptors has a unique detection mechanism. Nucleic acids, enzymes, and DNAzymes are the most common biomolecules used in the sensors. For the ligands, the functional groups such as –CN, –COOH, and –NS$_2$ have been widely utilized. In addition, in regard to the detection of nonmetallic ions, the LC H$^+$ sensors are important. They can not only measure the pH value via various mechanisms, but also detect the biomolecules. Furthermore, the halogen ion detection and arsenic ion detection have also been achieved via various LC sensors.

In spite of the rising research enthusiasm for the LC ion sensors, there still remain some challenging problems. Above all, more efforts are needed for fabricating the LC Na$^+$ and K$^+$ sensors. Na$^+$ and K$^+$ are the common blood electrolytes that are necessary for maintaining the cell physiology by adjusting the osmotic pressure and acid–base balance. In the release and delivery of the neurotransmitters, Na$^+$ and K$^+$ are also essential for the generation of membrane potential. A tiny concentration variation of Na$^+$ and K$^+$ can cause severe physiological disorders of the human body. As a result, it is of great significance to monitor the Na$^+$ and K$^+$ concentrations accurately. Although the LC sensors based on the crown ethers have been proposed to detect K$^+$, the LOD of the sensor still remains to be improved. This is because the steric hindrance change of the crown ether before and after combining K$^+$ is small. Therefore, new receptors that can recognize Na$^+$ or K$^+$ specifically with marked steric hindrance change should be explored. In addition, the LC Na$^+$ and K$^+$ sensors with satisfactory biocompatibility should also be investigated to lay the foundation for the detection of the membrane potential and neural signal in the human body.

In addition, in the LC sensors with irregular geometry, the mobility of the LC molecules is severely limited by the polymer matrix, therefore reducing the detection sensitivity. In the LC sensors with spherical/hemispherical geometries, the stability is suboptimal as the detection property will reduce with the volatilization of aqueous phase. To achieve the LC sensors with satisfactory stability and sensitivity simultaneously, a new type of LC material, known as the LC microcapsules (LC-Ms), has been proposed. The LC-Ms are composed of the LC core and the polymer shell and are usually fabricated via a two-step strategy. First, the LC droplets with monomers distributed either in the LC phase or in the aqueous phase should be obtained by emulsification techniques such as stirring emulsification, membrane emulsification, and microfluidics. Then, a polymerization reaction at the LC–aqueous interface is performed to process the monomers into polymerized shells. Such an emulsification–polymerization strategy is quite complex, hindering the development of the LC-Ms ion sensors. As a result, the bulk fabrication of LC-Ms with uniform size, good stability, and high optical performance has been an urgent task. In one way, the emulsification technique should be improved to enable the scale-up production of the monodispersed LC droplets. In another way, strategies that can realize the simultaneous emulsification and polymerization should be explored.

Another key requirement is to develop a precise procedure for the optical pattern classification and performance prediction, which are time consuming but of great importance. For a typical LC ion sensor, the tiny differences in the optical patterns usually imply the distinction on the ion type and ion concentration. Distinguishing such tiny differences is not manually feasible. In addition, the quantitative measurement of a wide range of ion concentrations is crucial but remains unfinished. Investigating the relationship between the ion concentration
and the gray level of the optical signal is an alternative approach to solving this problem. However, the task is also hard to achieve artificially. Aiming at solving the above problems, machine learning (ML)-based strategies, which can eliminate the human factors and process optical images efficiently, seem to be an ideal solution. In recent years, Abbott and his colleagues explored various ML algorithms, which can optimize the recognition accuracy and speed, providing guidance for integrating the LC ion sensors and ML technologies.\textsuperscript{1,6,18} Overall, current works have demonstrated the superiority of the LC ion sensors in a variety of applications. The sensors are of great practical value and hold promising application potential, especially after the remaining problems are solved.

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Conflict of Interest

The authors declare no conflict of interest.

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active optical components, biopotonic sensors, ion sensors, liquid crystal sensors, nanophotonic materials, optical sensing

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