ESIPT-based AIE luminogens: Design strategies, applications, and mechanisms

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Abstract
In this review, we present a systematic and comprehensive summary of the recent development and applications of excited-state intramolecular proton transfer-based (ESIPT-based) aggregation-induced emission luminogens (AIEgens), a type of promising materials that inherit the advantages of ESIPT and AIE, such as large Stokes shift, excellent photostability, and low self-quenching. We first summarize the backbones that have been used to construct the ESIPT-based AIEgens and classify the constructed ones based on the relation between ESIPT and AIE unit. According to the sensing mechanisms and design strategies, we have reviewed the applications of ESIPT-based AIEgens in bioimaging, drug delivery systems, organic light-emitting diodes, photo-patterning, liquid crystal, and the detection of metal cations, anions, small molecules, biothiols, biological enzymes, latent fingerprinting, and so on. We have also reviewed the recent advances in the development of new theoretical methods for investigating molecular photochemistry in crystals and their applications in ESIPT-based AIEgens. We discussed the remaining challenges in this field and the issues that need to be addressed. We anticipate that this review can provide a comprehensive picture of the current condition of research in this field, and promote researchers to make more efforts to develop novel ESIPT-based AIEgens with new applications.

KEYWORDS
AIE, ESIPT

INTRODUCTION

Excited-state intramolecular proton transfer (ESIPT) was first proposed by Weller in the 1950s to explain the dual fluorescence of methyl salicylate.¹,² Typically, ESIPT is a four-level phototautomerization process (Scheme 1). In the ground state, the molecule exists as enol form (E) with the intramolecular hydrogen bond X₁─H⋅⋅⋅X₂, where X₁ and X₂ are electronegative atoms, such as N or O, including O─H·⋅⋅⋅O, O─H·⋅⋅⋅N, and N─H·⋅⋅⋅N.³–¹⁵ Upon photoexcitation to the excited state of enol form (E*), proton transfer occurs from X₁ to X₂ to form the excited-state keto form (K*) with intramolecular hydrogen bond═X₁·⋅⋅⋅H─X₂. The K* can return to the ground state of keto form (K) by emission or nonradiative transition and then return to the initial E by ground state intramolecular proton transfer. Depending on the energy barrier of ESIPT, single fluorescence from E* or dual fluorescence from E* and K* can be observed experimentally. The energy barrier of ESIPT could be tuned by substituents, solvents, intermolecular hydrogen bonding, and crystallization.¹⁶,¹⁷ In addition, the coexistence of E and K may be observed when the relative Gibbs free energy difference between the two forms is less than 2 kcal mol⁻¹.⁸,¹⁸

One of the great advantages of ESIPT molecules is that the emission of K* possesses an extremely large Stokes shift, thereby suppressing self-absorption and making ESIPT molecules attractive materials as chemosensors, fluorescent probes, laser dyes, and optoelectronic devices.³–¹⁵ A variety of ESIPT-based systems have been developed and applied in the abovementioned fields. Moreover, extensive theoretical studies have also been performed to unravel the sensing mechanisms of ESIPT-based fluorophores, and reveal the effects of pH, temperature, substitutes, solvents, and intermolecular hydrogen bonding on the ESIPT process.¹⁹–²⁴

Conventional organic fluorophores may suffer from aggregation-caused quenching (ACQ) owing to the strong intermolecular π–π stacking or formation of excimers, limiting their applications in living cells where high concentration...
in aqueous medium is required and in optoelectronic devices where the materials need to be worked in the aggregated- or solid-state. The aggregation-induced emission (AIE) is an opposite phenomenon of ACQ and was first reported by Tang et al. in 2001.[25] The AIE luminogens (AIEgens) are nonemissive or emit weak fluorescence in dilute solutions, whereas they emit strong fluorescence upon aggregation in solutions with poor solubility or solid-state. The unique photophysical properties of AIEgens make them especially suitable for biological imaging and optoelectronic device fabrication.[26, 27] Endowing the ESIP-based fluorophores with AIE characteristics can inherit the advantages of both and thus extend their application scope. The development of ESIP-based AIEgens has attracted great attention in the fields of physics, chemistry, and biology science. A growing number of ESIP-based AIEgens have been developed and applied in the detection of cations,[28–57] anions,[34, 35, 41, 43, 58–68] and small molecules,[69–76] bioimaging in the living cell and in vivo,[77–116] drug delivery systems (DDS),[14, 117–119] liquid crystal,[120–122] white light emitters,[123–127] and latent fingerprinting.[56, 128–131]

Fluorescence quenching of AIEgens in dilute solutions resulted from the consumption of excited-state energies by intramolecular motions, including vibrational motions, rotational motions, and both of them. In aggregated states, these intramolecular motions will be restricted owning to the intermolecular interactions and AIE will be active. Restriction of intramolecular motions (RIM) has been widely accepted as the general working mechanism of AIEgens.[132–137] Typically, the formation of the H-aggregate with a face-to-face orientation leads to strong π–π stacking interaction and thereby quenches the fluorescence, whereas the formation of the J-aggregate with head-to-tail orientation is beneficial for the AIE.[27] However, the relation between the aggregate type and AIE is ambiguous. The formation of J-aggregate not always leads to AIE,[27] and the AIE due to the formation of H-aggregate has also been reported.[138] From the perspective of excited-state potential energy surface (PES), restriction of access to a conical intersection (RACI),[139–143] and restriction of access to a dark state[144] have also been proposed to complete the picture of AIE mechanisms. A prerequisite for ESIP is the formation of stable intramolecular hydrogen bonds. For ESIP-based AIEgens, the intermolecular interactions not only restrict the intramolecular motions but also stabilize the intramolecular hydrogen bonding and promote the ESIP process. Therefore, unraveling the working mechanism of ESIP-based AIEgens can help understand the nature of the coupling between the intermolecular and intramolecular interactions.

Except that ESIP-based AIEgens, some other ESIP fluorophores without involving the AIE can also emit strong fluorescence in solid-state, which have been reviewed well in refs. [9, 145]. Although more and more reviews on AIEgens and their applications have been published and discussions on ESIP-based AIEgens have been included in some of them as a part, a comprehensive and systematic review on ESIP-based AIEgens has not been presented.[146–158] In this review, we first summarize the commonly used ESIP and AIE units and how to use them to construct ESIP-based AIEgens, and then we discuss the applications of ESIP-based AIEgens in different fields and the related sensing or working mechanisms. We also present a brief discussion on theoretical advances in the mechanistic study of ESIP-based AIEgens. Finally, a summary and outlook are presented.

## 2 | BACKBONES OF ESIP-AIE LUMINOGENS

Depending on the relations between AIE and ESIP units, the reported ESIP-based AIEgens can be subdivided into three types.[108] In the first type, the AIE unit is identical to the ESIP unit. In Scheme 1, we show the structures of the reported ESIP-based AIEgens of this type.

As a typical AIE unit, the Schiff base may undergo C=N isomerization followed by a free intramolecular rotation. Moreover, the N atom of the Schiff base can act as a proton acceptor. When the phenolic hydroxyl group was utilized as a proton donor, the formed compound was usually referred to as salicylaldehyde-based Schiff base (SSB, Scheme 2A), which is a typical backbone of ESIP-based AIEgens. By changing the substituents on the benzene ring and the end of the Schiff base, various SSB derivatives have been developed as ESIP-based AIEgens.[29, 30, 32, 38, 43, 44, 58, 62, 116, 129, 130, 159–168] The introduction of the strong electron-withdrawing groups into SSB, such as −F and −NO2, may lead to a red-shift of the emission due to the separation of the electron cloud and an increase of the fluorescence quantum yield.[130] A similar effect can also be achieved by attaching an electron-donor diethyamine group and an electron-acceptor maleonitrile group at different sides of SSB.[116] In addition, the structure–activity relationship studies on a series of SSB derivatives have shown that the attaching of the dimethylamino group into the phenolic ring may increase the cell-penetrating capacity due to an increase of hydrophobicity.[164] The compounds may also possess two or more Schiff bases (Scheme 2B) with extending conjugation length, of which the emission color can be finely tuned from bluish-green to orange–red by changing the aromatic substituents with electron-donor or electron-withdrawing groups.[169, 170] Except that phenol, naphthol (Scheme 2C)[33, 50] and coumarin (Scheme 2G)[172] can also be utilized as a proton acceptor and combined with Schiff base to construct ESIP-based AIEgens. The extension of conjugation of the aromatic system by coumarin not only leads to a large red-shift of the emission wavelength but also increases...
SCHEME 2 Chemical structures of backbones of ESIPT-based AIEgens (I). (A) SSB. (B) Compound with two Schiff bases. (C) 3-hydroxy-\(N^2\)-(2-hydroxy-1-naphthalene methylene)-2naphthalene hydrazide. (D) SAA. (E) Symmetric SAA. (F) 1-((E)-((E)-5-bromo-2-hydroxy benzylidene)hydrazono)methyl)naphthalen-2-ol. (G) Coumarin-based Schiff bases. (H) 8,8’-(1E,1E’)-hydrazine-1,2-diylidenebis(methanylylidene))bis(7-hydroxy-4-methyl-2Hchromen-2-one). (I) HBT (X = S) and HBI (X = NH). (J) 2-(2’-aminophenyl)benzothiazole (ABT). (K) 2’-hydroxychalcone (HC). (L) Hydroxyphenylquinazolinone (HPQ). (M) 1,5-benzodiazepin-2-one. (N) 2-hydroxy-1-naphthal-4-aminoantipyrine. (O) (2-hydroxyphenyl)propenone. (P) BOPYIN. (Q) Coumarin-pyrazole. (R) Quinazoline.

the fluorescence lifetime to \(\approx 8 \mu s\). It should be noted that the recent studies by Pramanik and Das have demonstrated that the AIE of the most reported Schiff bases resulted from the aldehydes due to the hydrolysis of the molecules by water. However, this is not the case for SSB derivatives because the studies by Pramanik and Das have also demonstrated that the presence of intramolecular hydrogen bonding can prevent the hydrolysis of the molecules.

Akin to Schiff base, azine can also act as an AIE unit and proton acceptor to form intramolecular hydrogen bonding with the \(\alpha\)-hydroxyl group on benzene (Scheme 2D,E). Among these compounds, symmetric salicyaldehyde azine derivatives (SAA, Scheme 2E) have gained the most popularity in construction of ESIPT-based AIEgens because they are easily synthesized from salicyaldehyde derivatives and hydrazine hydrate even in one step. A significant advantage of symmetric SAA is that the hydroxyl group can be easily modified by various protecting and targeting groups, making it suitable in the detection of small and biological molecules. Moreover, a series of asymmetric SAA derivatives including keto-salicyaldehyde
The emissions of HBT derivatives are easily tunable (ABT, Scheme 2I) have been reported. Geometric to be applied in bioimaging. Moreover, other ESIPT-based AIEgens bearing O=H−⋯N or N=H−⋯N intramolecular hydrogen bonds have also been developed and reported, in which the proton acceptor N is located on five- or six-membered rings, including hydroxyphenylquinazolinone (HPQ, Scheme 2L), 1,5-benzodiazepin-2-one (Scheme 2M), or red-shifted. As the second transition-metal ion in the human body, zinc ion (Zn²⁺) plays a significant role in various biological processes and is essential for human health. Deficiency or excess of Zn²⁺ may cause health issues, including undergrowth, Alzheimer’s, and Parkinson’s disease. Therefore, almost all the reported ESIPT-based AIEgens for detection of metal cations involve SSB or SAA scaffolds, or at least, involve Schiff base or azine bearing an intramolecular hydrogen bond O=H−⋯N which may cause health issues, including undergrowth, Alzheimer’s, and Parkinson’s disease. Hence, it is of vital importance to develop new chemosensors to detect Zn²⁺ in the environment and biological systems. Coordination of Zn²⁺ with ESIPT-based AIEgens usually induced a new emission peak with a significant enhancement of intensity by disturbing the intramolecular hydrogen bond and inhibition of nonradiative decay pathways, such as intramolecular rotations and photo-induced electron transfer (PET). Compared with the emission from K⁺ of ESIPT-based AIEgens, the induced new peak by coordination of Zn²⁺ may be blue- or red-shifted. A representative example of ESIPT-based AIEgens for the detection of Zn²⁺ and its possible sensing mechanism is shown in Figure 1. Compound 1 is a 2-naphthol-based derivative bearing azine unit (Figure 1C). The experimentally measured emission spectrum of compound 1 contains two-humped bands and is not a mirror image to the absorption spectrum, confirming the occurrence of the ESIPT process. In DMSO, compound 1 shows good solubility and a weak
emission at around 505 nm. Increasing the content of water in DMSO/H₂O to ≈90% afford a ≈52-fold of emission intensity with a red-shift to 520 nm, suggesting that compound 1 possesses AIE characteristics. The detection of Zn²⁺ has been performed in DMSO/H₂O (9:1 v/v, 5 µM, HEPES, pH 7.2) mixture solution, in which compound 1 has not shown AIE behavior. Upon addition of Zn²⁺, a prominent fluorescence enhancement is observed at around 527 nm, whereas the effect of other metal ions on the fluorescence spectrum is negligible (Figure 1A,B). The further experimental study demonstrates that compound 1 can also detect Zn²⁺ in the living cell.

The fluorescence quenching of compound 1 in dilute solutions may result from the C=N isomerization of azine accompanied by a PET from the nitrogen atom of azine to the naphthalene ring. Coordination of Zn²⁺ will completely block the C=N isomerization and inhibit the PET process because the lone-pair electron of nitrogen has been involved in coordination with the metal, thereby causing a chelation-enhanced emission (CHEF). Such a type of CHEF mechanism should also apply to most ESIPT-based AIEgens for the detection of Zn²⁺.
An exception to the CHEF mechanism has recently been reported by Pariat and coworkers.\textsuperscript{53} They developed and synthesized a 2-(2′-hydroxybenzofuranyl) benzoxazole derivative (compound 2, Figure 2), which is an ESIPT-based AIEgen and can be utilized to selectively detect Zn\textsuperscript{2+} in CH\textsubscript{2}Cl\textsubscript{2}/CH\textsubscript{3}CN (9:1 v/v), in which compound 2 show distinct dual emission from E* and K*. Upon addition of Zn\textsuperscript{2+} gradually, the emission intensity will decrease, and the dual emission bands will convert to a single band from K*. Such an unusual fluorescence behavior of compound 2 coordinated with Zn\textsuperscript{2+} results from the fact that the coordination does not disturb the intramolecular hydrogen bonding (Figure 2),\textsuperscript{53} which has not been observed for any other ESIPT-based AIEgens for detection of Zn\textsuperscript{2+}.\textsuperscript{28, 30, 32, 33, 43, 46, 49, 52, 55, 57}

Recently, Wu and coworkers reported a new fluorescent probe (compound 3, Figure 3A) for the detection of Zn\textsuperscript{2+} based on a chelation-induced AIE mechanism.\textsuperscript{56} Compound 3 is a hydrazone-based chemosensor with ESIPT property but does not possess AIE characteristics. Upon coordination of compound 3 with Zn\textsuperscript{2+}, the formed complex shows
3.1.2 Detection of Cu²⁺

Copper is the third transition metal in the human body and plays an essential role in human health. An imbalance of copper in the body has been associated with a series of diseases, such as Wilson’s disease, Alzheimer’s disease, and heart disease. Accurate, highly selective, and sensitive detection of intracellular Cu²⁺ is beneficial for the early diagnosis of these diseases. Unlike Zn²⁺, coordination of Cu²⁺ with ESIPT-based AIEgens will quench the fluorescence via chelation-enhanced quenching (CHEQ) mechanism. Therefore, detection of Cu²⁺ needs to be performed in poorly soluble solvents or aggregate state where the ligand has shown distinct AIE characteristics. Compound 4 (see Figure 4A) is an SSB derivative and shows AIE characteristics in the aqueous solution (see Figure 4B). The addition of Cu²⁺ will induce a remarkable fluorescence quenching, whereas the other metal ions do not interfere with the binding of compound 4 to Cu²⁺ (see Figure 4C). The fluorescence quenching by Cu²⁺ has also been observed for other ESIPT-based AIEgens and may result from ligand-to-metal charge transfer, as has been demonstrated by density functional theory calculations. The computed highest occupied molecular orbital and lowest unoccupied molecular orbital of a ligand–Cu²⁺ complex are localized on ligand and metal center, respectively.

A novel sensing strategy for the detection of Cu²⁺ by ESIPT-based AIEgens has been proposed by Jiang and coworkers. First, the hydroxyl group of HC (see Scheme 1K) was replaced with a picolinoyl-ester subunit (compound 5, see Figure 5B), thereby providing three coordination sites with one “N” and two “O” atoms to catch Cu²⁺ via forming a ligand: Cu²⁺ (2:1) intermediate (compound 6, see Figure 5B). Then the compound 6 will undergo a hydrolysis process and releases an ESIPT-based AIEgen HC, which exhibits a strong near-infrared emission at 648 nm as a result of the AIE and ESIPT effect (see Figure 5C). Further imaging experiments indicated that compound 5 can ratiometric image Cu²⁺ in living HeLa cells.

3.1.3 Detection of other metal ions

The ESIPT-based AIEgens has also been developed and applied to detect other metal ions, including Al³⁺, Cd²⁺, Pb²⁺, Fe³⁺, and Hg²⁺. Some ESIPT-based AIEgens may detect two or more metal ions. Typically, the detection of different ions by the same ESIPT-based AIEgen was performed in different solutions. For example, compound 1 can detect Zn²⁺ in DMSO/H₂O (9:1 v/v, 5 µM, HEPES, pH 7.2) mixture solution, whereas it can detect Al³⁺ in MeOH/H₂O (9:1 v/v, 5 µM, HEPES, pH 7.2) mixture solution, whereas it can detect Al³⁺ in MeOH/H₂O (9:1 v/v, 5 µM, HEPES, pH 7.2) mixture solution (see Figure 1C). When two ions being detected follows the same CHEQ mechanism as that of Cu²⁺, whereas the detection of Fe³⁺ and Fe²⁺ follows the same CHEQ mechanism as that of Cu²⁺. Some ESIPT-based AIEgens may detect two or more metal ions. Typically, the detection of different ions by the same ESIPT-based AIEgen was performed in different solutions. For example, compound 1 can detect Zn²⁺ in DMSO/H₂O (9:1 v/v, 5 µM, HEPES, pH 7.2) mixture solution, whereas it can detect Al³⁺ in MeOH/H₂O (9:1 v/v, 5 µM, HEPES, pH 7.2) mixture solution (see Figure 1C). When two ions being detected follow different mechanisms, the detection process may be performed sequentially. For example, the addition of Cu²⁺ to compound 1 in the aqueous solution will cause a significant fluorescence quenching, whereas further addition of Hg²⁺ will restore the fluorescence (see Figure 4D). Based on the fluorescence “off–on” via the addition of Cu²⁺ and Hg²⁺, compound 4 can be applied as logic gates with Cu²⁺ and Hg²⁺ as input and fluorescence intensity as output.
solution and will trigger a hydrolysis process, and then release compound 8 with AIE and ESIP effect (see Scheme 4). Therefore, compound 7 can selectively detect Hg²⁺ in THF/H₂O (1:1 v/v, PBS 20 mM, pH = 8.5) and living MCF-7 cells.

3.2 Detection of anions

The ESIP-based AIEgens have been developed and applied in the detection of F⁻, CN⁻, S²⁻, CO₃²⁻, ONOO⁻, CNO⁻, and ClO⁻ with three different sensing mechanisms. In the first mechanism, the anions will disturb the intramolecular hydrogen bonding or deprotonate the hydroxyl group of ESIP-based AIEgens, thereby inducing a new emission band with enhanced intensity. An example of this mechanism is the detection of F⁻ by compound 9 (see Figure 6A).

The emission band of compound 9 in CH₃CN was observed at 540 nm with a large Stokes shift of 170 nm. Addition of F⁻ first induced a new emission band at 490 nm and then red-shifted to 565 nm with the increasing of F⁻ concentration.

The ¹H NMR titrations experiments show that the signal of proton of the hydroxyl group at 13.28 ppm will disappear with increasing of F⁻ concentration, whereas the signals of other protons remain unchanged, confirming the deprotonation proton of the hydroxyl group.

In the second mechanism, the proton of the intramolecular hydrogen bond of ESIP-based AIEgens was protected by a special group that is active for the detected anions. The fluorescence of the protected probe will be quenched owing to the blocking of the ESIP process. After reaction with the detected anion, the protecting group will be removed via a hydrolysis process, and the intramolecular hydrogen bond is restored. Then, the released ESIP-based AIEgen will exhibit a strong fluorescence. Two examples of this mechanism are the detection of F⁻ and ONOO⁻ by protected HBT (compound 10, see Figure 6B) and SAA (compound 11, see Figure 6C), respectively. The HBT and SAA are protected by dimethylphosphinothionyl and diphenylphosphinate groups, respectively.

The third sensing mechanism for the detection of anions by ESIP-based AIEgens is based on an indirect manner. Compound 12 (see Figure 7D) is an SSB derivative with ESIP and AIE properties, which can be used to detect Cu²⁺ by virtue of the CHEQ mechanism (see Figure 7A). After that, the formed 12-Cu²⁺ complex can selectively discriminate S²⁻ by restoring the fluorescence of compound 12 (see Figure 7B). This is because that the strong affinity between Cu²⁺ and S²⁻ will cause decomposition of
FIGURE 5  (A,B) Probe design and the predicted mechanism of Cu$^{2+}$ sensing. (C) Photographs of compound 5 with various metal ions under daylight and 365 nm UV irradiation. Reprinted with permission.[51] Copyright 2021, The Royal Society of Chemistry

SCHEME 4  The detection mechanism of probe 7 for Hg$^{2+}$. Reprinted with permission.[36] Copyright 2017, Elsevier B.V

12-Cu$^{2+}$ complex and releasing of the free 12.[47] The IMPLICATION logic gate can be constructed based on the fluorescence “on–off–on” characteristics of 12 toward Cu$^{2+}$ and S$^{2-}$ (see Figure 7C). Moreover, 12-coated filter paper can be used as a sensing device for on-site detection of Cu$^{2+}$ and S$^{2-}$.[47]

3.3 Detection of biothiols

Biological thiols such as cysteine (Cys), homocysteine (Hcy), and glutathione (GSH) play significant roles in various kinds of physiological and pathological processes. The abnormal level of these biothiols in the human body may lead to some diseases such as cancer, cardiovascular diseases, and hematopoiesis reduction.[104–114] Thus, it is essential and meaningful to establish practice methods for the detection of biothiols in biological systems. Various ESIPT-based AIEgens have been developed and applied in the detection of biothiols, and most of them are based on a sensing mechanism of cleavage reaction.[104–114]

Similar to the second mechanism for the detection of anions, the hydroxyl group of ESIPT-based AIEgens is caged
by a biothiols-reactive fluorescence quencher such as 2, 4-dinitrobenzenesulfonyl (DNBS) group,\textsuperscript{104, 107, 108, 111, 113} acryloyl group,\textsuperscript{105–107, 109, 110} and maleimide group.\textsuperscript{113} When the ESIPT-based AIEgen is protected by DNBS, the protected probe can react with biothiols and then release the free ESIPT-based AIEgen, DNBS, and sulfur dioxide (SO\textsubscript{2}) (see Figure 8A). This reaction is not selective for biothiols. Therefore, usually more than one biothiols could respond to the DNBS-protected probe, as has been observed for the detection of biothiols by compound 13 (see Figure 8B).\textsuperscript{104} Figure 8C shows the reaction mechanism between an acryloyl-protected probe (compound 15) with biothiols, which begins with the formation of a thioester intermediate by Michael addition reaction. The intramolecular cyclization then occurs followed by the cleavage of the ester bond. Finally, the free ESIPT-based AIEgen and a seven-membered ring product are released when the Cys act as the reactant. This reaction is fast and kinetically favored by Cys, whereas it is slow or kinetically unfavored by other biothiols such as Hcy and GSH. Therefore, the acryloyl-protected probes can distinguish Cys from Hcy and GSH (see Figure 8D).\textsuperscript{105–107, 109, 110} Although the maleimide-protected compound 17 can also kinetically discriminate Cys from other biothiols, it follows a different reaction mechanism (see Figure 8E,F).\textsuperscript{114} The reaction between 17 and biothiols involves a Michael addition reaction followed by an S, N-intramolecular rearrangement cascade reaction. This reaction is fast for Cys because the involved transition state is an easily formed five-membered cyclic ring. However, it is slowed down for Hcy owning to the additional carbon-chain extension, and is kinetically unfavored by GSH because it needs to form a 10-membered cyclic transition state.\textsuperscript{114} An indirect method for the detection of Cys by using 2-hydroxy-1-naphthal-4-aminoantipyrine (compound 18, see Scheme 2N) has also been reported by Fang and coworkers.\textsuperscript{112} Similar to the third mechanism for detection of anions,\textsuperscript{47} compound 18 can also selectively detect Cu\textsuperscript{2+} by the CHEQ mechanism. The quenched fluorescence of the 18-Cu complex can only be restored by the addition of Cys owing to the low pKa value and less steric hindrance effect of –SH group.\textsuperscript{112} Finally, it should be mentioned that almost all of these probes can detect biothiols in the living cell.\textsuperscript{104, 106–114} 3.4 Detection of biological enzymes As an important biomarker, the abnormal serum alkaline phosphatase (ALP) activity is closely related to many serious diseases, making the detection of ALP is of great importance.\textsuperscript{77–79, 195, 212} The detection of ALP by ESIPT-based AIEgens follows the same mechanism as that of the direct method for the detection of biothiols, whereas the phosphate group has been used as the protecting group.\textsuperscript{177–79, 195, 212} Among the reported ESIPT-based AIEgens for the detection of ALP, compound 20 is completely insoluble in water with intense K* emission in the aggregated state, whereas the phosphate-protected compound 19 is well soluble in water without fluorescence (see Figure 9A).\textsuperscript{212} This unique property can overcome the diffusion problem of conventional probes and make the released compound 20 concentrates near the active site, thereby providing an enhanced bioimaging contrast. The compound 19 has been successfully applied in the visualization of ALP.
FIGURE 7  (A) Photograph of compound 12 with various metal ions under UV light at 365 nm. (B) Colorimetric detection of S\(^{2-}\) by 12-Cu\(^{2+}\). (C) Reversible sensing nature of 12 toward Cu\(^{2+}\) and S\(^{2-}\) under a UV lamp, and construction of truth table of IMPLICATION logic circuit. Reprinted with permission.[47] (D) Structure of compound 12. Copyright 2021, American Chemical Society

in living cells (see Figure 9B), osteosarcoma cells, and tissues.[212] Although the protection of the ESIPT-based AIEgens with the phosphate group usually suppresses fluorescence by prohibiting the ESIPT process, the phosphate-protected HC (see Scheme 2K) can emit greenish-yellow fluorescence in buffer solutions, whereas the released HC emits red fluorescence and possess poor water solubility.[177]

When the hydroxyl group of ESIPT-based AIEgens is protected by the β-galactopyranoside group, the protected probes can be used to detect β-galactosidase in living cells[97, 100, 102] and β-glucuronidase in Escherichia coli.[104] The same ESIPT-based AIEgen may be used to detect different biological enzymes. The phosphate-protected and β-galactopyranoside-protected SAA have been used to detect ALP[79] and β-galactosidase,[103] respectively. Moreover, compound 13 (see Figures 8A and 9C), a chlorine-substituted SAA, which has been used to directly detect β-galactosidase,[104] can also be used to indirectly detect β-lactamase.[98] Introducing a cephalosporin substrate into the system can release a thiol compound from β-lactamase via two reaction steps (see Figure 9C). Then, the problem of detecting β-lactamase becomes the problem of detecting thiol, which is what compound 13 is good at.[98, 104]

As previously mentioned, hyperoside (see Figure 9D) is a natural product that can be easily purified from Hedyotis diffusa.[102] Upon reaction with β-glucuronidase, ESIPT-based AIEgen quercetin will be obtained (see Figure 9D and Scheme 3AB). Therefore, hyperoside can be used as a light-up fluorescent probe for the detection of β-glucuronidase.[102]

Acetoxy, L-leucine amide, and γ-glutamate can be used as protecting groups to detect esterases,[115, 116] leucine aminopeptidase,[81] and γ-glutamyl transpeptidase (GGT),[101] respectively. To detect a special esterase, not only the protecting group, but a targeting group is also needed. By introducing acetoxy and morpholines into SAA to act as an esterase reactive group and a lysosome-targeting group, respectively, compound 21 (see Figure 9E) has been applied in the detection of lysosomal esterase and monitoring of the lysosomal movements in living cells.[115]

3.5 Cell imaging

Without introducing any special protecting or targeting groups, various ESIPT-based AIEgens have been demonstrated their abilities to penetrate cell membranes,[44] and selectively accumulate in the cytoplasm[88, 90, 93, 96] or liquid droplets (LDs),[82, 84, 85, 87, 91] indicating their potential applications in cell imaging. The structure of an HBT-based compound 23 and its imaging mechanism is shown in Figure 10A.[90] Compound 23 is nonemissive in low concentration. After quickly penetrating cell membranes, probe 23 will selectively concentrate in the cytoplasm and light up its fluorescence, probably owing to the formation of hydrogen
(A) Cleavage of sulfonyl bond of compound 13 by thiols and production of AIE fluorophore 14. (B) Fluorescence spectra of DNBS-CSA (30 mM) upon addition of 10 Equiv. of various amino acids, MPA (3-mercaptopropionic acid), and ABT (2-aminobenzenethiol) in 30% DMSO-10 mM PBS buffer at 7.4. Inset: the corresponding fluorescence intensity of DNBS-CSA upon addition of various amino acids and analytes. Reprinted with permission. Copyright 2014, Elsevier B.V. (C) The proposed reaction mechanism of compound 15 and Cys. (D) Fluorescence spectra of compound 15 (10 μM) after being treated with various 100 μM amino acids in PBS/DMSO system (99:1 v/v, pH 7.4). Reprinted with permission. Copyright 2018, Elsevier B.V. (E) Proposed sensing mechanisms of compound 17 toward Cys, Hcy, and GSH. (F) Fluorescence spectra (λex = 350 nm) of compound 17 (10 μM) with the addition of various amino acids (10 μM for Cys, 100 μM for GSH, Hcy, Pro, Ser, Glu, Lys, Gly, Tyr, Phe, Asp, and Arg) in water containing 0.5 % DMSO for 15 min. Inset: fluorescence images of adding Cys, blank, GSH, and Hcy under UV light (365 nm). Reprinted with permission. Copyright 2020, Elsevier B.V.

bonding between the carboxyl group of 23 and active components in the cytoplasm. Compound 24 (see Figure 10B) is an SAA-based fluorophore, which can penetrate membranes of both live and apoptotic cells and then light up its fluorescence by selectively aggregating in LDs. Upon zinc coordination, compound 25 can distinguish between different stages of apoptosis and selectively target and kill bacteria without harming mammalian cells (see Figure 10C). Compound 25 is positively charged, whereas cell membranes in the early stages of apoptosis and bacteria are generally negatively charged. Electrostatic interactions between them lead to selective imaging and activation of AIE plus ESIPT emission. The killing of bacteria of compound 25 is achieved by generating reactive oxygen species (ROS) under light irradiation. By introducing special targeting groups, the ESIPT-based AIEgens have been utilized to selectively image mitochondria, lysosomes, and cell membranes. By incorporation of pyridinium and triphenylphosphine groups with positive charges into the SAA skeleton, compounds 26 (see Figure 11A) and 27 (see Figure 11B) can trace the differentiation process of brown adipose cells and discriminate cancer cells from normal cells, respectively, via selectively accumulating in mitochondria. In particular, compound 27 can produce ROS in the absence of light and be applied in cancer therapy. As mentioned earlier, the morpholine ring can be used to construct lysosome-targeting probes. By conjugating the morpholine group with the SSB-carbazole skeleton, compound 28 (see Figure 11C) has...
been utilized in the visualization of the lysosome-related autophagy process.\cite{89} Pyridinium with positive charges can be used to selectively locate not only mitochondria but also cell membranes. Compound 29 (see Figure 11D) with pyridinium is a membrane-specific probe that can also generate ROS to kill bacteria and fungi upon light irradiation.\cite{80}

Although the vast majority of ESIPT-based AIEgens can be used for living cell imaging, few have been reported for in vivo imaging. As an ESIPT-based AIEgen, flavonoid quercetin (QC, see Figure 11E) can be easily obtained from *Sophora japonica* and show crystallization-induced K* emission. The prepared QC nanocrystals with the size of ≈5 nm have been successfully applied in vivo bioimaging in mice (see Figure 11F).\cite{86} Preparing QC from *Sophora japonica* avoids using toxic reagents during time-consuming synthesis. Moreover, the obtained QC is cheap and green with good biocompatibility. More efforts should be put forward in this direction to pursue better ESIPT-based AIEgens.

### 3.6 Detection of small molecules

The ESIPT-based AIEgens have also been developed and applied in the detection of small molecules that play vital roles in the environments and biological systems, such as hydrogen peroxide (H$_2$O$_2$),\cite{70} hydrogen sulfide (H$_2$S),\cite{72,73} SO$_2$,\cite{76} hydrazine,\cite{74} Pd$0$,\cite{75,160} perborate,\cite{75} phosgene,\cite{185} and 2-thiobarbituric acid.\cite{69} Most of these probes follow the “first protecting and then releasing” mechanism that has been described in the detection of anions, biothiols, and biological enzymes. In Figure 12, we show some reported ESIPT-based AIEgens for the detection of small molecules, as well as the target analyte and the corresponding protective group. The involved ESIPT-based AIEgens are HPQ (see Figure 12A and Scheme 2L), TPE-based derivatives (see Figure 12B,D), SAA-based derivatives (see Figure 12E), HBT-based derivatives (see Figure 12C,D,G), and SSB-based derivatives (see Figure 12F). For further details please refer to the corresponding references.

An alternative method for the detection of small molecules is achieved by the direct reaction between the ESIPT-based AIEgens and the target analyte, which will block the ESIPT process and thereby quench the fluorescence. Sharma and coworkers have developed a carbazole-based compound with ESIPT and AIE characteristics for selectively detection of 2-thiobarbituric acid.\cite{69} It has been proposed that the interactions between the S atom of 2-thiobarbituric acid and the phenolic proton of the probe disturb the intramolecular hydrogen...
**FIGURE 10** (A) The imaging mechanism of compound 23 in the cytoplasm. Reprinted with permission.©2015, The Royal Society of Chemistry. (B) Chemical structures of compound 24 and 25, and a schematic illustration of compound 24 for intracellular LDs staining and 25 for the detection of cell apoptosis. Reprinted with permission.©2015, The American Chemical Society. (C) The schematic illustration of 25 for selective targeting, imaging, and killing of bacteria over mammalian cells. Reprinted with permission.©2015, Wiley Periodicals, Inc.

**FIGURE 11** The structures of compounds (A) 26, (B) 27, (C) 28, and (D) 29. Reprinted with permission.©2014, The Royal Society of Chemistry; Copyright 2014, Wiley Periodicals, Inc.; Copyright 2016, Wiley Periodicals, Inc.; and Copyright 2021, The Royal Society of Chemistry. (E) Schematic illustration of preparation of QC AIEgen with ESIPT and QC nanocrystals with AIE fluorescence. (F) Schematic illustration of imaging cellular cytoplasm and in vivo bioimaging using QC nanocrystals with AIE fluorescence. Reprinted with permission.©2015, Wiley Periodicals, Inc.
bonding and suppress the ESIPT process.[69] The reaction between probe 43 and its target analyte hydrazine can lead to a conversion of $-\text{C}=\text{N}$ group to $-\text{CH}_2\text{NH}$ group (see Figure 13A), which has been confirmed by $^1$H NMR and can block the ESIPT process (see Figure 13B).[74]

### 3.7 Other applications

Recently, Singh’s group has made much effort on exploring the potential applications of ESIPT-based AIEgens in DDS.[117–119] They have developed three compounds (44, 46, and 49 in Figure 14) that can act as DDS but with different advantages. All these compounds possess $p$-hydroxyphenacyl ($p$HP) as a phototrigger and only can release the drugs in their aggregated state. Owning to the involvement of the SAA scaffold, compound 44 can deliver two drugs sequentially.[117] According to the proposed mechanism of photorelease of drug molecules (see Figure 14A), upon photo-excitation, the DDS was excited to its first singlet excited state accompanied by the ESIPT process. Then, the DDS will decay to the triplet excited state via intersystem crossing. The release of drug molecules occurs in the triplet excited state. Introducing the TPE endows compound 46 and its released product 47 the ability to generate ROS (see Figure 14B), thereby showing photodynamic therapy and chemotherapy activities simultaneously.[118] A combination of naphthalene moiety and $p$HP can enhance the two-photon absorption cross section, allowing compound 49 to work in the phototherapeutic window as a two-photon responsive DDS (see Figure 14C).[119] Since the DDSs and their released product possess different emission wavelengths, the release of drug molecules can be monitored in real-time.[117–119]

Owing to the high fluorescence quantum yield in solid-state and easily tunable color, the ESIPT-based AIEgens are ideal candidates for the construction of organic light-emitting diodes (OLEDs). Recently, numerous OLEDs based on the ESIPT-based AIEgens have been developed by using Schiff base,[172] SAA,[176] HBT,[123, 126, 187] and TPE[127, 213] derivatives. Although pyrene is a typical ACQ unit due to the strong $\pi-\pi$ interactions, Niu et al. have designed and developed three ESIPT-based AIEgens by conjugation of pyrene with HBT and demonstrated their potential applications in OLEDs.[187] Samanta et al. have designed an AIE-active bis-imine compound bearing pyrene group, which shows dual emissions in the methanol–water mixed solvent and a
FIGURE 13  (A) The detection mechanism of probes 43 for hydrazine hydrate. $^1$H NMR of 43 (B) before and (C) after hydrate was added. Reprinted with permission.[74] Copyright 2019, Elsevier B.V.

FIGURE 14  (A) Possible mechanism of photorelease of the dual DDS 44. Reprinted with permission.[117] Copyright 2018, The Royal Society of Chemistry. (B) TPE-based single-component nanoparticles for synergistic combination therapy (PDT and chemotherapy). Reprinted with permission.[118] Copyright 2018, The Royal Society of Chemistry. (C) Working protocol of the DDS 49 in the phototherapeutic window. Reprinted with permission.[119] Copyright 2020, The Royal Society of Chemistry
white-light emission can be achieved by adjusting the fraction of water.\textsuperscript{[124]} The short- and long-wavelength emissions have been demonstrated to result from the formation of excimer and occurring of the ESIPT process.\textsuperscript{[124]} The formation of exciplex between an ESIPT-based AIEgen and an AIE-active compound bearing pyrene has been observed by Bhat-tacharyya et al. and proved to play a vital role in generating white-light emission.\textsuperscript{[125]} Chen et al. have developed a series of HBT derivatives (see Figure 15A) with AIE and ESIPT characteristics by changing the substitutes in the benzene moiety.\textsuperscript{[126]} The emission spectra of these compounds cover the entire visible region (see Figure 15B) and white-light emissions in toluene and polydimethylsiloxane film have been obtained by the combination of three fluorophores with different molar ratios.\textsuperscript{[126]}

Photo-activable and photochromic materials have received much attention owing to their potential applications in photopatterning, molecular switches, logic gates, anticounterfeiting, etc. Recently, various ESIPT-based AIEgens have been developed as photo-activable\textsuperscript{[75, 175]} and photochromic\textsuperscript{[37, 162, 186, 193, 205]} materials. Typically, the photo-activable fluorophores are constructed by replacing the proton of the hydroxyl group in the intramolecular hydrogen bonding with a photo-activable group to block the ESIPT process and quench the fluorescence. Upon photo-excitation, the photo-activable group will be released and the intramolecular hydrogen bonding is restored to light up the fluorescence. The photo-excitation wavelength can be tuned by attaching different substitutes. Based on this design strategy, Peng et al. have designed a series of SAA derivatives as photo-activatable fluorophores and tested their applications in photo-patterning.\textsuperscript{[175]} Compound 38 (see Figure 12E) is another SAA-based photo-activable fluorophore caged by a 2-nitrobenzyl group, which will be converted to SAA upon 365 nm UV illumination. Since the photorelease reaction is irreversible, the photo-patterning is therefore unerasable. This problem can be overcome by using photochromic materials.

Photochromic materials are usually based on cis–trans isomerization or ring open–close. By simple conjugation of TPE with SSB, Wang et al. developed a photochromic fluorophore 51 (see Figure 16A) with AIE and ESIPT properties.\textsuperscript{[162]} Upon UV irradiation, the enol form of 51 will be converted to trans-keto form by a combination of ESIPT and cis–trans isomerization. The absorption and emission spectra of trans-keto form are significantly different from those of enol form, thereby inducing a color change. The trans-keto form can return to the enol form thermally or upon irradiation with visible light. Based on the photochromism of 51, an erasable photopatterning can be obtained (see Figure 16B).\textsuperscript{[162]} By introducing the methoxy group into 51, the obtained compound 52 (see Figure 16C) shows a polymorph-dependent photochromism.\textsuperscript{[205]} Two polymorphs, 52-a and 52-b (see Figure 16D,F) can be obtained in different concentrations of dichloromethane/methyl alcohol mixtures. Surprisingly, reversible photochromic behavior can be observed for 52-a, but not for 52-b. Further analysis of crystal packing indicates that a more close packing style (see Figure 16E,G)
may suppress the photoisomerization process and lead to the absence of photochromism.\textsuperscript{[205]} The 52-a can also be used as an erasable photopatterning and the combination of 52-a and 52-b can be applied in data encryption.\textsuperscript{[205]} Based on the ring open–close, Tu et al. developed a diarylethene derivative bearing HBT skeletons, which can be acted as a photo-switchable probe and be applied in cell imaging.\textsuperscript{[193]} In addition, different polymorphs of the same ESIPT-based AIEgen can also be converted by grinding, melting, vapor, annealing, and so on.\textsuperscript{[178, 179, 214]} As a result, the ESIPT-based AIEgens will change the color and can be applied as stimuli-responsive materials.

The detection of latent fingerprints by employing the ESIPT-based AIEgens has also been reported recently.\textsuperscript{[128–131]} However, the underlying sensing mechanism and structure–activity relations remain unexplored. In addition, several ESIPT-based AIEgens based on HBT have been developed and applied as liquid crystalline materials.\textsuperscript{[120–122]}

4 | RECENT ADVANCES IN THEORETICAL STUDIES

Although an increasing number of experimental studies on ESIPT-based AIEgens have been reported, theoretical studies on exploring the sensing mechanisms and the interplay between intermolecular and intramolecular interactions have been rarely reported. A few theoretical studies focusing on the computing of the energy barrier of the ESIPT process in solution and crystal have been reported,\textsuperscript{[215–218]} in which the crystal environment was treated by employing the ONIOM method. It is well-known that in the aggregated state the intermolecular interactions will decrease the energy barrier of ESIPT and promote the keto emission of the ESIPT-based AIEgens. This conclusion has been confirmed by theoretical studies from Shi’s\textsuperscript{[216, 217]} and Zheng’s\textsuperscript{[218]} groups. However, the theoretical studies on a diphenylethylene-modified HBT compound by Lin et al.\textsuperscript{[215]} provide a result that is inconsistent with the experimental observations,\textsuperscript{[188]} in which the computed energy barrier of the ESIPT process in crystal (0.44 eV) is larger than that in solution (0.06 eV).\textsuperscript{[215]} This inconsistency may result from the limitations of the conventional ONIOM method with an electronic embedding scheme. Recently, Rivera et al. have assessed the performance of different embedding schemes, including point charge embedding (PCE), ONIOM Ewald embedded cluster (OECC), and ONIOM embedded cluster as implemented in fromage package,\textsuperscript{[219]} in describing the excited state PES of molecules in solid-state.\textsuperscript{[220]} The results demonstrated that the PCE scheme can only be applied when the molecule possesses a rigid structure with small exciton couplings, otherwise the OECC model should be used.\textsuperscript{[220]}

By employing the static quantum chemical calculations with different methods, including time-dependent density functional theory (TDDFT), complete-active-space self-consistent-field (CASSCF), CASPT2, ADC(2), and CC2, and surface hopping nonadiabatic dynamics simulations with TDDFT and ADC(2) methods, Crespo-Otero’s group have performed a series of theoretical study on excited-state decays of HC (see Scheme 2K) and 2-hydroxyphenylpropenone derivatives.\textsuperscript{[220–223]} HC is a typical ESIPT-based AIEgen, whereas attaching a methoxy group in benzene ring makes the HC-OMe (see Figure 17A) be nonemissive in both solution and solid-state. For HC and HC-OMe in the vacuum, two minimal energy conical intersections (MECIs) have been located and are related to the intramolecular rotation (CIROT, see Figure 17B) and carbonyl pyramidalization (CIPYR, see Figure 17B).\textsuperscript{[221]} The CIROT is easily accessible and accounts for the fluorescence quenching of HC and HC-OMe in solutions, whereas the CIPYR is inaccessible. In the solid-state, the CIROT is completely blocked and only the CIPYR can be obtained for HC and HC-OMe. The CIPYR of HC-OMe is easily accessible whereas it is difficultly accessible for HC (see Figure 17C).\textsuperscript{[221]} The larger stability of CIPYR of HC-OMe results from the electronic effects
of the methoxy group. These results can explain well the fluorescence behavior of HC and HC-OMe in solution and solid-state. A similar RACI mechanism has also been observed for HPQ by employing the TDDFT, MS-CASPT2/CASSCF, and ONIOM methods, in which the MECI related to the rotation of the C=C bond is completely blocked in crystal (see Figure 17D)\(^{[224]}\)

5 | SUMMARY AND OUTLOOK

Thanks to the large Stokes shift of ESIPT and high fluorescence quantum yield in the solid-state of AIE, ESIPT-based AIEgens has shown its great potential in various fields. Among the reported ESIPT-based AIEgens, most of them are based on SSB, SAA, HBT, and conjugation of TPE with these three skeletons. Developing the new platforms for the construction of novel ESIPT-based AIEgens remains a significant challenge. When used as chemical and biological sensors, almost all ESIPT-based AIEgens have been successfully applied in living cells, whereas only very few can be applied in vivo. As the only two ESIPT-based AIEgens extracted from nature, myricetin\(^{[68]}\) and quercetin\(^{[86]}\) have demonstrated their potential applications in in vivo bio imaging. Therefore, the development of new ESIPT-based AIEgens based on these two compounds or the search for new ESIPT-based AIEgens that can be directly extracted from nature may be a promising direction.

Despite various sensing mechanisms that have been proposed, most of them involve disturbing or protecting intramolecular hydrogen bonding. Disturbing the intramolecular hydrogen bonding by the target analyte will induce a permanent change of fluorescence. The first protection of intramolecular hydrogen bonding will quench the fluorescence by blocking the ESIPT process, upon reaction with the target analyte then restore the intramolecular hydrogen bonding and light up the fluorescence as a result of AIE and ESIPT. The applications in bio imaging involve an introduction of a target group that can be selectively targeted to the target analyte without disturbing the intramolecular hydrogen bonding. Moreover, we also review some sensing mechanisms based on an indirect manner, which possess some unique advantages and deserve more attention.

Theoretical studies on the sensing mechanisms and excited-state decays of ESIPT-based AIEgens not only help the researcher understand the underlying mechanism for tuning the fluorescence behavior but also provide a theoretical guide for further developing new ESIPT-based AIEgens. However, only a few theoretical studies have been reported, which has greatly slowed the development of new ESIPT-based AIEgens with promising properties. The recently developed new ONIOM(QM:QM\(^\dagger\)) method with different embedding schemes has enabled us to obtain an accurate excited-state PES of molecules in solid-state.\(^{[219, 220]}\) More theoretical studies by employing this and other methods should be performed to unveil the nature of the interplay between intermolecular and intramolecular interactions and provide instructive design strategy for improving the performance of ESIPT-based AIEgens and developing new ones.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.
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dynamics of organic molecules and solid-state materials, as well as the mechanism of synthesis and decomposition of energetic materials.

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