An Intelligent AIEgen with Nonmonotonic Multi-responses to Multi-stimuli

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ABSTRACT: Intelligent stimulus-response (S/R) systems are the basis of natural process and machine control, and have been intensively explored in biomimetic design, analytical chemistry and biological applications. However, nonmonotonic multi-S/R systems are still rarely studied so far. Now, we propose a rational design strategy to achieve such a unique S/R system by integrating opposite luminescence behaviors in one molecule. When solvent polarity increases, many heterocycles often become more emissive due to the suppression of the proximity effect. However, molecules with donor-acceptor (D-A) structures tend to be less emissive because of the twisted intramolecular charge transfer. Meanwhile, protonation on D/A moieties will weaken/strengthen the D-A interaction to result in blue/red-shifted emissions. By combining a protonatable heterocyclic acceptor and a protonatable donor together in one molecule, we can easily achieve nonmonotonic brightness responses to polarity stimuli and nonmonotonic color responses to pH stimuli. In this work, a simple molecule, namely ASQ is chosen as the model compound to verify the design strategy feasibility. It successfully shows two opposite trends of responses to polarity and pH stimuli, and aggregation-induced emission (AIE) with a nonmonotonic AIE curve. Moreover, the acidified ASQ solution is also a pure organic up-conversion and white-light-emitting system. A new mechanistic viewpoint is established to explain its unique anti-Stokes emission. Besides, ASQ shows multivalent functionalities including albumin protein sensing, ratiometric pH sensing, and amine gas sensing, etc. Therefore, ASQ is proved to be a fundamentally important and versatile functional "intelligent" AIE luminogen with nonmonotonic multi-responses to multi-stimuli.

INTRODUCTION

Living systems and machines are controlled by input-output (stimulus-response) systems (Table 1). In simple cases, one input results in one output (1/1). As a matter of fact, the real world is based on rather complex manipulations. To achieve intelligent control of systems either naturally or artificially, multiple inputs no matter whether they are independent, synergistic or antagonistic are thus needed to give one or more outputs (n/1 or n/n). For example, the evolution from simple irritability, unconditioned reflex, to conditioned reflex, or the development from the electronic diode, triode, to complicated circuits.

In a single stimulus to a single response (1/1) systems, their stimulus-response behaviors could be monotonic or nonmonotonic (Table 2). If a positive trend of stimulus generates a positive trend of response (e.g. increased input → increased output), the corresponding S/R mode is a syn-mode (+/+). Conversely, it is an anti-mode (+/−). In many cases, the situation is so sophisticated that the response curve may be sectionalized or "zone-dependent". As a result, the S/R mode could be syn-anti (+/+ −), anti-syn (+/− +), and so on. Examples include: 1) enzymes have an optimum pH and temperature ranges, and they would be deactivated in higher or lower ranges; 2) either insufficient or excessive intake of nutrients would reduce the crop yield and only an appropriate amount of fertilizer is beneficial to food production and 3) a low dose of auxin would accelerate the growth of plants whereas a high dose of auxin would suppress the growth of plants. Nature is an incredible source of inspiration. However, these kinds of nonmonotonic responses are rarely explored in artificial molecular systems. Therefore, the biomimetic design of controllable nonmonotonic multi-responses to multi-stimuli systems is of high
scientific value and essential to the further exploration of emerging “intelligent” applications in analytical chemistry, biology, medicine, local environmental sensing, etc.

Table 1. I/O System

<table>
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<tr>
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<td>1/1</td>
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<td>n</td>
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Table 2. S/R Mode

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<th>R</th>
<th>Zone A</th>
<th>Zone B</th>
<th>S/R</th>
<th>Mode</th>
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<td>→ (+)</td>
<td>← (−)</td>
<td>← (−)</td>
<td>+/+</td>
<td>Syn</td>
</tr>
<tr>
<td>Non-monotonic</td>
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<td>→ (−)</td>
<td>← (+)</td>
<td>← (+)</td>
<td>+/−</td>
<td>Anti</td>
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Figure 1. Different types of emission responses to stimuli.

Table 1. I/O System

- I = input, 0 = output, n = 1,2,3...

Table 2. S/R Mode

- S = stimulus, R = response.

To realize the goal, we chose fluorescence signal as the output signal since fluorescence shows high sensitivity to environmental stimuli such as polarity, pH, temperature, viscosity, aggregation state, etc. Among the present fluorescent S/R systems, scientists always aim to design (1/1) system with (+/+ ) mode. Fluorescent probes with multifunctionality (n/1) are also explored. However, the (n/n) system with nonmonotonic modes is seldom reported (Fig. 1). Herein, we proposed a rational design strategy to realize the expected behaviors and built a simple molecular system to verify its feasibility.

In luminescence research, twisted intramolecular charge transfer (TICT) is a common solvent-dependent phenome-

non observed in systems with electron donor (D) -acceptor (A) structures. This effect is featured with large red-shifted and weakened emission as the polarity of the surrounding environment increases.

However, people always ignored the opposite solvent effect. Proximity effect is a widely observed quenching effect in many heterocyclic or carbonyl-containing molecules. In nonpolar solvents, the low-lying (n,π*) dark state with a quite small oscillator strength (J) and the (π,π*) bright state with a relatively large J are in close proximity to quench the light emission of these molecules. However, in polar/aprotic solvents, the lone pairs or n orbitals are stabilized and the energy gap of n → π* transition becomes larger, thus the (n,π*) state is destabilized and blue-shifted. On the contrary, the (π,π*) state would be stabilized and red-shifted. The net effect is the decoupling of the two close-lying states or the reversal of the (n,π*)/(π,π*) ordering, leading to the recovery of (π,π*) emission with a small red shift. Herein, such a solvent effect is coined as suppression of proximity effect (SOPE) (Fig. 2).

We are curious about what is the consequence if we combine the two opposite solvent effects together by integrating a carbonyl-containing heterocycle with a D-A structure. Since a carbonyl-containing heterocycle is inherently an electron acceptor, we can easily obtain the desired molecule by attaching an electron donor on it. Moreover, if both the donor and acceptor are nitrogen-containing moieties, they are anticipated to be proton-responsive. Protonation on the donor can weaken the D-A interaction (WDAI) to result in blue-shifted emission while protonation on the acceptor can strengthen the D-A interaction (SDAI), to give rise to red-shifted emission. Therefore, by assembling a protonatable electron acceptor obeying SOPE effect and a protonatable electron donor, the resulting molecule may exhibit SOPE + TICT and WDAI + SDAI properties and shows a nonmonotonic brightness (intensity, I) response to polarity change, and a nonmonotonic color (wavelength, λ ) response to pH change.

In addition, aggregation is another facile approach to induce fluorescence changes by altering the local molecular environment and the freedom of molecular motions. Aggregation-induced emission (AIE) luminogens have attracted much research interest in these few decades for their wide applications in OLED display, chemosensing, bioimaging and therapy, etc. More importantly, some TICT molecules are already reported to be AIE-active with a nonmonotonic response to the stimulus of poor solvent addition.

Taking all the considerations together, 4-(dimethylamino)styryl]quinolin-2(1H)-one (ASQ) was chosen as the model compound (Fig. 1) and its opposite trends of responses to polarity, pH and aggregation were studied. Results show that the molecule is a good demonstration of the biomimetic design of nonmonotonic multiple S/R systems. We also studied its unique up-conversion and white-light emission behaviors, established a new mechanism of anti-Stokes emission, developed multiple sensing applications including albumin protein sensing, ratiometric pH sensing, and biogenic amine gas sensing. All these make ASQ a fundamentally important and versatile functional “intelligent” material.
RESULTS AND DISCUSSION

During the screening for a compound which fulfills the design criteria, we found a carbonyl-containing and electron-accepting nitrogen-heterocyclic compound, namely, 3-methylquinoxalin-2(1H)-one (MQ) whose fluorescence intensity in methanol is higher than that in n-hexane. The plot of quantum yield (QY) versus the normalized Reichardt’s parameter ($E_T$) is a monotonic increasing curve (Fig. 3A, Table S1). In contrast, TICT molecules such as the well-known dimethyaminobenzonitrile (DMABN) show intense emission in n-hexane but very faint emission in methanol. The QY vs $E_T$ plot is a monotonic decreasing curve (Fig. 3B, Table S2). As for ASQ, it perfectly reproduces the solvent responses of MQ and DMABN. As the solvent polarity gradually increases, its PL intensity first increases then decreases (Fig. 3C). The QY vs $E_T$ plot is a nonmonotonic concave curve (Fig. 3D, Table S3). The fluorescence lifetimes changes in a similar way. The lifetime in THF solution is higher than that in n-hexane or methanol (Fig. S2). Therefore, the S/R mode is (+/−).

To understand the zone-dependent polarity response, we performed computational studies on multiple excited states of the MQ, DMABN and ASQ compounds. The calculation results indicate that MQ possesses a pair of close-lying ($n,\pi^*$) dark state ($f \sim 0.000$) and ($\pi,\pi^*$) bright state ($f > 1$) (Fig. 4Aa, Table S4). Its solvent effect obeys the SOPE mechanism. The solvent with high polarity weakens the quenching effect of ($n,\pi^*$) dark state to enhance its emission. For DMABN, there is a locally excited (LE) bright state ($f > 1$) and a charge transfer (CT) dark state ($f \sim 0.0000$) where the dimethyamino group (-NMe$_2$) is coplanar and perpendicular to the phenyl ring, respectively (Fig. 4Ab, Table S4). The high polar solvent stabilizes the CT state and facilitates the CT dark state to weaken the light emission. The excited states of ASQ largely resemble the MQ and DMABN. There are one bright state and dual dark states: 1) a LE ($\pi,\pi^*$) bright state whose HOMO is on the whole molecule ($f > 1$); 2) a LE ($n,\pi^*$) dark state whose HOMO is localized on the acceptor moiety ($f \sim 0.000$), and 3) a CT dark state whose HOMO is localized on the donor part ($f \sim 0.0000$) (Fig. 4Ac, Table S5). The triplet states were not considered to simplify our model. Since the major pathway of intersystem crossing is from the low-lying ($n,\pi^*$) to ($\pi,\pi^*$), it’s acceptable to regard the triplet-related non-radiative decay as a part of ($n,\pi^*$) dark-state quenching.

A better understanding of ASQ’s polarity-responsive behavior could be obtained via the potential energy surfaces...
When the solvent polarity is low, the proximity effect dominates to give rise to weak emission. When the solvent polarity increases, the \((\pi,\pi^*)\) is destabilized and \((\alpha,\pi^*)\) is relatively stabilized, the energy gap between \((\pi,\pi^*)_{\text{max}}\) and \((\alpha,\pi^*)_{\text{min}}\) enlarges to gradually enhance the emission intensity (Fig. S7). However, the emission enhancement is not unlimited. When the polarity continues to increase, the CT dark state starts to take over and plays a dominant role in governing the light emission behavior. The twisting of the -NMe₂ group occurs and charge transfer is generated to gradually weaken the emission intensity.

In short, the dual dark states are responsive to the non-radiative decay in low and high polarity solvents. SOPE and TICT, which are two antagonistic effects, jointly determine the nonmonotonic responses of ASQ to polarity stimuli.

![Figure 4](image)

**Figure 4.** (A) Frontier molecular orbitals and bright/dark states transitions of (a) MQ, (b) DMABN, and (c) ASQ. (B) Schematic PESs of ASQ.

The polarity of the molecular microenvironment not only can be tuned by changing different solvents but also can be modulated by the state of aggregation. TICT molecule, which acts as a branch of AIE lumigen, shows weak emission in the aqueous environment but turns out to be emissive after aggregate formation. Once a poor solvent such as water is added into the ethanol solution of ASQ, the emission first decreases and red-shifts due to the increased polarity (Fig. 5A/B, \(f_w = 0 \sim 60\%\)). On the one hand, as aggregate forms, the local environment of the inner part of aggregates becomes less polar because the molecules are now "surrounded by themselves" rather than "surrounded by neighbor water molecules" so the polarity-sensitive TICT dark state is thus thermodynamically less accessible. On the other hand, the molecular motion that leads to the dark state minimum, namely the -NMe₂ group twisting can be effectively restricted by intermolecular interactions from the rigid surroundings, making the TICT dark state is also kinetically less accessible. Due to the restriction of intramolecular motion (RIM), and restriction of access to dark state (RADS) mechanism (Fig. 5C), the aggregate emission is enhanced and blue-shifted (Fig. 5A/B, \(f_w = 60\%\sim 75\%\)).

Similarly, the emission enhancement is not unlimited. As the water fraction continues to increase, the sizes of nanoaggregates decline and their fluorescence also become weaker (Fig. 5A/B, \(f_w = 75\%\sim 90\%\); Fig. S3). Such a phenomenon is commonly observed in AIE+TICT systems. For ease understanding of the phenomenon, we define the aggregate as an idealized core-shell model (Fig. 5C). On the one hand, as the particle size (aggregate radius, \(R\)) decreases and the specific surface area increases, the ratio of ambient semi-free molecules (shell depth \(d\)) to the inner rigid molecules (core radius \(r\)) increases. Therefore, the entire emitting species will be greatly reduced. On the other hand, the photothermal effect is intensively studied in AIE+TICT systems. The local heat generated by the non-radiative decay of the semi-free layer could probably dissipate into the emitting core (thermal-agitated depth \(d\)) and enhance the motions of the molecules. As \(R\) decreases, the proportion of thermal-agitated layer might increases to exert influence on the core emitting species. Above all, the decreased aggregate size and enhanced molecular motions lead to the decline in fluorescence intensity.

In short, the different states of aggregation will determine the degree of freedom of molecular motions. RIM and IM, which are two sides of a balance, control the nonmonotonic emission intensity responses towards water addition.

Protein encapsulation is another pathway to manipulate the local polarity and molecular freedom of ASQ. Albumin protein is a substance carrier in blood with multiple binding sites. Fortunately, ASQ was found to be a suitable substrate of albumin. When albumin was added to ASQ in PBS buffer, the solution became more emissive and the emission was blue-shifted (Fig. 5D). It is readily comprehensible that both the emission phenomenon and working mechanism are the same as the AIE process. There is a very good linear relationship between the fluorescence intensity and the albumin concentration (Fig 5E). Meanwhile, ASQ shows a good selectivity towards albumin because its emission fails to be turned on by binding with other common biomolecules such as hemoglobin (Fig 5F).

The detection of blood and urine albumin is clinically significant to examine health status and monitor chronic kidney diseases. However, the present instrument or immunoassay-based techniques are expensive and time-consuming. In consideration of its good linearity and selectivity, ASQ is promising in specific and quantitative analysis of albumin and serves as a fluorescent assay for cheap and fast detection of albumin in-time and on-site. Moreover, the nanocomposites of AIEgen–albumin hybrids are biocompatible materials and have been increasingly used in drug delivery, bioimaging, photothermal therapy, etc. The quinoxalin-2(1H)-one moiety is reported to be an anti-HIV/tumor/bacterial agent. Therefore, the ASQ-albumin complex possesses high potential in fluorescence therapy and pharmaceutical applications, which have been studying in our lab.
The above-mentioned solvent effect, AIE effect, or albumin sensing, are all related to the fluorescence responses to polarity stimulus. ASQ is also designed by the criteria that both the donor and acceptor are protonatable to alter the D-A interaction. As predicted, either in the solution state or the solid state, ASQ shows exactly two appearance color and fluorescence color change upon the continuous addition of trifluoroacetic acid (TFA) or TFA gas fuming (Fig. 6A/C). The process is reversed by the addition of triethylamine (TEA) or TEA gas fuming. Fig. 6B and 6D show the absorption and fluorescence changes during the sequential protonation process. The DCM solution of ASQ shows an absorption peak at 445 nm ($\lambda_{ab}@445$ nm) and a fluorescence peak at 570 nm ($\lambda_{f}@570$ nm). When the [TFA]/[ASQ] ratio increases from 0 to around 200, the $\lambda_{ab}@445$ nm gradually drops while the $\lambda_{ab}@643$ nm rises up. The $\lambda_{f}@570$ nm also declines but the $\lambda_{f}@447$ nm intensifies. When the [TFA]/[ASQ] ratio further increases from 1500 to 65000, the $\lambda_{ab}@643$ nm goes down and the $\lambda_{ab}@435$ nm increases. It seems that the absorption spectrum is gradually switched back to the original pattern. The fluorescence spectrum undergoes a similar “backward” shift that the $\lambda_{f}@447$ nm declines and the $\lambda_{f}@512$ nm increases. In summary, upon decreasing pH, the fluorescence blue-shifts and then red-shifts, so the S/R mode is syn-anti (−/− +). To clearly understand the nonmonotonic responses, we need to identify the protonation sequence. However, the basicity of donor and acceptor cannot be easily distinguished. According to our logical reasoning, the blue emission is ascribed to the donor-protonated species because the protonation of the donor will weaken the D-A interaction. On the contrary, the $\lambda_{f}@512$ nm is attributed to the further protonation on the acceptor which will strengthen the D-A interaction. The hypothesis makes sense, yet a question emerges: the $\lambda_{ab}@643$ nm and the $\lambda_{f}@447$ nm increase upon molecular protonation. And it is quite abnormal that a long-wavelength absorption gives rise to a short-wavelength emission.
To make a comparison, we synthesized a donor-free molecule called styrylquinoloxalin-2(1H)-one (SQ) and studied its absorption and fluorescence upon TFA addition. As shown in Fig. S4, only a single-color change was observed and both absorption and fluorescence peaks red-shift upon TFA addition as only the acceptor is protonated. Similarly, the acceptor protonation of ASQ should be responsible for the \( \lambda_{\text{ab}} @ 643 \text{ nm} \) and the weak and easily ignored \( \lambda_{\text{f}} @ 720 \text{ nm} \). Therefore, the above question can be answered: the blue color appearance is due to the acceptor-protonated species (D-AH\(^+\)) which absorbs red light and the blue fluorescence is due to the donor-protonated species (H\(^+\)D-A).

The \(^1\)H NMR spectra of original and acidified ASQ samples also indicate the coexistence of two kinds of monoprotonated species because both the donor and acceptor-related proton resonances shift downfield simultaneously (Fig. 7A). Now, the complete protonation process can be summarized as Fig. 7B. In order to clearly see the original D-A / red-shifted D-AH\(^+\) / and blue-shifted H\(^+\)D-A fluorescence peaks, we captured three PL spectra during TFA addition (Fig. 8A). In fact, the red-shifted emission peak does appear. However, it is so weak that it misleads us that the emission of ASQ only blue-shifts upon protonation.

Considering that the monoprotonated ASQ mixture exhibits long-wavelength absorption and short-wavelength emission, we wondered whether the mixture would display up-conversion property. To our surprise, when the mixture was excited at 600 nm, both blue emission and red emission can be recorded, in which the blue emission is an abnormal anti-Stokes emission (Fig. 8B). Generally speaking, the sensitized triplet-triplet annihilation (TTA) mechanism is used to explain the up-conversion phenomenon.\(^{36}\) A pair of energy-level-matched emitter and sensitizer should be present in contact so that the triplet-triplet energy transfer is possible to occur. Also, the intersystem crossing of both components must be efficient. So far, organic up-conversion materials usually contain either heavy-metal or planar aromatic hydrocarbons. We thought that the TTA mechanism may not be applicable to this metal-free heterocyclic system in a dilute solution. Therefore, another mechanistic hypothesis on this unusual up-conversion system was attempted to propose.

According to our analysis of the absorption and emission spectra, the \( \lambda_{\text{ab}} @ 600 \text{ nm} \) corresponds to the absorption of D-AH\(^+\) and the \( \lambda_{\text{f}} @ 447 \text{ nm} \) corresponds to H\(^+\)D-A. We can reasonably assume that after \( \lambda_{\text{ab}} @ 600 \text{ nm} \), D-AH\(^+\) undergoes a proton transfer to generate H\(^+\)D-A to result in \( \lambda_{\text{f}} @ 447 \text{ nm} \). It doesn’t matter whether the proton transfer takes place by intramolecular A-to-D or intermolecular proton replacement between the ASQ molecule and the nearby acid molecule. Indeed, a clearer hypothesis could be obtained by the proposed PESs (Fig. 8C). The energy gap between \( S_{0,\text{min}} \) and \( S_{1,\text{min}} \) of D-AH\(^+\) is smaller than that of H\(^+\)D-A. After excitation of D-AH\(^+\), the excitons can go through the proton transfer reaction coordinate and radiatively decay to the H\(^+\)D-A ground state, resulting in an anti-Stokes blue emission. At the D-AH\(^+\) ground state minimum, the -NMe\(_2\) group is non-twisted, while at the H\(^+\)D-A ground state minimum, the protonated -NMe\(_2\) group is highly twisted. Therefore, the nuclear motion axis of the PESs can also be regarded as the -NMe\(_2\) group twisting.

To prove our hypothesis, we performed theoretical calculations and the results were provided in Table S6. As indicated in Fig. 8C and 8D, the D-AH\(^+\) first undergoes a LE excitation. Then along the PES in the excited state, the \( \text{-NMe}_2 \) group starts to twist which will result in several consecutive transitions: 1) the lone pair on the twisted -NMe\(_2\) group no longer participates in conjugation and the donor becomes more basic and prone to be protonated; 2) the electron-donating ability of the non-conjugated donor is weakened and the protonated acceptor becomes less stable and prone to be deprotonated; and 3) the \( S_1 \) becomes a CT transition whose HOMO energy is much elevated to give rise to
red emission. So far, the emission still obeys the rule of Stokes shift. The turning point appears when the donor is protonated. According to the calculation result, once the lone pair of -NMe₂ group is occupied, the transition goes back to a LE transition again. Since the D-A interaction of H⁺D-A is weaker than that of D-AH⁺, the transition energy of H⁺D-A is larger than that of D-AH⁺. Therefore, by the merit of the excited-state proton transfer or replacement, the D-AH⁺ absorption can lead to an anti-Stokes H⁺D-A emission.

In some sense, the LE → TICT → LE change seems to be a nonmonotonic response as well. The design strategy of this work not only can help us design nonmonotonic multi-S/R systems but also provide us a new and easy approach to obtain a pure organic up-conversion system, which is fundamentally important for broadening the research area of up-conversion materials and the related applications in bioassays, optoelectronics, etc.\textsuperscript{37-39}

**Figure 9.** (A) PL spectra of ASQ in aqueous buffers with different pH. (B) PL spectra of ASQ in pH4, 5 and 6; [ASQ] = 10 μM. (C) ASQ solutions in acetic acid with concentrations of 0.5, 0.0125, and 0.0313 mM. (F) CIE graph at pH = 5 (0.326,0.368), and solution concentration = 0.0125 mM (0.305,0.338).

Besides the unique up-conversion phenomenon, the acidified ASQ mixture was also found to be a white-light-emissive system. When the pH of the PBS buffer of ASQ decreases from 6 to 4, the fluorescence color changes from orangish-yellow D-A to blue H⁺D-A. Therefore, ASQ is able to serve as a ratiometric pH sensor (Fig. 9A, S5) for in-vivo imaging of local pH value.\textsuperscript{40} Particularly, at pH = 5, the solution is nearly white-light-emissive with a CIE coordinate of (0.326,0.368) (Fig. 9B/D). The pH can be further fine-tuned on a small scale to obtain more pure white light (Fig. S6). More simply, white light emission could be achieved by directly dissolving the ASQ in weak acid (e.g. acetic acid). The lower the ASQ concentration, the more intense is the blue emission. At the ASQ concentration of 0.0125 mM in acetic acid, the CIE coordinate of the white emission is (0.305,0.338) (Fig. 9C/D). As a simple and readily prepared single molecular white-light-emitting system, ASQ shows a potential to be fabricated as a white light-emitting diode (WOLED).\textsuperscript{41}

The pH-responsive behavior of ASQ not only makes it a ratiometric pH sensor and a white-light emitter, but also a sensor for volatile basic gas such as biogenic amine gas. The deterioration of protein gives rise to smelly amine species which are indicators of food spoilage.\textsuperscript{24} The pre-acidified ASQ-2H⁺ exhibits a yellow appearance and emits yellow fluorescence. When a test paper loaded with ASQ-2H⁺ is exposed under the ammonia atmosphere, gradual deprotonation of ASQ-2H⁺ to form ASQ-H⁺ with a blue appearance and blue fluorescence, and ASQ with an orange appearance and orange fluorescence occurs (Fig. 10A). The two trends of nonmonotonic changes can help people distinguish the freshness of perishable food in an easy and straightforward way. We used the eatable salmon meat and eviscerated dead fish as a demonstration. After 24 h storage under the same condition, the test paper in the salmon meat package turns to blue, whereas that in dead fish package changes to orange. This means that a high level of amine gas is generated by the dead fish (Fig. 10B). Therefore, unlike the previous reports that only one trend of color or intensity change was observed (Scheme S2), the ASQ system can not only tell us whether the food goes bad but also tell us how severe the food spoilage is by the distinct color change gradient. In this scenario, the nonmonotonic S/R system can certainly do more than the normal (+/+ mode). Now the performance optimization of the test paper and productization are systematically studied in our lab.

**CONCLUSION**

To accomplish the biomimetic design of intelligent nonmonotonic multiple response-stimulus systems, we proposed a rational approach to achieve zone-dependent fluorescence responses to multiple local-environmental stimuli including polarity, pH, state of aggregation, etc. The design strategy is to combine units with opposite luminescence behaviors in one molecule, examples of which include SOPE+TICT, RIM+IM, SDAI+WDAI, etc. In this work, the ASQ molecule was designed as an excellent demonstration by assembling a protonatable heterocyclic acceptor and a protonatable donor together. ASQ was found to exhibit a nonmonotonic concave change in brightness (intensity) in response to increasing solvent polarity or increasing water fraction (+/+ mode) and a nonmonotonic convex change in color (wavelength) in response to decreasing pH (−/− mode). Theoretically, the ordering and arrangement of three excited states, namely, LE (\(\pi,\pi^*\)), LE (\(n,\pi^*\)) and TICT states play a key role in the photophysics of nonmonotonic responses of ASQ.
More interestingly, the acidified ASQ solution was found to display anti-Stokes emission and white-light emission, making the proposed design strategy an easy approach to achieve pure organic up-conversion and white-light-emitting system. The up-conversion behavior is related to an excited-state proton transfer/replacement process together with a LE→TICT→LE nonmonotonic excited-state change, which provides a new viewpoint to understand the up-conversion mechanism.

Practically speaking, ASQ is proved to have multifunctionalities in this work including albumin protein sensing, ratiometric pH sensing, and biogenic amine gas sensing. The potential applications in albumin quantification-based disease diagnosis, imaging and therapy of AIEgen-albumin nanocomposite, in-vivo ratiometric pH mapping, and productization of food spoilage test strips were progressively explored in our lab.

ASSOCIATED CONTENT
Supporting Information. Summary of albumin protein sensors and amine gas sensors; detailed experimental and computational data of MQ, DMABN, (protonated)ASQ, supplementary characterizations including UV-vis, lifetime, DLS, etc. This material is available free of charge via the Internet at http://pubs.acs.org."


