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Multiple control of azoquinoline based molecular photoswitches†

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Multi-addressable molecular switches with high sophistication are creating intensive interest, but are challenging to control. Herein, we incorporated ring–chain dynamic covalent sites into azoquinoline scaffolds for the construction of multi-responsive and multi-state switching systems. The manipulation of ring–chain equilibrium by acid/base and dynamic covalent reactions with primary/secondary amines allowed the regulation of *E/Z* photoisomerization. Moreover, the carboxyl and quinoline motifs provided recognition handles for the chelation of metal ions and turning off photoswitching, with otherwise inaccessible *Z*-isomer complexes obtained *via* the change of stimulation sequence. Particularly, the distinct metal binding behaviors of primary amine and secondary amine products offered a facile way for modulating *E/Z* switching and dynamic covalent reactivity. As a result, multiple control of azoarene photoswitches was accomplished, including light, pH, metal ions, and amine nucleophiles, with interplay between diverse stimuli further enabling addressable multi-state switching within reaction networks. The underlying structural and mechanistic insights were elucidated, paving the way for the creation of complex switching systems, molecular assemblies, and intelligent materials.

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Introduction

As one of the most employed photochromic switches, azobenzene has received unabated attention due to the simple structure, facile synthesis, large geometric differences between *E/Z* isomers, and high fatigue-resistance.^{1–4} In particular, the change in the molecular shape of azobenzene upon photo-activation offers a powerful strategy for manipulating guest recognition,^{5–8} molecular machines,^{9–12} supramolecular assemblies,^{13–16} and nanoparticles.^{17–20} Azoheteroarenes obtained by replacing one or both phenyl with a heteroaryl,^{21–24} such as pyridine,^{25–28} pyrazole,^{29–31} imidazole,^{32–34} and thiazole,^{35–37} are recently generating strong interest. Many research efforts have focused on the extension of new heterocycles and the modulation of their photoswitching properties through substituent effects.^{38,39} However, six-membered ring heterocycles beyond pyridine have been less studied.^{40–42} Azoquinoline has a phenyl directly attached to the azo group, but with an adjacent fused pyridyl group, which makes it

intermediate in nature between azobenzene and azoheteroarene. In this context, photoinduced *E* → *Z* isomerization and thermal *Z* → *E* isomerization of azo compounds derived from hydrogenated quinolines and 8-quinolinols have been explored,^{43,44} but the direct use of quinoline moieties as azo photoswitches is rarely reported.

The intercorrelation between azoarene switching motifs and different responsive sites was harnessed for obtaining novel structures and functions.^{45–48} For example, the attachment of azobenzene onto artificial transporters enabled the fabrication of smart membranes with light-driven transport properties.^{49–51} Photocontrol over the equilibrium of boronic ester formation and further the stiffness of polymeric hydrogels was achieved with *ortho*-boronic acid substituted azobenzene.^{52,53} The incorporation of azobenzene and two dihydroazulene units into a macrocycle allowed the realization of hexa-state switching.⁵⁴ Moreover, out-of-equilibrium coordination^{55–58} or dynamic covalent cages^{59–61} were constructed by making use of azobenzene connected building blocks. A versatile platform for diverse regulation of azoarene switches would be highly desired. While the combination of various switching units and stimuli would build up systematic complexity and enrich chemical information stored in multi-state processes,^{62–65} it is challenging to develop multi-controllable molecular switching systems with high sophistication and precision. Compared to conventional azobenzene derivatives, azoheteroarenes not only retain the photochromic properties, but also introduce additional basic nitrogen sites that further affect the switching properties through acid–base stimulation, hydrogen bonding,

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and metal coordination, which would afford ample opportunities for multi-responsive molecular switches.^{66–70}

Along our longstanding efforts in the flourishing field of dynamic covalent chemistry (DCC),^{71–76} we developed a general concept of dual reactivity based DCC through regulating equilibrating tautomers.^{77–83} The selection of reaction pathways allowed the creation of switchable reaction networks,^{78,79} discrete assemblies,⁸⁰ fluorescent materials,⁸¹ as well as dynamic polymers.^{82,83} Inspired by the controllable switching patterns and abundant signaling outputs, we propose merging azoquinoline photoswitches and ring–chain tautomerism toward the ultimate goal of multi-responsive and multi-state switching systems (Fig. 1a). We envisioned that the incorporation of 2-formylbenzoic acid and quinoline motifs would provide diverse recognition handles, such as acid–base stimulation and metal ion coordination, accordingly influencing ring–chain equilibrium, dynamic covalent reactions (DCRs),^{84–86} and photoswitching. As a result, the intricate interaction within chemical networks would induce multi-mode responses and enhanced complexity. In the current work multiple control of azoquinoline photoswitches was achieved, including light, pH, metal ions, and amine nucleophiles. The underlying structural and mechanistic foundation was explored, with the interplay between triggers toward modulating switching behaviors in complex systems elucidated and setting the scene for future studies.

Results and discussion

Design, synthesis, and structures

To realize the strategy a modular synthesis route was developed with 3-nitrophthalic anhydride as the starting material (Scheme S1† and Fig. 1b).⁸⁷ The ring-opening esterification followed by selective reduction of carboxylic acid and then oxidation of benzylic alcohol afforded methyl 2-nitro-6-formylbenzoate (Scheme S1†). The protection of the aldehyde as a cyclic acetal, reduction of the nitro group, and subsequent nitrosation furnished the key nitroso intermediate (Fig. 1b). The azoarene scaffolds were constructed *via* azo-coupling reactions from corresponding aromatic amines, and the target compound (*E*-1) was finally obtained after the hydrolysis of the acetal and the ester groups. A control compound (*E*-2) without the formyl group was also prepared (Scheme S2†).

With the compounds in place, their solution structures were studied. The appearance of a broad peak around 6.8 ppm suggests that *E*-1 existed mainly in the cyclic hemiacetal form in DMSO-*d*₆, in equilibrium with the open aldehyde. High-quality single crystals of *E*-1 were further obtained for XRD analysis (Fig. 1b and S24†). The hemiacetal structure falls in line with solution studies, and quinoline nitrogen orients away from the lactone unit. In addition, both arene groups rotate out of the azo plane (torsion angle around 17°). A supramolecular chain supported by hydrogen bonding between quinoline nitrogen and

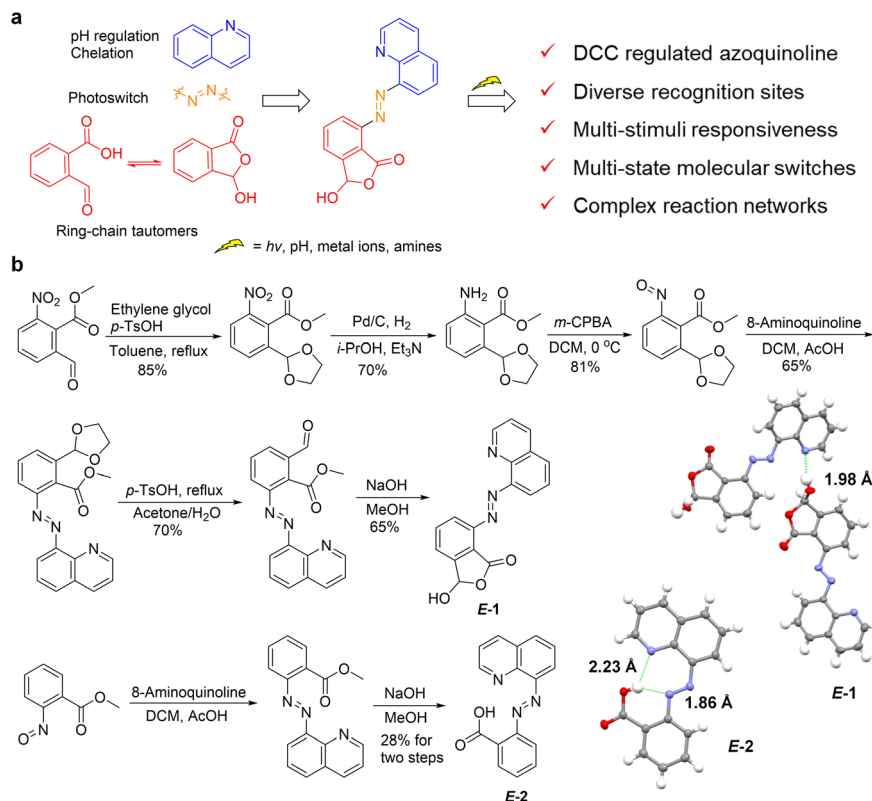


Fig. 1 (a) Proposed strategy for merging azoquinoline photoswitches with ring–chain tautomerism toward the goal of multi-addressed and multi-state switching. (b) Synthesis of target compounds *E*-1 and *E*-2 and their corresponding X-ray structures, with the distance (Å) of hydrogen bonding listed.



hydroxyl hydrogen (OH \cdots N 1.98 Å) offers additional stabilizing force. In the solid-state structure of *E*-2, multiple hydrogen bonding between carboxyl OH and two nitrogen atoms (OH \cdots N 1.86 and 2.23 Å) was found in a planar structure (Fig. 1b).

Photoswitching behavior

We next set to examine photochromic switching of azoquinoline. The hemiacetal methine hydrogen and the hydrogen next to the quinoline nitrogen were used to determine the ratio of *E*/*Z* isomers due to their characteristic chemical shifts. When *E*-1 (a of Fig. 2A) was subjected to photoisomerization at 365 nm for 1.5 h, the *Z* isomer (60%) was detected in DMSO-*d*₆, and the cyclic hemiacetal form was maintained, as evidenced by the presence of a broad peak at about 6.9 ppm, partially overlapping with *E*-1 (b of Fig. 2A). The irradiation at 425 nm allowed the recovery of the *E* isomer (80%, c of Fig. 2A). Despite the realization of *E*/*Z* switching, the thermal stability of *Z*-1 was modest, with a half-life around 5.4 h (Fig. S25–S27[†]). Among azoarenes with six-membered heterocycles that have been reported, *E*-1 has comparable bidirectional switching efficiency and thermal

stability,^{41–44,88–90} but the photoisomerization rate is lower than that of representative azoarenes with five-membered pyrazoles that are nearly quantitatively switchable.^{29,30} Photoinduced *E* → *Z* (82% *Z* isomer) and *Z* → *E* (85% *E* isomer) isomerization of *E*-2 in CDCl₃ was also attained. The measurement of UV-vis spectra validated *E*/*Z* photoswitching, and multiple cycles of bidirectional photoswitching were feasible, demonstrating great reversibility and fatigue-resistance (Fig. 2B and S28, S29[†]).

pH effects

The regulation of ring–chain tautomerism and photoswitching of the cyclic hemiacetal attached azoquinoline by changing the pH was then explored (Fig. 3A). The addition of methanesulfonic acid (MA) to *E*-1 gave the protonated form of *E*-1 (*i.e.*, *E*-1-H⁺, Scheme S3[†]). Both cyclic hemiacetal (6.8 ppm) and open aldehyde (10.2 ppm) forms were observed in DMSO-*d*₆, with a ratio of 5 : 1. XRD analysis (Fig. 3B) verified the lactone form of *E*-1-H⁺. Furthermore, an extended planar structure was found, with intramolecular NH \cdots N hydroxyl hydrogen bonding (2.43 Å).

The titration of MA into *E*-1 further confirmed the domination of the ring tautomer for *E*-1-H⁺, and the H₃ signal of *E*-1-H⁺ moved downfield by 0.4 ppm compared to the H₃ signal of *E*-1 at 8.6 ppm (Fig. S30[†]). The titration of DBU into *E*-1-H⁺ (a of Fig. 3C and S31[†]) gave rise to the deprotonation of quinolinium (*i.e.*, *E*-1, b of Fig. 3C) followed by ring opening to afford the conjugate base of the open aldehyde (*E*-1_{OCB}, c of Fig. 3C). The reverse acid-triggered switching from *E*-1_{OCB} to *E*-1 and then *E*-1-H⁺ was also verified (Fig. S32[†]). Similar photochromic switching behaviors were also obtained for *E*-1-H⁺ in DMSO-*d*₆ (44% *Z* isomer for *E* → *Z* and 87% *E* isomer for *Z* → *E*), albeit with a shorter half-life (1.7 h) for *Z*-1-H⁺ over *Z*-1 (Fig. 3D and S33–S36[†]), which is likely due to the protonation of the azo group *via* intramolecular hydrogen transfer from the quinolinium.^{91,92} Moreover, the cyclic hemiacetal was maintained in *Z*-1-H⁺. When the photochromic switching of *E*-1_{OCB} was investigated in DMSO-*d*₆ (Fig. S37–S41[†]), it was found that *E*-1_{OCB} has a relatively high photoisomerization efficiency (69% *Z* isomer for *E* → *Z*) and thermal stability (half-life 20.6 h) over *E*-1/*Z*-1. This was attributed to the fact that the use of a base converts *E*-1 to the ring-opened form *E*-1_{OCB}, which limits the formation of hydrogen bonds.

Coordination effects

Metal ion coordination was then employed to diversify the switching system (Fig. 4A). Interestingly, the cyclic hemiacetal form (a of Fig. 4B) was converted to an open aldehyde upon the addition of Zn(OAc)₂ to *E*-1, as the methine peak moved from 6.8 to 10.2 ppm (b of Fig. 4B and S42[†]). Crystal analysis revealed the chelation of zinc with quinoline nitrogen, adjacent azo nitrogen, as well as carboxylate of *E*-1_{OCB} (Fig. 4C). The additional monodentate coordination by water and the carboxylate from a second molecule of *E*-1_{OCB} gives a distorted bipyramidal geometry. In order to accommodate metal binding, the carboxyl group rotates out of the arene plane. As compared to *E*-1-H⁺, the rotation of one C–N single bond would be needed to facilitate

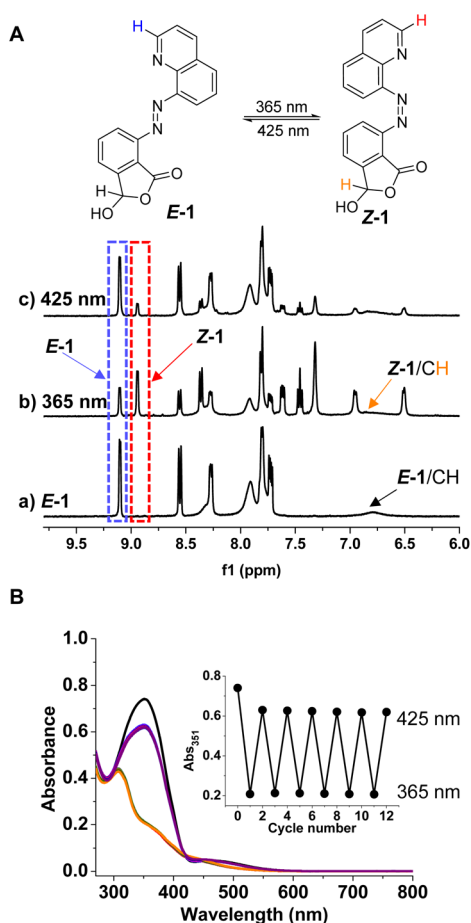


Fig. 2 Photoswitching behavior of *E*-1. (A) ¹H NMR spectra of *E*-1 in DMSO-*d*₆ (10 mM, a), and after irradiation for 1.5 h at 365 nm (b) and then for 0.5 h at 425 nm (c). (B) UV-vis spectra of *E*-1 (75 μM in DMSO) after alternative irradiation at 365 and 425 nm. The inset shows the multiple cycles of switching in response to 365 and 425 nm light.



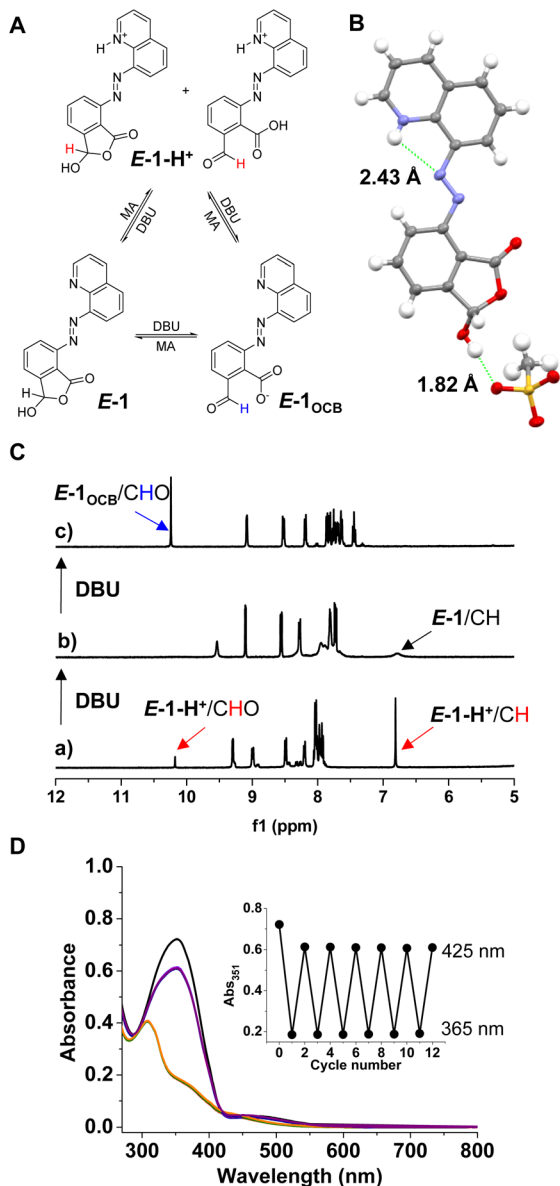


Fig. 3 (A) Controlling the ring-chain tautomerization with acid/base. (B) X-ray structure of $E-1-H^+$, with the distance (Å) of hydrogen bonding listed. (C) 1H NMR spectra of $E-1-H^+$ in $DMSO-d_6$ (10 mM, a), its mixture with DBU (1 equiv., b), and following addition of DBU (1 equiv., c). (D) UV-vis spectra of $E-1-H^+$ (50 μM in $DMSO$) after alternative irradiation at 365 and 425 nm, with the inset showing the multiple cycles of switching in response to light.

zinc chelation in $E-1-Zn^{2+}$. The distinct binding mode of a proton and metal ion by $E-1$ can be attributed to the significantly different size of the guest. Moreover, supramolecular chains of zinc complexes linked by π -stacking and hydrogen bonding stabilize crystal packing. Since carboxylate engages in zinc binding, the adjacent formyl unit would be exposed, resulting in the shift of ring-chain tautomerization equilibrium. With the proton displaced by zinc ion from $E-1$, acetic acid would also be released. The addition of EDTA enabled the formation of $E-1$, with additional cycles of complexation/de-complexation feasible (Fig. S43–S45[†]).

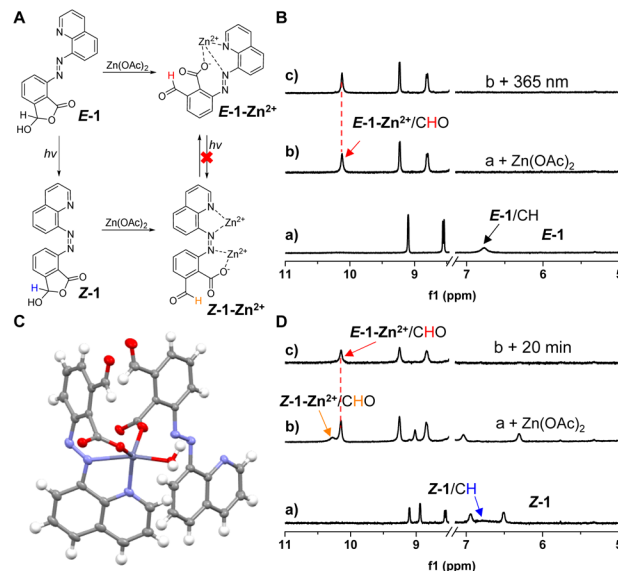


Fig. 4 (A) Illustration of the modulation of $E-1$ with coordination and light. (B) 1H NMR spectra of $E-1$ in $DMSO-d_6$ (10 mM, a), its mixture with $Zn(OAc)_2 \cdot 2H_2O$ (1.5 equiv., b), and after irradiation for 1.5 h at 365 nm (c). (C) X-ray structure of $E-1-Zn^{2+}$. (D) 1H NMR spectra of Z -enriched solution of 1 (created by irradiation of $E-1$ for 1.5 h at 365 nm) in $DMSO-d_6$ (10 mM, a), its mixture with $Zn(OAc)_2 \cdot 2H_2O$ (2.5 equiv., b), and after 20 min (c).

Furthermore, analogous metal binding induced reversal of ring-chain tautomerism was also realized with $Co(OAc)_2$. The coordination of Co^{2+} by two molecules of $E-1_{OCB}$ allows the creation of an approximately octahedral configuration according to the crystal structure of $E-1-Co^{2+}$ (Fig. S24[†]). In addition, photoswitching was suppressed for $E-1-Zn^{2+}$ (c of Fig. 4B) and $E-1-Co^{2+}$ in $DMSO-d_6$ (Fig. S46 and S47[†]), likely due to the locking of the E isomer in the form of metal chelation. Such a gating phenomenon is consistent with the regulation of E/Z isomerization within azobenzene complexes.⁹³ Nevertheless, when $Z-1$ was generated first followed by the addition of excess amounts of $Zn(OAc)_2$, a similar open aldehyde form was generated for the zinc complex ($Z-1-Zn^{2+}$) though it converted back to $E-1-Zn^{2+}$ after 20 min (Fig. 4D and S48[†]). This is reasonable because Zn^{2+} could be chelated by carboxylate and neighboring azo nitrogen and thus induce ring-opening of the lactone (Fig. 4A). Despite the low thermal stability, the otherwise inaccessible high-energy state ($E-1-Zn^{2+}$) was thus attained through a detour. As a result, the sequence of photoirradiation and coordination further built up the complexity of the switching system.

Dynamic covalent chemistry

The next goal was to tune photoswitching with dynamic covalent reactions (DCRs) of amines in conjunction with metal coordination (Fig. 5A). With the cyclic hemiacetal present in $E-1$, its reactivity is reminiscent of 2-formylbenzoic acid,^{84–86} giving open imine $E-3$ with 1-butylamine (3 equiv.) (Fig. S49[†]). $E-3$ showed higher photoisomerization efficiency under 365 nm irradiation (78% Z isomer) than $E-1_{OCB}$, and no



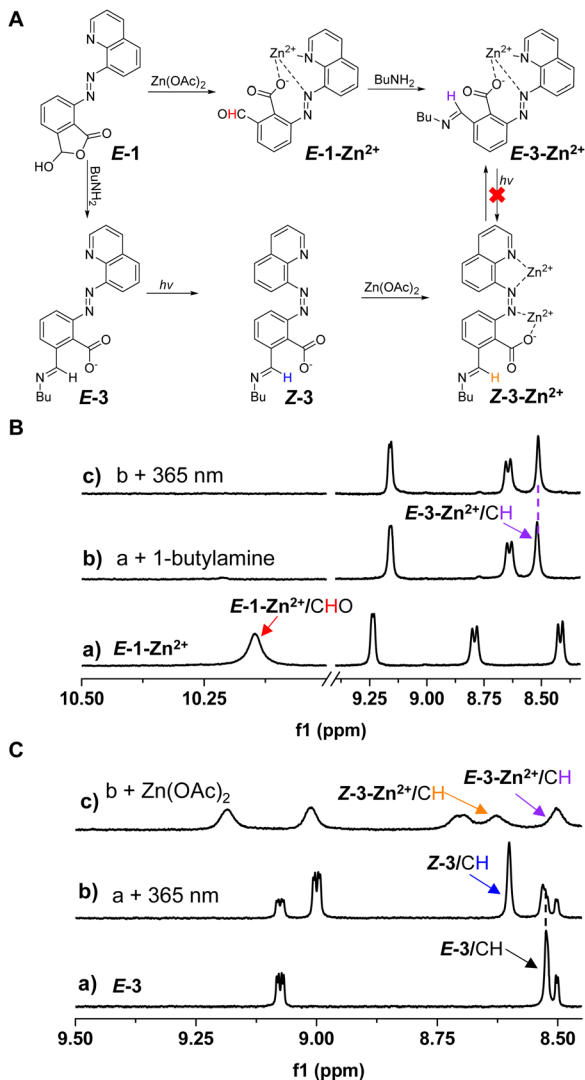


Fig. 5 (A) Illustration of the modulation of *E*-1 with primary amine, light, and coordination. (B) ^1H NMR spectra of *E*-1- Zn^{2+} in $\text{DMSO}-d_6$ (10 mM, a), its mixture with 1-butylamine (3 equiv., b), and after irradiation for 1.5 h at 365 nm (c). (C) ^1H NMR spectra of *E*-3 in $\text{DMSO}-d_6$ (10 mM, a), after irradiation for 1.5 h at 365 nm (b), and its mixture with $\text{Zn}(\text{OAc})_2$ (2.5 equiv., c).

photoisomerization of imines was observed (Fig. S50 \dagger).^{94,95} The $Z \rightarrow E$ switching at 425 nm (81% *E* isomer) was also attained. As for the thermal stability, *Z*-3 exhibited a shorter half-life (9.0 h) than *Z*-1_{OCB} in $\text{DMSO}-d_6$ (Fig. S51 \dagger). We speculated that *n*-butylammonium, created from excess *n*-butylamine and carboxyl, acts as a guest to bind with *Z*-3 *via* hydrogen bonding, thus reducing its stability. Therefore, DBU (1 equiv.) was used to capture the protons in *n*-butylammonium. The half-life was significantly prolonged to 85.6 h, further demonstrating the importance of hydrogen bonding in modulating the thermal stability of azoquinolines (Fig. S52 \dagger). Moreover, excellent fatigue-resistance was found when a dilute solution of *E*-3 was irradiated *via* alternative illumination at 365 and 425 nm (Fig. S53–S55 \dagger). When *E*-1- Zn^{2+} (a of Fig. 5B) was subjected to reaction with 1-butylamine (3 equiv.), imine *E*-3- Zn^{2+} was afforded (b

of Fig. 5B). The ability of photoswitching was turned off for *E*-3- Zn^{2+} (c of Fig. 5B and S56 \dagger), consistent with *E*-1- Zn^{2+} . When *Z*-3 was generated first followed by the addition of $\text{Zn}(\text{OAc})_2$, *Z*-3- Zn^{2+} appeared and was then converted to *E*-3- Zn^{2+} after 30 min (Fig. 5C and S57 \dagger). Thus, a complex chemical network was constructed through the intricate interaction with the stimulation of light, metal ions, and amines. The dynamic covalent bonding enables our system to be efficiently post-modified by the imine formation reaction, while the high photoisomerization efficiency after the reaction and abundant recognition sites would show potential applications in smart materials, such as artificial membranes,⁴⁹ multi-stimuli responsive polymers,⁹⁶ and nanocapsules.^{18,20}

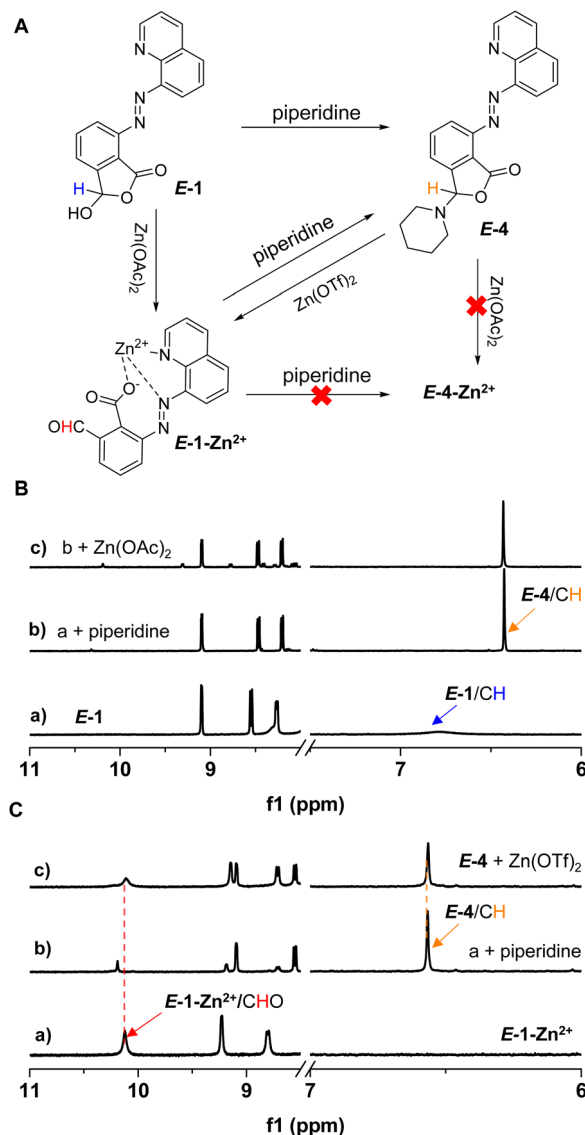


Fig. 6 (A) Illustration of the modulation of *E*-1 with secondary amine and coordination. (B) ^1H NMR spectra of *E*-1 in $\text{DMSO}-d_6$ (10 mM, a), its mixture with piperidine (1.5 equiv., b), and its mixture with $\text{Zn}(\text{OAc})_2$ (1.0 equiv., c). (C) ^1H NMR spectra of *E*-1- Zn^{2+} in $\text{DMSO}-d_6$ (10 mM, a), its mixture with piperidine (1.5 equiv., b), as well as the mixture of *E*-4 and $\text{Zn}(\text{OTf})_2$ (3 equiv., c).



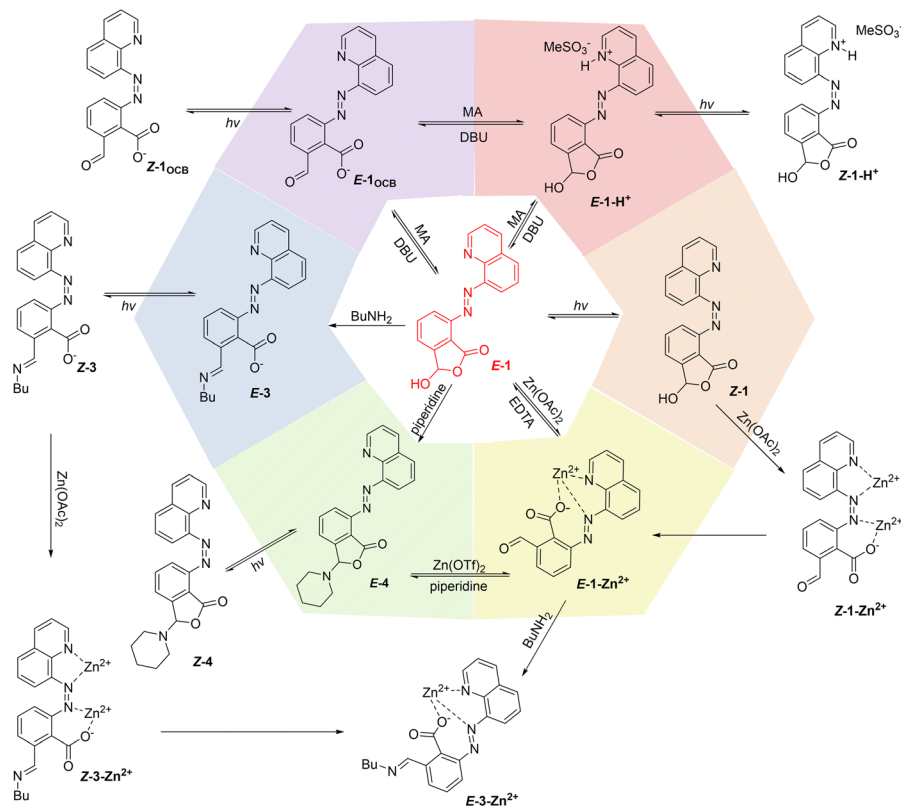


Fig. 7 Illustration of the modulation of *E-1* with light, pH, coordination, and amine nucleophiles, and the reaction network created by the interaction between different stimuli.

Reaction networks were further created with secondary amines (Fig. 6A). The reaction of *E-1* and piperidine was readily realized, giving cyclic hemiaminal ether *E-4* (b of Fig. 6B and S58†). Similar photochromic switching behaviors were obtained for *E-4* (60% *Z* isomer for *E* → *Z* and 80% *E* isomer for *Z* → *E*) with multiple cycles of switching successful, but a much shorter half-life (2.3 h) for *Z-4* over *Z-3* (Fig. S59–S63†). Different from *E-3-Zn*²⁺, a combination of *E-1-Zn*²⁺ and piperidine resulted in the formation of *E-4* and concomitant release of metal ion (b of Fig. 6C and S64†). Moreover, no metal binding was apparent upon the titration of Zn(OAc)₂ into *E-4* (c of Fig. 6B and S65†). Nevertheless, upon mixing Zn(OTf)₂ and *E-4* the decomposition of *E-4* occurred accompanied by the appearance of *E-1-Zn*²⁺, likely due to the higher Lewis acidity of Zn(OTf)₂ (c of Fig. 6C and S66†). As a result, the selection of metal salts offered a facile means for control over dynamic covalent reactivity.

The discrimination between primary and secondary amines can be attributed to the ring–chain equilibrium of *E-3*, which renders the carboxyl ligand feasible for engaging in the chelation of Zn²⁺. In contrast, the cyclic hemiaminal ether for *E-4* would give a more rigid scaffold, with zinc binding unlikely. Thus, the distinct metal binding mode of primary and secondary amine derived adducts provided a handle for regulation of the switching behaviors of azoquinolines. Tying it all together, through the interaction between different stimuli we realized multiple control of azoarenes and constructed a multi-state reaction network (Fig. 7).

Conclusions

In summary, we developed a multi-responsive molecular switching system through combining an azoquinoline photo-switching unit with ring fusion dynamic covalent sites. The incorporation of a cyclic hemiacetal and quinoline into the azoarene scaffold was realized in a multi-step synthetic sequence. Acid/base stimulation allowed the modulation of ring–chain equilibrium between the cyclic hemiacetal and open aldehyde and *E/Z* photoswitching behaviors. Furthermore, metal ion chelation by carboxylate as well as azo and quinoline nitrogen was attained, resulting in the reversal of ring–chain equilibrium and turning off the photoswitching. The inaccessible metal ion-containing *Z* isomer was instead created by changing the stimulation order. Dynamic covalent reactions of primary amines along with light and metal coordination further enhanced the complexity of the system. Differently, reactions with secondary amines prohibit the ring–chain tautomerism and thus complexation. In essence, multiple control of the switching system was achieved with light, pH, metal ions, and amine nucleophiles, with the intricate interaction between different stimuli further affording addressable multi-state switching within the complex network (Fig. 7). This work demonstrates diverse dynamic covalent and non-covalent binding sites as powerful tools to induce abundant triggers in multi-state switching systems, which will open new possibilities in molecular switches, information encoding, and smart materials.



Data availability

All experimental data and detailed experimental procedures are available in the main text and ESI.†

Author contributions

Y. L. carried out the synthetic work, photoswitching studies, and dynamic covalent reactions. H. Y. carried out the theoretical calculation. L. Y. designed the project and wrote the manuscript. All authors discussed the results and have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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