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Sheng Ding, Yuanyuan Che, Yuming Yu, Lang Liu, Dianzeng Jia, and Jianzhang Zhao J. Org. Chem., Just Accepted Manuscript • DOI: 10.1021/acs.joc.9b00495 • Publication Date (Web): 10 May 2019 Downloaded from http://pubs.acs.org on May 10, 2019

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# An interactive aggregation-induced emission system controlled by dynamic covalent chemistry

Sheng Ding,<sup>1</sup> Yuanyuan Che,<sup>1</sup> Yuming Yu,<sup>1,2</sup> Lang Liu, \*<sup>1</sup> Dianzeng Jia,<sup>1</sup> Jianzhang Zhao<sup>1,2</sup>

<sup>1</sup> Key Laboratory of Energy Materials Chemistry, Ministry of Education; Institute of Applied Chemistry, Xinjiang University, Urumqi, 830046 Xinjiang, China

<sup>2</sup> School of Chemistry and Chemical Engineering, Xinjiang University, Urumqi, 830046 Xinjiang, China.

**Abstract:** Aggregation-induced emission (AIE) molecule shows all kinds of application in biological research, chemical sensing and medical study. However, most of the reported molecules are based on the performance of the single molecular entity. In this paper, a molecular system for real time sensing through combination of dynamic covalent chemistry and aggregated induced emission was rationally designed and tested. The aggregated particles exhibit different fluorescence emission color upon the addition of various kinds of chemical reagents. The LC-MS analysis reveals that the breakage, formation and exchange of the disulfide bonds in the molecular system occurs spontaneously upon different reagents (base/acid and cysteine), which leads to proportion of different components in the system changed accordingly. Meanwhile, the fluorescence emission of the AIE system exhibits blue/redshift accompanying with intensity changes. Moreover, the particle size of the aggregated molecules gradually increased with the

change of chemical environment, which could be the result of the nucleus growing through intermolecular hydrogen bonding among molecular components. Thus, the chemical environment change results in the interactions of molecular structures, which further leads to the variation of dynamic fluorescence emission and morphology. The result represents a promising future of dynamic AIE molecular system in bio-imaging and sensing study.

### **1. INTRODUCTION**

Since the concept of AIE was first coined in 2001, AIE molecules exhibit fluorescence emission in aggregation state together with excellent dispersibility, high resistance to photobleaching and biocompatibility.<sup>1</sup> Thus, large amount of related compounds and systems have been reported, which have been widely used in different research areas, for example, chemical sensing, biological probes, optoelectronic systems and so on.<sup>2-4</sup> Recently, many works are focused on combining AIE with other functional groups to obtain AIE molecules that show multi-responsive properties in photochromism, mechanical force, evaporation or complexation. These compounds can be used in anti-counterfeiting, chemical sensing, etc.<sup>5-11</sup>

Despite the outstanding properties and novel functions of the recent AIE molecules, they still have many puzzles to be solved. Because the molecular structures are specifically designed, which cannot response to different chemical reagents. Moreover, most of the reported studies mainly centered on the effect of intramolecular structure changes on AIE properties. The relationship between AIE properties and the interaction among molecules still remains unexplored.

Thus, we decided to employ dynamic covalent chemistry (DCC), which is an important constituent of systems chemistry that originated from biological system.<sup>12,13</sup> It focused on the interaction of multiple chemical components in a molecular system. DCC exhibits advantages in

the study of equilibrium system of various kinds of chemical species. Based on the breakage and formation of dynamic covalent bonds, the molecule can respond to outside stimulus (light, pH, temperature, electric fields, etc.) through inter-/intramolecular interaction.<sup>14-17</sup> The dynamic processes have been applied in receptor synthesis, catalysts, bio-macromolecule recognition, self-healing polymers and sensors.<sup>18-22</sup>

Scheme 1. Synthesis route of the compound DS-2.



In consideration of the features of DCC, it is reasonable to combine it with luminogens exhibiting AIE properties (AIEgen),<sup>1</sup> resulting in a new AIE system that can respond to chemical environment changes specifically through dynamic covalent bonding, breaking and exchanging. Herein, we synthesized 2, 2'-disulfanediylbis(N'-((E)-4-(1,2,2-triphenyl-vinyl)benzylidene) acetohydrazide) (**DS-2**), which includes typical dynamic covalent bond, -S-S-, and a standard AIEgen, tetraphenylethene (TPE) (Scheme 1). Its AIE responses to base, acid and cysteine (Cys) were tested and the mechanism were systematically studied.

### 2. RESULTS AND DISCUSSIONS



**Figure 1**. (a) Fluorescence spectra of the compound in DMF/H<sub>2</sub>O mixture ( $1 \times 10^{-5}$  mmol/mL, fraction of water,  $f_w$ : 0% - 90%); fluorescence spectra changes with increasing the concentration of (b) DBU ( $1 \times 10^{-5}$  mmol/mL,  $f_w$ : 90%), (c) TFA ( $1 \times 10^{-5}$  mmol/mL,  $f_w$ : 90%, DBU: 1.34 mmol/mL) and (d) cysteine ( $1 \times 10^{-5}$  mmol/mL,  $f_w$ : 90%, DBU: 1.34 mmol/mL) in DMF/H<sub>2</sub>O mixture; (e-h) photoluminescence photos of each AIE states under irradiation with a hand-held UV-lamp (365 nm).

With the addition of water, as shown in Figure 1a, fluorescence emission of **DS-2** DMF/water mixed solution with maximum at 500 nm gradually intensified, which reveals typical AIE property. In solid form, **DS-2** also showed cyan fluorescence emission and high quantum yield ( $\phi$  =22.26%,  $\lambda_{ex}$  = 397 nm) (Figure S1). The corresponding UV-vis spectra of **DS-2** DMF solution upon different water fraction is shown in Figure S2. The decrease of UV-vis absorption intensity upon the increasing of water fraction is attributed to the aggregation of dissolved molecules. Herein, we chose **DS-2** DMF solution with 90% fraction of water as the original state (**DS-2**: 1 × 10<sup>-5</sup> mmol/mL, Figure 1a, black line). The aggregations of the original state emitted intense cyan fluorescence with a quantum yield of 6.46 % ( $\lambda_{ex}$  = 365 nm, Figure 1e). Based on the instability of the -S-S- bond under basic condition, the response of the aggregated **DS-2** to 1, 8-diazabicyclo [5.4.0]undec-7-ene (DBU) was firstly studied. It can be observed that the intensity of the emission peak ( $\lambda$  = 500 nm) was gradually decreased through treatment with DBU and the emission band

showed an obvious blueshift to 410 nm. Subsequently, the intensity of the emission peak ( $\lambda = 410$ nm) was further increased (**DBU state**,  $1 \times 10^{-5}$  mmol/mL,  $f_w$ : 90%, DBU: 1.34 mmol/mL, Figure 1b, blue line) and the system showed deep blue luminescence (Figure 1f), accompanied by the complete disappearance of peak at  $\lambda = 500$  nm. The quantum yield of the **DBU state** was increased from 6.46% in the original state to 11.08% ( $\lambda_{ex} = 330$  nm). The 'state' here refers to the final state of mixed solution since a kind of reagent was introduced (such as DBU, TFA and cysteine). It can be inferred that DS-2 transforms to the monomer which diminishes the conjugation effect because of the breaking of -S-S- bonds and only one TPE structure was remained in the monomer. Secondly, trifluoroacetic acid (TFA) was employed to study the multi-response of **DS-2** in the aggregated form. After the **DBU state** was treated with TFA, the intensity of the emission peak at 410 nm was gradually increased together with the maximum emission wavelength shift to  $\lambda = 420$  nm (TFA state,  $1 \times 10^{-5}$  mmol/mL,  $f_w$ : 90%, 1. DBU: 1.34 mmol/mL, 2. TFA: 2.42 mmol/mL, Figure 1c, pink line). The quantum yield of **TFA state** was determined to be 4.45% ( $\lambda_{ex} = 330$  nm). In Figure 1g, the photoluminescence color was changed from dark blue to light blue accordingly. Finally, to further dig into the feature of -S-S- bonds, we studied the response of DS-2 to other molecules with -SH group, cysteine. Dithiothreitol (DTT) was firstly employed under basic condition (DBU state) to facilitate the breakage of disulfide bonds before the addition of cysteine.<sup>23</sup> Only tiny decrease of the emission intensity is shown in Figure 1d (orange dotted line). Then the intensity was continually decreased by adding cysteine and finally the emission peak red shift to  $\lambda = 475$  nm and the quantum yield was measured to be 1.12%,  $\lambda_{ex} = 320$  nm (Cys state, 1 × 10<sup>-5</sup> mmol/mL,  $f_w$ : 90%, 1. DBU: 1.34 mmol/mL, 2. DTT: 0.003 mmol/mL, 3. cysteine: 1.65 mmol/mL, Figure 1d, orange line). The photoluminescence color was turned to light blue simultaneously (Figure 1h). Therefore, the AIE of **DS-2** can respond to outside chemical environment changes in real time

through breakage and re-formation of the disulfide linkages and exhibits different fluorescence color. The tiny changes of UV-vis spectra upon different reagents are shown in Figure S3. A weak absorption band centered at 500 nm was observed in the **TFA state** (blue line). Moreover, with increasing the amount of cysteine, absorption intensity between 400-600 nm was slightly increased in the **Cys state**. The absorption changes may result from the structure changes of the components that induced by intermolecular interaction.



**Figure 2**. Product distribution over the amount of different chemical reagents in various states monitored by UPLC: (a) **DBU state**, (b) **TFA state**, (c) **Cys state**.

UPLC-MS experiments have been applied to analyse the mechanism of dynamic covalent bond changes in different AIE states. Due to the concentration of each states is too dilute to be detected by liquid chromatogram, we prepared the DMF solution of **DS-2** with higher concentration ( $2.5 \times 10^{-3}$  mmol/mL, original state). The liquid chromatogram of the original state shows the three isomers of **DS-2** (Figure S4, S5, *cis*-isomer (1), *cis-/trans*-isomer (2), *trans*-isomer (3)).<sup>24</sup> The corresponding cation fragments (*m/z* 512.19 and 474.60) of the isomers are demonstrated in Figure S6-S9.<sup>25,26</sup> When the solution was treated with increasing amount of DBU, the monomer was emerged and the amount of dimer was decreased at the same time (Figure 2a, Figure S10). Cation fragment with mass of 374.18 that corresponds to the monomer can be observed in Figure S11, S12. After 200 eq. of DBU was added to the system, the proportion of the monomer was increased rapidly and accounts for over 60%. The transformation is resulted from the breaking of -S-S- bond

of **DS-2** under alkaline environment. The amplification of the monomer with only one TPE unit in the system further leads to the blueshift of fluorescence emission from 500 nm to 410 nm (Figure 1b).<sup>27</sup>

In addition, after TFA was introduced into the system, it can be observed that the proportion of the dimer was increased well over 60% at the cost of monomer conjugation (Figure 2b, Figure S13). The ratio change between the dimer and the monomer results in the tiny redshift of the emission wavelength in Figure 1c. However, excessive amount of TFA led to the decomposition of the dimer, which was transformed into the monomer and other components. Therefore, the breakage and re-formation of the disulfide bond can be controlled through pH modulation.

In Figure 2c, the introduction of cysteine into the **DBU state** firstly resulted in the decrease of the dimer obviously. The exchange reaction between the dimer and cysteine generated a new product (mono-cys, Scheme 2). After 10 eq. of cysteine was introduced, the monomer became the main component of the AIE system. Then cysteine preferably combined with the monomer and the mono-cys dominated in the whole system. It can be further increased through consuming the dimer and the monomer (Figure S14). An ion fragmentation with a unique mass of 489.60 (mono-cys) verifies that the exchange reaction between the dimer (**DS-2**) and cysteine has occurred (Figure S15, S16). The continuous increasing of the amount of mono-cys finally led to redshift of the emission wavelength from 410 nm to 475 nm (Figure 1d).

Scheme 2. The mechanism of AIE transformation among different states.



Based on the above results, we summarized the variation of dynamic covalent bond (-S-S-) under different chemical environments (Scheme 2). In the original state, **DS-2** with two TPE AIEgen structures shows a fluorescence emission peak at 500 nm. With the increase of DBU, the -S-S-bonds in the dimer are broken gradually and the proportion of the monomer with less  $\pi$ -conjugation structure is increased, which results in the obvious blueshift of the emission (**DBU state**,  $\lambda = 410$  nm). The monomer can be partially transformed into the dimer by controlled addition of TFA for the acid neutralized the DBU in the solution. However, excessive amount of TFA directly leads to the decomposition of the dimer. This process induces tiny red shit of the emission peak together with the increase of intensity (**TFA state**,  $\lambda = 420$  nm). In the **Cys state**, on the one hand, cysteine favors the exchange reaction with the dimer and yields a new product (mono-cys) under alkaline environment. On the other hand, a portion of cysteine can also conjugate with the monomer to form mono-cys. Compared to the dimer and the monomer, the mono-cys contains only one TPE AIEgen structure and longer molecular chain, it shows an emission peak centered at 475 nm, which is located between 410 nm and 500 nm.



**Figure 3**. (a) The comparison histogram of particle size distribution in different aggregated states; TEM images of aggregated particles: (b) original state (scale bar: 500 nm; inset: 100 nm), (c) **DBU state** (scale bar: 1 μm; inset: 300 nm), (d) **TFA state** (scale bar: 3 μm; inset: 100 nm), (e) **Cys state** (scale bar: 5 μm; inset: 2 μm).

It is well known that AIE originates from the intra-/intermolecular rotation or vibration restriction among molecular aggregations. Thus it is necessray to explore the change of molecular aggregations. Firstly, we measured the particle size of each states. In Figure 3a, the aggregations of the original state revealed good monodispersity with sizes around 100 nm. After the introduction of DBU, in Figure S17, the proportion of the initial particles was gradually decreased and novel particles with sizes around 375 nm emerged. All the particles were aggregated into bigger ones with sizes about 500 nm. Similarly, the particle sizes were further increased to around 1.2  $\mu$ m and 2.25  $\mu$ m in the **TFA state** and the **Cys state** (Figure S18, S19).

To further analyze the morphology of the aggregations, transmission electron microscopy (TEM) images are shown in Figure 3. In the original state, we can still observe that large amount of nano particles gather around bigger cores (~100 nm) (Figure 3b). The inset shows a growing nanocore which gathered smaller particles together. Furthermore, in Figure 3c, it can be observed that all the smaller nanocores were transformed into nanoclusters with sizes around 500 nm in basic solution (**DBU state**). Due to the nanoparticles were gradually aggregated into bigger ones, less nano cores can be observed compared to the orginal state. After the introduction of TFA, molecular aggregations with larger sizes were observed (Figure 3d, **TFA state**). Remarkably, each aggregation was consisted of several smaller particles (inset, around 50 nm) that stick together. The smaller particles may resulted from dissolution of the bigger particles in **DBU state** after the introduction of TFA. Moreover, the nanoclusters in the **DBU state** were further gathered together and finally formed into microparticles after the addition of cysteine (~2 µm, Figure 3e, **Cys state**). We observed that two smaller microcores merged together in the inset. Ostwald ripening process may occur during the growing of particles. Smaller nanoparticles were dissoloved in the solution because of the breakage and bonding of the disulfide bond that induced by chemical reagents. The

components in the solution redeposited onto larger particles during nucleation process. In addition, molecules in the central part of the particles may have little effect on the entire system's AIE performance because the molecules cannot take part in the interaction with other components in the AIE system. Thus, the growing of particle results in the decrease of the fluoresence emission intensity of the **DBU** and **Cys states**. On the contrary, the nanoparticles in the **TFA state** were dissolved in the acidic solution and thus the molecules were released into the solution, which further led to the emission intensity increase. The changes in the morphology are accord with the particle size analysis.

# **3.** Conclusions

In summary, based on the breakage, bonding and exchange of intrinsic -S-S- bonds in molecules, we designed a new AIE system that shows specific fluorescence emission upon different chemical reagents. The changes in the -S-S- linkages lead to the interaction among different molecules in the system. Then the interaction further changes the proportion of the molecules and produces new one with different AIE performance. Therefore, the system's fluorescence emission that results from these molecules is changed accordingly. That is to say, the AIE system responses to various kinds of chemical environment in real time. Moreover, the interaction among molecules also influences the nucleation process of the nanoparticles in the system. Smaller nanoparticles are easily dissolved in the solution and the dissolved molecules can be re-deposited onto the larger ones, resulting in different sizes and morphologies for the aggregations in each states.

The system verifies the feasibility to control the AIE properties through dynamic covalent chemistry. The combination of multiple intra-/intermolecular DCC strategies with all kinds of AIEgen structures is on the way in our lab. We expect to produce practical AIE system controlled

by dynamic covalent chemistry, which are able to complete multi-stimuli response and real time sensing in biomedicine.

# 4. Experimental section

**4.1 Materials and Reagents.** All the reagents were obtained from commercial sources and used without further purification.

**4.2 Synthesis.** 2,2'-disulfanediyldi(acetohydrazide), **DS-1** (white powder, 463.7 mg, 73.60%). m. p. 217.6 – 218.5 °C. The precursor of **DS-1**, ethyl 2-mercaptoacetate, was synthesized according to the literature.<sup>28</sup> White solid compound **DS-1** was recrystallized from the reaction mixture through air oxidation.

<sup>1</sup>H NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  9.19 (s, 2H), 4.34 (s, 4H), 3.41 (s, 4H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz,  $d_6$ -DMSO)  $\delta$  167.2 (s), 40.5 (s). HRMS (ESI) m/z: [M + H]<sup>+</sup> Calcd. for C<sub>4</sub>H<sub>11</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> 211.0318; Found: 211.0315.

2, 2'-disulfanediylbis(N'-((Z)-4-(1,2,2 triphenylvinyl)benzylidene) acetohydrazide), **DS-2** (faint yellow powder, 584.0 mg, 65.30%). m. p. 217.6 – 218.5 °C. 4-(1,2,2-triphenylvinyl)benzaldehyde was prepared according to the literature.<sup>29</sup> 1 mmol of **DS-1** and 4 mmol of 4-(1,2,2-triphenylvinyl)benzaldehyde were dissolved in ethanol solution and refluxed under 80 °C for 1h. The reaction was monitored by TLC analysis. After cooling down, the solvent was evaporated under reduced pressure. The crude product was further purified by column chromatography (ethyl acetate/dichloromethane = 1 : 20) to afford the compound **DS-2** as faint yellow powder.

<sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  11.52 (d, *J* = 17 Hz, 3H), 11.52 (d, *J* = 17 Hz, 2H), 8.08 (d, *J* = 7 Hz, 2H), 7.85 (s, 2H), 7.49 – 7.32 (m, 4H), 7.26 – 7.07 (m, 16H), 6.98 (ddd, *J* = 9 Hz, 8.0, 3.5 Hz, 14H), 5.32 (t, *J* = 5 Hz, 2H), 3.59 (d, *J* = 16 Hz, 2H), 0.85 (t, *J* = 7 Hz, 2H) (the different chemical shifts of NH, CH lines are attributed to the *cis-trans* isomerization).<sup>26 13</sup>C {<sup>1</sup>H} NMR (101

MHz,  $d_6$ -DMSO)  $\delta$  174.7 (s), 164.7 (s), 145.3 (s), 143.3 (d), 141.6 (s), 140.4 (s), 132.5 (s), 131.5 (s), 131.1 (d), 130.1 (s), 128.3 (d), 127.1 (s), 126.7 (s), 35.6 (s), 31.7 (s), 29.6 – 28.7 (m), 27.0 (s), 25.5 (s), 22.5 (s), 14.4 (s) (overlapping has been observed for some aromatic carbon atoms).<sup>30</sup> HRMS (ESI) m/z: [M+H]<sup>+</sup> Calcd for C<sub>58</sub>H<sub>47</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub> 895.3135; Found: 895.3124.

4.3 General Characterization. ESI-MS characterization were made on an Ultimate 3000/Q-Exactive UPLC-MS/MS. <sup>1</sup>H NMR, <sup>13</sup>C NMR spectra were measured with an INOVA-400 NMR spectrometer with  $d_6$ -DMSO as solvent. Melting points were measured with a B-540 melting point apparatus without correction. Fluorescence spectra were performed on a Hitachi F-4500 spectrometer equipped with an integrating sphere accessory. Irradiation of 365 nm UV light was provided by a hand-held ultraviolet lamp (15 W). The absolute fluorescence quantum yields of each states and the solid sample were determined using a FluoroLog-3 (Horiba-Jobin-Yvon, Edison, NJ, USA) fluorescence spectrophotometer. The particle sizes of samples were measured on a Malvern Zetasizer Nano S90. The transmission electron microscopy (TEM) images were taken by JEM-2100 at 100 kV. UPLC-MS spectra were measured using an Agilent 1290 coupled to a Thermo Scientific TSQ Quantum Ultra. The UPLC analyses were performed using a reversed phase UPLC column (Thermo Scientific C18 Hypersil GOLD,  $2.1 \times 100$  mm,  $1.9 \mu$ m), using an injection volume of 5.0 µL, with elution at a flow rate of 0.25 mL/min (column temperature, 25 °C). Positive ion mass spectra were acquired with the electrospray ionization (ESI) source (Vaporizer temperature: 350 °C; sheath gas pressure: 30 arb.; Spray Voltage: 4000 V). All the samples were analysed using the method in Table S1.

# ASSOCIATED CONTENT

**Supporting Information**. UV-vis spectra and fluorescence spectrum of **DS-2**, UPLC-MS analyses, hydrodynamic size analysis of each states and NMR spectra of the related compounds.

This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

AUTHOR INFORMATION

**Corresponding Author** 

#### \* llyhs1973@sina.com

### ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21362037, 51672235), National "Ten Thousand People Plan"(2017), Xinjiang "Tianshan Elite Plan"(2017), the Program for Changjiang Scholars and Innovative Research Team in the University of Ministry of Education of China (IRT1081), and Xinjiang University Doctoral Innovative Research Program (XJUBSCX-2015011).

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Table of contents

