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Synthesis of isoniazid-substituted tetraphenylethylene stereoisomers with dramatic differences on aggregate morphologies, optical and mechanocharomic properties

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Graphical abstract

Highlights

- The pure *E*/*Z* isomers isoniazid-substituted TPE derivatives with high yields was synthesized and the structure was confirmed by single crystal, mass spectrometry and NMR spectroscopy.
- The structure-property relationships of these molecules have been systematically investigated by the combining the spectroscopic methods, theoretical calculations and single crystal data analysis.
- •The *E*/*Z* isomers possessed dramatic differences in fluorescent properties and distinct aggregate self-assembly morphologies, they exhibited diverse changes in response to stimuli. Meanwhile, they can be used as efficient fluorescent probes for the detection of copper in the environment.

Abstract

Stereoisomers play an irreplaceable prominent role in life sciences. In molecular engineering, the isomers have been continuously designed and synthesized, and their interrelationships among structure-property-function have also been explored. However, the difficulties in purification and structural confirmation of tetraphenylethene (TPE) derivatives' stereoisomers hinder their structural diversity and

scope of functions. Meanwhile, there were few researches on the macroscopic optical differences about TPE derivatives isomers. Herein, isoniazid-substituted TPE derivatives stereoisomers have been synthesized, as confirmed by single crystal data, mass spectrometry and NMR spectroscopy. The different photophysical properties were caused by the introduction of functional group isoniazid on the periphery of TPE. These isomers possessed dramatic differences in fluorescent properties, and exhibited diverse changes in response to stimuli. They also have distinct aggregated selfassembly morphologies because of different intermolecular hydrogen bonding, and they can be used as efficient fluorescent probes for detecting copper. Based on the coordination-driven sensing system, the morphologies of isomers aggregates changed significantly after interaction with copper, and the stoichiometry between them is 2:1. The theoretical calculation demonstrated that they have obvious intramolecular charge transfer behavior. Our research provided a good strategy for designing different substituted groups that can produce various functions and have more potential applications.

Key words

Aggregation induced emission, Optical difference, Self-assembly morphologies, Mechanochromism, Fluorescent probe.

1. Introduction

Molecular research plays a crucial role in the creation of new functional materials, from design to investigation of their performance, behavior and interrelationships [1-4]. Researchers have modified multitudinous molecular structures with TPE core to construct functional applications in chemical sensing, bioimaging, optical materials and biomedical therapies and so on [5-8]. Modifying and controlling the spatial configuration of a molecule is an efficient strategy for adjusting the macroscopic properties [9-11]. Isomers have the same molecular formula but different geometric configurations in space, which play a vital role in current life and materials science [12-13]. For example, the E-isomer of entacapone can be used as a new generation COMT (catechol-oxygen-methyltransferase) inhibitor for the treatment of Parkinson's disease, while the Z-isomer has no effect for therapy [14]. Therefore, designing new stereoisomers and elucidating their structure-property-function relationships are worthy in molecular engineering. The exploration of E/Z isomers is of great significance and application value in understanding the working mechanism of various new molecules and materials [15-17].

Since the aggregation induced emission(AIE) phenomenon was first reported in 2001 [18], it has rapidly become hot research topics of molecular materials. What's more, TPE and its derivatives are a class of typical fluorescent molecules with outstanding AIE characteristic. TPE has the advantages of easy modification, meanwhile it possesses high-efficiency optical properties. To date, multiple functional group-substituted TPE derivatives have been applied to bioimaging, optoelectronic devices, biosensing and therapeutic applications [19-23]. Designing and developing

new AIE molecules based on TPE and expanding their scope of applications are important development directions of AIE research.

Nowadays, the stereoisomers of TPE and its derivatives can be obtained by the McMurry unsymmetrical coupling reaction [24-25]. In the present research reports, macroscopic differences in optical properties of pure isomers were scarce. Tang et al. have successfully synthesized pure isomers of ureidopyrimidinone-functionalized tetraphenylethenes ((Z)-TPE-UPy and (E)-TPE-UPy), which they showed distinct fluorescence in the aggregate state and different self-assembly behaviours [26]. The apparently different stereoisomers of TPE derivatives were currently rare, which were invaluable.

As is well-known, luminescent stimuli-responsive materials are extensively applied in sensing, photoelectric device devices, drug release and optical recording because of their unique performance [27-30]. Mechanochromic materials as stimuli-responsive luminescent material that can change their fluorescence emission colors or intensity exposed to appropriate external force stimulus such as grinding, shearing, pressing or crushing [31-33]. In general, mechanical forces can destroy the pristine packing of molecules, including phase transitions from the crystalline state to the amorphous state, or transition from one crystal stage to another one, and change intermolecular interactions or molecular structures, which resulting in mechanochromism [34-35]. The specifically distinct isomers possess mechanochromic property will induce different color change or intensity response, which must attract more attention.

The presence of intramolecular hydrogen bonding causes the molecules to accumulate in different pattern or the rotation of the bond, so the photophysical properties will be also very various [36-37]. Isoniazid contains rich heteroatoms, which has large electronegativity and small radius. Intramolecular interactions will be formed when it was designed as functional molecules. At the same time, the N atoms on isoniazid provide the possibility of coordination with metals [38-39].

Here, the isoniazid group was modified on the TPE core unit by covalent connection, and the E/Z isomers (TPE-INH-E and TPE-INH-Z) were identified by single crystal Xray diffraction, 2D COSY NMR and 2D ROESY NMR. The stereoisomer displayed markedly differences in optical properties. This dramatic difference was rare between the E/Z isomers of TPE derivatives. Intermolecular hydrogen bonding interaction promotes the formation of different polymers in the aggregated state of TPE-INH-E and TPE-INH-Z. These two isomers have different response to mechanochromic phenomenon and intramolecular charge transfer behaviors. In addition, TPE-INH emitted strong fluorescence in the aggregate state, which can be applied to the detection of Cu^{2+} in aqueous solution.

2. Experimental section

2.1 Materials

4-Methylbenzophenone, Titanium tetrachloride, Anhydrous tetrahydrofuran, NBromosuccinimide(NBS), Dibenzoyl peroxide (BPO) were purchased from Aladdin. Anhydrous tetrahydrofuran (THF), silver trifluoroacetate and sodium acetate were

purchased from Energy Chemical. All other reagents were of analytical grade and used as received. Ultrapure water was prepared using a Milli-Q water purification system.

2.2 Apparatus

The NMR spectra were recorded using a AVANCEDRX600 NMR spectrometer (Bruker, Germany) operated at 600 MHz. High resolution mass spectrometry was measured by Agilent 6540 Q-TOF mass spectrometer. The crystallographic data collection was performed on a Bruker SMART APEX-II CCD area detector using graphitemonochromated Mo-K α radiation ($\lambda = 0.71073$ Å). The data reduction and integration and global unit cell refinements were performed using the INTEGRATE program of the APEX2 software package. Semiempirical absorption corrections were applied using the SCALE program for the area detector. Fluorescence spectra were performed on a Hitachi High-Technologies Corporation Tokyo Japan 512-0004 model F-7000 FL spectrofluorometer. UV-Vis absorption was characterized using a UV/Vis/NIR spectrophotometer (Shimadzu, Japan). The Fourier transform infrared (FT-IR) spectra were obtained on a FT-IR spectrophotometer (Thermo Nicolet 365). X-ray powder diffraction patterns were taken using a D/max-TTR III X-ray diffractometer (Rigaku, Japan) with a scan speed of 0.1 s per step and a step size of 0.01°.

2.3 Synthesis

2.3.1 Synthesis of compound 1 1,2-bis-(4-methylphenyl)-1,2-diphenylethene

1,2-bis-(4-methylphenyl)-1,2-diphenylethene was synthesized referred to the previous reported. Zinc powder (1.0 g, 15.3 mmol) was added into a 100 mL doubleneck flask. 15 mL anhydrous THF was added under an N2 atmosphere, which cooled to -5 °C, and then TiCl₄ (1.1 mL, 10 mmol) and pyridine (0.05 mL, 0.6 mmol) were added dropwise. The mixture was refluxed at 75 °C for 2 hours, then 20 mL THF solution of 4-methylbenzophenone (1.0 g, 5 mmol) was added. The solution was further refluxed at 75 °C for 12 hours. Upon completion of the reaction, the solution cooled to room temperature and 40 mL 30 % water solution of K₂CO₃ was poured into it, which was stirred strongly for 5 minutes and then filtered. The filtrate was extracted with ethyl acetate, washed with water and brine successively, and dried with Na₂SO₄. A white solid was obtained by rotary evaporation, and purified by column chromatography (silica gel, petroleum ether) to result in a white product 1 (Yield, 85 %). The ¹H NMR and ¹³C NMR spectrum of product 1 (400 MHz, CDCl₃, 25 °C), δ (TMS, ppm) were showed in Figure S1 and S2, respectively. ¹H NMR: 7.105-7.016(10 H, m), 6.928-6.905(8 H, m), 2.276(3 H, s), 2.258(3 H, s);¹³C NMR: 144.528, 141.294, 140.766, 136.270, 131.738, 131.704, 131.599, 131.545, 128.759, 128.701, 127.974, 127.916, 126.560, 21.580, 21.538. High resolution mass spectrometry of product 1 is showed in Figure S3, (m/z): calculated for C₂₈H₂₄[[]M+Na]⁺ 383.1770, found 383.1771.

2.3.2 Synthesis of (E)-4,4'-(1,2-diphenylethene-1,2-diyl)dibenzaldehyde and (Z)-4,4'-(1,2-diphenylethene-1,2-diyl)dibenzaldehyde

1,2-bis-(4-methylphenyl)-1,2-diphenylethene 720 mg (2 mmol) obtained in the previous step was added into a 100 mL round bottom flask, and then NBS (700 mg, 4

mmol), BPO (32 mg, 0.125 mmol) and CCl₄ (30 mL) were added. Under an N₂ atmosphere, the mixture was reacted at 80 °C for 2 hours. Then, NBS (700 mg, 4 mmol) and BPO (32 mg, 0.125 mmol) were added into the mixture every two hours for twice. After 24 hours, the mixture was filtered, and the solid was washed with ethyl acetate. The filtrate was concentrated by rotating evaporation. Next, the yellow solid (1.5 g), sodium acetate trihydrate (750 mg, 9 mmol), silver trifluoroacetate (2.0 mg, 10 mmol), THF (25 ml) and H₂O (5 ml) were placed in a 100 mL round bottom flask. The mixture was further refluxed at 75 °C for 24 hours, the solution was cooled to room temperature and filtered. The filtrate was extracted with ethyl acetate, washed with water and brine successively, and dried with Na₂SO₄. A light vellow viscous liquid was obtained by rotary evaporation, and purified by column chromatography (silica gel, petroleum ether/ ethyl acetate=20:1) to result in a yellow-green product (TPE-2CHO-E and TPE-2CHO-Z, yields were 15 % and 10 %). The ¹H NMR and ¹³C NMR spectra of TPE-2CHO-E (600 MHz, DMSO-d6, 25 °C) were showed in Figure S4 and S5, respectively. ¹H NMR: 9.886 (2 H, s), 7.686 (4 H, d, *J* = 8.4 Hz), 7.208 (4 H, d, *J* = 8.4 Hz), 7.183-7.152 (6 H, m), 7.006 (4 H, d, J = 8.4 Hz); ¹³C NMR: 192.549, 149.079, 141.892, 141.291, 134.425, 131.334, 130.652, 129.071, 128.206, 127.341. HRMS(ESI) calculated for C₂₈H₂₀O₂ [M+H]⁺ 389.1536, found 389.1537, as shown in Figure S6. The ¹H NMR and ¹³C NMR spectrum of TPE-2CHO-Z (600 MHz, DMSO-d6, 25 °C) were showed in Figure S7 and S8, respectively. ¹H NMR: 9.895 (2 H, s), 7.699 (4 H, d, J =8.4 Hz), 7.226 (4 H, d, J = 7.8 Hz), 7.177-7.153(6 H, m), 7.012 (4 H, d, J = 5.4 Hz);¹³C NMR: 192.391, 148.861, 141.923, 141.140, 134.435, 131.320, 130.492, 129.081,

127.972, 127.087. HRMS(ESI) calculated for $C_{28}H_{20}O_2$ [M+H]⁺ 389.1536, found 389.1535, as shown in Figure S9.

2.3.3 Synthesis of TPE-INH

TPE-2CHO-E (40 mg, 0.1 mmol) and TPE-2CHO-Z (40 mg, 0.1 mmol) were severally added to 10 mL round bottom flasks, followed by isoniazid (42 mg, 0.3 mmol), and methanol (2 mL) as a solvent, refluxing at 75 ° C for 5 hours. The solid was centrifuged and washed with methanol, then the light yellow solid (TPE-INH-E, yield, 90 %) and the light pink solid (TPE-INH-E, yield, 70 %) were obtained by drying at 60 °C for 24 hours. The ¹H NMR and ¹³C NMR spectrum of TPE-INH-E (600 MHz, DMSO-d6, 25 °C) were showed in Figure S10 and S11, respectively. ¹H NMR: 12.066(2 H, s), 8.778(4 H, d, J = 4.8 Hz), 8.371(2 H, s), 7.812(4 H, d, J = 4.8 Hz), 7.517 (4 H, d, J = 8.0 Hz), 7.179-7.162 (6 H, m), 7.061 (4 H, d, J = 8.0 Hz), 7.024 (4H, d, J = 7.2 Hz); ¹³C NMR: 161.456, 150.231, 148.586, 145.069, 142.495, 140.784, 140.378, 132.245, 131.078, 130.6539, 127.950, 126.902, 126.673, 121.401. HRMS(ESI) calculated for C₄₀H₃₀N₆O₂ [M+Na]⁺ 649.2322, found 649.2321, as shown in Figure S12. The ¹H NMR and ¹³C NMR spectrum of TPE-INH-Z (600 MHz, DMSO-d6, 25 °C) were showed in Figure S13 and S14, respectively. ¹H NMR: 12.059(2 H, s), 8.770 (4 H, d, J = 5.6 Hz), 8.369(2 H, s), 7.804(4 H, d, J = 7.8 Hz), 7.546(4 H, d, J = 8.4 Hz), 7.164-7.119 (6 H, m), 7.078 (4 H, d, J = 8.4 Hz), 7.008 (4 H, d, J = 6 Hz). ¹³C NMR: 161.448, 150.211, 148.576, 148.046, 142.490, 140.768, 140.387, 132.353, 131.120, 130.590, 127.845, 126.750, 121.397, 120.898. HRMS(ESI) calculated for C₄₀H₃₀N₆O₂ [M+Na]⁺ 649.2322, found 649.2319, as shown in Figure S15.

3. Results and discussion

3.1 Design, synthesis and characterization of all compounds.

The compound 1 (1,2-bis-(4-methylphenyl)-1,2- diphenylethene) was prepared from starting material 4-methylbenzophenone through the McMurry unsymmetrical coupling. TPE-2CHO was obtained by NBS under the induction of a free radical initiator (BPO) in CCl₄ at 80 °C and with silver trifluoroacetate as catalyst. The pure TPE-2CHO-E and TPE-2CHO-Z were separated and purified by column chromatography. High resolution mass spectrometry revealed that the two new compounds have the same molecular weight as the target molecule, demonstrating that they are E/Z isomers. Then, yellow TPE-INH-E and pink TPE-INH-Z were synthesized by Schiff base condensation reaction with isoniazid, respectively. The configuration of TPE-2CHO did not alter when heated in methanol, and the spatial configuration remained unchanged after the reaction with isoniazid. The synthetic routes were shown in Scheme 1, their related NMR data were detailed in supporting information.

The single crystal of *E* isomers can be obtained by solvent diffusion method. *E* isomers could be identified by single crystal test, and the detailed single crystal data and structure were shown in Table 1 and Fig. 1, respectively. TPE-2CHO-E and TPE-INH-E were both monoclinic systems, and the space groups were P 2₁ and C 2/c, respectively. All the single crystal data were submitted to the Cambridge Crystallographic Data Centre (CCDC), and each compound has its corresponding number, 1955284 (TPE-2CHO-E) and 1955283 (TPE-INH-Z).

The geometry structures of E/Z isomers were further affirmed by 2D COSY and ROESY NMR spectroscopy, which certified these structures shown in Fig.2 and Figure S16. The spatial difference of E/Z isomers mainly depends on the spatial correlation of hydrogen atoms on TPE. The 2D COSY and ROESY NMR of TPE-2CHO-E and TPE-2CHO-Z were shown in Figure S16, H 1 and H 11 (δ = 9.886 ppm) were used as correction reference values. According to this assignment and the explicit correlations in the 2D COSY spectrum, δ = 7.693 and 7.215 ppm belong to H 2, H 3, H 12, H 13 and H 4, H 5, H 14, H 15, respectively. These protons signal of $\delta = 7.183-7.152$ ppm are attributed to H 8, H 9, H 10, H 18, H 19, H 20, δ = 7.013 ppm is assigned to H 6, H 7, H 16, H17, respectively, because they have a strong correlation in 2D COSY NMR. As shown in Figure S16C, the cross-peaks in the blue circles indicate obvious correlation between H 4/ H 5/H 14/H 15 and H 6/H 7/H 16/H 17, which indicates ring A and ring C is very close in space, and means they are on the same side of the double bond. However, there are no correlations for those hydrogens in COSY NMR spectroscopy (Figure S16B). In the meantime, we cannot find clear correlations between H 4/ H 5/H 14/H 15 and H 6/H 7/H 16/H 17 in Figure S16F, because ring A/C are far from ring B/D in Z isomers. Consequently, the 2D ROESY and COSY NMR spectra confirmed the geometrical structures of the E/Z isomers of TPE-2CHO molecule.

The 2D COSY and ROESY NMR of TPE-INH-E and TPE-INH-Z were shown in Fig.2 and Figure S17-20. The resonance at $\delta = 12.066$ ppm corresponds to the H5 and H20 protons as a reference for correction. $\delta = 8.371$ ppm is attributed to H 6 and H 21, $\delta = 8.784$ ppm is ascribed to H 1, H 3, H 16 and H 17, $\delta = 7.818$ ppm belongs to H 2, H

4, H 18, and H 19, because H 1, H 3, H 16, H 17 and H 2, H 4, H 18, H 19 have strong correlation in 2D COSY NMR. δ = 7.527 ppm is attributed to H 9, H 10, H 24 and H 25, δ = 7.179 ppm is ascribed to H 7, H 8, H 22 and H 23, because of their strong correlation in 2D COSY NMR. These proton signals with δ = 7.162-7.051 ppm belong to H 13, H 14, H 15, H 28, H 29, H 30, δ = 7.015 ppm was assigned to H 11, H 12, H 26, H 27, respectively. As shown in Fig. 2C, the cross-peaks in the blue circles suggest distinguished correlation between H 9, H 10, H 24, H 25 and H 11, H 12, H 26, H 27, which reveals ring A and ring C is very adjacent in space, and verifies they are on the same side of the double bond. At the same time, the correlation of these hydrogen was not observed in the 2D COSY NMR spectrum. In Fig.2F, since the A / C ring is far from the B / D ring in the Z isomer, there is no significant correlation between H 9, H 10, H 24, H 25 and TPE-INH-Z have the same molecular formula and different spatial configurations, therefore, their FTIR spectra are almost the same (Figure S22).

3.2 Photophysical properties in solution

After the structure was confirmed, the AIE properties of TPE-INH-E and TPE-INH-Z were investigated. They have good solubility in DMF and almost no fluorescence, but the hydrophobicity of aromatic rings makes them insoluble in aqueous solution and tend to aggregation. With the increasing of the water fractions (f_w) in the mixed solvent, TPE-INH-E and TPE-INH-Z gradually aggregate, and their fluorescent intensity progressively enhances at 510 nm thanks to the restriction of intermolecular rotation (Fig.3). When f_w was up to 99 %, its fluorescent intensity of TPE-INH-E was 35-fold

higher than that in pure DMF. The fluorescence enhancement of TPE-INH-Z at $f_w = 99$ % was 45 times stronger than that in pure DMF. Clearly, they displayed the same phenomenon under UV light (Figure S21). These results indicated that they have highlighted AIE characteristic. As shown in Fig.3C/F, the excitation spectrum of the TPE-INH-E was a narrow one, while the TPE-INH-Z was a broad spectrum when $f_w =$ 99 %, indicating that the excitation light source of the TPE-INH-Z was wider than TPE-INH-E. The UV absorption of TPE-INH-E and TPE-INH-Z have dramatic differences when they were dissolved in DMF, as shown in Fig.4B. The maximum UV absorption wavelength of TPE-INH-E were 286 nm and 355 nm, while that of TPE-INH-Z was 322 nm. Interestingly, the two isomers exhibited the similar AIE properties in the aggregated state, but obviously different UV absorption in the solution state.

Furthermore, the different photophysical properties of the isomers inspire us to research their self-assembly behaviors in the aggregation state (50 μ M, $f_w = 99$ %). TPE-INH-E formed nanofibers and TPE-INH-Z formed a sheet-like particle that can be observed by SEM (Fig. 5 C/D). We believed that TPE-INH-E and TPE-INH-Z may form polymers with different structures upon linking their molecules through intermolecular forces. To gain more insight into the structure-property correlations, we analysed the single crystal structures of TPE-INH-E and the theoretical calculation of TPE-INH-Z according to density functional theory (DFT) on the basis of the B3LYP / 6 311G(d) method in the Gaussian 09 program. As shown in Fig. 5, TPE-INH-E has a strong hydrogen bond interaction with adjacent molecules, and this intermolecular force make it forms long periodic linear polymers by side-by-side association, thus, it

tends to form nanofibers. The optimization of theoretical results demonstrated that TPE-INH-Z is easy to form dimer, which aggregation is apt to form particles. The different aggregation morphologies of isomers are consistent with their differences in polymerization, which indicates that the slight change of TPE configuration will have a great influence on the self-assembly behavior.

3.3 Mechanochromic property

Interestingly, the isomers displayed distinctly different emission in the solid-state. TPE-INH-E was light green-emitting, with fluorescent spectrum peaked at 489 nm, while TPE-INH-Z presented light blue fluorescence at 469 nm. The excitation spectrum of TPE-INH-E was broad (370-440 nm), while that of the TPE-INH-Z was narrow (370 nm), as shown in Fig.4A. The excitation wavelength of the two molecules in the aggregation state was significant different with that the solid state. Compared with TPE-INH-Z, the emission wavelength of TPE-INH-E has a red shift of 20 nm, which may be due to the large interaction (C-H \cdot \cdot N) between the TPE-INH-E molecules, while TPE-INH-Z has strong intramolecular (C-H· · · N) and molecular-molecular interactions (C-H \cdot · N, C-H \cdot · O) (Fig.5A/B). The fluorescence radiative rate constant (k_r) and non-radiative rate constant (k_{nr}) were estimated by combining the results of quantum yield [$\Phi = k_r / (k_r + k_{nr})$] and fluorescence lifetime [$\tau = (k_r + k_{nr})^{-1}$]. TPE-INH-Z (20.20 %, 2.69 ns) has a longer fluorescence lifetime than TPE-INH-E (31.69 %, 1.86 ns), but it has a low fluorescence quantum yield. The macroscopic optical difference E/Z isomers powder is relatively obvious, which was rarely reported. According to the formula, the $k_{\rm r}$ of TPE-INH-E isomer is calculated to be $0.75 \times 10^8 \ {\rm s}^{-1}$ and $k_{\rm nr}$ is

calculated to be $2.96 \times 10^8 \text{s}^{-1}$ in the pristine state. However, the k_r of TPE-INH-Z isomers is $1.70 \times 10^8 \text{ s}^{-1}$, which is higher than that of TPE-INH-E isomers. The k_{nr} of TPE-INH-Z isomers is $3.68 \times 10^8 \text{ s}^{-1}$, which is lower than that of TPE-INH-E isomers. These suggests that the molecular packing of isomers produces different optical properties by combining the non-radiative decay process with the radiative transition (Table 2).

The controllable mechanochromic behaviour of organic molecules have attracted much attention because of their potential applications in sensors, logic gate units, memories and security inks, etc [31-35]. The two isoniazid-substituted TPE derivatives have prominent fluorescent response when they suffered from grinding stimuli. As shown in Fig.6, the fluorescence changed from light green to yellow when TPE-INH-E was subjected to grinding, while the fluorescence of TPE-INH-Z transformed from light blue to yellow, and then the fluorescence turned back to its original after being fumed by DCM vapor.

The mechanocharomic properties of TPE-INH-E and TPE-INH-Z were studied by emission and UV absorption spectrum in detail. In Fig. 7C/D, the solid UV absorption indicated that the maximum absorption wavelength showed blue shifted after grinding, which could be caused by the destruction of the π - π stack between molecules and the change of the packing mode. The TPE-INH-E isomers at the pristine state emitted at 489 nm, which displayed red-shifted emission peak at 520 nm upon grinding. It can return back to the original state after being fumed by DCM vapor. Under the same conditions, the fluorescent emission red-shifted of TPE-INH-Z isomers solid from 469

nm to 520 nm. The red shift wavelengths of they are 31 nm and 51 nm, respectively (Fig. 7A/B). Their fluorescent emission change was reversible and recyclable when TPE-INH-E and TPE-INH-Z repeated grinding-fuming by DCM process, as shown in Figure S24.

After being subjected to grinding stimuli, the fluorescence quantum yield, fluorescence lifetime of TPE-INH-E and TPE-INH-Z were all decreased. In addition, their non-radiative rate constant increased, these results indicated that the non-radiative decay process of the two isomers was activated when stimulated by grinding (Table 2 and Figure S23).

To better explain the different spectral properties between the luminogens, we further analyzed their structure by powder X-ray diffraction (XRD) measurement. As shown in Fig. 8A/B, the XRD patterns revealed that significant difference between TPE-INH-E and TPE-INH-Z powders but both of them have a series of sharp diffraction peaks. Upon grinding, their crystalline structure almost completely transformed into the amorphous state. The ground samples underwent recrystallization process with the original peak intensity and peak position recovery when the sample was fumed with DCM vapor. Distinctly, the reversible conversion between ordered crystal and amorphous state is very crucial to the switchable response of luminophor.

3.4 Theoretical study

We performed theoretical calculations on their energy levels by DET method at B3LYP/6-311G(d) basis in the Gaussian 09. The theoretical calculation results include

optimized molecular configuration, energy levels, electron distribution of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of TPE-INH-E and TPE-INH-Z, as shown in Fig. 9A/B. The electron of TPE-INH-E LUMO is mainly distributed on the isoniazid and benzene ring connected with isoniazid, while the electron cloud of HOMO is mainly distributed on the TPE center and conjugated bonds. The electron cloud of TPE-INH-Z LUMO is mainly distributed on the conjugated bond and benzene ring connected with isoniazid, and the electron cloud distribution of HOMO is the same as that of TPE-INH-E. The energy gaps of TPE-INH-E and TPE-INH-Z are 3.37 eV and 3.43 eV, respectively. Theoretical results distinctly declared that TPE-INH-E and TPE-INH-E and TPE-INH-E and TPE-INH-E and TPE-INH-E.

3.5 Fluorescence Probe for Cu²⁺

As a fundamental element of human body, copper was used by many enzymes to perform the functions of energy generation, neurotransmitter and pigment synthesis based on its redox activity [40]. The balance regulation of copper in the body is also connected with many diseases, including cancer, neurodegenerative alzheimer's disease and Parkinson's disease [40-41]. Copper ion is an important analytical material in biochemistry, medicine and environment, because of its bio-accumulation and destruction of the central nervous system, blood components, lungs, kidneys and liver in the human body [42]. Therefore, it is of great significance to establish a highly selective and sensitive method to detect Cu^{2+} in the environment [43-45].

The isoniazid contains rich heteroatoms, which provides the possibility of coordination with metal ions for TPE-INH-E and TPE-INH-Z. To demonstrate this possibility, metal ions such as Ag⁺, Cu²⁺, Ca²⁺, Co²⁺, Cr³⁺, Pd²⁺, Fe²⁺, Fe³⁺, Hg²⁺, Zr²⁺, Mn²⁺, Sn²⁺, Ni²⁺ and Zn²⁺ were added to the TPE-INH-E and TPE-INH-Z solutions of DMF/H₂O (4 μ M, 1/99, v / v), respectively. From the fluorescence spectrum (Fig. 10D and Figure S26D), it can be seen that there was a higher fluorescence quenching selectivity for Cu²⁺ in comparison with other metal ions, and the quenching efficiency of the TPE-INH-Z to the copper ions was higher than the TPE-INH-E, as shown in Figure S24.

In order to determine the conditions under which TPE-INH-E and TPE-INH-Z were used to detect copper ions, we investigated the response time of their fluorescence signals, as shown in Fig. 10C and Figure S26C. The fluorescence was almost completely quenched by adding copper ions to the TPE-INH-E and TPE-INH-Z aggregation solutions in about 1 minute. Then the fluorescence intensity remained stable for 5 minutes, which proved that the response was fast and stable. To evaluate the detective range of copper ion detection in the sensing system, the effects of Cu^{2+} on the fluorescence intensity of TPE-INH-E and TPE-INH-Z aggregation solutions were explored, as shown in Fig. 10A/B and Figure S26A/B. The fluorescence intensity of TPE-INH-E and TPE-INH-Z aggregation solutions decreased gradually at 510 nm with the increase of Cu^{2+} concentration, respectively. There is a linear relationship of log[(F- F_0)/ F_0] = 0.553 log (Cu^{2+})-0.212 and log[(F- F_0)/ F_0] = 0.648 log (Cu^{2+})-0.219 from 0.01 to 4 μ M for TPE-INH-E and TPE-INH-Z, respectively. The detection limit is 2

nM and 5 nM on the basis of a signal-to-noise ratio of 3:1, respectively. The presence of Cu^+ has no effect on the fluorescence signal, that it could be an excellent Cu^{2+} ion sensing material (Figure S27).

To investigate the practicability of Cu²⁺ sensing system, it was applied to detect the concentration of copper ions in the Green Lake water sample. When TPE-INH-E as detector, an average value of $0.59 \pm 0.05 \ \mu$ M of Cu²⁺ was found for n = 3 determinations, using this developed approach with good recovery (99.14 ± 1.19 %). The average concentration of copper detected was $0.54 \pm 0.07 \ \mu$ M (n=3) and the standard recovery rate was 99.59 ± 1.84 % when TPE-INH-Z was used as fluorescence probe (Table S1 and S2). It is indicated that TPE-INH-E and TPE-INH-Z have good reliability as probes for detecting copper ions in environmental samples.

Based on the response sensing mode driven by coordination. The morphology of TPE-INH-E and TPE-INH-Z aggregates changed significantly after the addition of Cu^{2+} , which changed from nanofibers to spherical and flaky structures to prismatic shapes, as shown in Fig. 11. The morphology of isomer aggregates in Cu^{2+} changed solution obviously after self-assembly due to the difference of spatial configuration. The fluorescence lifetime of TPE-INH did not change after the addition of copper ions, which revealed static quenching process (Figure S28).

In order to demonstrate the difference between the different isomers with the copper, we further studied their coordination of TPE-INH-E and TPE-INH-Z in the dissolved state with copper. TPE-INH-E and TPE-INH-Z (60 mg, 0.1 mmol) were dissolved in

(1 mL) DMF, and methanol solution containing copper nitrate trihydrate (15 mg, 0.05 mmol) was added into it, respectively. The green solid was obtained by static reaction for 2 days at 75 °C, and were successively washed by DMF and methanol for centrifugation. The green powder was dried overnight at 75 °C. They assembled into different complexes with significantly different peak positions by XRD measure (Figure S29). The two complexes did not emit fluorescence (Figure S30). In the FTIR spectrum, TPE-INH-E and TPE-INH-Z have the same absorption peak. The formation of intermolecular hydrogen bonds of TPE-INH-E in solid state caused two absorption peaks of N-H stretching vibration, which are 3442.46 cm⁻¹ and 3279.37 cm⁻¹(TPE-INH-Z 3422.77 cm⁻¹ and 3277.07 cm⁻¹), respectively. After coordinating with copper ions, the absorption peak of TPE-INH-E at 3279.37 cm⁻¹(TPE-INH-Z 3277.07 cm⁻¹) disappeared because the intermolecular hydrogen bond weakened or disappeared. The absorption peak of TPE-INH-E at 1288.69 cm⁻¹ (TPE-INH-Z 1292.62 cm⁻¹) is attributed to the interaction between the bending vibration of N-H and the stretching vibration of C-N. This interaction weakened after coordination, so this peak disappeared. The C =O absorption peak of TPE-INH-E at 1663.37 cm-1 (TPE-INH-Z 1665.74 cm⁻¹), and the electron cloud density around C=O changed after coordination, which led to the change of carbon-oxygen double bond force constant that caused the absorption to decrease. The C-N expansion vibration of TPE-INH-E at 1542.96 cm⁻¹ (TPE-INH-E 1546.26 cm⁻¹ ¹), the distribution of N-electron cloud after coordination changed, resulting in change of the C-N bond force constant so that the peak moved to 1384 cm⁻¹, and the absorption

is enhanced. These results indicated that the coordination between copper ions and ligands leads to the change of infrared absorption peak (Figure S22).

MALDI-TOF-MS also suggested the composition of the Cu-TPE-INH product (Figure S31). Unfortunately, only Cu-TPE-INH-E was detected. The peak at m/z =1501.999 was assigned to [Cu(TPE-INH-E)₂6H₂O(DMF)]+4H⁺, and the other two peaks were assigned to [Cu(TPE-INH-E)₂3H₂O(DMF)]+2H⁺(m/z = 1440.992) and [Cu(TPE-INH-E-8H)₂(DMF)]+H⁺ (m/z = 1382.373). Combined with fluorescence Job's plot, we recommend the stoichiometry of TPE-INH-E to Cu²⁺ may be 2:1. Cu-TPE-INH-Z has the similar Job's plot as Cu-TPE-INH-E, so we inferred that the stoichiometric ratio may be also 2:1(Fig. 10E and Figure S26E). The possible coordination structures as show in Figure S32.

4. Conclusions

In summary, pure stereoisomers of isoniazid-substituted TPE derivatives were synthesized with high yields and characterized by different spectroscopic techniques. The optical properties and aggregate self-assembly behaviours of the stereoisomers strongly depend on the configuration of TPE. They form different polymers due to intermolecular hydrogen bonding interactions. The stereoisomers with dramatic difference in fluorescence properties provide excellent references for further design and preparation of optical systems through covalent bonding strategies. Both compounds exhibited significant mechanocharomic behavior with different color change responses. Interestingly, such changes could be well recovered under mild fuming in DCM,

indicating their great potential for applications in practical devices. The two E/Z isomers compounds can function as fluorescent sensors for specific detection of Cu²⁺ due to the heteroatoms offered by the isoniazide unit. We believed that this work may open up a rational approach for developing a broad class of novel functional materials with photophysical functions. Considering that E/Z isomerization of TPE may change under special stimulation, the construction of smart materials using TPE-INH-E and TPE-INH-Z, whose photophysical properties and corresponding morphologies could be controlled by external stimuli, is of great significance and will be carried out in the future.

5. Conflicts of interest

There are no conflicts to declare.

6. Acknowledgements

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Scheme 1 Synthetic routes of TPE-INH-E and TPE-INH-Z.



Fig. 1 Crystal structures of TPE-2CHO-E (A) and TPE-INH-E (B).



Fig. 2 2D COSY-NMR (B/E) and 2D ROESY-NMR(C/F) of TPE-INH-E and TPE-INH-Z (A/D).



Fig. 3 Fluorescent spectra of TPE-INH-E (A) and TPE-INH-Z (D) (10 μ M, Ex=380 nm) in DMF/H₂O mixtures with different water fractions. The plot of the relative fluorescent intensity of TPE-INH-E (B) and TPE-INH-Z(E). Excitation and emission spectra of TPE-INH-E (C) and TPE-INH-Z (F) at f_w = 99 %.



Fig. 4 Fluorescence spectra (A) of TPE-INH-E and TPE-INH-Z in the solid state and UV spectrum (B) in DMF at a concentration of 10 μ M. Photographs of TPE-INH-E (C) and TPE-INH-Z(D) under UV light (Ex = 365 nm).



Fig. 5 (A) Intermolecular interactions of TPE-INH-E; (B) Optimized dimers formed by TPE-INH-E calculated on the basis of the B3LYP/6-311G(d) method in the Gaussian 09 program; SEM images of TPE-INH-E (C) and TPE-INH-Z (D) (50 μ M) in a mixed solvent of DMF/H₂O (f_w = 99 %).



Fig. 6 Fluorescent images of TPE-INH-E (A) and TPE-INH-Z (B) in different treatments: Pristine; Grinding at one side; Grinding all; Fumed by DCM.



Fig. 7 Fluorescent spectra of TPE-INH-E (A) and TPE-INH-Z (B): pristine, grind, and fumed by DCM. Solid UV absorption of TPE-INH-E (C) and TPE-INH-Z (D): pristine and grind.



Fig. 8 XRD patterns of TPE-INH-E (A) and TPE-INH-Z (B): pristine, grind, and fumed by DCM.



Fig. 9 Energy levels of LUMO and HOMO, energy gaps, and electron cloud distributions of TPE-INH-E (A) and TPE-INH-Z (B).



Fig. 10 (A)Fluorescence spectra of TPE-INH-E (4 μ M) in DMF/H₂O (1/99, v / v) in the presence of increasing concentration of Cu²⁺ (from 0 to 4 μ M). (B) Variation of the intensity ratio of TPE-INH-E (4 μ M, in DMF/H₂O) with increase in the concentration of Cu²⁺ for the determination of the detection limit, where F₀ and F are the intensities at 510 nm when the metal ion concentration is zero, each metal ion concentration was tested during titration, respectively. (C) Time-dependent fluorescence response of the TPE-INH-E (4 μ M) to Cu²⁺ in DMF/H₂O (1/99, v / v). (D) Bars denote the fluorescence intensity difference (F₀-F) in presence of a series of metal ions (20 μ M). (E) Job's plot showing 2:1 binding of TPE-INH-E with Cu²⁺.



Fig. 11 SEM images of TPE-INH-E (A)and (B) TPE-INH-Z after addition of Cu²⁺, respectively.

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	ТРЕ-2СНО-Е	TPE-INH-E			
Formula	$C_{28}H_{20}O_2$	C ₄₀ H ₃₀ N ₆ O ₂ , CH ₄ O			
<i>f</i> w [g∙mol ⁻¹]	388.44	658.74			
crystal color	Yellow	Yellow			
crystal system	Monoclinic	Monoclinic			
space group	<i>P</i> 2 ₁	<i>C</i> 2/c			
a [Å]	9.906(3)	17.187(4)			
b [Å]	9.130(3)	11.132(3)			
c [Å]	12.122(4)	35.991(10)			
β [deg]	105.470(9)	90.131(9)			
V [Å ³]	1056.6(6)	6886(3)			
Z	2	8			
ρ _{calcd} [g/cm ³]	1.221	1.271			
μ [mm ⁻¹]	0.076	0.082			
T [K]	150 K	100 K			
θ _{min} -θ _{max} [deg]	0.96-26.886	0.964- 24.407			

R/w*R* [I >2 $\sigma_{(1)}$] 0.0520 / 0.1325

0.1139- 0.2590

Table 1. Selected crystallographic data for TPE-2CHO-E and TPE-INH-E.

Name	Treatment	Em(nm)	Δλ (nm)	${\it I} \!$	τ (ns)	$k_{\rm r}/10^8({\rm s}^{-1})$	
$k_{\rm nr}/10^8({\rm s}^{-1})$							
TPE-INH-E	Pristine	489	31	20.20	2.69	0.75	2.96
	Grind	520		16.55	1.60	1.03	5.22
TPE-INH-Z	Pristine	469	51	31.69	1.86	1.70	3.68
	Grind	520		5.64	1.67	0.34	5.65

Table 2. Photophysical parameters of TPE-INH solids after different treatments.