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Research Article

Keywords: Intramolecular Charge Transfer, 1,3,4-thiadiazole, Schiff base, pH Fluorescent probe, Solvent-free grinding

Posted Date: September 18th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10776841/v1>

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Additional Declarations: No competing interests reported.

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ABSTRACT

A phenyl-1,3,4-thiadiazole Schiff base pH fluorescent probe TDP is fabricated via a green synthetic route based on intramolecular charge transfer (ICT). The aminothiadiazole intermediate is first obtained through cyclization catalyzed by concentrated hydrochloric acid, followed by solvent-free grinding to accomplish Schiff base condensation. This strategy avoids the use of large amounts of organic solvents, featuring a simple and efficient synthesis process. The response performance, photostability, reversibility and anti-interference capacity of the probe under various pH conditions are systematically investigated. The results reveal that the probe exhibits a pK_a value of 5.40, accompanied by obvious shifts of emission peaks with varying pH values, and it realizes sensitive, reversible and specific recognition towards acidic and alkaline environments. This synthetic route possesses the merits of controllable reaction, green efficiency and easy operation, and the as-prepared probe holds promising application prospects in practical samples.

Key words: Intramolecular Charge Transfer, 1,3,4-thiadiazole, Schiff base, pH Fluorescent probe, Solvent-free grinding

1. Introduction

pH is a core detection indicator in environmental monitoring, food analysis and biological microenvironment characterization. Industrial acid pickling wastewater, fruit and vegetable juices, as well as cellular lysosomes represent typical acidic systems. Accurate and rapid acidity detection is of great significance for ecological protection and food safety. Conventional pH detection techniques, including potentiometry, acid-base test strips and acid-base titration, generally suffer from limited sensitivity, incapability of in-situ fluorescence imaging and cumbersome operation. In contrast, small-molecule fluorescent probes have emerged as a research hotspot in the sensing field in recent years, owing to their fast response, low detection limit, visual readout and low sample consumption.

1,3,4-thiadiazole is a five-membered aromatic heterocycle containing two nitrogen atoms and one sulfur atom. The 1,3,4-thiadiazole skeleton possesses a unique conjugated delocalized system. The N and S heteroatoms on the ring exert strong electron-withdrawing inductive effects and p- π conjugation, endowing the ring with both electron-donating character and electron-deficient active sites. Functional groups such as aldehyde, amino and hydroxyl moieties can be introduced at the reactive C2 and C5 positions to construct structurally tunable derivatives with extended π -conjugation. Compounds based on 1,3,4-thiadiazole exhibit rigid planar molecular conformations, excellent photochemical stability, efficient charge transfer capability,

and abundant hydrogen-bonding and metal-coordination sites. Benefiting from the above structural merits, thiadiazole derivatives have been widely exploited in pH sensing, ion recognition, organic dyes, as well as pharmaceutical and agrochemical intermediates ^{Error! Unknown switch argument.}.

Traditional Schiff base probes suffer from poor reproducibility, signal drift ^{Error! Unknown switch argument.}, and severe interference from metal ions and organic impurities in aqueous media ^{Error! Unknown switch argument.}. Their conventional synthesis relies on ethanol reflux, which entails prolonged reaction duration, massive solvent consumption and complicated post-treatment, failing to comply with the principles of green chemistry ^{Error! Unknown switch argument.}. The solvent-free solid-state grinding method promotes reactions via intermolecular mechanical friction at room temperature, featuring straightforward manipulation, high yield and low pollution ^{Error! Unknown switch argument.}.

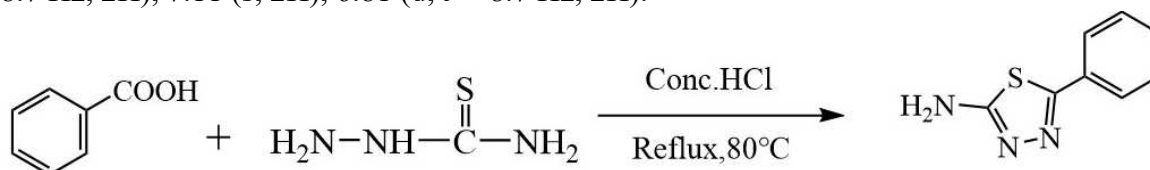
2 Materials and Methods

2.1 Instruments and Reagents

All chemical reagents used in the experiments were purchased from commercial suppliers and used without further purification. Melting points were measured on an X5 melting point apparatus (Taikang, Beijing) without temperature correction. Room-temperature UV-vis absorption spectra were recorded on a UV-1000 spectrophotometer. Fluorescence emission spectra were acquired using a Horiba FluoroMax-4 spectrofluorometer. Fourier-transform infrared (FT-IR) spectra ranging from 500 to 4000 cm⁻¹ were collected on a JEOL FT/IR-6800 spectrometer. ¹H nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker NMR spectrometer operating at 600 MHz with dimethyl sulfoxide (DMSO-d₆) as the deuterated solvent.

2.2 Synthesis of Intermediate DP

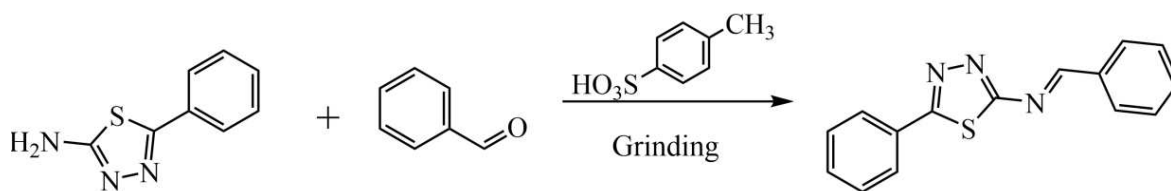
Scheme 1: 0.456 g thiosemicarbazide and 0.733 g benzoic acid were added into a round-bottom flask, followed by slow addition of 1 mL concentrated hydrochloric acid under stirring. The mixture was heated under reflux for 6–8 h with reaction progress monitored by thin-layer chromatography (TLC). Upon completion of the reaction, the system was cooled to room temperature. Distilled water was added to form a slurry, and dilute aqueous ammonia was dropwise added to adjust the pH to 8. The precipitate was collected by suction filtration and dried, then purified via recrystallization with an appropriate solvent to afford white solid DP (Figures S1–S2). Yield: 83% (0.736 g), m.p. 220–228 °C. IR (KBr pellet, cm⁻¹): 3375 (s), 3265 (s), 3174 (s), 1653 (s), 1530 (s), 1320 (s). ¹H NMR (600 MHz, DMSO-d₆): δ 7.78 (d, J = 8.7 Hz, 2H), 7.11 (s, 2H), 6.81 (d, J = 8.7 Hz, 2H).



Scheme 1 Synthetic route of DP

2.3 Synthesis of Target Probe TDP

Scheme 2: The solvent-free grinding method was adopted. 0.177 g 2-amino-5-phenyl-1,3,4-thiadiazole intermediate and 0.189 g p-toluenesulfonic acid (p-TSA) were placed in a dry mortar and ground to achieve homogeneous mixing. Subsequently, 0.127 g benzaldehyde was added, and grinding was continued until the reaction reached completion as verified by TLC. After the reaction, the crude mixture was transferred to a beaker, washed with deionized water and filtered under suction. The filter cake was dried and purified by recrystallization to yield white solid TDP (Figures S3–S4). Yield: 89% (0.236 g), m.p. 154–162 °C. IR (KBr pellet, cm^{-1}): 3060 (s), 1635 (s), 1544 (s), 1213 (s). ^1H NMR (600 MHz, DMSO- d_6): δ 8.48 (s, 1H), 7.99 (d, $J = 7.4$ Hz, 2H), 7.80 (d, $J = 3.6$ Hz, 2H), 7.64–7.59 (m, 6H).



Scheme 2 Synthetic route of TDP

2.4 Optical Performance Measurements

A 1 mmol/L stock solution of probe TDP was prepared with pure N,N-dimethylformamide (DMF). The fluorescence spectra of TDP in five solvents (methanol, ethanol, acetonitrile, DMF and DMSO) were compared. DMF was selected as the optimal single solvent due to its highest characteristic absorption intensity and stable spectral baseline (Figure S5). However, pure DMF exhibits poor water miscibility and cannot satisfy aqueous pH detection requirements. Therefore, Britton–Robinson (BR) buffer solution was introduced, and a DMF:BR volume ratio of 6:4 was determined as the optimal testing medium (Figure S6). Stock solutions (0.1 mmol/L) of various analytes, including cations (Li^+ , K^+ , Ca^{2+} , Ba^{2+} , Zn^{2+} , I^- , CH_3COO^- , F^- , SO_4^{2-} , $\text{S}_2\text{O}_8^{2-}$, SiO_3^{2-}) and amino acids (Gly, Ala, Val, Pro, Ile), were prepared with deionized water. UV–vis absorption spectra (200–600 nm) and fluorescence emission spectra (422–550 nm) of TDP were measured in DMF/BR mixed media (6:4, v/v) with different pH values. The excitation and emission slit widths were both set to 5 nm, and the excitation wavelength was fixed at 345 nm.

3 Results and Discussion

3.1 Molecular Design and Synthetic Mechanism of the Probe

The TDP probe was synthesized via a classic aldehyde-amine condensation route and features a typical push-pull D- π -A electronic configuration. The electron-rich 1,3,4-thiadiazole unit serves as the electron donor (D), the $-\text{CH}=\text{N}-$ imine bond and heterocycle form a continuous π -conjugated bridge, and the terminal phenyl group acts as the electron acceptor (A). The Schiff base $-\text{CH}=\text{N}-$ imine moiety functions as

the ion recognition site to modulate the intramolecular charge transfer (ICT) effect, ultimately generating spectral signal variations. The synthetic mechanism is illustrated in Figure 1.

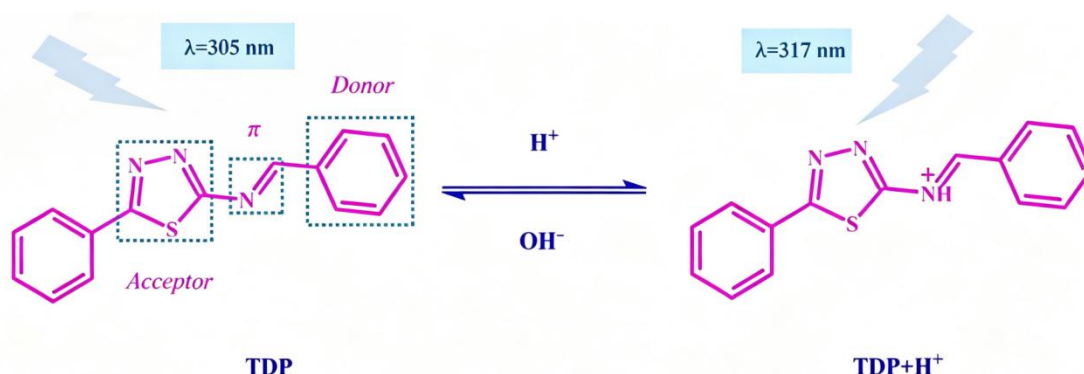


Figure 1 Protonated structure of TDP under acidic conditions

3.2 Spectral Performance Investigation

UV-vis absorption and fluorescence spectra of TDP were recorded at varying pH values to explore its pH-responsive behavior (Figures 2a and 2b). Under acidic conditions, the absorption and fluorescence emission peaks of the probe intensified, accompanied by a red shift of the UV-vis absorption band. To further characterize the pH response regularity of TDP, standard pH titration experiments were carried out over the pH range of 2.80–9.55, and fluorescence spectra were collected accordingly (Figure 2c). Reversible protonation occurs at the imine nitrogen atom; stronger acidity leads to a higher protonation degree of nitrogen and enhanced ICT efficiency, thus improving the fluorescence radiative efficiency. Consequently, the fluorescence emission intensity of TDP at 434 nm rises significantly with decreasing pH. The inset shows a magnified view of the main emission band, intuitively demonstrating the gradual attenuation of fluorescence intensity along the pH gradient. This observation indicates that the TDP probe realizes intensity-based pH response via reversible protonation–deprotonation equilibria, enabling quantitative discrimination of acidic and alkaline environments.

Fluorescence intensities at the primary emission peak were plotted against corresponding pH values, followed by nonlinear fitting with a sigmoidal S-type function (Figure 2d). The fitting equation is expressed as $y = A_2 + (A_1 - A_2) / (1 + \exp((x - x_0)/dx))$, with a correlation coefficient $R^2 = 0.9933$, revealing excellent consistency between experimental data points and the fitting curve and high fitting reliability. The fitted half-response parameter x_0 was determined to be 5.40 ± 0.08 , corresponding to the probe's $pK_a = 5.40$, which demonstrates that the optimal response window of the probe centers on weakly acidic conditions. The complete descending S-shaped fitting curve shows that fluorescence intensity declines smoothly and continuously as pH increases, proving that this thiadiazole Schiff base probe achieves continuous and sensitive quantitative acid-base identification within the pH range of 2.80–9.55.

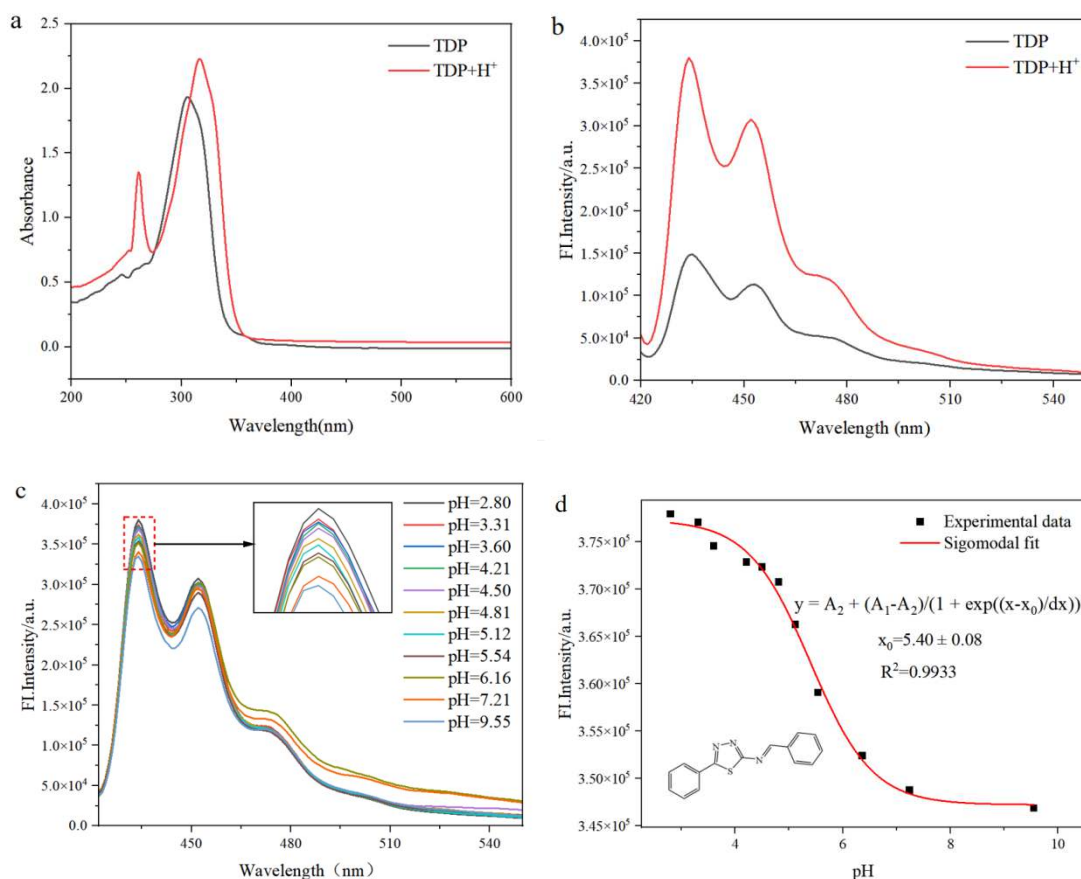


Figure 2 (a) UV-vis absorption spectra and (b) fluorescence spectra of 0.1 mmol/L TDP under different pH conditions; (c) Fluorescence spectra of 0.1 mmol/L TDP in buffer solutions with gradient pH values; (d) Sigmoidal fitting curve analysis.

3.3 Density Functional Theory (DFT) Calculations

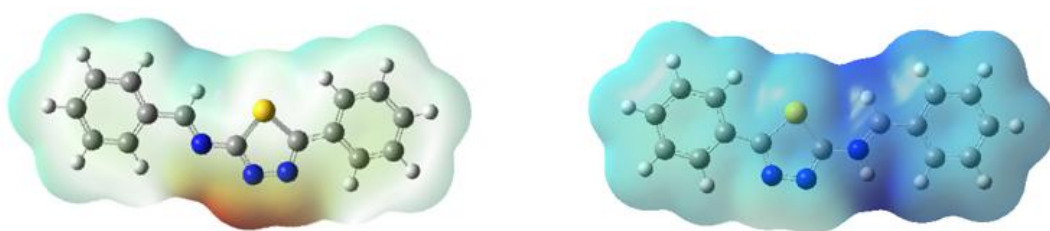
Density functional theory calculations were performed using Gaussian 09 software at the B3LYP/6-31+G(d,p) level to further elucidate the optical properties of TDP under acidic environments. Frequency analysis was conducted after geometric optimization to verify the absence of imaginary frequencies for all steady-state structures.

As displayed in Figure 3a, electrostatic potential calculations reveal prominent negative electrostatic potential distributed over the 1,3,4-thiadiazole heterocycle, which can attract hydrogen ions from the solution through electrostatic interactions to form hydrogen-bonded intermediates. Nevertheless, nitrogen-protonated thiadiazole species exhibit poor charge delocalization capacity and low thermodynamic stability, failing to stably capture hydrogen ions and produce reversible optical signals. Although the static negative electrostatic potential of the $-\text{CH}=\text{N}-$ imine nitrogen in the Schiff base is relatively weak, it bears lower steric hindrance. Moreover, positive charges generated upon imine nitrogen protonation can be effectively delocalized along the entire conjugated molecular skeleton, rendering the protonation-deprotonation process reversible. Therefore, the dominant binding site for pH

recognition in this probe is the imine nitrogen of the Schiff base -CH=N- double bond, while the thiadiazole ring nitrogen only assists hydrogen ion enrichment via electrostatic hydrogen bonding and does not govern the fluorescent pH response.

The optimized molecular geometries, HOMO/LUMO electron cloud distributions and orbital energy levels of neutral TDP and protonated TDP+H^+ are presented in Figure 3b. For neutral TDP, the HOMO electron cloud is mainly localized on the electron-donating 1,3,4-thiadiazole unit, whereas the LUMO orbital concentrates on the -CH=N- imine bond and the terminal phenyl acceptor segment, directly confirming the intrinsic intramolecular charge transfer (ICT) characteristic. The HOMO–LUMO energy gap of neutral TDP reaches 3.61 eV. After binding H^+ via protonation, both HOMO and LUMO energy levels shift downward dramatically to -9.62 eV and -7.17 eV, respectively, accompanied by obvious localization of orbital electron clouds and a narrowed energy gap of 2.45 eV. The reduced energy gap directly verifies the significantly strengthened ICT effect upon acidification, consistent with the red shift observed in absorption spectra. The sensing mechanism responsible for the reversible spectral pH response of the thiadiazole Schiff base probe is clarified at the theoretical level.

a



b

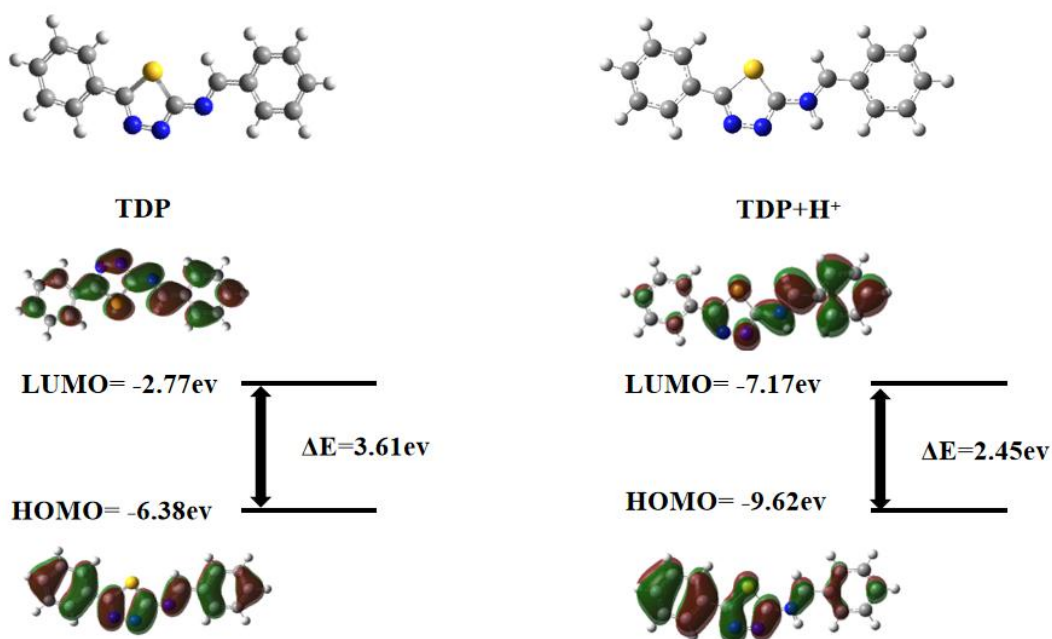


Figure 3 DFT calculation results of TDP and its protonated derivative TDP+H⁺

3.4 Anti-Interference Performance

At pH=3.60 and pH=7.24, various interfering species including Li⁺, K⁺, Ca²⁺, Ba²⁺, Zn²⁺, I⁻, CH₃COO⁻, F⁻, SO₄²⁻, S₂O₈²⁻, SiO₃²⁻, Gly, Ala, Val, Pro and Ile were separately introduced into probe solutions. Fluorescence intensities at 434 nm were recorded, as shown in Figure 4. No obvious variations in the characteristic emission peak position, peak shape or intensity were observed after addition of the above substances compared with blank control groups, demonstrating favorable specific recognition and robust anti-interference capability of the probe.

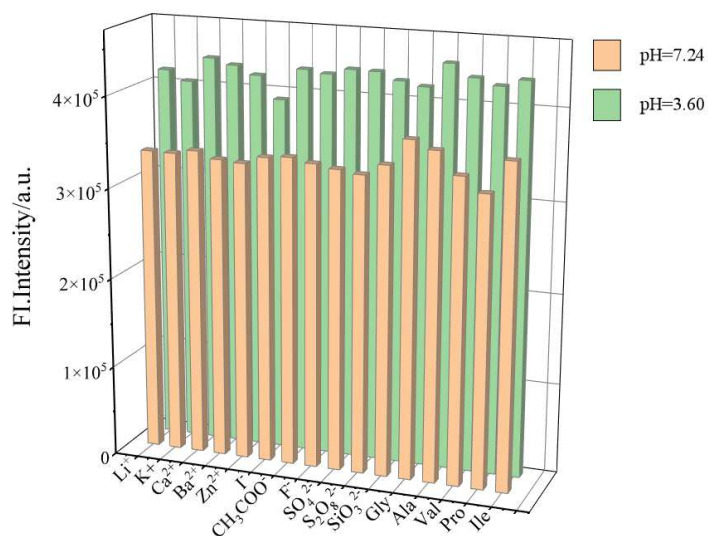


Figure 4 Anti-interference histograms measured at pH=3.60 and pH=7.12

3.5 Photostability and Reversibility

Photostability tests were carried out at pH=3.60 and pH=7.24. Fluorescence intensities at 434 nm were determined every 5 min at room temperature for a total duration of 90 min (Figure 5a). No obvious attenuation or drift of fluorescence intensity was detected, indicating outstanding photostability of the probe. Reversibility experiments were implemented by alternately adjusting the solution pH between 3.60 and 7.24 with BR buffer for five switching cycles (Figure 5b). Stable switching between high and low fluorescence signals with nearly identical response amplitudes was maintained throughout multiple acid-base cycles, without evident signal decay or response lag. This result confirms the fully reversible protonation–deprotonation reaction and recyclable utilization potential of the probe.

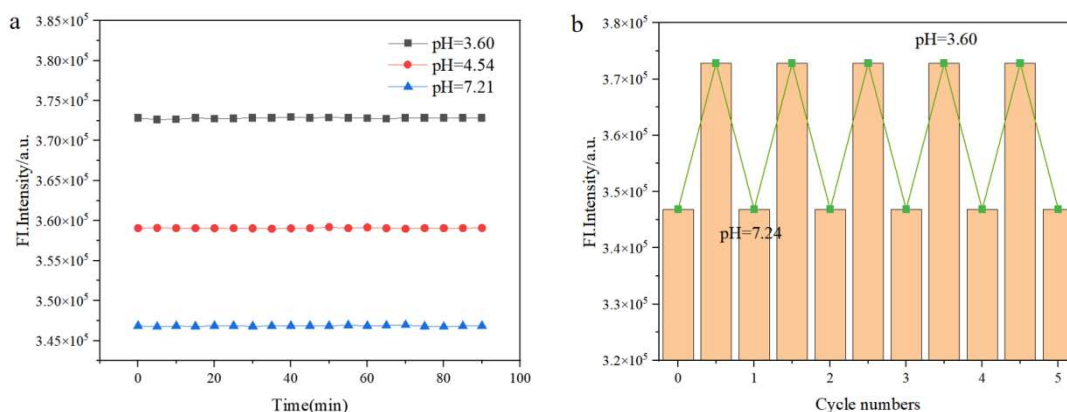


Figure 5 (a) Photostability curve of the probe; (b) Reversible acid-base cycling profile of the probe.

3.6 Sensing Mechanism

^1H NMR titration experiments were performed to clarify the pH-sensing mechanism of TDP toward acidic media (Figure 6). Upon protonation of TDP, the characteristic imine proton (H6) of the $-\text{CH}=\text{N}-$ group exhibits an obvious upfield shift. After the imine nitrogen atom captures a proton, redistribution of electron density across the molecular conjugated system occurs, triggering synchronous chemical shift displacements of aromatic proton signals on the adjacent aromatic rings (H1–H3, H4, H5, H9–H11). Particularly remarkable signal variations are observed for hydrogen atoms on the phenyl ring linked to the imine moiety, which verifies that protonation mediates electron transmission along the Schiff base conjugated skeleton. The reversible binding of hydrogen ions modulates molecular structures, and the ^1H NMR results confirm at the molecular level that the probe realizes fluorescent pH recognition via imine nitrogen acting as the primary binding site.

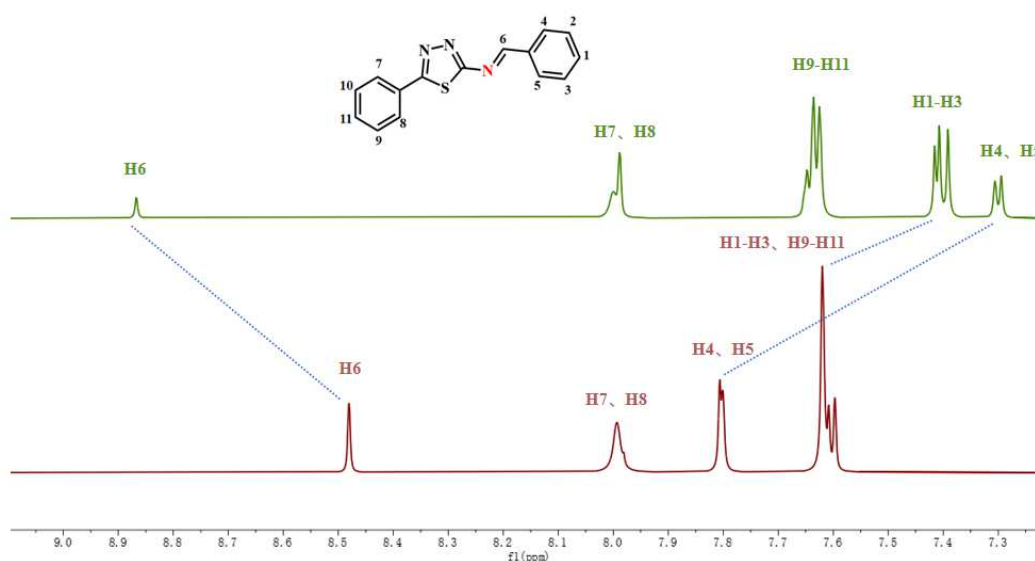


Figure 6 Comparative ^1H NMR spectra of free and protonated TDP. Red curve: pristine probe; green curve: protonated probe

3.7 Practical Sample Detection

The probe TDP was applied to pH detection of four commercial acidic beverages. Appropriate volumes of undiluted beverage samples were mixed with TDP stock solution, and fluorescence intensities at the characteristic emission wavelength of the probe were measured. As illustrated in Figure 7, stable and comparable fluorescence signals at 434 nm were obtained for all four acidic beverage matrices, which implies that coexisting additives and organic acids in drinks impose negligible interference on probe recognition. The measured pH values match well with those determined by a commercial pH meter. Combined with the analytical data summarized in Table 1, the relative standard deviations of parallel detection by the probe are all below 3%, reflecting excellent detection precision. These results prove that the probe can be utilized for rapid acidity quantification of real beverage samples.

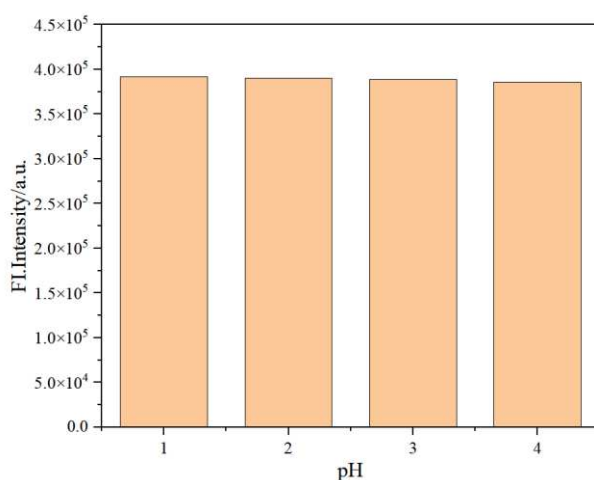


Figure 7 Fluorescent response of probe TDP in different beverage samples: (1) kumquat lemon flavored drink; (2) C100 lemon fruit juice; (3) lemon honey water; (4) Alien lime electrolyte drink.

Table 1 pH values of different beverage samples determined by probe TDP

Sample	PH-meter	PH-found
1	2.85±0.04	2.56±0.03
2	2.93±0.02	2.70±0.02
3	3.05±0.03	2.88±0.02
4	3.38±0.02	3.12±0.03

4 Conclusions

A novel 1,3,4-thiadiazole-based Schiff base fluorescent pH probe (TDP) was successfully synthesized via a green two-step route combining hydrochloric acid-catalyzed cyclization and solvent-free mechanical grinding. The proposed synthetic method features eco-friendliness, simple operation and high efficiency, affording TDP with a yield of 89%. The molecular structures of the intermediate and target probe were systematically characterized by FT-IR and ¹H NMR spectroscopy.

Spectral tests and DFT calculations revealed that TDP exhibits sensitive, reversible and specific fluorescence responses to pH variations in the range of 2.80–9.55, with a pK_a value of 5.40. The pH-sensing mechanism originates from the reversible protonation–deprotonation of the imine nitrogen atom on the –CH=N– bond, which modulates the intramolecular charge transfer (ICT) effect and regulates molecular orbital energy gaps, as further verified by ¹H NMR titration. The TDP probe possesses excellent photostability, cycling reversibility and prominent anti-interference performance against common coexisting ions and amino acids. Moreover, the probe achieves precise and reliable pH detection of commercial beverage samples with high accuracy. Benefiting from its green synthesis and excellent sensing performance, the TDP probe is a promising candidate for rapid pH monitoring in food safety and environmental water analysis.

Author Contributions

Yuting Liu: Writing-review & editing, Validation, Supervision, Project administration. Jiale He: Writing-original draft, Visualization, Formal analysis, Data curation. Dawei Yin: Resources, Supervision, Funding acquisition. Liangyan Qiao: Validation, Data curation. Qian Yu: Validation, Formal analysis. Shuaiqi Wang: Validation, Formal analysis.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are thankful to the Instrument analysis center of the Shaanxi University of Science & Technology for FT-IR, UV-Vis, Fluorescent, and ¹H NMR. The authors gratefully acknowledge the financial support from the Key R & D Program in Shaanxi Province of China (2026GY-162, 2022NY-070)

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