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A TURN-OFF FLUORESCENT CHEMOSENSOR FOR DETECTING FORMALDEHYDE BASED ON PYRIDINE DERIVATIVE

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Abstract

Formaldehyde in solution, commonly known as formalin, is often utilized. In Indonesia, there is widespread misuse of formalin as a food preservative. Formaldehyde has been identified as a carcinogenic substance by the International Agency for Research on Cancer (IARC) and the Environmental Protection Agency (EPA). Based on this background, the present study developed a sensor compound capable of detecting formaldehyde obviously. The compound 3'-(4-(3,4-dimethoxyphenyl)pyridine-2,6-diyl)dianiline (ChP-2A) has been successfully synthesized through the reduction reaction of the compound 4-(3,4-dimethoxyphenyl)-2,6-bis(3-nitrophenyl)pyridine (ChP-0A) using 80% hydrazine hydrate and 10% Pd/C as a catalyst. The ChP-2A compound in acetonitrile exhibits a significant decrease in fluorescence intensity (turn-off) after the addition of formaldehyde, and it has been successfully applied in the form of a test paper for the detection of formaldehyde qualitatively.

INTRODUCTION

At the end of 2005, Indonesian society was concerned about the discovery of a chemical substance known as formalin in food products such as tofu, meatballs, wet noodles, chicken, and fresh fish. The addition of formalin is intended to preserve food so that it does not spoil easily. Formalin is 37% formaldehyde in water and a basic ingredient for making biocides, preservatives, plastics, building materials, adhesives, medicines, and cosmetics [1]. In 2004, the International Agency for Research on Cancer (IARC) and the Environmental Protection Agency (EPA) stated that exposure to formaldehyde over a long period could endanger human health because it is carcinogenic [2]. Based on this background, it is important to develop a sensor that can be used to detect formaldehyde. A chemosensor is a chemical compound that can function as a sensor due to the interaction between the analyte and the sensor molecule. The interaction is followed by a change in color, emission, or reduction potential [3]. A chemosensor has two important sites: the binding site, which is employed to bind to the analyte, and the signaling site, which plays a role in the change of spectroscopic characteristics (color or fluorescence) or electrochemistry. The response of the color change can be observed qualitatively and quantitatively using a spectrophotometer.

Formaldehyde can be detected by several methods, namely spectrophotometry, chromatography, and enzymatic. Chromatographic and enzymatic methods require complex equipment, making the analysis relatively expensive and time-consuming [4]–[9]. On the other hand, spectrophotometry is more economical, simple, and quick for routine formaldehyde analysis. Spectrophotometry in formaldehyde detection is divided into two methods: colorimetry [10]–[16] and fluorometry [17]–[35]. Some literature studies have shown that fluorometric has greater sensitivity than colorimetric [36]–[38].

In previous work, we reported on the formaldehyde sensor based on a pyridine derivative, 3,3'-(4-(2-amino-4,5-dimethoxyphenyl)pyridine-2,6-diyl)dianiline (**ChP-3A**), which exhibited a turn-on fluorescence response. Computationally, the amino group positioned at *the para* and *meta* positions of the methoxy group on the phenyl ring did not participate in the reaction with formaldehyde when the **ChP-3A** sensor compound was exposed to formaldehyde. Based on these research findings, we have developed a new pyridine derivative sensor compound, 3,3'-(4-(3,4-dimethoxyphenyl)pyridine-2,6-diyl)dianiline (**ChP-2A**), which features two amino groups as the binding sites for the chemosensor. This new sensor compound exhibits an opposite response compared to the previous sensor, as it demonstrates turn-off

fluorescence for formaldehyde detection (**Figure 1**).

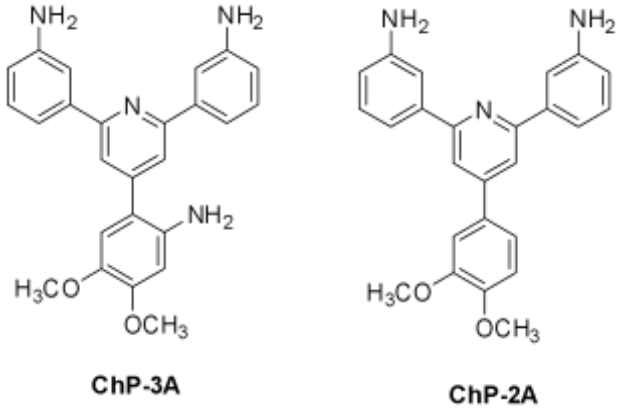


Figure 1. Chemical structure of **ChP-3A** and **ChP-2A.**

EXPERIMENT

Materials

The materials used for synthesis include veratraldehyde, ammonium acetate, glacial acetic acid, 80% hydrazine hydrate, 10% Pd/C catalyst, and ethanol solvent. The solvents used for formaldehyde sensor testing via fluorometry are a 37% formaldehyde solution, acetonitrile solvent, and dimethyl sulfoxide (DMSO). All the materials and solvents used are pro-analysis grade from Merck, except for distilled water.

Procedures

*Synthesis of 4-(3,4-dimethoxyphenyl)-2,6-bis(3-nitrophenyl)pyridine (**ChP-0A**)*

Compound 4-(3,4-dimethoxyphenyl)-2,6-bis(3-nitrophenyl)pyridine was synthesized based on the modification method by [39]. Ammonium acetate (1 g) and glacial acetic acid (2.5 mL) were added to a three-necked flask. The mixture was then heated and stirred at approximately 60°C until the solid completely dissolved. The compound *m*-nitroacetophenone (2 mmol) and veratraldehyde (1 mmol) were gradually added to the mixture. After the addition was complete, the mixture was refluxed at 110°C for approximately 3 hours according to the TLC (Thin Layer Chromatography) control results. The refluxed result was cooled to room temperature and filtered with two washing processes. The first wash was performed using a 50% acetic acid solution, approximately 10 mL, followed by a second wash using cold ethanol (40 mL). The solid obtained from the filtration was purified through ethanol recrystallization and then dried in a desiccator. (Greenish white powder, 61.96%, 0.75 g, mp 217-218 °C). FT-IR (KBr) υ (cm^{-1}) 1142 and 1026 (C-O-C), 1258 (C-N), 1605 (C=N), 2943 (C-H sp^3); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 3.97 (s, 3H), 4.02 (s, 3H), 7.05 (d, *J*=8.3 Hz, 1H), 7.23 (d, *J*=2.2 Hz, 1H), 7,35 (dd, *J*=8.3, 2.2 Hz, 1H), 7.72 (t, 2H), 7.96 (s, 2H), 8.32 (ddd, *J*=2.5, 5.5, 2.0 Hz, 2H), 8.56 (ddd, *J*=3.0, 8.0, 2.0 Hz, 2H), 8.98 (dd, *J*=2.0, 1.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C (ppm): 55.64, 55.84, 110.68, 112.09, 112.51, 114.77, 114.81, 115.87, 119.69, 129.12, 130.61, 139.83, 148.94, 148.97, 149.23, 149.85, 157.11; MS (EI) for $C_{25}H_{19}N_3O_6$ m/z: 457.0 (M^+).

*Synthesis of 3,3'-(4-(3,4-dimethoxyphenyl)pyridine-2,6-diyl)dianiline (**ChP-2A**)*

The reduction reaction of **ChP-0A** was carried out based on the modification method [39]. A solid of **ChP-0A** (1.2 mmol) was added to a three-necked flask containing 20 mL of ethanol. The mixture was heated and stirred at approximately 50°C and then added a Pd/C catalyst (0.08 g). The solution of hydrazine hydrate (1 mL in 2 mL of ethanol) was added slowly for 1 hour through a dropping funnel. After adding hydrazine hydrate was completed, the mixture was refluxed for approximately 2 hours at 78 °C. TLC (Thin Layer Chromatography) control was performed to ensure the formation of the reaction product. Once the reflux process was finished, the reaction mixture was filtered while still hot. The filtrate was cooled to induce a solid appearance. Then the solid was filtered and purified through a recrystallization process using a 50:50 mixture of ethanol and water. The obtained solid was subsequently dried in a desiccator. (White powder, 70.22%, 0.13 g, mp 206-207 °C). FT-IR (KBr) υ (cm^{-1}): 1142 and 1026 (C-O-C), 1258 (C-N), 1519 (C=N), 3456 and 3387 (NH_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H (ppm): 3.84 (s, 3H), 3.92 (s, 3H), 5.21 (s, 4H), 6.68 (ddd, *J*=1.5, 7.8, 2.0 Hz, 2H), 7.12 (d, *J*=8.5 Hz, 1H), 7.18 (t, 2H), 7.41 (ddd, J=2.5, 8.0, 3.5 Hz, 2H), 7.50 (t, 2H), 7.55 (d, J=2.0 Hz, 2H), 7.94 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C (ppm): 55.60, 55.80, 110.70, 112.1, 112.5, 114.8, 114.8, 115.9, 119.7, 129.1, 130.6, 139.8, 148.9, 149.0, 149.2, 149.9, 157.1; MS (EI) for $C_{25}H_{23}N_3O_2$ m/z: 397.0 (M^+).

*The Solvatochromic test of the **ChP-2A** toward Formaldehyde*

The synthesized chemosensor of **ChP-2A** was dissolved respectively in DMSO and

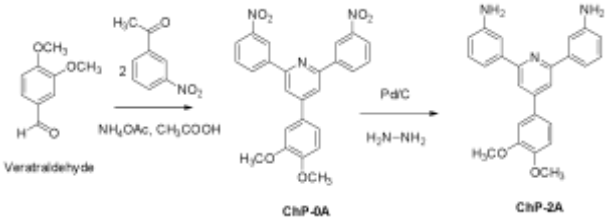
acetonitrile with a concentration of 1×10^{-4} M. Subsequently, 50 µL of 37% formaldehyde was added to each sensor solution (3 mL). The chosen solvents were capable of completely dissolving the chemosensor solid and providing significant color changes before and after the addition of formaldehyde. Observations were made directly by the naked eye and indirectly through a 365 nm portable UV lamp.

*Fluorescence spectra measurement of **ChP-2A***

The synthesized chemosensor of **ChP-2A (Scheme 1)** was dissolved in the appropriate solvent (based on solvatochromic test results) to make a concentration of 2.5×10^{-4} M. Each of the chemosensor solutions (4 mL) was transferred into a vial. Then 100 µL of a 37% formaldehyde solution was added. The intensity of the chemosensor solution was measured before and after adding formaldehyde using a spectrofluorophotometer.

Application of ChP-2A as test paper

The application of **ChP-2A** as a test paper was begun by preparing a sensor compound solution at a concentration of 1×10^{-3} M in an appropriate solvent. Whatman filter paper no. 42 is cut into a circular shape with a diameter of 2 cm. The paper circle is soaked in the prepared sensor solution for 15 minutes. After the soaking period, the paper circle is dried in an oven at approximately 78 °C for 1 hour. The dried paper circle can be used directly for formaldehyde testing.



Scheme 1. Synthesis route of **ChP-2A.**

RESULT AND DISCUSSION

The chemosensor of 3,3'-(4-(3,4-dimethoxyphenyl)pyridine-2,6-diyl)dianiline (**ChP-2A**) is the result of the reduction of the compound 4-(3,4-dimethoxyphenyl)-2,6-bis(3-nitrophenyl)pyridine (**ChP-0A**). The successful reduction process of **ChP-0A** to **ChP-2A** is shown by the characteristic absorption of the amine ($-NH_2$) at wavenumbers 3456 and 3387 cm^{-1} in the FT-IR spectrum. It is further confirmed by the appearance of a molecular ion peak at m/z 397 in the MS spectrum. The m/z value corresponds to the molecular weight of **ChP-2A**, which is 397 g/mol. The ^{1}H-NMR and ^{13}C-NMR spectra strengthen the success of the reduction process. The complete FT-IR, MS, and NMR spectra are in the supplementary file.

The solvatochromic test aims to select a solvent that can completely dissolve the sensor compound and provide significant color changes in the sensor solution before and after the addition of formaldehyde. This change is evidenced by the shift in wavelength or changes in fluorescence intensity. Based on the solvatochromic test in various solvents, the synthesized compound of **ChP-2A** dissolves completely in acetonitrile and DMSO. Between these solvents, acetonitrile exhibits significant changes before and after the addition of formaldehyde.

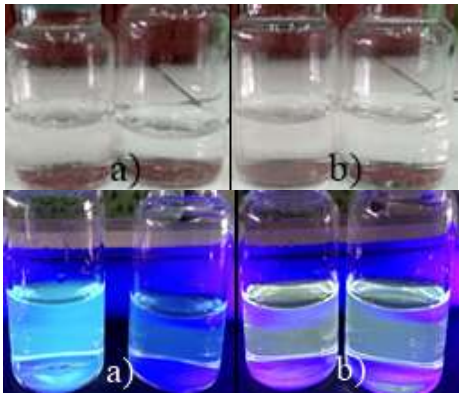


Figure 2. Photographs of **ChP-2A** solution (1×10^{-4} M in: **a)** acetonitrile, **b)** DMSO, before (**left**) and after (**right**) addition of 37% formaldehyde solution in daylight (**up**) and under 365 nm UV lamp (**down**).

Based on **Figure 2**, the **ChP-2A** solution in acetonitrile before and after adding formaldehyde shows a noticeable difference when observed under a 365 nm UV lamp. However, there is no apparent change when observed with the naked eye. The sensor solution before the addition of formaldehyde exhibits a bright blue fluorescence, while the addition of formaldehyde makes the solution dim and almost non-fluorescent. The results of the solvatochromic test were further confirmed using fluorescence spectra. The spectra were done to ensure that the binding site of the sensor compound, specifically the amine group, reacts with formaldehyde as a covalent bond to form an imine.

The fluorescence spectra in **Figure 3** show no significant wavelength shift at 478 nm before and after the addition of formaldehyde at an excitation

wavelength of 280 nm. However, an interesting observation is a drastic decrease in fluorescence intensity and the appearance of a small peak at a wavelength of 564 nm after adding formaldehyde. Based on the spectra, it can be concluded that the interaction between the chemosensor and formaldehyde quenched the fluorescence intensity. Therefore, the **ChP-2A** compound can be classified as a formaldehyde chemosensor with a "turn-off" response.

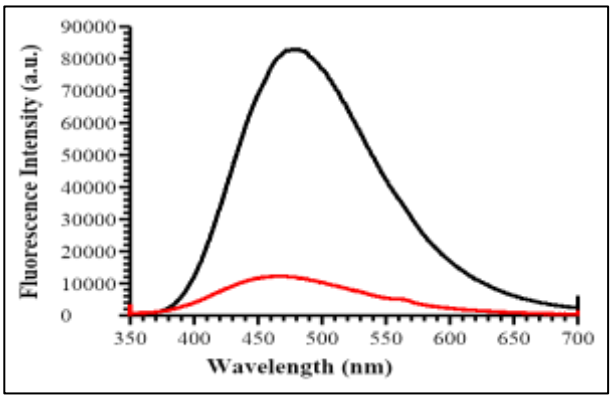


Figure 3. Fluorescence spectra of **ChP-2A** solution in acetonitrile (5×10^{-5} M) before (**black**) and after (**red**) addition of 2 M formaldehyde solution (100 µL) with excitation at 280 nm.

The sensor compound of **ChP-2A** was subjected to ^{1}H-NMR titration with formaldehyde solutions at concentrations of 0.4 and 1.2 M. The signal proton from the amine group (-NH_2) of the **ChP-2A** appears at a chemical shift (δ) of 5.21 ppm. The amine group in the chemosensor of formaldehyde is a bonding site that covalently bonds with formaldehyde, forming an imine. As shown in **Figure 4**, after adding 0.4 M and 1.2 M formaldehyde, new peaks appear in the ^{1}H-NMR spectra. The new peaks that appear at around δ 3.62 and 4.43 ppm correspond to the proton peaks of the formaldehyde compound [40]. In addition to the formaldehyde proton peaks, new peaks with smaller intensities appear in the ^{1}H-NMR spectrum of **ChP-2A** after adding formaldehyde at chemical shifts around 5.80 and 6.20 ppm. These two peaks indicate the proton signals of the imine resulting from the Schiff base reaction between the sensor of **ChP-2A** and formaldehyde. They appear as two peaks because the two protons from the methylene (=CH_2) have different chemical environments [28]. The addition of formaldehyde concentration affects the intensity of the imine and amine proton peaks. The higher the concentration of added formaldehyde, the greater the intensity of the imine proton peaks, and the smaller the intensity of the amine proton peaks detected in the ^{1}H-NMR. Based on the titration results of the proton NMR spectra of the **ChP-2A** chemosensor compound with formaldehyde, the possible reaction between the chemosensor and formaldehyde is presented in **Scheme 2**.

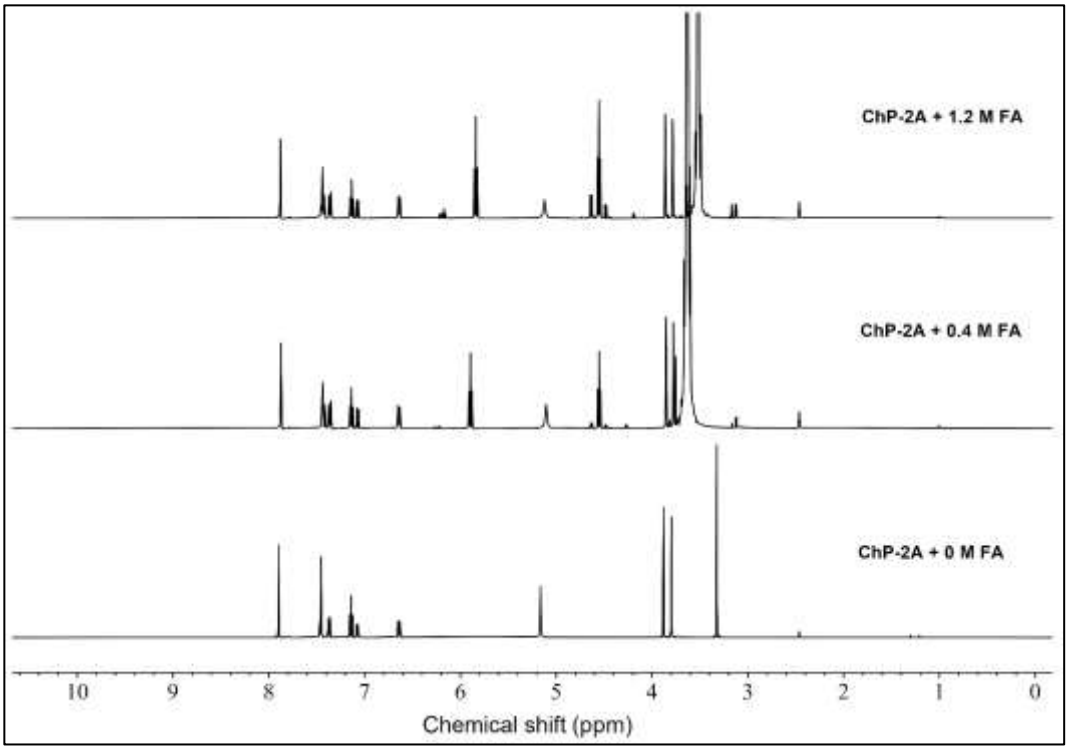
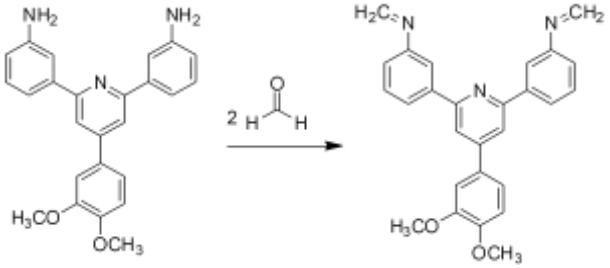


Figure 4. ^{1}H-NMR titration of **ChP-2A** toward formaldehyde in DMSO-d_6.



Scheme 2. Reaction of **ChP-2A** with formaldehyde.

A test paper was developed to support the qualitative detection ability of formaldehyde using the chemosensor **ChP-2A**. The test paper was filter paper that was loaded with a synthesized chemosensor. Water was added as a control since formaldehyde solutions are formaldehyde in water. **Figure 5** demonstrates that the test paper exhibited very weak fluorescence when treated with a formaldehyde solution, whereas the test paper treated with water as a control exhibited strong fluorescence. This phenomenon indicates that the chemosensor **ChP-2A** can be used to detect formaldehyde qualitatively.

Based on the fluorescence spectra, supported by proton NMR and the application of the test paper, it can be concluded that the imine compound resulting from the covalent interaction between formaldehyde and chemosensor **ChP-2A** quenched the fluorescence intensity. Therefore, the **ChP-2A** compound can be utilized as a "turn-off" chemosensor for formaldehyde detection.

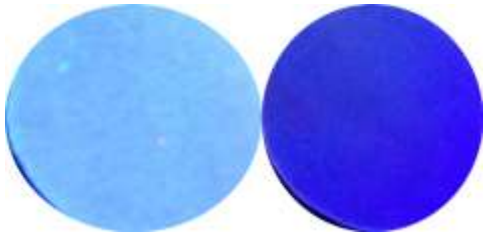


Figure 5. Photographs of **ChP-2A** as test paper after the addition of 2 M formaldehyde (**right**) and water (**left**) under 365 nm UV lamp.

CONCLUSION

The compound of 3,3'-(4-(3,4-dimethoxyphenyl)pyridine-2,6-diyl)dianiline **ChP-2A** can be used for the qualitative detection of formaldehyde and has been successfully applied to a test paper. The **ChP-2A** solution in acetonitrile shows a significant change before and after the addition of formaldehyde. Before the addition of formaldehyde, the **ChP-2A** exhibits strong fluorescence, while after the addition of formaldehyde, the **ChP-2A** solution exhibits very weak fluorescence.

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