Colorimetric chemosensor of symmetrical benzoylthiourea derivatives as for detection of Cu$^{2+}$ in aqueous solution

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Abstract. A novel receptor, designed with a combination of oxygen (O), nitrogen (N) and sulfur (S) -binding sites for metal ions was synthesized. Ortho (A), meta (B) and para (C) bearing benzyl thiourea were designed and synthesized with triamine group to apply as colorimetric chemosensors for detection of Cu$^{2+}$. The structure was confirmed by characterized the compound using Elemental analysis, Fourier Infrared (FTIR) and proton Nuclear Magnetic Resonance ($^1$H NMR) spectroscopy. Functional groups of C=O, N-H, C=N and C=S were found at 1677 cm$^{-1}$, 3240 cm$^{-1}$, 1591 cm$^{-1}$, 1024 cm$^{-1}$ respectively while $^1$H NMR shows peaks of alkane (CH$\_2$), benzene (Ar-H), CONH, CSNH at 3.68 – 4.14, 7.16 – 7.86, 8.74, and 9.2 respectively. Elemental analysis for A, B and C $C_{30}H_{33}N_{6}O_{8}S_{2}B_{2}$ found was compatible with the expected theoretical calculation. For an application, all of these three sensors showed excellent colorimetric specific selectivity and high sensitivity for Cu$^{2+}$ in acetonitrile/water binary solutions, so only A was selected for further studies towards sensitivity. When Cu$^{2+}$ was added to the solution of A, a dramatic color change from yellow to green, while other cations Fe$^{2+}$; Zn$^{2+}$, Ni$^{2+}$, Co$^{2+}$, Cr$^{3+}$ and Mn$^{2+}$ did not interfere with the recognition process for Cu$^{2+}$. The detection limit of the sensor C toward Cu$^{2+}$ was 1.15 x 10$^{-5}$ M, which is less sensitive that sensor A and B with a detection limit of 6.2 x 10$^{-6}$ M and 1.5 x 10$^{-6}$ M respectively. This indicated that the sensor A and B might be useful as an efficient chemical sensor.

1. Introduction
Thiourea derivatives are organosulfur compounds with the general formula (R$^1$R$^2$N)(R$^3$R$^4$N)C=S. In organic synthesis, thiourea derivatives are continuously increasing in numbers, due to their unique properties and synthetic simplicity. They have been extensively studied in coordination chemistry, and are known for various applications in the field of material science, agriculture, biological studies and pharmaceutical. The ability of thiourea derivatives to bind with metal ions via thiono group (C=S) make them applicable as ion sensors and transition metals extractors. In recent years, there were different types of sensor designed and synthesized to sense different types of metals such as multisubstituted hydrazone based Schiff bases as a sensor to detect F$^-$ and Cu$^{2+}$ [1], thiosemicarbazone-appended 3-hydroxynaphthalimide detect Cu$^{2+}$ [2], naphthalimide-based fluorescent chemosensor that detect Zn$^{2+}$ [3] and calix[4]arenes to detect Hg$^{2+}$ ion [4]. Copper (Cu) is an essential trace metal that is used as a catalytic cofactor for many enzymes. Copper is also a vital dietary nutrient, although only small amounts of the metal are needed for well-being. Although copper is the third most abundant trace metal in the body [behind iron and zinc], the total amount of copper in the body is only 75-100 milligrams. Copper is present in every tissue of the body, but is stored...
primarily in the liver, with fewer amounts found in the brain, heart, kidney, and muscles [5]. Despite this, Cu is dangerous when it is present in excess, mainly because it can participate in the Fenton reaction and produce free radical species. Many studies have reported that copper overload leads to the overproduction of reactive oxygen species (ROS) and the establishment of an oxidative stress condition that is responsible for the pro-oxidative damage of key proteins, lipids and DNA structure [6]. The present study aimed at the determination of the isomerization effect of the methyl group at ortho, meta and para positions of the three newly synthesized bromobenzoyl thiourea isomers, namely 1-(2-Bromo-benzoyl)-3-(2-{2-[3-(2-bromo-benzoyl)-thioureido]-ethylamino}-ethyl)-thiourea A, 1-(3-Bromo-benzoyl)-3-(2-{2-[3-(3-bromo-benzoyl)-thioureido]-ethylamino}-ethyl)-thiourea B and 1-(4-Bromo-benzoyl)-3-(2-{2-[3-(4-bromo-benzoyl)-thioureido]-ethylamino}-ethyl)-thiourea C on the spectroscopic data (UV-vis, NMR, FTIR and EA).

2. Methods

2.1. Reagents and physical measurements

The inorganic salts Fe(SO$_4$)$_2$.6H$_2$O, Mn(SO$_4$)$_2$, Cr(SO$_4$)$_3$.XH$_2$O, Co(Cl$_2$)$_3$.6H$_2$O, Ni(NO$_3$)$_2$.6H$_2$O, Cu(NO$_3$)$_2$.3H$_2$O and Zn(Cl$_2$)$_2$ were purchased from Sigma-Aldrich. All solvents and other reagents were of analytical grade. $^1$H NMR spectra were recorded on a Bruker Avance III 300 Spectrometer at room temperature. $^1$H chemical shifts were reported in ppm downfield from tetramethylsilane (TMS), d scale with the solvent resonances as internal standards. UV-vis spectra of compounds were recorded on a Perkin Elmer LAMBDA 25 UV-Vis spectrometer. Melting points were measured using BÜCHI Melting Point B-545 and the elemental analyses were conducted using CHNS Analyzer Flash EA 1112 series. The infrared spectra were performed using FTIR Perkin Elmer 100 Spectrophotometer in the spectral range of 4500-600 cm$^{-1}$.

2.2 General Procedure for UV-Vis spectroscopy

All the UV-Vis experiments were carried out in Acetonitrile solution on a Perkin Elmer LAMBDA 25 UV-Vis spectrometer. Any changes in the UV-vis spectra of the synthesized compound were recorded on the addition of sulfate, chloride, and nitrate metal salts while the ligand concentration was kept constant in all experiments.

2.3 Binding constant

The binding constant values for receptor towards Cu$^{2+}$ were calculated from the UV–Vis titration results using Benesi–Hildebrand (B–H) Eq. (1).

\[
\frac{1}{\Delta A} = \frac{1}{b\Delta e[G_0][H_0]K_a} + \frac{1}{b\Delta e[G_0]}
\]

where $\Delta A$ is the change in absorbance, $[G_0]$ is the concentration of the guest molecule, $[H_0]$ is the concentration of the host molecule and $K_a$ is binding constant. The plot can be made with $1/\Delta A$ as a function of $1/[H_0]$. $\Delta e$ can be derived from the intercept while $K_a$ can be calculated from the slope.

2.4 Synthesis and characterization of sensors A, B and C.

Preparation of 1-(2,3,4-Bromo-benzoyl)-3-(2-{2-[3-(2,3,4-bromo-benzoyl)-thioureido]-ethylamino}-ethyl)-thiourea (A-C). The 2,3,4-bromobenzoyl chloride (1.2 mL, ten mmol) was added dropwise to a stirring acetone solution (40 mL) with ammonium thiocyanate (0.76 g, 10 mol). A white precipitate of
NH₄Cl was formed immediately and was filtered. The filtrate then was taken to be added dropwise into diethyleneetriamine (0.5 mL, five mmol) in 40 mL acetone then put at reflux with constant stirring for 4 hours. The solution was poured into a beaker containing some ice blocks. Then, the resulting yellow precipitate was filtered and washed with little cold methanol, then dried in a vacuum desiccator. Finally, the crude product was purified by recrystallization from methanol to afford the title compound as colorless single crystalline solids.

**STEP 1** Preparation of benzoyl isothiocyanate

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{X} \\
\end{array}
+ \text{NH}_4\text{SCN} \rightarrow
\begin{array}{c}
\text{NCS} \\
\text{O} \\
\text{X} \\
\end{array}
+ \text{NH}_4\text{Cl}
\]

**STEP 2** Preparation of symmetrical ligand

\[
\begin{array}{c}
\text{NCS} \\
\text{O} \\
\text{X} \\
\text{X} \\
\end{array}
\text{H}
\text{H}
\text{N}
\text{N}
\text{H}
\text{H}
\text{H}
\text{H}
\text{N}
\text{N}
\end{array}
\]

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{O} \\
\text{S} \\
\text{S} \\
\text{X} \\
\text{X} \\
\end{array}
\text{X} = o/m/p- \text{Br}
\]

**Scheme 1** Synthesis of the symmetrical benzoylthiourea derivatives

A: Yield 52.8%; pale yellow solid, m.p 80°C. IR (cm⁻¹): \(\nu(C=O) 1673, \nu(N-H) 3230, \nu(C=C) 1589, \nu(C=S) 1025\). \(^1\)H NMR (600 MHz, CDCl₃-\(d_6\)) \(\delta 10.65 \text{ (s, CSNH, 1H)}, 8.98 \text{ (s, CONH, 1H)}, 7.14-7.66 \text{ (m, Ar-H, 6H)}\). Anal. Calc. for C\(_{21}\)H\(_{26}\)N\(_5\)OSBr: C, 40.90; H, 3.60; N, 11.92. Found: C, 41.42; H, 3.39; N, 11.83.

B: Yield 61.4%; pale yellow solid, m.p 158°C. IR (cm⁻¹): \(\nu(C=O) 1713, \nu(N-H) 3343, \nu(C=C) 1622, \nu(C=S) 1065\). \(^1\)H NMR (600 MHz, CDCl₃-\(d_6\)) \(\delta 10.85 \text{ (s, CSNH, 1H)}, 8.95 \text{ (s, CONH, 1H)}, 7.19-8.32 \text{ (m, Ar-H, 6H)}\). Anal. Calc. for C\(_{21}\)H\(_{26}\)N\(_5\)OSBr: C, 40.90; H, 3.60; N, 11.92. Found: C, 40.46; H, 3.62; N, 10.02.

C: Yield 54.2%; pale yellow solid, m.p 95°C. IR (cm⁻¹): \(\nu(C=O) 1668, \nu(N-H) 3263, \nu(C=C) 1589, \nu(C=S) 1008\). \(^1\)H NMR (600 MHz, CDCl₃-\(d_6\)) \(\delta 10.87 \text{ (s, CSNH, 1H)}, 8.98 \text{ (s, CONH, 1H)}, 7.28-8.06 \text{ (m, Ar-H, 6H)}\). Anal. Calc. for C\(_{21}\)H\(_{26}\)N\(_5\)OSBr: C, 40.90; H, 3.60; N, 11.92. Found: C, 41.12; H, 3.99; N, 12.26.
3. Results and Discussions

3.1 Absorption studies of receptors A, B and C.

The experimental maximum absorption bands of benzoylthiourea isomers A, B and C are showed in Figure 1 and Table 1. The experimental spectra were recorded in acetonitrile solvent (c \(5 \times 10^{-5}\) M). The maximum absorption bands at 250, 250 and 246 nm in A, B and C respectively, correspond to \(\pi \rightarrow \pi^*\) electronic transition. The solvent effect induces a hypsochromic shift (blue shift) of \(\lambda_{\text{MAX}} (\pi \rightarrow \pi^*)\) from ortho and meta (250nm) to para (246nm), which was shifted to shorter wavelength and higher energies. According to Woodward-Fieser Rules for Aromatic, it stated that a substituent will have a different effect depending on whether it is ortho, meta or para substituents. This rules also noted that the strongest effect is observed for para substituent. According to Chetana and co-workers, the electronic absorption spectra of compounds N, N’- disubstituted thiourea show two intense broad bands with maxima in the range of \(\sim 270\) and \(\sim 325\) nm; the high energy band can be attributed to ligand \(\pi \rightarrow \pi^*\) transitions on the pyridine and benzene aromatic rings, whereas the lower energy band can be considered as a thione originating calf thymus (CT) transition at the C=S bond [7].

![Figure 1 UV spectra of A, B and C; c= 5 x 10^{-5} M in acetonitrile, cell length = 1mm.](image)

**Table 1.** Experimental \(\lambda_{\text{MAX}}\) (nm) of \(\pi \rightarrow \pi^*\) transition of A, B and C benzoylthiourea derivatives.

| Sensor | \(\lambda_{\text{MAX}}\) (nm) |
|--------|-----------------|
| A      | 250             |
| B      | 250             |
| C      | 246             |

3.2 Absorption studies of receptors A B and C toward various cations.

All ligands A, B and C are more sensitive sensor towards Cu\(^{2+}\) ion than other metals such as Mn\(^{2+}\), Cr\(^{3+}\), Fe\(^{2+}\), Co\(^{2+}\), Ni\(^{2+}\) and Zn\(^{2+}\). The cation binding abilities of the different receptors were investigated by UV-vis spectroscopic titration in ACN/ H\(_2\)O (10:1/v:v) at pH 7.0. The colorimetric sensing abilities were primarily investigated by adding various cations (Cu\(^{2+}\), Mn\(^{2+}\), Cr\(^{3+}\), Fe\(^{2+}\), Co\(^{3+}\), Ni\(^{2+}\) and Zn\(^{2+}\)) to the ACN/ H\(_2\)O (10:1/v:v, pH 7.0) solutions of sensors. Addition of Cu\(^{2+}\) to the solutions (5.0 \(\times 10^{-5}\) M), was responded sensors with dramatic color changes from yellow to green while other cation did not induce any changes (Fig. 3) which is compatible with the UV-Vis results indicated that only Cu\(^{2+}\) ion...
can be detected by the sensors A, B and C. In the corresponding UV-vis spectrum (Fig. 2), the absorption peak of Cu$^{2+}$ were shifted from 250nm (A), 250nm (B) and 246nm (C) to a new peak appeared at visible spectra at 800 nm of Cu$^{2+}$ complexes formed, which attributed to the color change from yellow to green.

Fig. 2. UV-vis absorption spectra of A (a), B (b) and C (c) in the presence of various cations in ACN/H$_2$O (10:1, v:v, pH 7.0) solution at room temperature.

In order to exclude the possibility of these results being due to Cu$^{2+}$ self-absorption, a blank test were carried out via adding the same amount of Cu$^{2+}$ to blank ACN/ H$_2$O solution (without containing A, B or C) as a result, no color change were observed. In corresponding UV-vis spectra, there is no absorption peak appeared in the visible region (Fig. 2). It was confirmed that all sensor A, B and C
could colorimetrically detect Cu$^{2+}$ in ACN/ H$_2$O binary solution [8]. B and C show same result as A so only A was selected for further studies towards sensitivity to Cu$^{2+}$. A series of experiments was carried out to investigate the Cu$^{2+}$ recognition capability and mechanism of A.

![Color changes observed upon the addition of various cations to the solutions of sensor A (1.5 x 10$^{-3}$ M) in ACN/H$_2$O (10:1, v:v, pH 7.0) solutions. Left to right : free A, Co$^{2+}$, Fe$^{2+}$, Cr$^{3+}$, Mn$^{2+}$, Zn$^{2+}$, Ni$^{2+}$ and Cu$^{2+}$.](image)

Fig. 3. Color changes observed upon the addition of various cations to the solutions of sensor A (1.5 x 10$^{-3}$ M) in ACN/H$_2$O (10:1, v:v, pH 7.0) solutions. Left to right : free A, Co$^{2+}$, Fe$^{2+}$, Cr$^{3+}$, Mn$^{2+}$, Zn$^{2+}$, Ni$^{2+}$ and Cu$^{2+}$.

Job’s plot studies (Fig. 3) were done to find out the stoichiometry of the complex formed between the receptors and cations and it was found that the complex formed was in 2:1 stoichiometries. The molar fraction found of the complex A-Cu$^{2+}$ was 0.7. Moreover, the recognition mechanism of the sensor A with Cu$^{2+}$ was investigated by IR spectra titration methods. Based on IR spectra of A, the stretching vibration absorption peaks of cyanide C=N, acyl C=O and thiourea C=S appeared at 1589, 1673 and 1025 cm$^{-1}$ respectively. However, when A coordinated with Cu$^{2+}$, the stretching vibration absorption peaks of acyl C=O were shifted to 1698 cm$^{-1}$ while stretching vibration absorption peaks of cyanide C=N and thiourea C=S didn’t take place any shift. According to IR spectrum, it shows left shifted (higher wavenumber) with the higher energy of C=O that indicated A complexed with Cu$^{2+}$ via Cu$^{2+}$- N coordination bond only near to C=O as shown in Scheme 2. The secondary amine near to C=O will bind to the Cu$^{2+}$ because it may affect the C=O through back-bonding theory. The addition of metal should form a lower energy but for peak C=O, the higher energy of C=O formed might be affected by the back bonding of Cu$^{2+}$- N coordination bond that may shorten the C=O bond, lower the vibration or frequency of the bond. Due to the equation of $E=hc$, the frequency is directly proportional to the energy. The higher the frequency, the higher the energy present.

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Fig. 3. A Job plot of A and Cu$^{2+}$, which indicated that the stoichiometry of A-Cu$^{2+}$ complex was 2:1.
Scheme 2. The proposed reaction mechanism of the sensor A with Cu$^{2+}$.

From the UV-Vis absorption measurements, the binding constant ($K_a$) of the copper complex of the receptor is calculated from the variation in the absorbance at 800nm, respectively and is found to be 1.04 x 10$^4$ M. This may be due to the presence of electron withdrawing group (–Br) in it. This suggests that the receptor forms strong binding with Cu$^{2+}$ ion [1].

The detection limit for C (para) is lower than A and B that correspond to the maximum absorption bands of C which is shifted to shorter wavelength and higher energy. Higher energy may have a lower detection limit towards metal. The detection limit of metal ions by A, B and C was calculated from the plot of UV–Vis absorbance versus metal ions concentration. From the plot, detection limit was calculated using the formula $3\sigma/m$. Where ‘$\sigma$’ is the standard deviation and ‘m’ is the slope of the straight line. A calibration curve was obtained from the plot of UV-Vis absorbance with the addition of Cu$^{2+}$ concentration. The curve equation as shown in Fig. 5 was $R^2=0.9987$. The linear range of quantitative detection for Cu$^{2+}$ was determined as $2.5 \times 10^{-4}$ to $1.95 \times 10^{-2}$ M with a detection limit of $6.2 \times 10^{-6}$ M (sensor A), $1.5 \times 10^{-6}$ M (sensor B) and $1.15 \times 10^{-5}$ M (sensor C) for Cu$^{2+}$ from the curve in the used aqueous solution system. Thus all A, B and C can be utilized as an efficient Cu$^{2+}$ ion sensor at micromolar level. According to World Health Organization (WHO-1984), 1 mg/l of copper present in drinking water. Our sensor A detects copper in micromolar levels ($10^{-6}$ M/L) which is lower or equal to maximum permitted amount of copper in drinking water defined by World Health Organization [9].
Fig. 4. (a) UV spectra titration of sensor A, B and C (5 x 10^{-5} M) with Cu^{2+} (2.5 x 10^{-6} M - 1.5 x 10^{-4} M) in 10:1 ACN/H_{2}O (v/v) solution. (b) Visible spectral titration of sensor A, B and C (5 x 10^{-5} M) with Cu^{2+} (7.5 x 10^{-4} M - 1.95 x 10^{-2} M) in 10:1 ACN/H_{2}O (v/v) solution.
4. Conclusion

In conclusion, A, B and C benzoylthiourea derivatives were designed and synthesized to apply as a colorimetric sensor for Cu$^{2+}$ ion. This sensor showed specific selectivity for Cu$^{2+}$ in ACN/H$_2$O binary solutions indicated that benzoylthiourea also may act as a chemosensor and played a crucial role in the process of colorimetric recognition. Only sensor A was chosen for further studies due to the same selectivity towards metal of Cu$^{2+}$ ion. Investigation of the recognition mechanism indicated that the sensor A recognized Cu$^{2+}$ by forming a stable 2:1 A- Cu$^{2+}$ complex. The coexistence of other cations did not interfere with the Cu$^{2+}$ recognition process. Moreover, the detection limit of the sensor C toward Cu$^{2+}$ was 1.15 x 10$^{-5}$ M, which is less sensitive that sensor A and B with a detection limit of 6.2 x 10$^{-6}$ M and 1.5 x 10$^{-6}$ M respectively. The sensitive detection indicated that the sensor A and B may be useful for preliminary detection of Cu$^{2+}$ ions by simple solvent extraction in chemical and environmental applications.

Acknowledgements

We would like to thanks the Malaysian Ministry of Education (KPM) for providing generous financial support under RAGS grants: 600-RMI/RAGS 5/3 (2/2013) in conducting this study and Universiti Teknologi Mara (UiTM) for providing all the needed facilities.

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