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# Synthesis and Characterization of Iron(II)-4-aminobenzoic acid complex as Potent Antibacterial agent

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**Abstract :** Iron(II)-4-aminobenzoic acid complex was synthesized by mixing metal and ligand with a ratio of 1:6 in methanol and continue for drying at room temperature to obtain a dark-brown powder. According to spectrometry and thermogravimetry analysis, the complex formula is $Fe_3(PABA)_6.nH_2O$ with n=2. The conductivity measurement indicates a 2 to 1 ratio of cation to anion charge. The complex formula is estimated as $Fe_2[Fe(PABA)_6].2H_2O$. Infrared spectra and magnetic moment indicate that the complex is paramagnetic with octahedral geometry where PABA carboxyl group is coordinated to the Iron(II) center ion. Antibacterial activity test has been performed for 4-aminobenzoic acid (PABA) and $Fe_2[Fe(PABA)_6].2H_2O$. The results showed that the complex has a synergistic antibacterial activity against *S. aureus*and *E. coli.*
**Keywords :** 4-aminobenzoic acid, antibacterial activity, iron complex.

## Introduction

A 4-Aminobenzoic acid or simply PABA is an isomeric form of aminobenzoic acid, which consists of a carboxylic and amine functional group. PABA can exist in three forms (neutral, anion, and cation) according to the pH of the environment. PABA often found and as ligand bind to a metal ion. PABA has been applied to medical interest in the past decade, particularly related to its effects on microorganism metabolism. It has been reported that PABA has antibacterial activity against *E. coli* at lower pH. The inhibitory effect on bacterial growth is known related to the carboxylic functional group.Inhibition of bacterial enzymes is one common mechanism to induce the antibacterial activity of antibacterial compounds in drugs. Incorporating PABA into whey protein-based film led to inhibition of *L. monocytogenes, E. coli, and S. Typhimurium*at pH 5.2. The



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interactions of PABA in that edible film resulted in different diffusion rates leading to varying degrees of inhibition.PABA can enhance the antibacterial activity of antibiotics and other primary antibacterials in both topical and systemic use against *P. aeruginosa, E. cloacae,* and *S. aureus*by sub inhibit concentration combination which resulted in the synergistic effect[1].It is identified that PABA is a good candidate for imaging a broad range of bacterial infections. A radio-fluorinated analog of PABA has been developed for a rapid and noninvasive diagnostic tool to detect and locate *S. aureu*s infection and guide antimicrobial selection[2].PABA derivatives were reported for their potential inhibitory property against novel antibacterial targets. Thiosemicarbazones of PABA were synthesized and the hydroxamatederivates found to have good antimicrobial activity against *E. coli, K. pneumoniae, S. aureus, V. cholerae, and B. subtilis*[3].

The development of antimicrobial agents through structure design and modification is important to overcome widespread bacterial and fungal infection cases. The various synthetic methods mostly used to connect two or more active derivative compounds into the new structures to improve activity compared to the initial compounds. Synthesis and characterization of the metal-para-aminobenzoic acid complex have been studied as they possess antimicrobial activity against pathogenic microorganisms. The widespread use of metal transition complex as an antimicrobial in medicine has been developed for many years. The complexation of metal ions and ligands increases their biopotential activity compared to their simple form as the changes in their shape, size, charge density distribution, and/or redox potential [4]. These complexes consist of an array of ligand that has available electrons for donating towards positively charged metal ions, forming covalent bonds. The complex properties are associated with the nature and structure of the complexes. The mechanisms of action against the microorganism can be different depending on the complex, i.e. by occupy surface sites, penetrate the cell wall, and disturb different molecule targets. The different examples of selected metals with antimicrobial activity applications have been reported, including Cu(II), Zn(II), and Fe(II) complexes. The studies were performed to compare the antimicrobial activity of complexes with a specific ligand and different metal ions or vice versa as the nature of different metal ions and the donor sequence of the different ligands reveal can affect the biological activity of the compounds[5,6].

Some Metal(II)-PABA derivatives complexes were synthesized and tested for antimicrobial activity against *Staphylococcus sp.*, *Escherichia spp.*,and *Streptococcus spp.* The result showed that Mn(II), Fe(II), and Zn(II) complexes of dimethyldithiocarbamic and PABA had very good antimicrobial activity against these microbes which proving their potentials as broad-spectrum antimicrobial agents *in-vitro*[7].Metal(II) complexes derived from *β-diketone*and PABA were synthesized and characterized include infrared (IR) and electronic spectra measurement. Furthermore, the study result showed that Mn(II) and Fe(II) complexes have good reactivity that might be significant in the development of drugs against pathogenic microorganisms[8].Synthesis of Cu(II)-PABA complex had been performed and it was tested for antimicrobial activity by diffusion techniques. The result showed the complexation of PABA with Cu(II) has significant antimicrobial activity against *E. faecalis, S. aureus, B. subtilis,* and *L. monocytogenes* compared to PABA ligand[9].

Iron is an essential transition metal ion that can coordinate with organic molecules presentingantimicrobialactivity. This ion is possible to be used as an active drug carrier in the cell[5].Iron(II) participate in the Fenton reaction, which reacts with $H_2O_2$ to form reactive hydroxyl radical that can damage proteins and nuclear acids. Iron is an important element in the establishment of a pro-oxidant condition in the cell which led to cellular DNA damage. The microorganism's growth will be inhibited under the excessive concentration of iron. This exploration of the antibacterial mechanism of iron against bacteria becoming one of the bases used of Iron(II) complexes as antibacterial agents[10,11]. Thus, this study was performed to synthesize and characterize Iron(II)-PABA complex and observe its antibacterial activity against *E. coli* and *S. aureus*.

## Experimental

### Materials andInstrumentation

The chemicals and solvents used were analytical grades, purchased from Merck. Thechemicals used for synthesis materials include ferrous sulfate heptahydrate ($FeSO_4.7H_2O$), methanol, ammonia ($NH_3$), and 4-aminobenzoic acid (PABA). Other reagents such as dimethyl sulfoxide (DMSO), sodium hydroxide, MacConkey agar, and mannitol salt agar were used for the antibacterial activities test. Microorganisms tested in this study were *Staphylococcus aureus* and *Escherichia coli*.

The characterization was determined by appropriate instruments. The infraredmeasurement was done as KBR disc on Fourier Transform Infrared Spectroscopy (FTIR) prestige 21 Shimadzu from 4000 $cm^{-1}$ to 400 $cm^{-1}$. The elemental contents of ironwere analyzed by Atomic Absorption Spectrophotometer Shimadzu AA-6650. Crystal water content was measured with Diamond Perkin ElmerThermogravimetric Analysis. The determination of magnetic properties was tested using Magnetic Susceptibility Balance and electronic spectra were studied in the range 1000 - 200 nm with a Perkin Elmer spectrophotometer UV-Vis.

**Synthesis of Iron(II)-4-aminobenzoic acid complex**

Iron(II)-PABA complex was synthesized by mixing $FeSO_4.7H_2O$ and PABA in a mol ratio of 1:6. PABA was dissolved in methanol, then added with 1 M $NH_4OH$ topH 5.5. A 15 ml of $FeSO_4.7H_2O$in methanol solution(0.695 g; 2.5 mmol) was added dropwise to 30 mL methanol solution of PABA (2.055 g; 15 mmol) while stirring at Room Temperature. The solid product was filtered, washed with methanol, and dried in a desiccator. Yield: 77.56%. UV-VIS (MeOH, nm): 272. FTIR (cm−1): 3461 and 3363 ($NH_2$), 1312 (C-N) aromatic amine, 1675 (C=O), 1177 (C-O), 461 (M-O).

**Antibacterial Study**

The antibacterial activity of the metal, ligand, and Fe-PABA complex was determined with a disc diffusion technique according to the method described by Zakaria et al (2007)[12] with slight modifications. DMSO was used as a control. The compounds were dissolved in DMSO in 0.5, 5, 10, 25, 50,75,100% (m/v). A 10 µl of the solution was loaded into Whatman filter paper discs (6 mm diameter), dried, and placed in the Petri dishes which previously seeded with the test organisms(*S. aureus* in mannitol salt agarand *E. coli* in MacConcey agar). The plates were incubated for 1-3 days at 37$^oC$. After the incubation period, the size of the inhibitory zone around each disc was measurein mm. The average diameter of inhibitory zone was determined from the triplicate readings.

## Results and Discussion

**Synthesis of Complex**

Thecomplex of Iron(II)-4-aminobenzoic acid was obtained by the reaction of ferrous sulfate heptahydrate ($FeSO_4.7H_2O$) with 4-aminobenzoic acid (PABA)in methanol solution. The addition of ammonium hydroxide to PABAaims to control the pH.PABA found as anionic species at pH 5.5, shown in Figure 1[13].

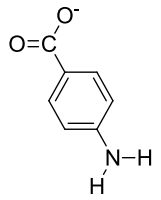


**Figure 1. Structure of PABA as anionic species**

Upon reaction, the color of the solution changed from a green Iron and a colorless PABA to dark brown powder. Complex precipitation was obtained with a yield of 77.56%. The molar conductance measurement of the complex corresponds to the 2:1 electrolytic nature of iron complex in methanol solution. The Iron(II) complex in methanol solution acts as $2Fe^{2+}$ : $[Fe(PABA)_6]^{4-}$. The analysis of iron content was 16.23% (cald. 16.43%). The electrolytic behavior further consolidated with the spectrometry analysis resulted in an agreement of the complex formulation as $Fe_2[Fe(PABA)_6].2H_2O$.

**Thermal Analysis**

The TG/DTA studies of the complexes were carried out in the temperature range 40-700$^oC$ with a sample heating rate of 10$^oC$/min under nitrogen atmosphere. Thermal degradation of the complexes occurred atfour stages presents in Figure 2.

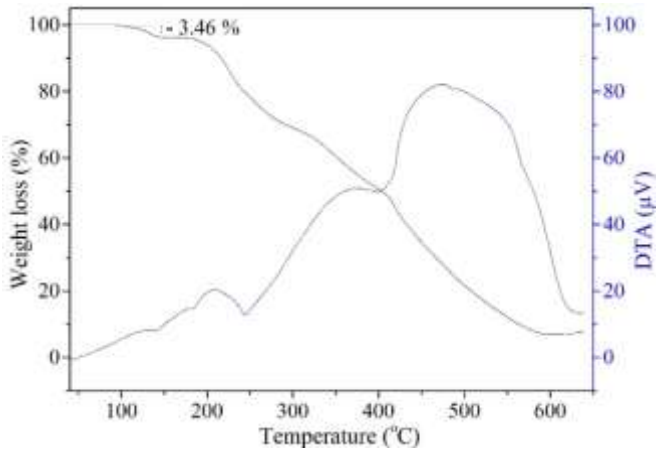


**Figure 2. Thermal analysis of $Fe_2[Fe(PABA)_6]. 2H_2O$**

The first decomposition stage occurred at a temperature range of 102-154°C with an endothermic peak at 138°C, which corresponds to the loss of uncoordinated lattice water.A loss of 3.46% agreed with the presence of two $H_2O$ molecules for $Fe_3(PABA)_6.2H_2O$ (cald. 3.53%). The further steps at178–564°C showed three endothermic peaks(186°C, 273°C, 428°C) and two exothermic peaksn(378°C, 504°C) as a result from the release of ligand moiety around the metal ion. Finally, the decomposition of the complex above 600°C has formed iron oxide.

**FT-IR Analysis**

4-Aminobenzoic acid (PABA) ligand is simple aromatic carboxylic acid and amine. It contains amino ($NH_2$) as donor group and the carboxyl acid ($COO^-$) as acceptor[14].Theν(C=O), $\nu_{sym}$(COO), and ν(C-O)stretching vibrations were observed at 1663, 1422, and 1773 for free ligand, while an aromatic amine was shown by two N-H stretching bands and C-N stretching band, listed in Table 1. The new ν($NH_2$) band in the metal complex did not shift significantly due to non-coordination of the PABA $NH_2$ to the metal ion.

**Table 1. Infra-reddata (4500-400 $cm^{-1}$) of PABA and $Fe_2[Fe(PABA)_6]. 2H_2O$**

| Compound | ν(N-H) | ν(C=O) | ν(COO) | ν(CO) | ν(C-N) | ν(M-O) |
|---|---|---|---|---|---|---|
| PABA | 3461 m<br>3364 m | 1663 s | 1422 s | 1173 s | 1312 s | - |
| $Fe_2[Fe(PABA)_6].2H_2O$ | 3461 m<br>3363 m | 1675 s | 1394 s | 1177 s | 1312 s | 461 w |

Band: s strong; m medium; w weak

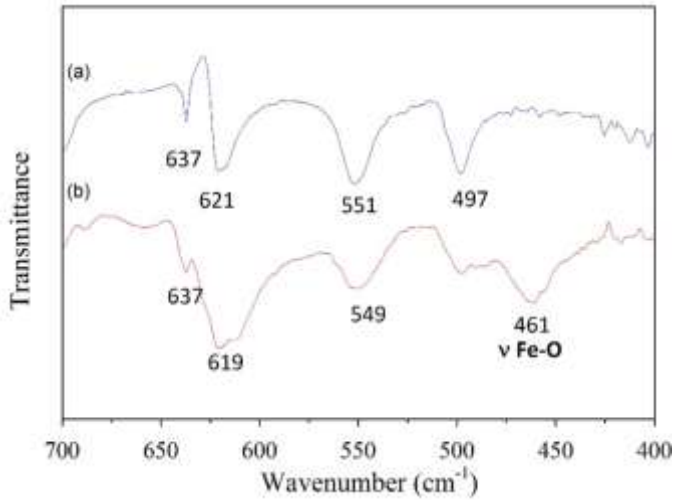


**Figure 3. Infrared spectra of PABA (a) and $Fe_2[Fe(PABA)_6].2H_2O$complex (b)**

The new band of the complex observed at 461 nm (Figure 3.). It can be attributed to ν(M-O) vibration[7].The participationof the PABA oxygen in coordination (M-O) is supported by the shifting ν(C=O) in free ligand tohigher 12 $cm^{-1}$wavenumbers in the complex. Therefore, the complex formation between ligand and metal occurred through the PABA carboxyl group,like the previous study of theMetal-PABA complex[7,9].PABA provides the lone pair electronsfrom the oxygen atom of carboxyl groups, resulting in a coordinate covalent bond to metal.

**Magnetic and Electronic Properties**

The $Fe_2[Fe(PABA)_6].2H_2O$ complex exhibits a moment ($\mu_{eff}$)at 4.81 B.M. It is lower than the $\mu_{eff}$of the high spin octahedral complex, which agreement of an octahedral geometry. In the splitting of *d* orbital in the octahedral field, the presence of unpaired electrons causes the paramagnetic characteristic of the complex with a magnetic moment of 4,9 BM ($\mu_{spin\ only}$).

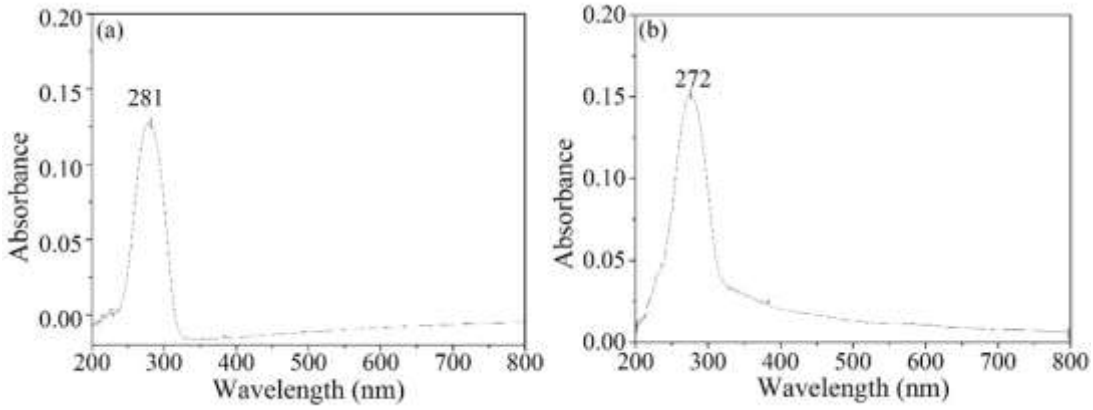


**Figure 4**. **Electronic spectra of PABA (a) and Fe-PABA complex(b) in methanolsolution**

The UV-Vis absorption spectra of PABA and complex were recorded inmethanol solution (Figure 4.). The band of PABA group that exhibited an absorption peak in the UV region at281 nm was shifted to 272 nm in complexation with metal, attributed to charge transfer (CT) transitions. Broadband observed in the spectrum of the complex was assignable to a combination of chargetransfer (CT) and weak *d-d* band transition which related to PABA involvement in complexation

**Antibacterial Activity**

Antibacterial activity test results showed that Dimethyl sulfoxide (DMSO) as negative control is a suitable inert solvent against tested bacteria, indicated by none of the clear zone found during the test. Based on inhibition zone diameter data, it showed that $FeSO_4.7H_2O$, PABA, and $Fe_2[Fe(PABA)_6].2H_2O$ complex have antibacterial activity against *S. aureus* and *E. coli* (Figure 5).Although no compounds showed antibacterial activity at a concentration of 0.5% for 24 hours but after 48 hours at the same concentration, only the complex produced a small inhibitory zone. Increased antibacterial activity is in-line with the concentration of compound used. The antibacterial activity for 48 hours and 72 hours werefound not significantly different. The optimum antibacterial activity was achieved on the 100% (m/v) $Fe_2[Fe(PABA)_6].2H_2O$ concentration for 48 hours diffusion time with inhibition zone against *S. aureus* and *E. coli* are 26 mm and 23 mm respectively.

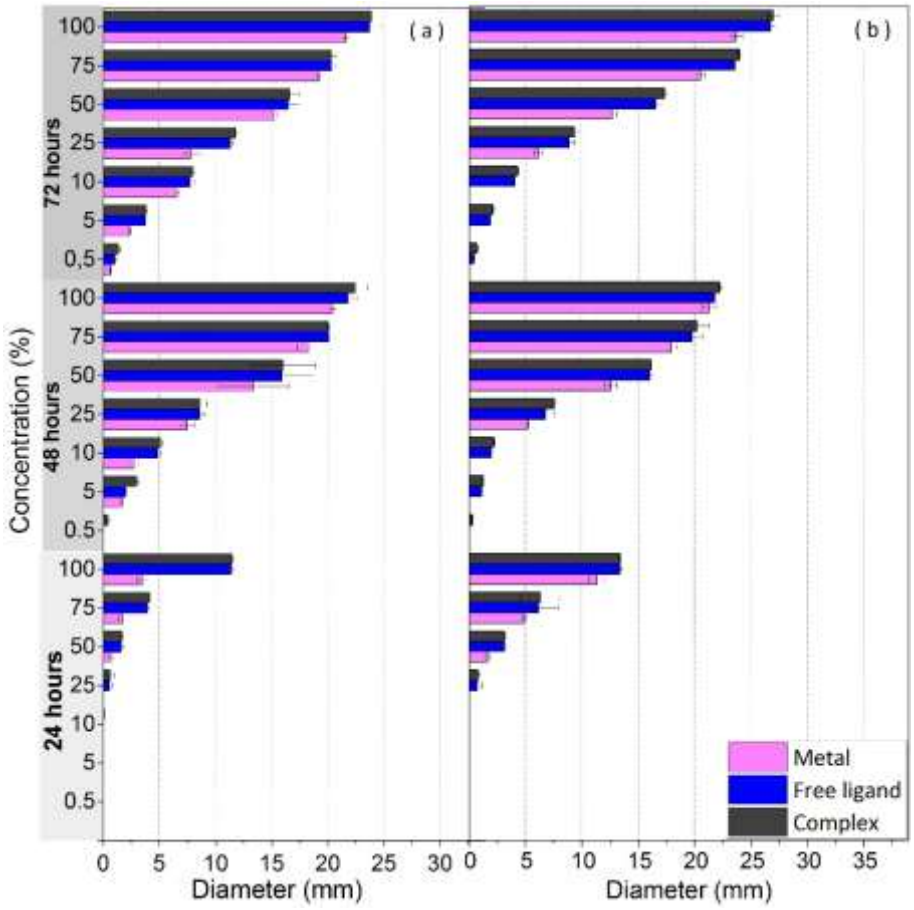


**Figure 5**.**Antibacterial activity test against *E. coli* (a) and *S. aureus*(b) for 24, 48, and 72 hours**

PABA is a weak acid and found most effective in the undissociated form that can increase its ability to penetrate the cytoplasmic membrane of bacteria. The damage of the bacterial cell membrane will disrupt cellular function leading to growth inhibition[15].PABA is applicable as a potent synergetic antibacterialfor the different bacterial strainsat low pH[16]. A lower pH increases the non-ionized PABA which enhances the compound absorption[17].It has been experimentally observed that the fastest PABA release kinetic was obtained at the acidic environment of pH 4[18]. In this study, Fe-PABA complex that dissolved in the dimethyl sulfoxide (DMSO) at pH 4.5 where$Fe_2[Fe(PABA)_6].2H_2O$ was ionized to Fe(II) and $[Fe(PABA)_6]^4$.Fe(II) further act as Fenton's reagent to introduce reactive oxygen species (ROS) through the reaction of peroxides with lipids and/or other macromolecules in the bacterial metabolism. This can induce hydroxyl radicals which are deleterious to cell and can damage DNA. It is suggested that they affect bacterial membranes, disrupting their vital activity, and causing cell death[19].

**Table 2.Antibacterial activities of PABA and Fe-PABA complex**

| **No** | **Compound** | ***S. aureus*** | ***E. coli*** |
|---|---|---|---|
| 1 | $FeSO_4.7H_2O$ | + + | + + |
| 2 | PABA | + + + + | + + + + |
| 3 | $Fe_2[Fe(PABA)_6].2H_2O$ | + + + + + | + + + + + |

Inhibition zone: + = 6-10 mm; + + = 10-14 mm; + + + = 14-18 mm; + + + + = 18-22 mm; + + + + + ≥ 22 mm

Based on the result presented in Table 2, $Fe_2[Fe(PABA)_6].2H_2O$ complex has better antibacterial activity than PABA ligand and Fe(II). PABA was active against *S. aureus* and *E. coli* with inhibitory zones range of 21-22 mm, while complex $Fe_2[Fe(PABA)_6]. 2H_2O$ shows better antibacterial activity with inhibitory zones of more than 22 mm. It shows the synergy of Fe(II) and PABA to

inhibit bacterial growth. The Fe-PABA complex was more active in the PABA ligand due to complexation reduces the polarity of the metal atom and increases lipophilic character. Thus supporting its permeation through lipid layers of the bacterial membrane[7,20].Most of the metal complexes of PABA had extra stability provided by hyper conjugation in the former related to the amino group at the 4$^{th}$ position[21].

The Inhibition activity of $Fe_2[Fe(PABA)_6].2H_2O$ complex against *S. aureus* (gram-positive bacteria) growth is higher than *E. coli* (gram-negative bacteria). Different bacterial cell walls structure and membrane components may affect the inhibition activity. Gram-negative bacteria are surrounded by outer membranes consist of lipopolysaccharides (LPS), lipoproteins, andphospholipids that form a penetration barrier whereas gram-positive bacteria contain a cytoplasmic membrane surrounded by a layer of peptidoglycan, teichoic acid, and pores that allow more easily penetration to damage cell membranes.LPS is the major component of the gram-negative bacteria outer membrane which creates an effective permeability barrier, while in contrast, teichoic acids that covalently linked to the peptidoglycan in the gram-positive bacteria bearing a strong negative charge[22].This allows a higher level of penetration of negatively charged free radicals causing antibacterial activity of Fe-PABA complex towards *S. aureus* is higher than towards *E.coli*[23].

## Conclusion

The synthesis and characterization of $Fe_2[Fe(PABA)_6].2H_2O$ complex has been described. PABA is coordinated with Iron(II) through carboxyl functional group. Fe(II), PABA ligand, and $Fe_2[Fe(PABA)_6].2H_2O$ complex were tested to assess their potencies as antimicrobial agents. The complex show greater antibacterial activity against *E.coli and S.Aureus* compared to parent compounds with inhibitory zones more than 22 mm. This suggested that the synergy of Iron(II) and PABA increases the capability to inhibit bacterial growth. Similar transition metal ion complexes can be good candidates for further synthesis and application as antibacterial agents.

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