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1. Journal of the Taiwan Institute of Chemical Engineers 68 (2016) 23–30
Contents lists available at ScienceDirect Journal of the Taiwan Institute of Chemical Engineers journal homepage: www.elsevier.com/locate/jtice
Synthesis, characterization, thermodynamics and biological studies of binary and ternary complexes including some divalent metal ions, 2, 3-dihydroxybenzoic acid and N-acetylcysteine Shella Permatasari Santoso a, Artik Elisa Angkawijaya b, Yi-Hsu Ju a,*

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ARTICLE INFO
Article history: Received 9 April 2016 Revised 1 July 2016 Accepted 1 August 2016 Available online 9 September 2016 Keywords: 2, 3-Dihydroxybenzoic acid Acetylcysteine Divalent metal Complex synthesis Metal–ligand Thermodynamic abstract The binary complexes with the [M(Dhba)]− core and ternary complexes with [M(Dhba)(Nac)]3− core have been synthesized and characterized by physical and spectral analyses, where M is 14valent metal (Mn2+, Co2+, Ni2+, Cu2+ or Zn2+) and Dhba and Nac are 2, 3-dihydroxybenzoic acid and N-acetylcysteine, respec- tively. The synthesized complexes are practical in biological applications since they are soluble in wa- ter. The synthesized complexes were found to possess enhanced antimicrobial activity, especially against Staphylococcus aureus, but reduced DPPH scavenging activity of Dhba. The binary and ternary complexes of Zn2+ were shown to possess the most remarkable properties thus their structures were further ex- amined. Thermodynamic properties of the Zn2+ complexes in aqueous solution at various temperatures were also determined

10with an ionic strength of 0.15 mol/
Synthesis of chelate complex drugs is one of the solutions to deal with pathogenic microbes which are becoming more and more drug resistance [1,2]. Bioactive organic ligands such as amino acids, phenolic acids and alkaloids coupled with essential metals are frequently employed in chelate complex synthesis [3–6]. 2, 3- Dihydroxybenzoic acid (Dhba) is an effective phenolic compound not only with regard to its biological ability such as antioxidant, antibacterial and anti-inflammatory [7,8], but also to its ability to form stable chelate complexes with various metal ions [9–11]. Therefore, Dhba was chosen as the ligand for the synthesis of metal–ligand binary complexes in this study. Ternary chelate complexes involving mixed ligands (Dhba and N-acetylcysteine (Nac)) were also synthesized. Nac was chosen as the consort ligand since it has been known to play an important role as a precursor of glu- tathione, an important antioxidant, and also known as potential sulfur replenishment for living organisms [12,13]. Moreover, Nac can form coordination compounds with metal ions [11,14,15]. In this study, binary and ternary complexes including Dhba, Nac and some divalent metal ions such as Mn2+, Co2+, Ni2+, Cu2+ and Zn2+ were synthesized and characterized. The chelate complexes were initially characterized by FTIR and UV–vis spectroscopy analyses. Scavenging activity and antibacterial activity of the complexes were examined. Subsequently, binary and ternary complexes with high biological activity were further studied using elemental analysis, 1H NMR and thermogravimetric analysis; their thermodynamic properties were also determined. 2. Experimental 2.1. Materials and instruments Copper chloride dihydrate (CuCl2·2H2O, 99% purity), cobalt nitrate hexahydrate (Co(NO3)2·6H2O, 98% purity), zinc nitrate hexahydrate (Zn(NO3)2·6H2O, 98% purity), Dhba (C7H6O4, 99% purity) and Nac (C5H9NO3S, 99% purity) were purchased from Sigma–Aldrich (St. Louis, MO); nickel chloride hexahydrate (NiCl2·6H2O, 98% purity) was obtained from Alfa Aesar (Lancashire, UK); manganese chloride tetrahydrate (MnCl2·4H2O, 99.8% purity) was supplied by Fisher Scientific (Bridgewater, NJ). Sodium hydroxide (NaOH, 96% purity) was supplied by Yakuri Chemical (Kyoto, Japan). Ethanol (C2H6O, 95% purity) was provided by Echo Chemical (Miaoli, Taiwan). All chemicals were analytical grade and were used without further purification. N, C, S and H analysis was performed using an Elementar Vario EL Cube analyzer (Hanau, Germany). Metal contents (Mn, Co, Ni, Cu, Zn and Na) of the complexes were determined by an ICP-AES JY 2000-2. The commercial

http://dx.doi.org/10.1016/j.jtice.2016.08.003 1876-1070/© 2016 Taiwan Institute of Chemical Engineers. Published by Elsevier B.V. All rights reserved.
ICP metal standard solution (1000 mg/l of metal in 0.5 mol/l HNO3) was used as the calibrant. Chloride content was determined by using an ion chromatograph Dionex ICS-1000. FTIR spectra were recorded with a Bio-Rad FTS-3500 on KBr disc with spectra range of 400–4000 cm⁻¹. UV–vis spectra of the complexes in H2O solvent were measured in the wavelength range of 200–500 nm by using a Jasco V-550 spectrophotometer. Conductivities of the complexes in water were measured using a Knick Konduktometer 703. Magnetic susceptibilities of powder samples at 300 K were measured using a MPMS7 Quantum Design SQUID Magnetometer.

7H NMR spectra were measured on a Bruker AVIII-600 MHz FT-NMR in D2O solution. Thermogravimetric analyses in the range of 30 to 900 °C were examined by using a Perkin Elmer Diamond TG/DTA. Thermodynamic proper-ties in 0.15 mol/dm³ NaCl ionic medium at various temperatures were measured potentiometrically under N2 atmosphere by using a Metrohm 888 Titrando potentiometer with Ecolrode Plus pH glass electrode. 2.2. Synthesis of binary and ternary complexes Binary complexes were synthesized by dissolving Dhiba (0.16 g, 1 mmol) in 14 ml H2O with the addition of 1 ml 95% ethanol. The ligand was allowed to dissolve by slowly adding a few drops of ±5 M NaOH solution until pH 11.0 was reached, NaOH solution was directly used without standardization. Five milliliters of 1 mmol metal salt solution (0.17 g CuCl2·2H2O; 0.30 g Zn(NO3)2·6H2O; 0.24 g NiCl2·6H2O; 0.30 g Co(NO3)2·6H2O; or 0.20 g MnCl2·4H2O) was added into the solution. The pH again was adjusted to 11.0 by using ±5 M NaOH. The mixture was allowed to react for 6 h with constant stirring. Any solid in the solution was removed by filtration. The solution was freezeed in −40 °C and then subjected to lyophilization. The dried complex then stored in a desiccator. Ternary complexes were synthesized similarly to that of binary complexes with the addition of Nac (0.16 g, 1 mmol). 2.3. Scavenging activity Scavenging activity of complexes was tested against the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) [16]. The tested com-plex was prepared at concentrations of 1 and 2 μg/ml. The com-plex was firstly dissolved in water, then methanol was added to a water to methanol ratio of 1: 19 (v/v).

DPPH solution was prepared at a concentration of 5 × 10⁻⁴ mol/l in aqueous solution with the same water to methanol ratio. DPPH solution (0.2 ml) was added to the prepared complex (0.8 ml). The tested complexes incubated at 37 °C for 30 min and its absorbance was measured at 517 nm against methanol blank. DPPH (0.2 ml) in methanol (0.8 ml) was used as the control. Percent DPPH inhibition was calculated as: % DPPH inhibition = ([Ac − As]/Ac) × 100 \( \text{(1)} \) where Ac and As are the absorbance of control and the absorbance of sample, respectively. Ascorbic acid was used as the positive controls. 2.4. Antimicrobial activity The antimicrobial potency of the complexes was tested against gram positive Staphylococcus aureus and gram negative Escherichia coli.

Broth macrodilution method was used for the inhibitory activ-ity determination [17]. Ampicillin (895.5 μg/ml potency) was used as the reference. The complex was prepared at four concentrations (100, 600, 1000 and 2000 μg/ml). The assay was performed in test tubes each containing the tested compound dissolved in Lysogeny Broth media. Fifteen microliters of the prepared bacteria suspen-sion (1 × 10⁸ cfu/ml) were injected into each tube. After incubated for 24 h at 37 °C, optical density at 600 nm wavelength (OD600nm) of each sample was measured. As the growth control, 15 μl of bac-teria suspension was injected into test tube containing no sample. The antimicrobial activity is expressed as %inhibition, calculated as: % inhibition = ([Ic − Is]/Ic) \( \text{(2)} \) where Ic is the absorbance of control and Is is the absorbance of sample.
Thermodynamic properties were determined potentiometrically by titrating 50 cm$^{-3}$ mixture of metal salts (0.001 mol/dm$^3$) and 0.001–0.003 mol/dm$^3$ of Dhba and/or Nac. The mixture was acidified to pH 2.5 by adding 0.003 mol/dm$^3$ HCl. The ionic strength was maintained by adding 0.15 mol/dm$^3$ NaCl. The mixture was titrated by 0.1 mol/dm$^3$ carbonate free-NaOH under N$_2$ atmosphere until pH 11.0 was reached. Stability constant of binary complex was determined at metal to ligand ratios of 1:1, 1:2 and 1:3 while ternary complex was determined from metal to ligand ratio of 1:1:1. Stability constants were determined at 25, 45 and 55 °C. Analyses of the titration data were done by using Hyperquad2008 [18].

Results and discussion

Metal–ligand complexes with deprotonated species as core (specifically [M(Dhba)]$^-$ and [M(Dhba)(Nac)]$^{3-}$, for binary and ternary species respectively) were synthesized at pH 11.0. This pH was chosen for the synthesis reaction since at this pH value core species were found to exist in the highest concentration, as shown in the distribution diagram in Supplementary Data Fig. S1 for Zn$^{2+}$ systems. The synthesized complexes were then characterized by FTIR and UV–vis spectra analyses. DPPH scavenging and antimicrobial activities of complexes were evaluated. The results of elemental analysis, conductivity and magnetic measurements of Zn$^{2+}$ binary and ternary complexes are presented in this section while the results of other metal ions complexes are summarized in the supplementary data (Table S1).

3.1. FTIR spectra

Binary complexes

The characteristic main bands in IR spectra of the ligands and binary complexes are listed in Table 1, while the IR spectra are presented in the supplementary data (Figs. S2 and S3). In the absence of metal ions, Dhba possessed bands at 3240 cm$^{-1}$ and 3048 cm$^{-1}$ corresponding to $\nu$(OH) of hydroxyl and carboxyl group, respectively. The IR spectrum of the free Dhba reveals a band at 1680 cm$^{-1}$ due to $\nu$(C=O) and $\nu$(C–OH) of protonated carboxyl group, respectively. The band at 1566 cm$^{-1}$ is attributed to the $\nu$(C=C) of Dhba aromatic ring, in the complexes this band is found at 1530–1548 cm$^{-1}$. Several new bands can be found in the metal complex system. The first is the $2\nu$(OH) band at 3478–3471 cm$^{-1}$ and 837–811 cm$^{-1}$ regions are due to coordinated water molecule [6,19]. Two new bands at 1618–1617 cm$^{-1}$ and 1473–1431 cm$^{-1}$ are contributed to $\nu$(COO$^-$)asy and $\nu$(COO$^-$)sym of deprotonated carboxylic group, $\nu$(C=O) of 145–187 cm$^{-1}$ suggests that this group is unbounded.

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Table 1

<table>
<thead>
<tr>
<th>Complex</th>
<th>IR spectra (cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhba</td>
<td>$\nu$(OH) 1680, $\nu$(C=O) 1617, $\nu$(C–OH) 1473</td>
</tr>
</tbody>
</table>
The \(2v(C-OH)\) band at 1191–1218 cm\(^{-1}\) is due to ethanol. The

2\(\text{cm}^{-1}\) are attributed to \(v(MO)\) for Cu\(^{2+}\), Zn\(^{2+}\), Ni\(^{2+}\), Co\(^{2+}\) and Mn\(^{2+}\), respectively.

3.1.2. Ternary complexes

The IR absorption bands of the ternary complexes are listed in Table 1 as well as binary complexes (the full spectra are presented in supplementary data Fig. S4). The ligand \(Nac\) \(v(NH)\) stretching and bending vibration was observed at 3376 and 796 cm\(^{-1}\), respectively. The stretch of \(v(OH)\), \(v(C=O)\) and \(v(CO)\) bond from protonated carboxylate group produced band at 2810 cm\(^{-1}\), 1718 cm\(^{-1}\) and 1229 cm\(^{-1}\) respectively. The thiol \(v(SH)\) frequency of \(Nac\) was characterized at 2548 cm\(^{-1}\), while in the complex this band dis-appeared, evidencing that this group was involved in chelation after deprotonation. The synthesized ternary complexes inherited the main spectra from both Dhba and \(Nac\). The \(v(OH)\) at 3449–3352 cm\(^{-1}\) and band at 834–806 cm\(^{-1}\) in all metal systems indicate the coordinated water molecule \([6,19]\). The bending of \(v(NH)\) at 758–745 cm\(^{-1}\) was still visible in the complexes, while the stretch- ing of \(v(NH)\) at higher region cannot be observed since the band is probably stacked with the \(v(OH)\) band. Two bands at 1659–1548 cm\(^{-1}\) and 1502–1440 cm\(^{-1}\) are contributed to \(v(COO^-)_{\text{asy}}\) and \(v(COO^-)_{\text{sym}}\) of the deprotonated carboxylic group.

**\(2\text{cm}^{-1}\) and band at 834–806 cm\(^{-1}\)**

The \(2v(C-OH)\) band at 1214–1228 cm\(^{-1}\) is due to ethanol. The

6\(\text{cm}^{-1}\) are contributed to \(v(COO^-)_{\text{asy}}\) and \(v(COO^-)_{\text{sym}}\) of the deprotonated carboxylic group.

**\(6\text{cm}^{-1}\) are contributed to \(v(COO^-)_{\text{asy}}\) and \(v(COO^-)_{\text{sym}}\) of the deprotonated carboxylic group.**

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Magnetic susceptibilities (\(\mu_{\text{eff}}\)) of the binary and ternary com-plexes were measured at 300 K and are summarized in Table S1. Low \(\mu_{\text{eff}}\) values (0.69–1.00 BM for binary and 0.62–1.75 BM for ternary complexes) suggest that the complexes only have one un- paired electron, and the complexes exhibit weak paramagnetic be- havior. In Zn\(^{2+}\) binary and ternary complexes, the results of \(\mu_{\text{eff}}\) indicate diamagnetic behavior of the complexes. Meanwhile, Co\(^{2+}\) ternary complex exhibits higher \(\mu_{\text{eff}}\) (2.38 BM) than other ternary metal complexes, this value is often observed for Co\(^{2+}\) complex with octahedral geometry and is also supported by the occurrence of the band at 499 nm in UV–vis spectra. The molar conductivity (\(\mu\)) measurements gave values of 153–179 S cm\(^2\)/mol for binary complexes, while for ternary com-plexes the values were 217–242 S cm\(^2\)/mol (Table S1). \(\mu\) of a complex indicates the electrolyte nature of the complex. The elec-trolyte behavior of a complex might be due to the presence of Na\(^+\) ions which were involved in the formation of the complex. Higher \(\mu\) of a ternary complex is because it contains more Na\(^+\) ions than a binary complex. 3.3. Biological activities

3.3.1. DPPH scavenging activity

Scavenging activity of the complexes at concentrations of 1 and 2 mg/l were evaluated against DPPH. The tests in scavenging ac- tivity were done in triplicate. The results are summarized as the average value, and the
difference between the three tests was indicated by the error bars, as shown in Fig. 2. The synthesized binary and ternary complexes did not show any increase in DPPH inhibition compared to Dhba. The possible reason is that originally Dhba inhibits DPPH by transferring H atom from —COO and meta —O group [23] while Nac inhibits DPPH by transferring H atom from —COO group [24]; in the formed complex H atoms of ligand which were originally inhibiting free radical formation disappeared thus inhibition activity actually decreased. Ternary complexes have higher inhibition activity than binary complexes. The enhancement in activity is due to the addition of Fig. 1. Spectra of the binary and ternary complexes at concentration of 187.5 mg/l. Fig. 2. DPPH scavenging activity of the complexes. Ascorbic acid is the standard reference. Nac, where amine group of Nac also contributes to bonding with DPPH through weak hydrogen bond. However for ternary complex of Cu2+, the inhibition activity is lower than that of binary Cu2+ complex which is known to produce free radical [25]. 3.3.2. Antimicrobial activity Antimicrobial activities of the synthesized complexes were evaluated against E. coli and S. aureus. The inhibition values are reported in Supplementary Data (Tables S2–S4). Dhba was shown to have better antimicrobial activity than Nac. For the synthesized complexes, some exhibited lower antimicrobial activity than that of Dhba. The complexes were found to be more effective in inhibiting S. aureus. It was found that in binary and ternary complexes, the complex of Zn possessed the highest inhibition activity against the growth of bacteria. Thus it is worthwhile to diagnose the efficacy of zinc complexes by determining the minimum inhibitory concentration (MIC) as shown in Table 2. The complexes of Zn gave higher inhibition activity than ligand alone (especially against S. aureus) as indicated by the smaller MIC values. The increase in bacterial growth inhibition of zinc complexes is perhaps due to the increase in solubility of the complexes. The solubility of Dhba in water is very low and becomes highly soluble in the form of chelate complex. The complexes were also found to be more effective to inhibit the growth of gram positive bacteria than gram negative bacteria. This is possibly due to differences in their cell walls [26,27]. As gram positive bacteria, S. aureus cell wall consists of thick peptidoglycan layer and plasma membrane while gram negative bacteria E. coli cell wall possesses an extra outer membrane layer which is high in lipid [28]. This lipid S.P. Santos

Nac (right). Table 2 MICa (μg/ml) of the tested compounds. Compound E. coli MIC50 MIC90 S. aureus MIC50 MIC90 Ampicilin Dhba Nac Binary zinc ternary zinc 4.1 49.1 589.8 1085.7 1293.9 >2000 383.8 554.8 1085.7 1293.9 >2000 603.5 867.0 773.9 971.6 0.3 702.0 >2000 149.3 347.1 2.6 932.6 >2000 383.8 554.8 1085.7 1293.9 >2000 603.5 867.0

3.4. Complexes of zinc Since the complexes of Zn show higher biological activity than other metal complexes, only Zn complexes were chosen for further characterization including elemental analysis, 1H NMR spectra, and thermogravimetric analysis. 3.4.1. Binary complex of zinc The binary complex of Zn has the chemical formula C9H11NNa2 O9Zn or Na2[Zn(NO3)(C7H3O4)(H2O)]·C2H6O, mw=595.70. It is dark green-brown in color. Elemental analysis. 3.4.2. Binary complex of zinc The binary complex of Zn has the chemical formula C9H11NNa2 O9Zn or Na2[Zn(NO3)(C7H3O4)(H2O)]·C2H6O, mw=595.70. It is dark green-brown in color. Elemental analysis. 3.4.2. Binary complex of zinc The binary complex of Zn has the chemical formula C9H11NNa2 O9Zn or Na2[Zn(NO3)(C7H3O4)(H2O)]·C2H6O, mw=595.70. It is dark green-brown in color. Elemental analysis.

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27 Fig. 3. Structure of ligand Dhba (left) and

Plasma mem- brane while gram negative bacteria E. coli cell wall possesses an extra outer membrane layer which is high in lipid [28]. This lipid S.P. Santos

Nac (right). Table 2 MICa (μg/ml) of the tested compounds. Compound E. coli MIC50 MIC90 S. aureus MIC50 MIC90 Ampicilin Dhba Nac Binary zinc ternary zinc 4.1 49.1 589.8 1085.7 1293.9 >2000 383.8 554.8 1085.7 1293.9 >2000 603.5 867.0 773.9 971.6 0.3 702.0 >2000 149.3 347.1 2.6 932.6 >2000 383.8 554.8 1085.7 1293.9 >2000 603.5 867.0

3), followed by new sig- nals at δH 3.69 (q, 2H, CH2, J=7.1Hz), 1.22 (t, 3H, CH3, J=7.1Hz). The 1H NMR signals are presented in Table 3, while the spectrums are presented in Figs. S5 and S6. The new 1H NMR signals in the complex were observed which corresponds to ethanol molecule. The attachment of ethanol molecule may also cause the shift in v(OH) IR spectra at 3471 cm–1. As indicated in the elemental analysis, Na+ molecules were involved in the formation of complex. Na+ molecules seem to help neutralizing the charge of the complex, which originally has a negative charge of 2, thus is insoluble in solid phase is possible. Result of elemental analysis suggests that there was one N atom corresponding to NO3 involved in complex formation. Thus the proposed structure of zinc binary complex is shown in Fig. 4. 3.4.2. Ternary zinc Ternary complex was found with chemical formula C14H18N2 Na4O12SZn or Na4[Zn(NO3)(C7H3O4)(C5H7NO3S)(H2O)]·C2H6O, mw=917382370

https://www.turnitin.com/newreport_printview.asp?eq=1&eb=1&esm=15&oid=917382370&sid=0&n=0&m=0&osv=330&r=30.21174670095176&lang=...
than attach to metal ion. Nac is designated as the primary ligand and Dhba as the secondary ligand since value. This point out that the secondary ligand (Dhba) prefers to attach at the binary complex Zn(Nac) rather stability of ternary complex. All of the ternary complexes exhibit positive log10 X greater than the statistical be- cause of electrostatic effect between the ligands thus lowering the stability of the complex. Meanwhile, formation of ternary complex is less preferred than binary complex. Such phenomenon probably occurred 127.29 114.14 112.17 24.64 22.68 128.89 129.06 94.14 92.41 242.91 244.57 27.86 29.40 192.37 193.48 22.99 16.33 129.07 33.04 91.19 22.77 240.15 28.36 29.93 11.43 193.56 65.78 97.04 23.19 23.11 128.39 62.44 62.96 100.58 101.23 37.71 38.02 72.98 74.84 97.59 97.46 8.49 22.85 19.45 128.35 41.80 – 11.24 98.11 37.28 37.00 69.14 71.09 94.71 97.28 15.84 15.96 59.95 61.64 77.49 79.17 19.01 19.60 57.39 58.62 1.08 1.34 Ternary–stability constant log10 βT 16.59 (8) σd 1.56 ?log10 K −0.49 log10 X 4.54 2.63 (4) 3.18 (2) 9.82 (2) 9.48 (5) 13.00 (2) −1.02 1.02 10.48 (4) 6.23 (8) 16.52 (9) 11.97 (6) 1.48 11.36 (8) 1.55 −0.33 4.27 2.60 (3) 3.12 (2) 9.84 (4) 9.42 (2) 12.72 (1) −1.05 1.26 10.25 (2) 6.19 (2) 16.51 (7) 11.98 (4) 1.40 1.21 16.02 (5) 1.61 −0.42 3.55 2.54 (1) 3.12 (1) 9.81 (4) 9.33 (2) 12.60 (2) −2.13 1.09 10.02 (5) 6.05 (5) 11.11 (3) 11.91 (4) 1.11 1.19 15.51 (6) 1.69 −0.58 3.00 A Standard deviations in parentheses at last decimal place represent the standard uncertainties of temperature u(T) = 0.1°C. b Values cited from Refs. [11] and [15], potentiometry method at I=0.15 mol/l NaCl. c Not defined. d Sigma (σ), the goodness of fitting in a system with expectation value of 1.00. Fig. 5. Proposed structure of zinc ternary complex. 3.4.4. Effect of temperature on thermodynamic parameters The dissociation constant (pKa) of Dhba and Nac as well as the stability constant (log10 β) of their binary and ternary complexes with Zn2+ in aqueous solution with I = 0.15 mol/l NaCl were de- termined at different temperatures (25 °C, 37 °C, 45 °C and 55 °C) and the results are presented in Table 4. Particularly for pKa3 of Dhba at 25 °C, a big error occurred during refinement thus result- ing in undefined value. The error may be caused by the decrease of the acidity of the ligand Dhba at low temperature resulting in delay in dissociation. The change of acidity is well demonstrated in Table 4, since pKa value decreased as the temperature was in- creased. In order to observe the capability of the ligand in pre- vening the formation of metal hydrolytic species, the hydrolysis constants were included in the determination of log10 β. No metal hydrolytic species were observed in the systems, indicating that the ligands were capable in preventing their formation (Fig. S1). The log10 β of binary and ternary complexes also decrease with increasing temperature indicating that complex is more likely to dissociate at higher temperature. Additional parameters ?log10 K and log10 X were determined with respect to the ternary species, where their values are calculated as: ?log10 K = log10 βZn(Dhba)(Nac) − [log10 βZn(Dhba) + log10 [Zn(Nac)](3) log10 X = 2log10 [Zn(Dhba)(Nac)] − [log10 [Zn(Dhba)]2 + log10 [Zn(Nac)]2] (4) Less negative ?log10 K indicates the formation of ternary species is more favorable than that of binary species [6,21]. At all temperatures, the complexes exhibit negative ?log10 K value S.P. Santoso et al. / Journal of the Taiwan Institute of Chemical Engineers 68 (2016) 23–30 Table 5 Thermodynamics properties of Dhba, Nac, binary and ternary complexes of Zn. Species −?G (kJ/mol) −?H (kJ/mol) ?S (J/K·mol) 25 °C 37 °C 45 °C 55 °C 25 °C 37 °C 45 °C 55 °C H2Dhba H3Dhba H2Nac HNac Zn(Dhba) Zn(Dhba)2 Zn(Nac) Zn(Nac)2 −?H (kJ/mol) −?H (kJ/mol) 25 °C 37 °C 45 °C 55 °C H3Dhba H2Dhba HDhba H2Nac HNac Zn(Dhba) Zn(Dhba)2 Zn(Nac) Zn(Nac)2 15.10 15.68 57.72 59.27 – 77.20 18.10 18.89 54.81 56.30 60.23 62.44 94.37 98.11 37.28 37.00 69.14 94.71 97.28 15.84 15.96 59.95 61.64 77.49 79.17 19.01 19.60 57.39 58.62 62.44 62.96 100.58 101.23 37.71 38.02 72.98 74.84 97.59 97.46 8.49 22.85 19.45 128.35 41.80 – 11.24 22.99 16.33 129.07 33.04 91.19 22.77 240.15 28.36 29.93 11.43 193.56 65.78 97.04 23.19 23.11 128.39 127.29 114.14 112.17 24.64 22.68 128.89 129.06 94.14 92.41 242.91 244.57 27.86 29.40 193.47 193.48 101.56 100.00 22.78 128.57 113.88 23.38 128.90 91.18 239.09 29.43 193.24 97.64 indicating that the formation of ternary complex is less preferred than binary complex. Such phenomenon probably occurred be- cause of electrostatic effect between the ligands thus lowering the stability of the complex. Meanwhile, for log10 X parameter, the value higher than statistical value (+0.6 for all geometries) indi- cates remarkable stability of ternary complex. All of the ternary complexes exhibit positive log10 X greater than the statistical value. This point out that the secondary ligand (Dhba) prefers to attach at the binary complex Zn(Nac) rather than attach to metal ion. Nac is designated as the primary ligand and Dhba as the secondary ligand since
the formation of Nac binary complexes took place at lower pH than that of Dhba binary complexes. The log10 X decreases with increasing temperature, indicating that ternary complex is less stable at higher temperature. This trend is supported by the log10 β values which also decreased with increasing temperature. Thermodynamic properties such as ?G (Gibbs free energy), ?H (enthalpy) and ?S (entropy) provide significant information related to the complex. ?G can be calculated as: ?G = −2.303 RT log10 β (5) ?H can be determined as the slope of the Van't Hoff plot which is defined as: log10 β = 2−.3?03HR 1/T + 2−.3?03SR ( ) (6) Thermodynamic properties of Dhba, Nac as well as the Zn binary and ternary complexes are given in Table 5. Negative values of ?G and ?H in the dissociation of the ligands and chelation of binary and ternary Zn complexes indicate that the reactions are spontaneous and exothermic, so that lower temperature is more favorable for complex synthesis. All ?S values are positive indicating that complex formation is favorable. 4. Conclusion Binary and ternary complexes of M/Dhba/Nac were synthesized. FTIR spectra and UV–vis spectra indicate that all complexes have similar structure. The complexes did not increase the scavenging activity of Dhba against DPPH. However in the antimicrobial evaluations against S. aureus and E. coli, the complexes were found to be more effective than that of Dhba which is caused by the enhancement of hydrophobicity of the complexes. The binary and ternary complexes of Zn gave the best enhancement in antimicrobial activity of Dhba and were characterized further. The binary complex was found to bind metal ion through ortho and meta —O group, which has the molecular structure C9H11Nax2O9Zn. The ternary complex was found to bind metal ion through ortho and meta —O group of Dhba, and —COO and —S of Nac, which has the molecular structure C14H18N2Na4O12SZn. The formation of binary and ternary complex was found to be spontaneous and exothermic. Acknowledgments This study was supported by a project (MOST 103-2221-E-011-148) from the Ministry of Science and Technology, Taiwan. The authors thank Shang-Ming Tseng of Instrumentation Center, National Taiwan University for magnetic (MPPMS7 Quantum Design SQUID Magnetometer) experiments.

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superoxide generation and translocation of p47phox and p67phox to cell membrane in human neutrophils
N-Acetyl cysteine attenuates copper overload–induced oxidative injury in brain of rat. Biol Trace Elem Res

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