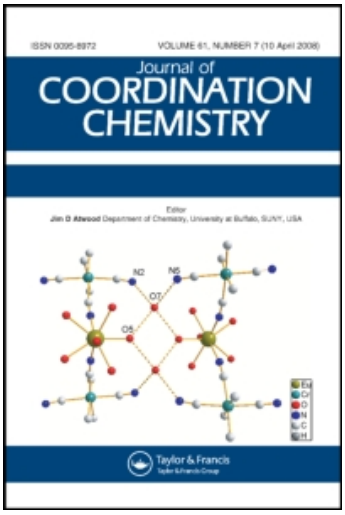

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Electrochemical Study of the Mixed Ligand Complexes of Co(II) and Ni(II) with Acetylsalicylic Acid and Nicotinamide

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ELECTROCHEMICAL STUDY OF THE MIXED LIGAND COMPLEXES OF Co(II) AND Ni(II) WITH ACETYLSALICYLIC ACID AND NICOTINAMIDE

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The interaction of acetylsalicylic acid (aspirin, aspH) and nicotinamide (NA) with Co(II) and Ni(II) ions was investigated using square-wave and cyclic voltammetry techniques. In the presence of Ni(II)/Co(II), nicotinamide gave new peaks at -0.85 V and -1.12 V, corresponding to the reduction of Ni(II)-nicotinamide (log $\beta_{1:2}=5.97$) and Co(II)-nicotinamide (log $\beta_{1:2}=5.19$) complexes, respectively. In the presence of Ni(II)/Co(II), acetylsalicylic acid gave new peaks at -0.91 V and -1.19 V, respectively, corresponding to the reduction of Ni(II)-salicylate (log $\beta_{1:2}=8.48$) and Co(II)-salicylate (log $\beta_{1:2}=8.14$) complexes. In the presence of nicotinamide, Ni(II)-salicylate and Co(II)-salicylate form mixed ligand complexes, reducing at -0.78 V (log $\beta_{1:2:2}=9.68$) and -1.14 V (log $\beta_{1:2:2}=8.64$), respectively.

Keywords: Electrochemistry; Acetylsalicylic acid; Nicotinamide; Mixed ligand complex

INTRODUCTION

Acetylsalicylic acid (aspH) and its derivatives are well known to have anti-inflammatory, anti-pyretic and anti-septic properties [1]. Therefore, they have found widespread application in medicine as a chemopreventative for many types of degenerative diseases such as cancers, cataracts, and circulatory diseases. The latter type of effects indicate that it is also an anti-oxidant, able to control damaging dioxygen metabolites, consisting of O_2^-, H_2O_2, HO. The reactive oxygen species occur in the presence of transition metals. *In vivo*, acetylsalicylic acid is rapidly hydrolyzed to salicylic acid. Salicylate aids in controling the flux and activity of metal ions by redox deactivation [2]. The transition metal complexes containing acetylsalicylic acid still draw considerable attention due to being more effective and desirable drugs than acetylsalicylic acid itself [3,4]. The copper(II) complex of acetylsalicylic acid, $(Cu_2(asp)_4)$, is more effective as an anti-inflammatory drug than free acetylsalicylic acid. In addition to this, the

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copper complex has anti-ulcer activity while acetylsalicylic acid is accepted to have ulcerogenic properties. Copper(II) complexes of salicylate derivatives with basic ligands containing a nitrogen donor, are of great interest in biological systems [5–9]. The $[Cu_2(asp)_2(py)_2]$ adduct has been reported to be an effective anti-inflammatory, anti-cancer and anti-convulsant agent [10–12].

Nicotinamide (NA), commonly known as vitamin B_3 (3-pyridine carboxylic acid amide) is a reactive moiety of the coenzyme nicotinamide adenin dinucleotide (NAD) [13–15]. Considering that nicotinamide is present in tissues of nearly all living organisms, its complexes with transition metals and biological ligands could play a very important role in oxidation–reduction processes of metabolic pathways [16,17], could help the body get rid of toxic and harmful chemicals, and help treat osteoarthritis and rheumatoid arthritis, insulin-dependent diabetes, insomnia, and migraine headaches. People with cancer are more likely to have vitamin B_3 deficiency. However, aspH prolongs the length of time that vitamin B_3 is in the body. On the other hand, both aspH and NA form complexes with metal ions and so help the transfer of metal ions to receptor sites in the treatment of some diseases (i.e. Alzheimer's disease). In this connection, the study of the interaction between Asp and NA in the presence and absence of metal ions is important.

Although many studies on the metal(II)-asp and its derivatives [3,4], metal(II)-nicotinamide [18–33] and mixed ligand metal complexes of acetylsalicylate and/or nicotinamide [34–40] have been reported, no electrochemical study dealing with the interaction of nicotinamide with acetylsalicylic acid in the presence and absence of Ni(II) and Co(II) ions in aqueous medium has appeared in the literature. Electrochemical techniques [41] have been extensively used to study the interactions between metal ions and various ligands [42]. Many of the most important biological processes are based on redox processes. There are similarities between electrochemical and biological reactions concerning electron transfer. Electrochemical studies may provide evidence regarding the mechanisms of biological processes.

In this work, acetylsalicylic acid and nicotinamide and the interaction of nicotinamide with acetylsalicylic acid and their mixed-ligand complexes with Ni(II) and Co(II) ions in aqueous solution are reported using square-wave and cyclic voltammetry techniques.

EXPERIMENTAL

Chemicals

Acetylsalicylic acid, nicotinamide, $NiCl_2$ and $CoCl_2$ were purchased from Merck. The reagents used were of analytical-reagent grade, 0.1 M borate buffer (pH 9.5) was used as supporting electrolyte. All solutions were prepared daily in ultrapure triply distilled water before use and protected from light and air.

Apparatus

Voltammetric experiments were performed with an EG&G PAR Model 384 B polarographic analyzer connected to an EG&G PARC Model 303 A polarographic stand (Princeton, NJ, USA) The cell was fitted with three electrodes, a static Hg drop

electrode (SMDE), a Ag|AgCl reference electrode with a saturated KCl salt bridge and a platinum counter electrode. The voltammograms were recorded with a Houston Instrument DMP-40 plotter (Austin, TX, USA). All measurements were performed at room temperature.

Electronic spectra were taken on an Unicam V2-100 UV–Vis spectrophotometer (cell length, 1 cm) in the 900–190 nm range.

Procedure

Before each polarographic measurement, 10 mL supporting electrolyte (0.1 M borate buffer, pH 9.5) was transferred to the polarographic cell. The solution was purged with oxygen-free nitrogen for 8 min and then a voltammogram was recorded. Throughout the investigations, pulse height of 20 mV, frequency of 100 Hz, drop size of medium and equilibrium time of 5 s were held constant. Addition of metal(II) to the cell containing acetylsalicylic acid or nicotinamide was carried out and the voltammograms were recorded. In another series of measurements, acetylsalicylic acid and metal(II) concentrations were held constant and nicotinamide concentration was raised.

Electronic spectra of mixtures with differing mole ratio of both Co(II)/Ni(II) and acetylsalicylic acid and/or nicotinamide in aqueous solutions were recorded. The changes in absorbance at the wavelength of the maximum absorption of these mixtures were observed.

RESULTS AND DISCUSSION

Co(II)/Ni(II)-Nicotinamide System

A square-wave voltammogram (SWV) of nicotinamide in 0.1 M borate buffer (pH 9.5) showed two peaks at -1.67 V and -1.78 V. It has been previously reported that nicotinamide is reduced in two stages, leading to the formation of aldehyde and carbinol derivatives, respectively [43]. A linear range for current-concentration relation of nicotinamide was found as 5×10^{-5}–1.25×10^{-3} M.

In 0.1 M borate buffer (pH 9.5), SWV of Co(II) and Ni(II) produced completely irreversible reduction peaks at -1.27 V and -1.10 V, respectively.

With addition of 2.5×10^{-5}–2×10^{-4} M cobalt(II) to the cell containing 4×10^{-4} M nicotinamide, the peak potential (-1.27 V) of the free cobalt ion shifted to more positive potential (-1.12 V) while the peak current of nicotinamide decreased (Fig. 1). The reduction of Co(II) complexes have shown that the metal ion, when bound to nitrogen donor(s), is reduced at more positive potentials than the aquation [44–46]. Thefore, the peak at -1.12 V can be attributed to the catalytic reduction of Co(II) ions in the Co(II)-nicotinamide complex.

On increasing Ni(II) concentration from 2×10^{-5} to 2×10^{-4} M in the bulk solution containing nicotinamide (4×10^{-4} M), a new peak at -0.85 V, at more positive potential than that of free Ni(II), was observed (Fig. 2). As nickel ion concentration increases, the peak current at -0.85 V increases, while the peak current of the nicotinamide reduction peak at -1.67 V decreases. The irreversible peak at -0.85 V (Fig. 2) can be assigned to the catalytic nickel reduction in the Ni(II)-nicotinamide complex.

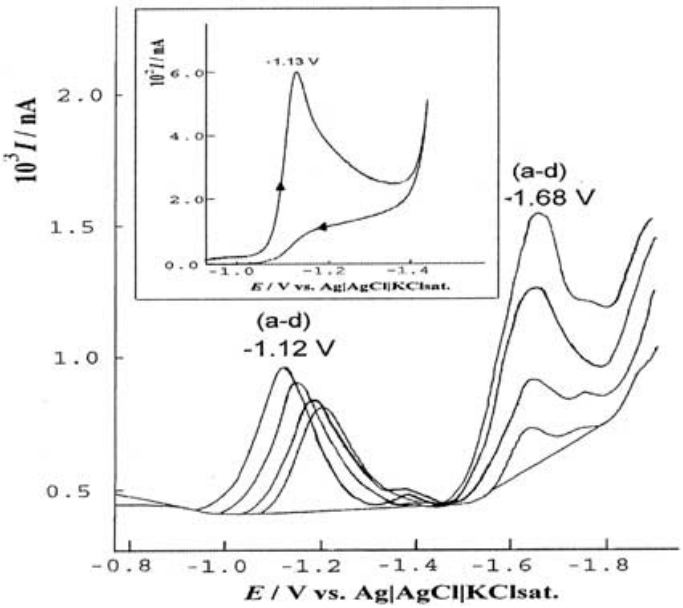


FIGURE 1 Square-wave voltammograms of 4×10^{-4} M nicotinamide solution containing 2.5×10^{-5} M (a); 4×10^{-5} M (b); 8×10^{-5} M (c); 2×10^{-4} (d) Co(II). *Inset*: Cyclic voltammogram of 4×10^{-4} M nicotinamide solution containing 2×10^{-4} M Co(II). Experimental conditions: scan rate 200 mV s^{-1}; pulse height, 20 mV; scan increment, 2 mV; equilibrium time, 5 s; frequency, 100 Hz; drop size, medium.

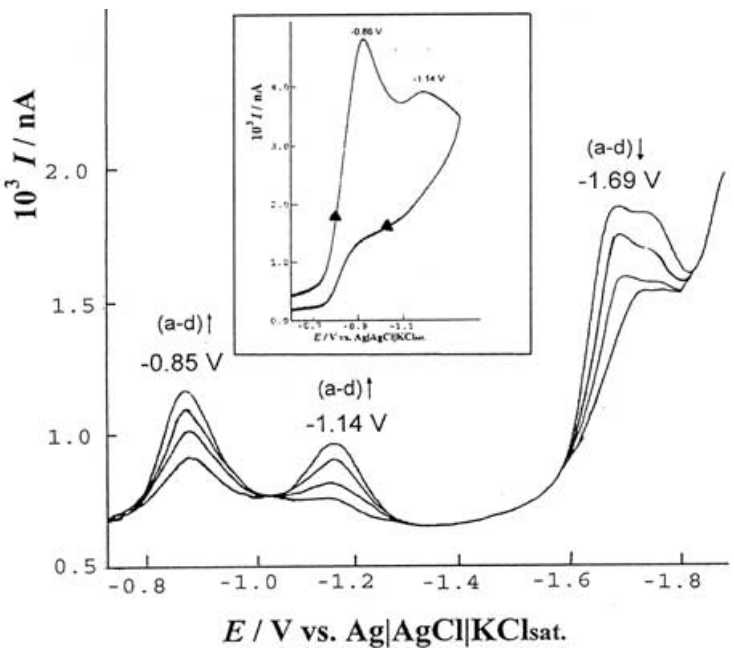


FIGURE 2 Square-wave voltammograms of 4×10^{-4} M nicotinamide solution containing 2.0×10^{-5} M (a); 8×10^{-5} M (b); 1.6×10^{-4} M (c); 2×10^{-4} M (d) Ni(II). *Inset*: Cyclic voltammogram of 4×10^{-4} M nicotinamide solution containing 2×10^{-4} M Ni(II). Other conditions as in Fig. 1.

Since the reducible ion is stabilized by complex formation, it is more difficult to reduce thermodynamically. Thus, increasing concentrations of a ligand generally shifts the potential of the voltammetric wave to more negative potentials. The reduction of cobalt/nickel ion requires high activation energy and electrode reaction occurs only with the application of a very large overvoltage [47]. However, in the presence of certain ligands present at trace levels, the overvoltage is decreased [48] and the reduction of the complexed cobalt/nickel ions occurs more readily at a more positive potential than that of the free metal ions. This pattern is usually termed the catalytic prewave. Thus, nicotinamide catalyzed the reduction of Co(II) and Ni(II) ions. It is well known that nitrogen coordination shifts reduction potential of the metal ions to the more positive values when compared to the aquaion [49].

Co(II)/Ni(II)-Acetylsalicylic Acid System

Acetylsalicylic acid is rapidly hydrolyzed to salicylic acid at pH 9.5. The SWV reduction of acetylsalicylic acid in the absence of metal(II) ions in 0.1 M borate buffer (pH 9.5) is characterized by one peak at -0.45 V. The linear range for the current-concentration relation of acetylsalicylic acid was determined as 1×10^{-4}–8×10^{-4} M.

Gradually increasing the Co(II) concentration from 1×10^{-4} to 2×10^{-4} M in the cell containing 4×10^{-4} M acetylsalicylic acid results in the occurrence of a new peak at more positive potential (-1.19 V) than that of free Co(II) (Fig. 3). The peak at -0.45 V corresponding to salicylate cathodic reduction decreases while the current of the peak at -1.19 V increases with increasing Co(II) concentration. The irreversible peak at -1.19 V results from complexation of Co(II) with salicylate (Fig. 3).

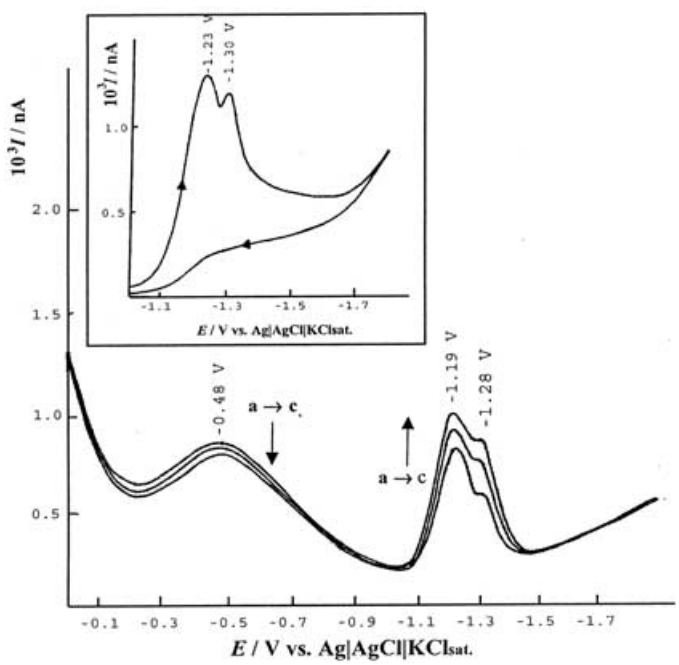


FIGURE 3 Square-wave voltammograms of 4×10^{-4} M acetylsalicylic acid solution containing 1.0×10^{-4} M (a); 1.5×10^{-4} M (b); 2.0×10^{-4} M (c); Co(II). Other conditions as in Fig. 1.

When Ni(II) in the range of 1.2×10^{-5}–4.0×10^{-4} M was added to the bulk solution containing acetylsalicylic acid (4×10^{-4} M), a well-established irreversible peak appears at -0.91 V, which indicates possible formation of the Ni(II)-salicylate complex (Fig. 4). With subsequent additions of Ni(II), a decrease in the peak current of salicylate and an increase in the peak current of the Ni(II)-salicylate complex was observed. The peak at -0.91 V corresponds to catalytic reduction of nickel ion from formation of the Ni(II)-salicylate complex. Also seen in Fig. 4 is the peak at -1.1 V from reduction of hydrated nickel ion in the solution.

The Interaction of Nicotinamide with Acetylsalicylic Acid

The peak current and peak potential of the peak of acetylsalicylic acid at -0.45 V were found to depend on the nicotinamide concentration. As soon as nicotinamide in the range of 5×10^{-5}–4×10^{-4} M was added to the bulk solution containing 3×10^{-4} M acetylsalicylic acid, an obvious change in SWV was observed. With gradual additions of nicotinamide, the peak current of the peak at -0.45 V decreased (Fig. 5). A decrease of the peak current is an indication of a physical interaction of acetylsalicylic acid and nicotinamide at the mercury electrode surface. The observed phenomenon can be explained by strong adsorption of nicotinamide itself on the mercury surface, which prevents acetylsalicylic acid from showing its voltammetric response. The peak potential shifted to more positive potential as a consequence of the interaction of acetylsalicylic acid with nicotinamide. This interaction is similar to the interfacial interactions between folates and thiols [50]. The nature of this interaction in the electrode/solution interface can be described as cooperative bonding in which various form of weak intermolecular forces take part [51].

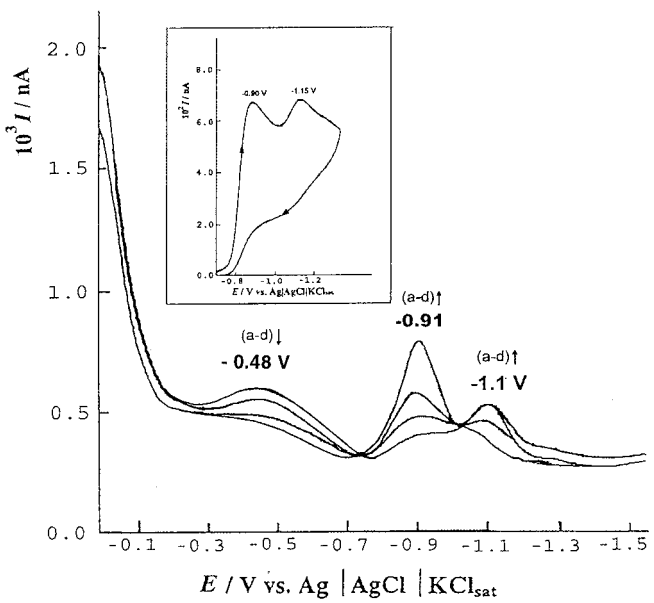


FIGURE 4 Square-wave voltammograms of 4×10^{-4} M acetylsalicylic acid solution containing 1.2×10^{-5} M (a); 1.6×10^{-4} M (b); 2.4×10^{-4} M (c); 4.0×10^{-4} M (d) Ni(II). *Inset:* Cyclic voltammogram 4×10^{-4} M acetylsalicylic acid solution containing 4×10^{-4} M Ni(II). Other conditions as in Fig. 1.

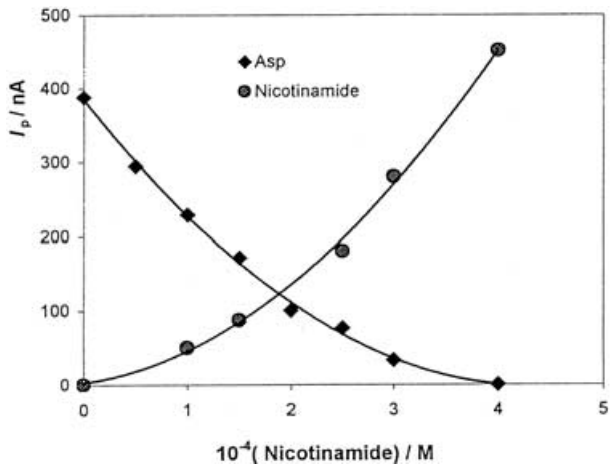


FIGURE 5 Peak currents of 3.0×10^{-4} M acetylsalicylic acid and nicotinamide as a function of nicotinamide concentration. Other conditions as in Fig. 1.

Co(II)/Ni(II)-Acetylsalicylic Acid the Presence of Nicotinamide

When increasing amounts of nicotinamide (1×10^{-4}–2×10^{-3} M) are added to the cell including Co(II)-salicylate (2×10^{-4} M Co(II); 4×10^{-4} M acetylsalicylic acid) or Ni(II)-salicylate (2×10^{-4} M Ni(II); 4×10^{-4} M acetylsalicylic acid), well-defined irreversible peaks, suggesting the formation of the new mixed ligand complexes of Co(II)/Ni(II) with acetylsalicylic acid and nicotinamide were observed at -1.14 and -0.78 V, respectively (Figs. 6 and 7). Voltammetry is a powerful technique for the study of complexation in solution. As can be seen, the peak potentials of the mixed ligand complexes are different from those of the binary complexes. The voltammograms (Figs. 6 and 7) are also agreement with the voltammograms recorded at the same supporting electrolyte by dissolving mixed-ligand complexes in water.

Electronic Spectra

The stoichiometries and overall stability constants of Co(II)/Ni(II)-salicylate, Co(II)/Ni(II)-nicotinamide and the mixed ligand complexes determined according to Job's method have been shown in Table I.

The electronic spectrum of acetylsalicylic acid in water exhibits three bands (at 224, 238 and 302 nm) due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transitions in the UV region. In the spectra of acetylsalicylic acid solutions containing Co(II) or Ni(II) ion, the band at 302 nm shifted to 282 and 276 nm, respectively. The observed bathochromic shifts of these maxima are probably due to formation of a complex. The bands at 282 and 276 nm can be assigned as metal-to-ligand charge-transfer transitions. However, in the visible region, Co(II) and Ni(II)-salicylate complexes *d–d* bands at 582 nm and 510 nm, respectively.

The electronic spectrum of nicotinamide consists of four bands at 227, 239, 274 and 347 nm. In the electronic spectra of the complexes of Co(II) or Ni(II) with nicotinamide, it has been shown that the band at 274 nm shifts to 261 nm for Co(II)-nicotinamide. In solution containing Ni(II), this band shifts slightly to 272 nm. On raising the

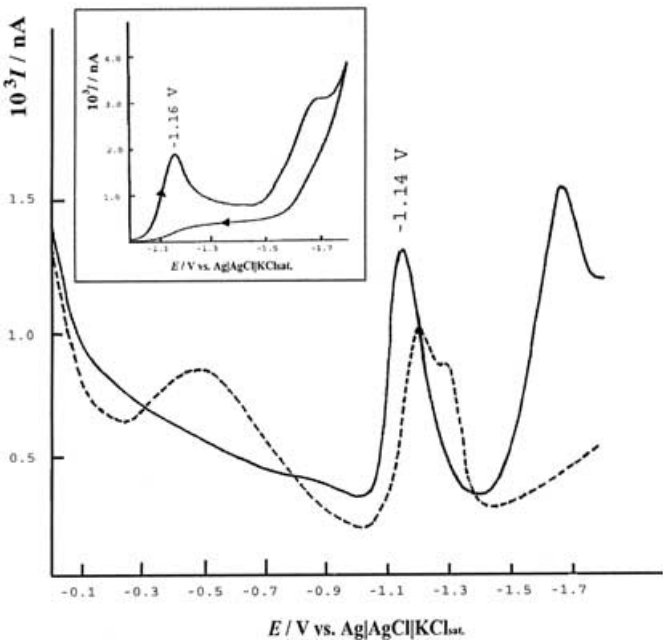


FIGURE 6 Square-wave voltammograms of 4×10^{-4} M acetylsalicylic acid and 2.0×10^{-4} M Co(II) in the presence (—) and absence (- - -) of 8.0×10^{-4} M nicotinamide. *Inset:* Cyclic voltammogram of 4×10^{-4} M acetylsalicylic acid and 2.0×10^{-4} M Co(II) containing 8.0×10^{-4} M nicotinamide. Other conditions as in Fig. 1.

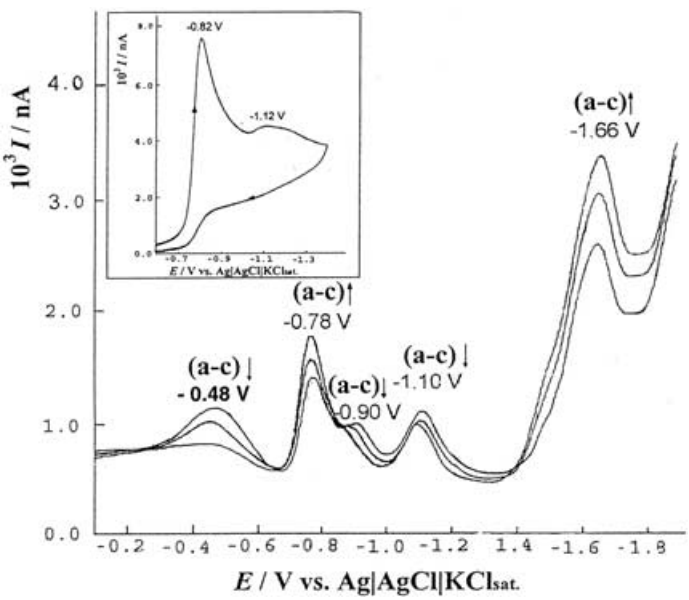


FIGURE 7 Square-wave voltammograms of 4×10^{-4} M acetylsalicylic acid and 2.0×10^{-4} M Ni(II) containing nicotinamide in concentrations 4×10^{-4} M (a); 6.0×10^{-4} M (b); 8.0×10^{-4} M (c). *Inset*: Cyclic voltammogram of 4×10^{-4} M acetylsalicylic acid and 2×10^{-4} M Ni(II) containing 8.0×10^{-4} M nicotinamide. Other conditions as in Fig. 1.

Co(II) and Ni(II) ion concentration, a distinct increase in the intensity of 261 nm and 272 nm band supports the assumption of binding to the rigid nicotinamide.

In the electronic spectra of mixed-ligand complexes of Co(II) and Ni(II) with acetylsalicylic acid and nicotinamide, Co(II)-salicylate-nicotinamide complex shows the maximum absorption at 371 and 511 nm, while Ni(II)-salicylate-nicotinamide complex has an absoption maximum at 374 nm (Table I).

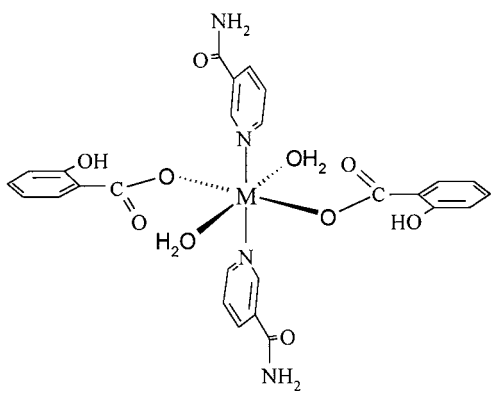
The stoichiometric ratios of the complexes in the aqueous medium determined by Job's method are collected in Table I. Table I shows the mixed ligand complexes of Co(II) ($\log \beta_{1:2:2} = 8.64$) and Ni(II) ($\log \beta_{1:2:2} = 9.68$) to be slightly more stable than the binary metal complexes (Co(II)-salicylate ($\log \beta_{1:2} = 8.14$), Co(II)-nicotinamide ($\log \beta_{1:2} = 5.19$), Ni(II)-salicylate ($\log \beta_{1:2} = 8.48$) and Ni(II)-nicotinamide ($\log \beta_{1:2} = 5.97$)).

In the mixed ligand complexes, nicotinamide binds to metal ions with pyridine N atom while salicylate ligands are coordinated by O atoms of the carboxylate group [21].

The proposed structures of Co(II)-salicylate-nicotinamide and Ni(II)-salicylate-nicotinamide complexes are shown in Scheme 1 due to relatively facile hydrolysis of the coordinated acetylsalicylate ligand.

TABLE I UV–Vis spectrophotometric characteristics of acetylsalicylic acid, nicotinamide and their cobalt and nickel complexes

Compounds	λ_{max}/nm (Exp.)	λ_{max}/nm (Lit. value[Ref.])	*Metal/ligand ratio*	*log β* (Exp.)
Acetylsalicylic acid	224, 238, 302	229, 276[52]		
Nicotinamide	227, 239, 274, 347	340[53]		
Co(II)-salicylate complex	282, 582		1:2	8.14
Ni(II)-salicylate complex	276, 510		1:2	8.48
Co(II)-nicotinamide complex	261, 505		1:2	5.19
Ni(II)-nicotinamide complex	272, 390		1:2	5.97
Co(II)-salicylate-nicotinamide complex	371, 511		1:2:2	8.64
Ni(II)-salicylate-nicotinamide complex	374		1:2:2	9.68



M = Co, Ni

SCHEME 1 The proposed structures of Co(II)-salicylate-nicotinamide and Ni(II)-salicylate-nicotinamide complexes.

CONCLUSIONS

The hydroxyl radical, OH reacts with extremely high rate constants with almost every type of molecule found in living cells. Hydroxyl radicals severely damage the bases and sugars of DNA and also induce strand breakage. If damage is repairable, mutations may result and if the damage is beyond repair, the cell will die. In the *Haber–Weiss* reaction, the hydroxyl radicals are produced by reaction of metal chelates with H_2O_2. The observation of DNA damage is hence mediated by some catalyzed *Haber–Weiss* reaction within the cell. However, metal complexes which include the NA or thiol compounds will not increase OH formation. Since NA prevents the formation of the OH radical from H_2O_2, and also aspH prolongs the length of time that vitamin B_3 is in the body, the presence of NA in free form or its mixed ligand complexes with aspH probably inhibits the formation of cancer cells despite its side effects.

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