Paper

# Electrochemical oligonucleotide detection based on probe DNA-modified gold electrode using cobalt phenanthroline complex

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Electrochemical detection of specific DNA sequence was investigated by using a gold electrode immobilized with probe DNA and tris(1,10-phenanthroline) cobalt (II) complex ($Co(phen)_3^{2+}$) as a hybridization indicator. 25-mer probe DNA modified with a thiol group at 5' end was immobilized on a gold electrode. After the probe DNA-modified gold electrode was hybridized with complementary target DNA, the anodic peak current of 0.1 mM $Co(phen)_3^{2+}$ increased as to the concentration of target DNA in the range from $10^{-7}$ M to $10^{-4}$ M. On the other hand, no current increase was observed when it was hybridized with poly-deoxy A as non-complementary DNA in the same range of concentration.

Keywords: DNA, Sensor, Gold electrode, Tris(1,10-phenanthroline) cobalt, Hybridization, Voltammetry,

## 1. Introduction

Today we are entering the post-humangenomic age. As detection technology of a certain sequence oligonucleotide plays an important role in the field of biology, medical science and diagnostic analysis, it has attracted a great deal of attention. DNA sensors have a potential to be applied not only to gene expression analysis but to mutation detection and pathogen identification. In DNA chip, arrays of single-stranded oligonucleotides are prepared utilizing microfabrication technologies. The complementary target DNA labeled by fluorescence dyes is hybridized with the single-stranded DNA and detected by fluorescent microscopy. Recently, electrochemical methods of oligonucleotide detection have been reported[1]~[18]. Electrochemical methods provide simple and quantifiable DNA determination. Schematic diagram of principle of electrochemical DNA sensor is shown in Fig. 1. Electrochemical DNA detection methods consist of an electrode immobilized with single-stranded probe DNA and an electroactive intercalator as a hybridization indicator. After the hybridization of complementary DNA with probe DNA on the electrode, electroactive intercalators which selectively bind to double-stranded DNA are concentrated in the vicinity of the electrode surface and redox current of the intercalator can be measured. The current should depend on concentration of complementary DNA. So far, various combinations of the modified electrode with a hybridization indicator have been reported.

Millan and Mikkelsen reported the possibility of electrochemical DNA sensor based on an electrode modified with DNA using tris(1,10-phenanthroline) cobalt complex and tris (2,2'-bipyridine) cobalt complex as an electroactive hybridization indicator[1]. 4000-mer target DNA was measured with use of tris(2,2'-bipyridine) cobalt complex in detection limit of $10^{-7}$ g/ml by cyclic voltammetry. 4000-mer probe oligonucleotide was covalently bound to stearic acid mixed in carbon paste electrode through deoxyguanosine residues by 1-[3-(dimethylamino)propyl] -3-ethyl carbodiimide and N-hydroxysulfo succinimide[3].

Interaction of 1,10-phenanthroline or 2,2'-bipyridine complex of metal ion with DNA has been investigated[19]. These metal complex was bound to DNA via intercalation into hydrophobic interior of DNA base stack and electrostatic interaction with the phosphate groups of DNA backbone.

J. Wang et al. immobilized probe DNA on a carbon paste electrode by adsorption and detected target DNA in $10^{-6}$ g/ml level using $Co(phen)_3^{3+}$ by chrono potentiometry[8].

M. Mascini et al. examined two manners of procedure for immobilizing probe DNA onto a graphite screen printed electrode [15]. One of those procedures involved the binding of avidin-biotinylated oligonucleotide and the other was adsorption at controlled potential. These sensors allowed to determine target DNA in the detection limit of $10^{-6}$ g/ml level using daunomycin as an indicator by chronopotentiometric stripping analysis.

Hashimoto et al. achieved higher sensitivity of DNA sensor[5]. They performed covalent immobilization of probe DNA, which has a mercaptohexyl group at the 5'-phosphate end, on a gold electrode. The use of Hochest 33258, DNA minor groove binder, as a hybridization indicator resulted in detection of target DNA in the range from $10^{-13}$ to $10^{-7}$ g/ml.

Maruyama et al. similarly used a gold electrode on which probe DNA with thiol group was immobilized and osmium methyl substituted phenanthroline complex as an indicator[16]. Target DNA could be measured in the detection limit of $6.9 \times 10^{-10}$ g/ml.

Among these investigations, DNA sensors based on a gold electrode on which probe DNA was immobilized through a mercaptohexyl group[5][16] showed higher sensitivity than electrodes prepared with other immobilization methods such as adsorption. It is considered that free end of probe DNA left in the immobilization procedure through a mercaptohexyl group on a gold electrode brings about higher efficiency of hybridization reaction than other immobilization methods. In this paper, therefore, we used a gold electrode immobilized with probe DNA having thiol group at 5' end for the purpose of preparing the DNA sensor which has high sensitivity.

For above mentioned DNA sensors based on a gold electrode,

Hochest 33258 or osmium methyl substituted phenanthroline complex was utilized as a hybridization indicator. Upon the hybridization detection, Hochest 33258 or osmium methyl substituted phenanthroline complex was oxidized at +0.55V and +0.59V, respectively. Background current and tailing of nucleotide oxidation peak is overlapping at +0.55V or more because nucleotide(guanine and adenine) is oxidized at +0.9~1.0V. It is expected that the lower redox potential of an electroactive hybridization indicator would lead to accurate measurement of target DNA hybridization, by the elimination of nucleotide oxidation current. In order to obtain an electroactive intercalator with lower redox potential, metal complex whose ligand is 1,10-phenanthroline or 2,2'-bipyridine is possible to change its property dramatically by exchanging metal ion. Therefore, as some phenanthroline metal complex were examined searching for an ideal hybridization indicator, cobalt complex oxidized at lower potential and can be prepared easier than other metal complex.

Synthetic single-stranded oligonucleotide modified with a mercaptohexyl group at 5' end is available easily today. We investigated electrochemical DNA detection in the combination of this modified electrode with tris(1,10- phenanthroline) cobalt (II) complex ($Co(phen)_3^{2+}$) as a hybridization indicator by cyclic voltammetry.

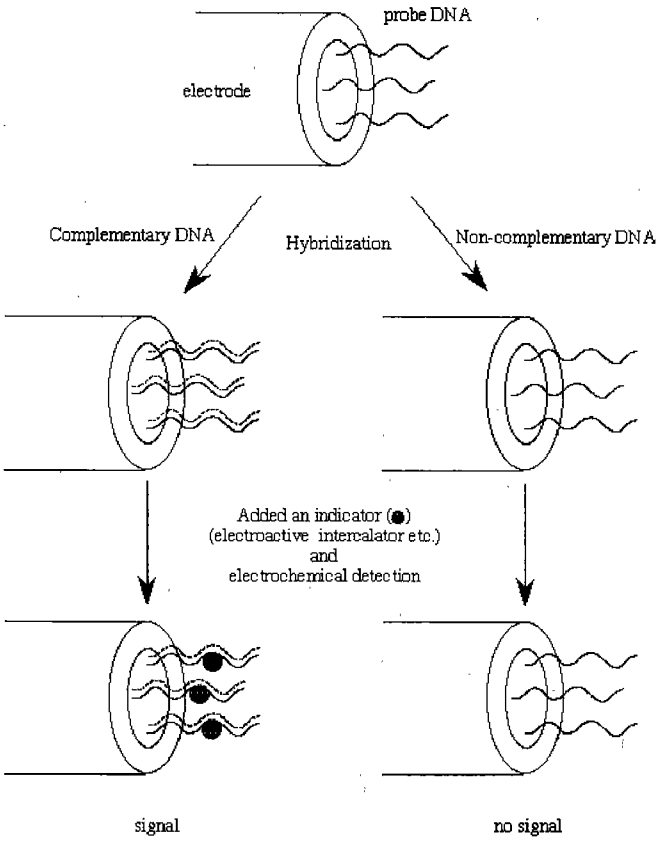


Fig. 1 Schematic diagram of principle of electrochemical DNA sensor.

## 2. Experiments

### 2.1 Materials and Instrumentation

Cobalt(II) sulfate, 1,10-phenanthroline, potassium ferrocyanide were purchased from KANTO Chemical Co., Inc.. Disodium ethylendiamine tetraacetic acid (EDTA) was obtained from Wako Pure Chemical Industries, Ltd.. Disodium hydrogenphosphate, Sodium dihydrogenphosphate (Wako Pure Chemical Industries, Ltd.) used were laboratory grade. High purity water (electric resistivity=18.3 MΩ·cm) was used in all experiments.

Electrochemical analyses were carried out using Bioanalytical Systems (BAS) CV-50W connected with a personal computer.

Gold electrodes (inner diameter 1.6 mm), Ag / AgCl (3 M NaCl) reference electrodes, platinum wire auxiliary electrodes and polishing materials were obtained from BAS.

All the measurements were carried out at room temperature in a glass vial (10 ml).

The probe DNA was targeted for Human Papillomavirus (HPV) type of eighteen, which is most frequently detected in cervical cancer.

The 25-mer probe DNA modified with thiol group at the 5'-phosphate end (HS-5'-TGA GAA ACA CAC CAC AAT ACT ATG G-3'), the 25-mer target DNA(5'-CCA TAG TAT TGT GGT GTG TTT CTC A-3') and 25-mer poly-deoxy adenosine (A) as non-complementary DNA were synthesized by amersham pharmacia biotech.

### 2.2 Preparation of tris(1,10-phenanthroline) cobalt (II) chloride

Tris(1,10-phenanthroline) cobalt (II) chloride was prepared according to previously reported procedure[20]. Three equivalence of 1,10-phenanthroline in ethanol was added to an aqueous solution of cobalt (II) sulfate and mixed. Sodium chloride (3 M) was added to precipitate the chloride salt of tris(1,10-phenanthroline) cobalt (II). The resulting precipitate was passed through a filter, and dried in vacuum over night.

### 2.3 Immobilization of probe DNA on gold electrode

A gold electrode was polished with 0.05 μm alumina on a polishing pad, and sonicated in distilled water prior to immobilization of probe DNA. Then, the electrode was repeatedly scanned in a 0.5 M sulfonic acid solution from 0 to 1.7V. After being rinsed with distilled water, the electrode was immersed in Tris·HCl - EDTA (TE) buffer (10 mM Tris·HCl (pH 8.0) - 1 mM EDTA) including the probe DNA for 20 h at 4 ℃. The electrode was washed with 0.2×standard saline citrate (SSC) buffer (2×SSC; 30 mM sodium citrate, pH 7.0 - 0.3 M sodium chloride) to remove probe DNA which is not immobilized on the electrode.

### 2.4 Examination of probe DNA concentration on immobilization step

In order to confirm the immobilization of probe DNA on a gold electrode, cyclic voltammetry was performed in 10 mM ferrocyanide / 0.1 M phosphate buffer (pH 7.0). The gold electrodes immobilized with probe DNA at various concentration of probe DNA solution were tested to compare the amount of probe DNA immobilized on the electrode.

### 2.5 Measurement of target DNA

The gold electrode immobilized with probe DNA was immersed into 2×SSC buffer containing target DNA. Hybridization reaction was performed for an hour at 65 ℃ with

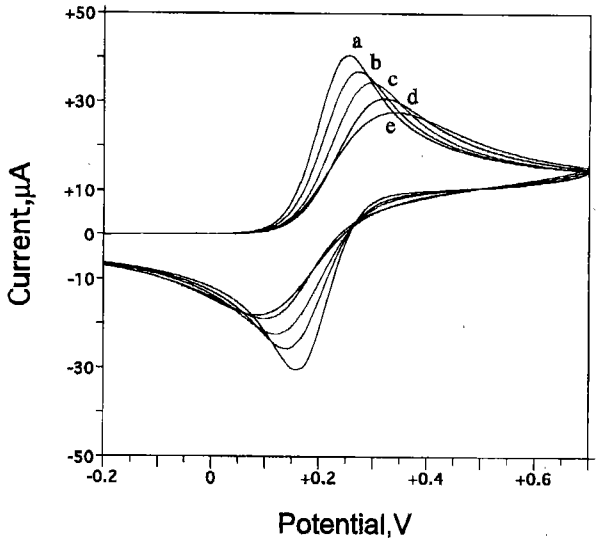


Fig. 2 Cyclic voltammograms of 10 mM potassium ferrocyanide in 0.1 M phosphate buffer (pH 7.0). scan rate; 100 mV / s. (a) bare gold electrode, the gold electrode immobilized with probe DNA at concentration of (b) 0.01 μM, (c) 0.1 μM, (d) 1.0 μM and (e) 20 μM.

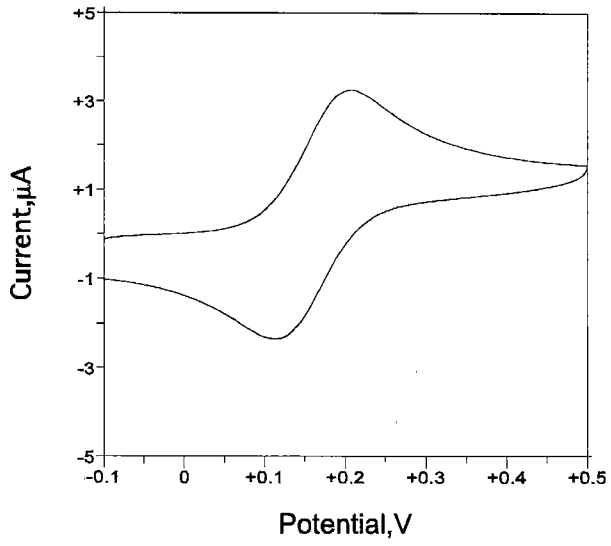


Fig. 3 Cyclic voltammogram of 1 mM $Co(phen)_3^{2+}$ in 0.1M phosphate buffer (pH 7.0). scan rate; 100 mV / s.

shaking. After that, the electrode was washed with 0.2×SSC buffer. Then, the electrode was immersed into $Co(phen)_3^{2+}$/ 0.1M phosphate buffer (pH 7.0). The anodic peak current of cyclic voltammogram in $Co(phen)_3^{2+}$ / 0.1 M phosphate buffer (pH 7.0) was calculated by CV-50W and used for detection of target DNA.

## 3. Results and Discussion

### 3.1 Immobilization of probe DNA to gold electrode

Probe DNA modified with thiol group at the 5'-phosphate end was immobilized to a gold electrode by chemisorption. Cyclic voltammetry was carried out in 10 mM ferrocyanide / 0.1 M phosphate buffer (pH 7.0) before and after the immobilization of probe DNA on a gold electrode. Cyclic voltammograms obtained using the gold electrode immobilized with probe DNA at the

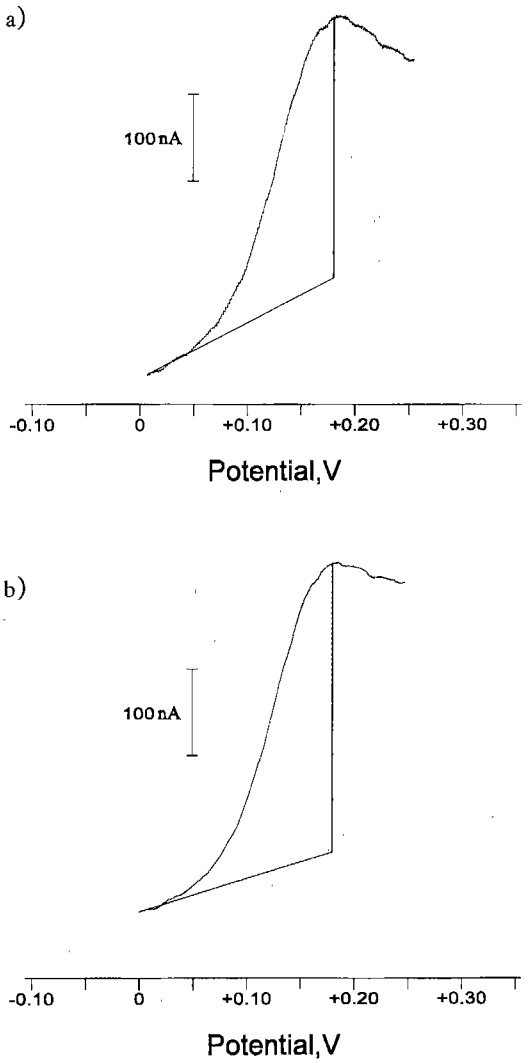


Fig. 4 Anodic peak of cyclic voltammograms of 0.1 mM $Co(phen)_3^{2+}$ / 0.1 M phosphate buffer (pH 7.0) using (a) the probe DNA-modified gold electrode and (b) the probe DNA-modified gold electrode hybridized with target DNA. scan rate; 100 mV / s. .

concentration of 0.01, 0.1, 1.0 and 20 μM probe DNA are shown in Fig. 2. As the concentration of probe DNA increased, the redox peak current of ferrocyanide decreased and the peak potential separation $\Delta E_p$ increased. The relation between redox peak current of ferrocyanide and the chemical modification of electrode surface was reported[5][21] and it is known that the modification by organic molecule tends to prevent the access of electroactive species such as ferrocyanide and results in the decrease of redox peak current. Therefore it was shown that probe DNA molecule on a gold electrode prevented electrochemical reaction of ferrocyanide by steric hindrance and electrostatic repulsion. Although it can be expected that higher density of probe DNA on a electrode provides higher sensor's sensitivity, taking account of hybridization efficiency of target DNA, probe DNA concentration of 1 μM was selected for further experiments.

### 3.2 Measurement of target DNA with cobalt phenanthroline complex

A cyclic voltammogram of 1.0 mM $Co(phen)_3^{2+}$ / 0.1 M

Table 1. Anodic peak currents of cyclic voltammograms at various $Co(phen)_3^{2+}$ concentrations. (n=3)

| $Co(phen)_3^{2+}$ conc. | Peak current |
|---|---|
| 0.1 mM | 294.0± 9.6 nA |
| 0.2 mM | 587.2± 17.9 nA |
| 0.3 mM | 874.9± 31.0 nA |
| 1.0 mM | 2964.5±151.9 nA |

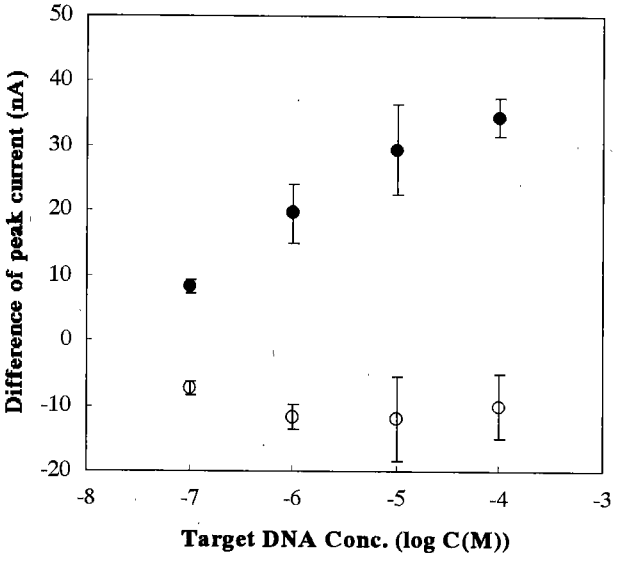


Fig. 5 Calibration plots for complementary DNA(filled circle) and poly-deoxyA(open circle) in 0.1 mM Co $(phen)_3^{2+}$ / 0.1 M phosphate buffer (pH 7.0). (n=3)

phosphate buffer (pH 7.0) is shown in Fig. 3. $Co(phen)_3^{2+}$ was reversibly reacted on the bare gold electrode with anodic peak potential at 180 mV and cathodic peak potential at 120 mV.

For the purpose of the determination of target DNA hybridized with probe DNA, the redox current of $Co(phen)_3^{2+}$ bound to double-stranded DNA was utilized as follows. After hybridization of target DNA with probe DNA bound to a gold electrode, the electrode was immersed into 1.0 mM $Co(phen)_3^{2+}$ / 0.1 M phosphate buffer (pH 7.0) for 5 min and rinsed with the buffer solution. Cyclic voltammetry of the resulting electrode was carried out in 0.1 M phosphate buffer (pH 7.0). Although redox reaction of $Co(phen)_3^{2+}$ was observed by this procedure, the anodic peak currents obtained by cyclic voltammograms of Co $(phen)_3^{2+}$ didn't depend on target DNA concentration. It is considered that most of cobalt phenanthroline complexes bound to DNA were washed out by rinsing the electrode.

In order to prevent desorption of $Co(phen)_3^{2+}$, another procedure was applied to target DNA determination. Cyclic voltammetry was performed in $Co(phen)_3^{2+}$ / 0.1 M phosphate buffer (pH 7.0) following hybridization reaction without rinsing the electrode. The result obtained in this procedure is described as follows.

Profile of cyclic voltammograms of $Co(phen)_3^{2+}$ / 0.1 M phosphate buffer (pH 7.0) using the probe DNA-modified gold electrode and the electrode hybridized with target DNA was similar to that obtained with the bare gold electrode (Fig. 3).

Anodic peak of 0.1 mM $Co(phen)_3^{2+}$ / 0.1 M phosphate buffer (pH 7.0) using the probe DNA-modified gold electrode and the probe DNA-modified gold electrode hybridized with target DNA was shown in Fig. 4. Anodic peak current of the electrode with hybridized DNA was larger than that of the electrode with probe DNA. In other word, the anodic peak current of $Co(phen)_3^{2+}$ increased by hybridization of target DNA to probe DNA on the gold electrode.

To optimize the concentration of $Co(phen)_3^{2+}$, the current increase and its correlation with the concentration of target DNA were examined at 0.1 mM, 0.2 mM, 0.3 mM, and 1.0 mM. Anodic peak currents obtained by cyclic voltammograms at each Co $(phen)_3^{2+}$ concentrations were shown in Table 1. At the concentration of 0.2 mM, 0.3 mM and 1.0 mM, the response currents did not clearly depend on target DNA concentration. Only at 0.1 mM $Co(phen)_3^{2+}$, the response currents depended on target DNA concentration. At the $Co(phen)_3^{2+}$ concentrations of 0.2 mM, 0.3 mM and 1.0 mM, indeterminate error might be larger than the current change by forming hybrids on probe DNA-modified gold electrode. Indeed, at $Co(phen)_3^{2+}$ concentration of 1 mM, approximately 3000 nA was observed and indeterminate error of 152 nA was much larger than the current change by forming hybrids at $Co(phen)_3^{2+}$ concentration of 0.1 mM.

Calibration curve for the DNA sensor in 0.1 mM $Co(phen)_3^{2+}$ was shown in Fig. 5. A vertical axis shows the difference between anodic peak current of the electrode with hybridized DNA and that of the probe DNA-modified electrode. The response currents increased relating to target DNA concentration in the range from $10^{-7}$ M ($7.7\times10^{-7}$ g/ml) to $10^{-4}$ M ($7.7\times10^{-4}$ g/ml). A slope of calibration curve was 10.5 nA / decade. Detection limit was calculated at $1.5\times10^{-8}$ M ($1.2\times10^{-7}$ g/ml).

Similar measurement was performed using the probe DNA-modified gold electrode reacted with 25-mer poly-deoxy A as non-complementary DNA. The response currents did not increased. On the other hand, all currents slightly decreased from that using probe DNA-modified electrode. It seems that the surface of DNA-modified electrode suffers from chemical alteration because the electrode was repeatedly used increasing the concentration of target DNA (or poly-deoxy A) after one measurement.

From these results, it was shown that a certain sequence of DNA, which is complementary to probe DNA, can be detected using cobalt phenanthroline complex and probe DNA-modified gold electrode.

We examined the combination of probe DNA-modified gold electrode with $Co(phen)_3^{2+}$ as a hybridization indicator for the purpose of detecting target DNA with high sensitivity. However, detection limit of target DNA using the sensor we prepared was $10^{-7}$ g/ml level. This detection limit was larger than that of the reported sensors based on the gold electrode immobilized with probe DNA through a mercaptohexyl group[5][16]. Performance of DNA sensor mostly depended on the hybridization indicator. Co $(phen)_3^{2+}$ have an advantage in low redox potential and easy preparation. However, binding constant (K) of $Co(phen)_3^{2+}$ with DNA is $3.0\times10^4$ $M^{-1}$ [19] and lower than that of osmium methyl substituted phenanthroline complex ($Os(5,6\text{-dimethyl-phen})_3^{2+}$ : $K = 4.2\times10^5$ $M^{-1}$ [16]). Moreover, the measurement method of the redox current of a hybridization indicator is associated with the sensitivity of the DNA sensor. Maruyama et. al. reported the use of square wave voltammetry for the sake of elimination of the background current. And, we determined target DNA hybridized with probe DNA by measuring the redox current in $Co(phen)_3^{2+}$ /

0.1 M phosphate buffer (pH 7.0), while Hashimoto et al. and Maruyama et al. measured the redox current of the hybridization indicator in the buffer solution after rinsing the electrode. It was considered that the oxidation of $Co(phen)_3^{2+}$ without binding to DNA decreased the sensitivity for detection of target DNA. Therefore, improvement of both an electroactive hybridization indicator and the method of measuring the redox current of a hybridization indicator would cause an increase of the sensitivity of the DNA sensor.

## 4. Conclusion

In this paper, we examined the DNA sensor which consisted of the gold electrode immobilized with probe DNA through a thiol group and tris(1,10-phenanthroline) cobalt (II) complex as a hybridization indicator. When cyclic voltammetry was performed in 0.1 mM $Co(phen)_3^{2+}$ / 0.1 M phosphate buffer (pH 7.0) followed by hybridization reaction, concentration of complementary target DNA was detected in the range from $10^{-7}$ M to $10^{-4}$ M. On the other hand, Poly-deoxy A as non-complementary target DNA was not detected in the same range. Sequence-specific DNA detection was achieved. The proposed procedure shall be applied to various field of DNA detection.

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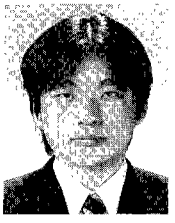

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