

# Voltammetric Recognition of $\text{Ca}^{2+}$ by Calix[4]arene Diquinone Diacid<sup>†</sup>

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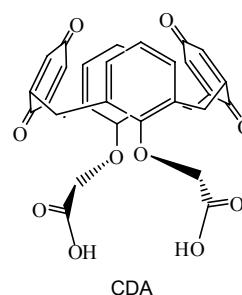
The voltammetric study on a water-soluble calix[4]arene-diquinone-diacid (CDA) in pH 7.4 in the presence of  $\text{Ca}^{2+}$  ion provided important information about the unique electrochemical behavior of CDA- $\text{Ca}^{2+}$  complex. Using CDA,  $\text{Ca}^{2+}$  ion in aqueous solution was recognized quantitatively by voltammetric techniques.

**Key Words:** Calixarene, Quinone, Calcium, Voltammetry, Ion recognition

## Introduction

Detection of electrolyte concentration in biological fluid, blood or urine is important for clinical diagnosis and treatment of diseases.<sup>1</sup> Especially, the development of selective sensors for  $\text{Ca}^{2+}$  ion in physiological samples is utterly important.<sup>2</sup> Conventional methods for the electrolyte measurements in biological fluids include optical and electrochemical analyses. Compared to conventional potentiometry and optical measurements of  $\text{Ca}^{2+}$  ion, voltammetric determination is very promising because of its high sensitivity, very small amount of sample needed and applicability for *in situ* monitoring.<sup>3,4</sup> For voltammetric determination of electrochemically inactive target ions such as  $\text{Ca}^{2+}$  ion, it is necessary to exploit an electroactive ionophore that can bind the ion and show characteristic electrochemical behavior. As one of the promising candidates for electroactive ionophores, extensive work on the synthesis and electrochemical behavior of quinone-derivatized calix[4]arene, in which one or more phenolic ring members are replaced by quinones, have been reported.<sup>5,6</sup> The quinone moiety in calixarene serves simultaneously not only as a redox center, but also as a ligating site.

The main difficulty in the determination of  $\text{Ca}^{2+}$  is to prepare water-soluble ionophore that can overcome the presence of  $\text{Na}^+$  ion of much higher concentration compared to that of  $\text{Ca}^{2+}$  ion in the biological fluids.<sup>7</sup> Due to the lack of a calixarene probe applicable to the determination of calcium ions in aqueous environment, we have attempted to design and synthesize calixarene-based probes that have a binding stability according to the activation energy for dehydration of the ion in the probe,<sup>8-12</sup> which are suited for measurements of biological samples by choosing a redox part on which ion binding is accomplished by a sufficient change of the electron distribution and thus the electrochemical properties of the redox site. The present study reports a water soluble calix[4]arene diquinone diacid (CDA) bearing two carboxylic acid groups (Figure 1), which exhibits a remarkably selective response to  $\text{Ca}^{2+}$  ion over various metal ions in neutral buffer solutions. Also analytical utilization of CDA for  $\text{Ca}^{2+}$  ion is demonstrated.



**Figure 1.** Structure of a water soluble calix[4]arene diquinone diacid (CDA).

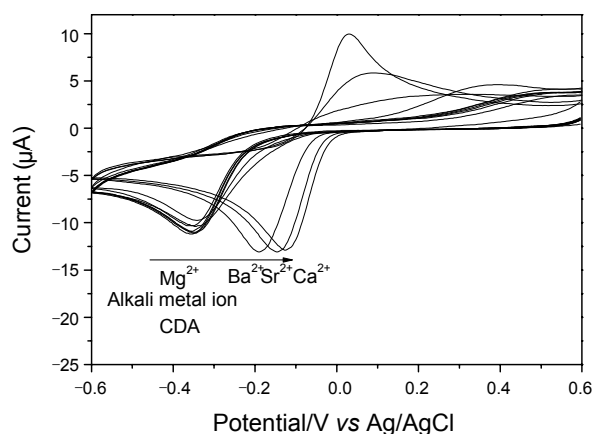
## Experimental Section

Electrochemical measurements were carried out with a Model 660 electrochemical workstation (CH Instruments, Austin, TX, USA). The three-electrode system consists of a glassy carbon working electrode, an Ag/AgCl (in KCl 3 M) reference electrode and a Pt wire counter electrode. The surface of the working electrode was polished with 0.3  $\mu\text{m}$  alumina (Buehler, Lake Bluff, MN) and rinsed with deionized water. Residual alumina particles were thoroughly removed by sonicating the electrode for 15 min. Then, the electrode was dried and washed with distilled water before use. Dissolved oxygen was removed by bubbling purified nitrogen gas. All experiments were carried out in nitrogen atmosphere at room temperature. Synthesis and identification of CDA was described in the previous paper.<sup>9</sup> Tetraethylammonium hydroxide aqueous solution (TEAOH, 20 wt % in aqueous solution, Acros Organic) was used as a base for controlling pH. Other reagents were purchased from Aldrich and were used without further purification.

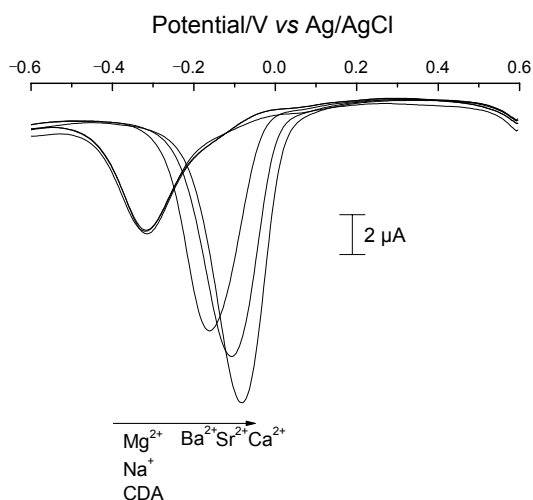
## Results and Discussion

Using this water-soluble and redox active CDA, the electrochemical recognition toward alkali and alkaline earth metal ions was investigated in aqueous HEPES buffer solution at pH 7.4 by cyclic voltammetry. This media was selected considering the practical application of physiological fluids. The electrochemical behavior of CDA is very similar to that of simple quinone derivatives such as *p*-benzoquinone in the same condi-

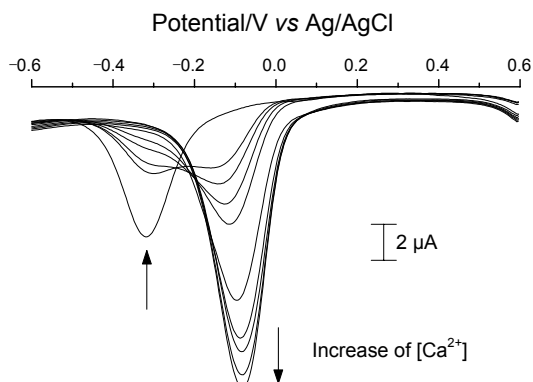
<sup>†</sup>This paper is dedicated to Professor Hasuck Kim for his outstanding contribution to electrochemistry and analytical chemistry.



**Figure 2.** Cyclic voltammograms (CVs) of CDA in the absence and presence of alkali and alkaline earth metal ions at pH 7.4 (HEPES buffer). [CDA] = 0.5 mM, [M(NO<sub>3</sub>)<sub>n</sub>] = 0.5 mM, scan rate = 50 mV/s.



**Figure 3.** Square wave voltammograms (SWVs) of CDA in the absence and presence of alkali and alkaline earth metal ions at pH 7.4 (HEPES buffer). [CDA] = 0.5 mM, [M(NO<sub>3</sub>)<sub>n</sub>] = 0.5 mM, scan rate = 50 mV/s.



**Figure 4.** SWVs of CDA upon the addition of increasing amount of Ca<sup>2+</sup> (0.01 mM ~ 1.5 mM).

tions.<sup>10</sup> The apparently irreversible redox wave of free CDA is due to the proton-coupled electrochemical reduction. Figure 2 and 3 show the effect of alkali and alkaline earth metal ions on the redox behavior of CDA.

**Table 1.** Voltammetric responses of CDA<sup>a</sup> in the presence of alkali and alkaline earth metal ions

Metal ions	$\Delta E_p^b$ (mV)
Li <sup>+</sup> , Na <sup>+</sup> , K <sup>+</sup> , Rb <sup>+</sup> , Cs <sup>+</sup> , Mg <sup>2+</sup>	0
Ca <sup>2+</sup>	216
Sr <sup>2+</sup>	196
Ba <sup>2+</sup>	152

<sup>a</sup>[CDA] = 0.5 mM (pH 7.4, 0.1 M HEPES/TEAOH Buffer). <sup>b</sup> $\Delta E_p$  (mV): difference between the reduction peak potentials in the presence of 0.5 mM metal ions. All data were obtained by cyclic voltammetry with a glassy carbon working electrode. Scan rate = 50 mV/s.

The addition of alkali metal ions to free CDA solution leads little change in both cyclic voltammograms (CVs) and square wave voltammograms (SWVs) of CDA. But the presence of alkaline earth metal ions alters both the reduction/oxidation peak potentials and currents of CDA. Especially, in the case of Ca<sup>2+</sup> ion, the redox behavior of CDA undergoes the most drastic change. With respect to the electrochemical behavior, the irreversible redox wave of free CDA undergoes a dramatic transition to a highly symmetric one upon the addition of Ca<sup>2+</sup> ion, as shown in Figure 2. The ratio of oxidation (*i*<sub>a</sub>) to reduction current (*i*<sub>c</sub>), *i*<sub>a</sub>/*i*<sub>c</sub>, is about 0.9 and the wave around +0.4 V attributed to the oxidation of protonated quinone moiety disappears.

The difference between potentials of the reduction peak ( $\Delta E_p$ ) in the absence and presence of metal ions is summarized in Table 1. In the presence of alkaline earth metal ion, the positive shift of reduction peak potential is similar to that due to redox-switching mechanism. Probably, metal ion is positioned so close to the quinone moiety that the reduction of the quinone should be facilitated by strong electrostatic interaction.<sup>10</sup> When benzoquinone instead of CDA was used, even a large amount of alkali and alkaline earth metal ions showed no significant influence on the electrochemical behavior of benzoquinone.<sup>12</sup> The results in Table 1 clearly show that CDA produces a very selective voltammetric response toward Ca<sup>2+</sup> ion over all alkali metal ions and other alkaline earth metal ions with some degree of interference.

To have an insight into the complexation behavior of CDA toward Ca<sup>2+</sup> ion, the redox changes of CDA were measured as a function of metal concentration in aqueous buffered solution of pH 7.4. Figure 4 shows the effect of the concentration of the Ca<sup>2+</sup> ion in the SWV. Upon interacting with Ca<sup>2+</sup> ion, CDA solution experienced a marked positive shift in its peak potential. The reduction peak at -0.3 V shifts to -0.1 V and grows largely at the expense of the reduction peak at -0.3 V. The peak current (*i*<sub>p</sub>) quantitatively increases as the concentration of the Ca<sup>2+</sup> ion increases.

In the presence of Ca<sup>2+</sup>, the irreversible redox wave of free CDA is transformed dramatically into a highly symmetric one, where the wave around +0.4 V due to the reduction of protonated quinone moiety disappears. This result implies that the protonation of reduced quinone is considerably inhibited when Ca<sup>2+</sup> is bound to CDA. Generally, it is well known that the process of electron transfer to quinone is coupled with proton transfer reaction in aqueous solution. The reaction mechanism consists of steps such as e<sup>-</sup>, H<sup>+</sup>, e<sup>-</sup>, H<sup>+</sup> or H<sup>+</sup>, e<sup>-</sup>, H<sup>+</sup>, e<sup>-</sup> depending on the

pH, where  $e^-$  and  $H^+$  represent electron transfer and protonation steps, respectively.<sup>13</sup> On the basis of the mechanism, the redox mechanism of CDA in this pH is well comprehended as a  $e^-$ ,  $H^+$ ,  $e^-$ ,  $H^+$  process although the difference between reduction and oxidation peak potentials is a little larger compared to that of *p*-benzoquinone.<sup>13</sup> However, in the case of CDA- $\text{Ca}^{2+}$  complex, the redox mechanism can no longer be applied. Thus, the positively shifted new reduction peak compared to free CDA appeared, and this stems from the facilitated electrochemical reduction of the diquinone associated with the  $\text{Ca}^{2+}$  ion in the aqueous phase.

### Conclusion

A water soluble calix[4]arene diquinone diacid is introduced and its electrochemical properties and complexation behavior in the presence of alkali and alkaline earth metal ions are investigated. Voltammetric studies show that CDA has high affinity toward alkaline earth metal ions, especially toward  $\text{Ca}^{2+}$  ions. Voltammetric recognition of  $\text{Ca}^{2+}$  by CDA does not suffer from significant interference by any alkali metal ions or  $\text{Mg}^{2+}$ .

When  $\text{Ca}^{2+}$  ion is entrapped by CDA, it stabilizes anion radical form of quinone significantly which is produced by the electrochemical reduction in aqueous media.

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