SYNTHESIS AND PROPERTIES OF NOVEL COENZYME-Q DERIVATIVES OBTAINED FROM COENZYME Q-0

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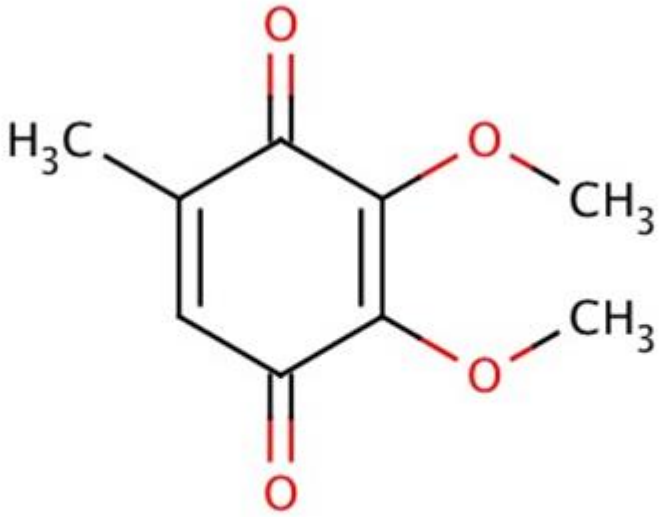
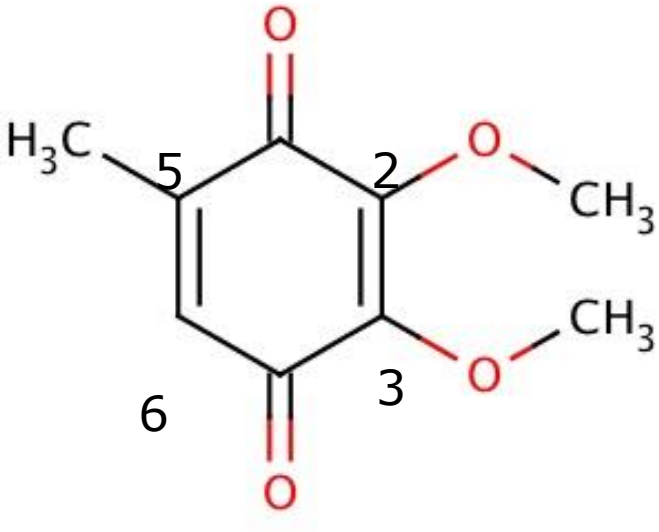
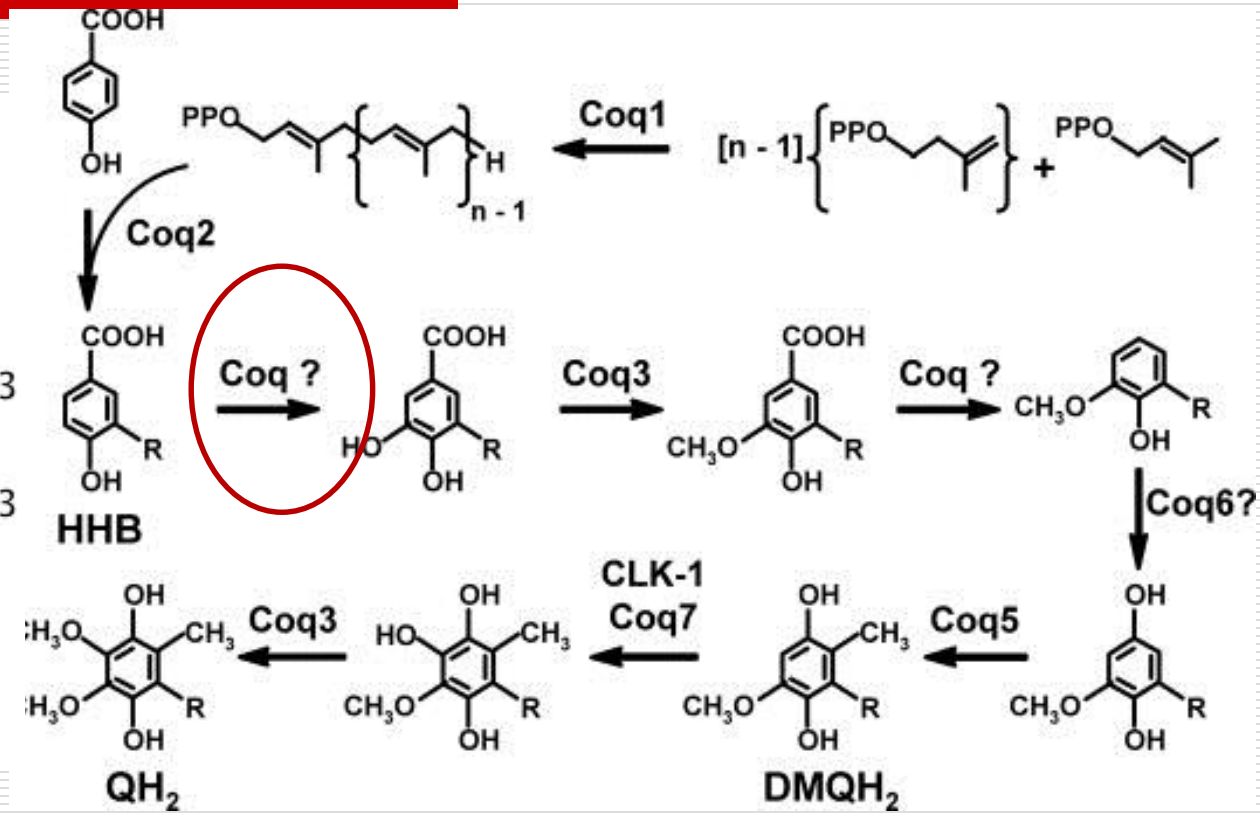
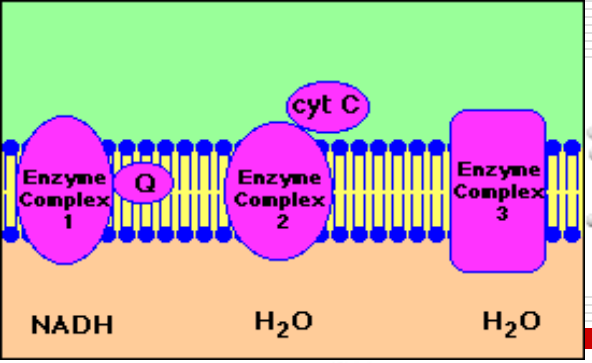


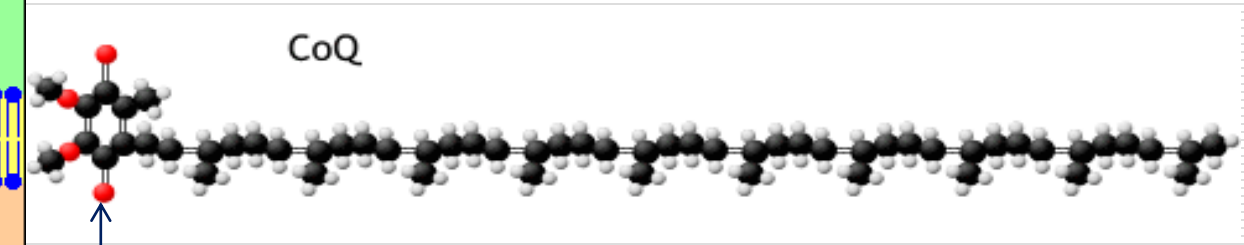
Coenzyme Q-0, 2,3-Dimethoxy-5-methyl-1,4-benzoquinone is an amphiphilic compound that is involved in the biosynthesis of Coenzyme Q-10

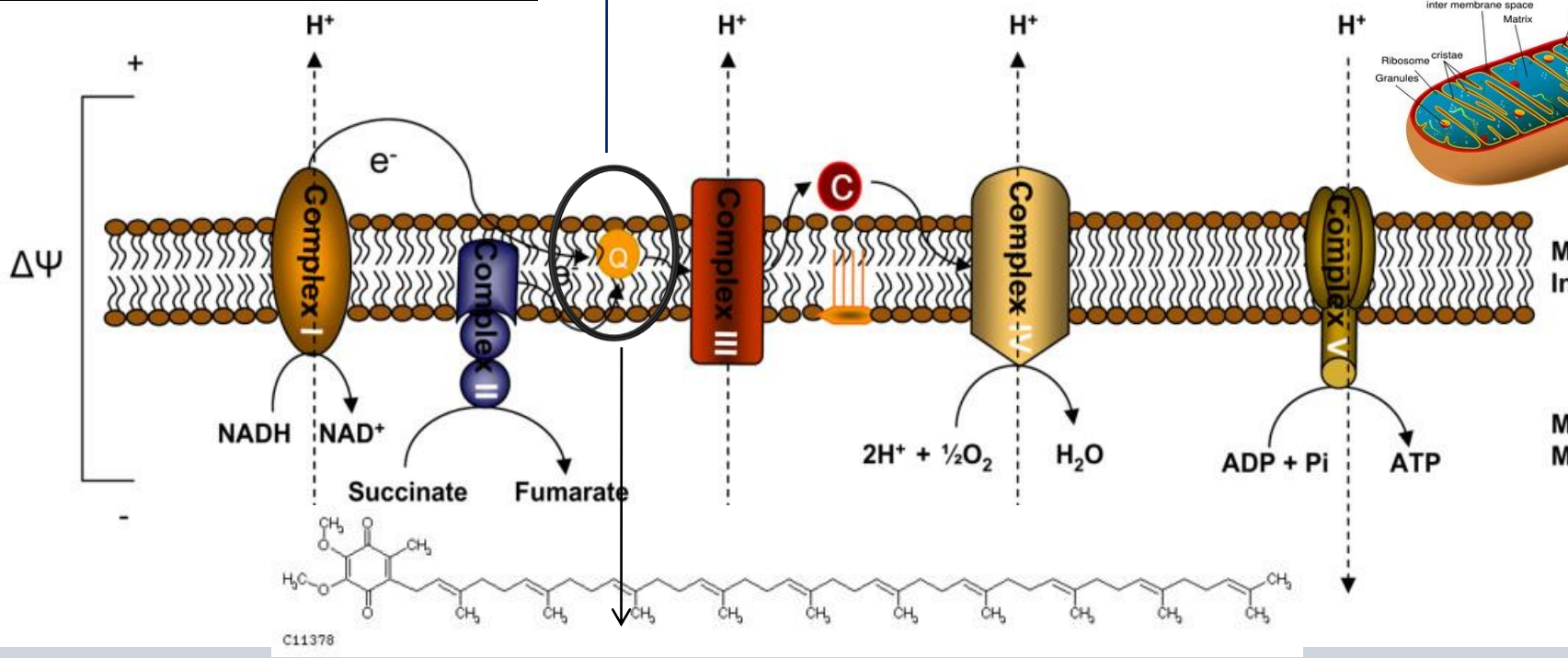


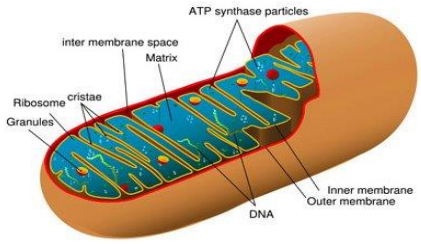
Coenzyme Q-0



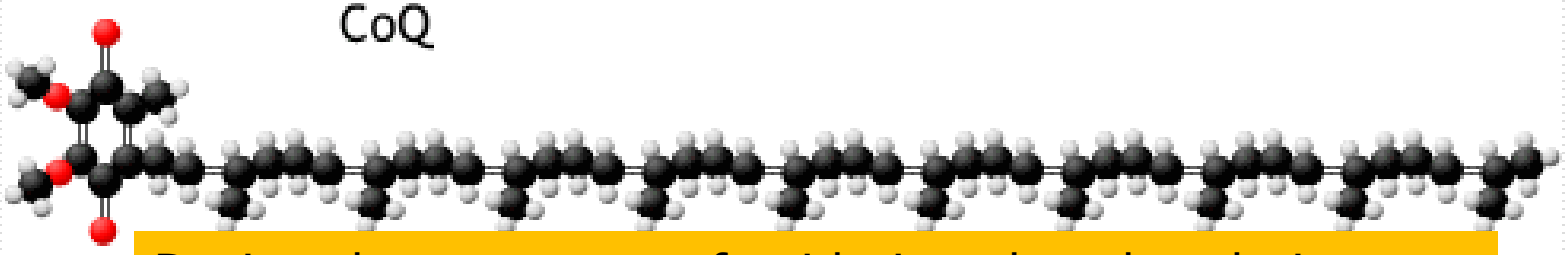






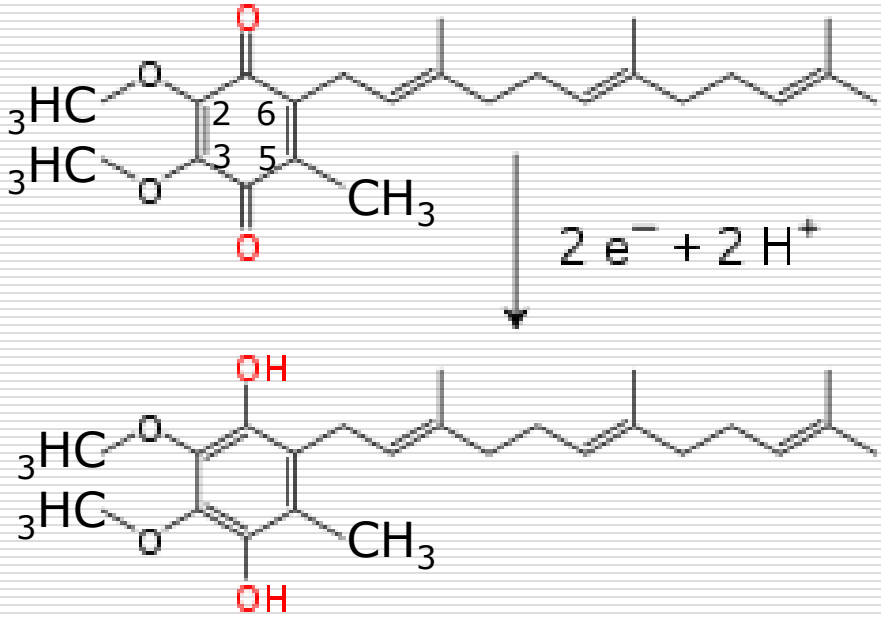


As we know, Coenzyme Q-10 is one of the crucial compounds taking part in the synthesis of ATP in mitochondrial Electron transport chain. Its role is to transfer electrons between complexes I, II and III, while also transferring protons across inner mitochondrial membrane



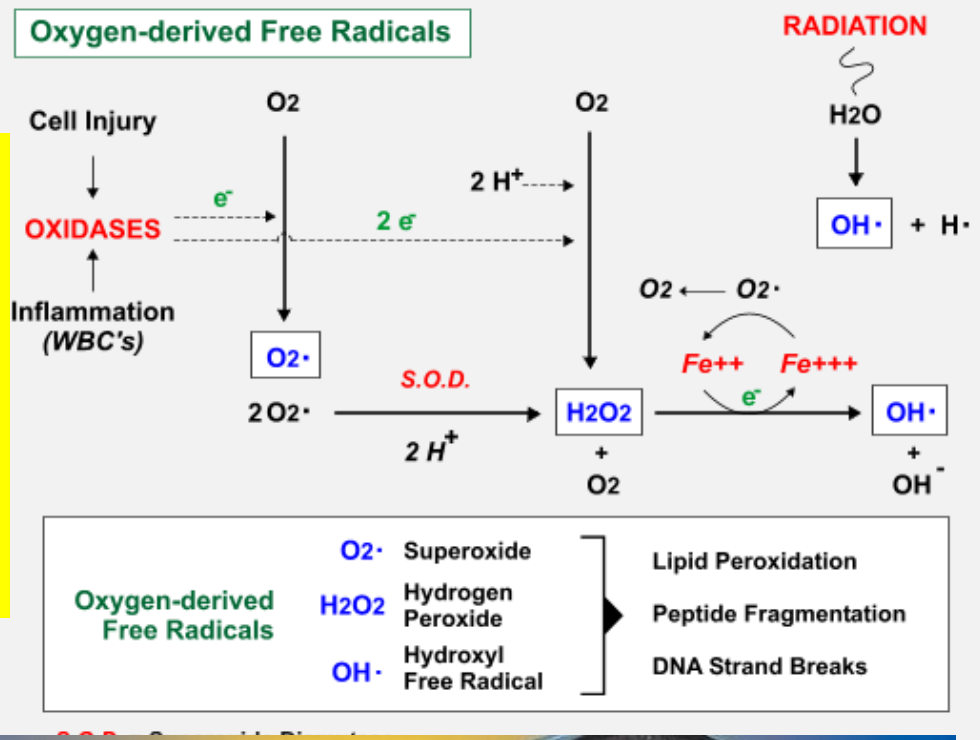
During the processes of oxidative phosphorylation, Coenzyme Q turns between two stable forms- **the oxidized Quinone** and the reduced ***Quinol form***

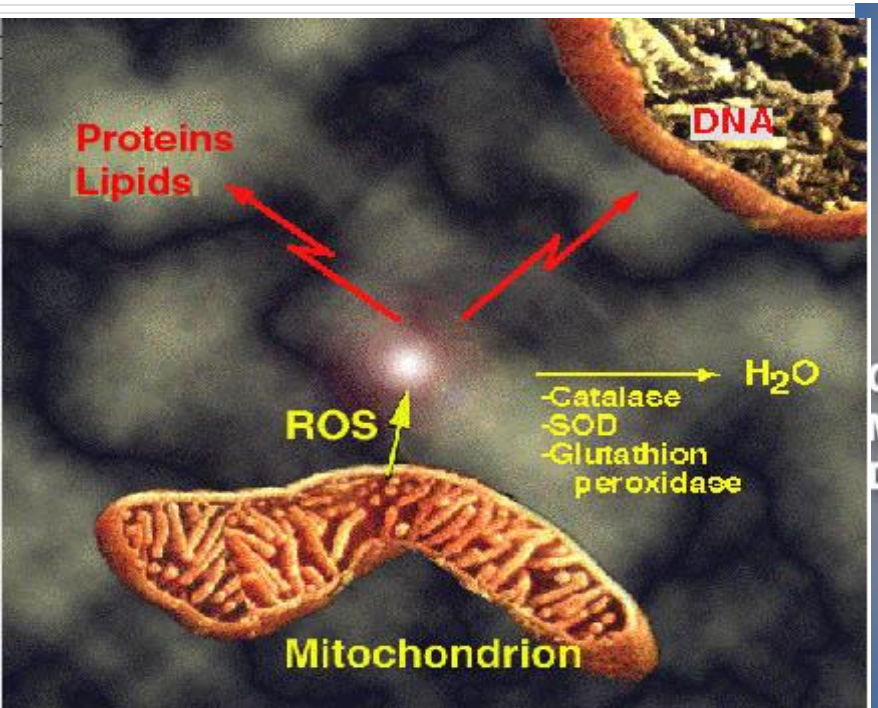
QUINONE (oxidized form)

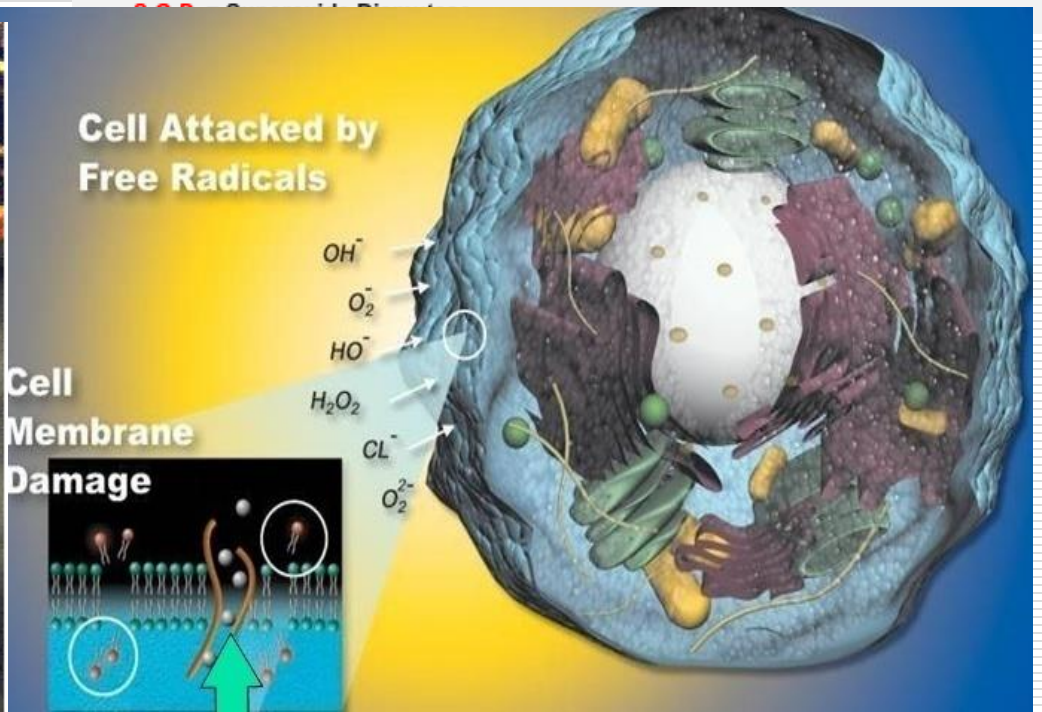


QUINOL (reduced form)

Next to its role as an electron&proton carrier, the **reduced form of Coenzyme Q-10** often **acts as a radical scavenger** for the **reactive oxygen species** generated during the processes of oxidative Phosphorilation







Two years ago, a paper of **Gulaboski, Mirceski et al. has been published in JACS**, where the chemical properties of novel Coenzyme Q 10-derivatives synthesized in alkaline media have been reported.

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Calcium Binding and Transport by Coenzyme Q

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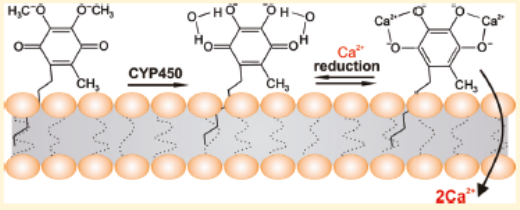
Supporting Information

ABSTRACT: Coenzyme Q10 (CoQ10) is one of the essential components of the mitochondrial electron-transport chain (ETC) with the primary function to transfer electrons along and protons across the inner mitochondrial membrane (IMM). The concomitant proton gradient across the IMM is essential for the process of oxidative phosphorylation and consequently ATP production. Cytochrome P450 (CYP450) monoxygenase enzymes are known to induce structural changes in a variety of compounds and are expressed in the IMM. However, it is unknown if CYP450 interacts with CoQ10 and how such an interaction would affect mitochondrial function. Using voltammetry, UV−vis spectrometry, electron paramagnetic resonance (EPR), nuclear magnetic resonance (NMR), fluorescence microscopy and high performance liquid chromatography−mass spectrometry (HPLC−MS), we show that both CoQ10 and its analogue CoQ1, when exposed to CYP450 or alkaline media, undergo structural changes through a complex reaction pathway and form quinone structures with distinct properties. Hereby, one or both methoxy groups at positions 2 and 3 on the quinone ring are replaced by hydroxyl groups in a time-dependent manner. In comparison with the native forms, the electrochemically reduced forms of the new hydroxylated CoQs have higher antioxidative



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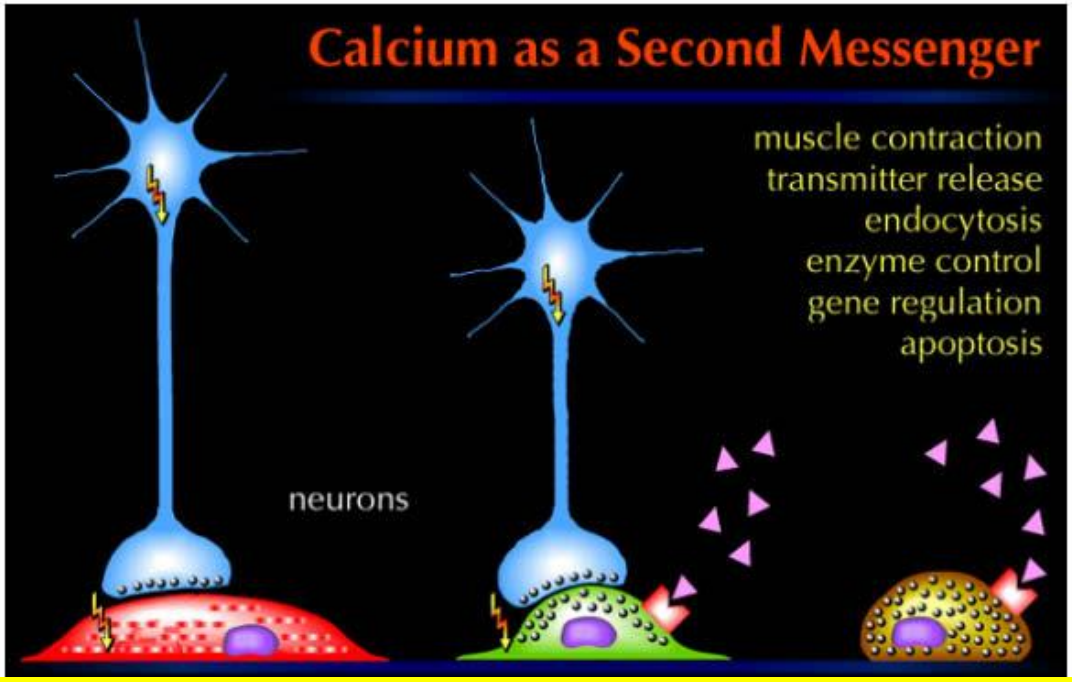
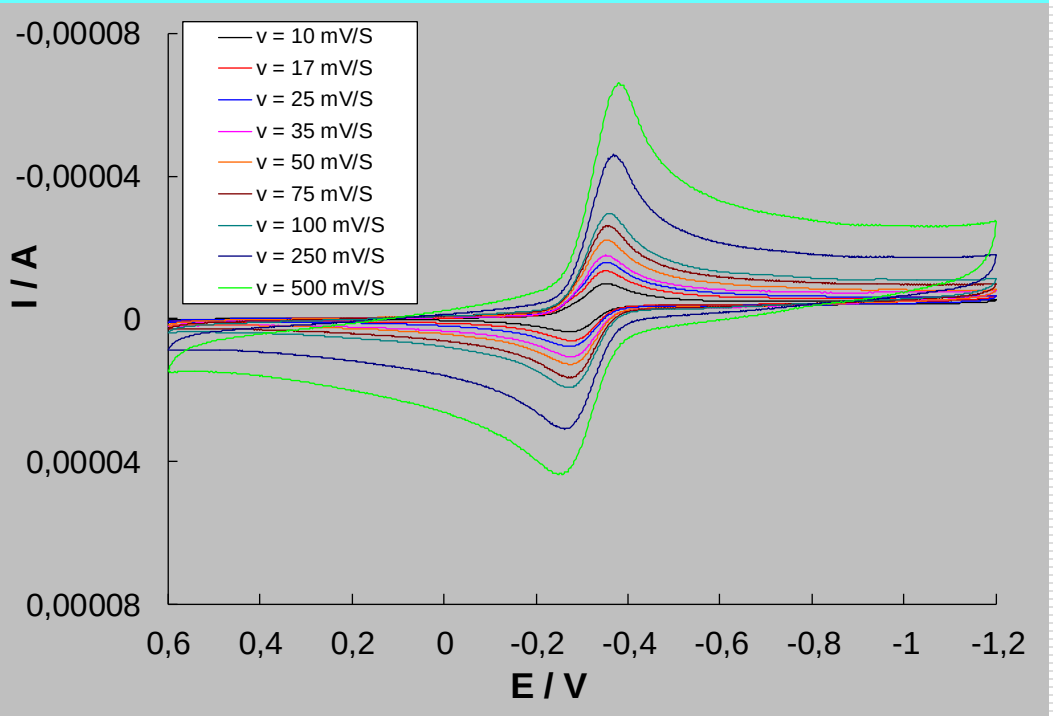
Our aim was to study the chemical features of Novel Coenzyme Q-0 derivatives obtained by reaction of Coenzyme Q-0 in alkaline media, and to study its metal-binding and antioxidative properties

Why Ca^{2+}?



Ca^{2+} -are one of the most important secondary messengers in many physiological processes!!!

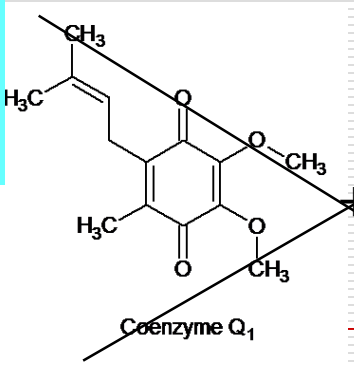
The cyclic voltammograms of Coenzyme Q-0 in neutral media consist of a single reversible signal having features of diffusional controlled redox reaction



Coenzyme Q-0 dissolves nicely in neutral, slightly alkaline and acidic media while giving yellow-colored solutions

Scan rate dependence of 0.1 mM Coenzyme Q-0 in pH of 7.00

One of our goals-to find whether native Coenzyme Q-0 can make complexes with ***Ca^{2+} ions***



+ 2e- + $2Ca^{2+}$=?

Native Coenzyme Q-0= ***Insensitive to Ca^{2+}***

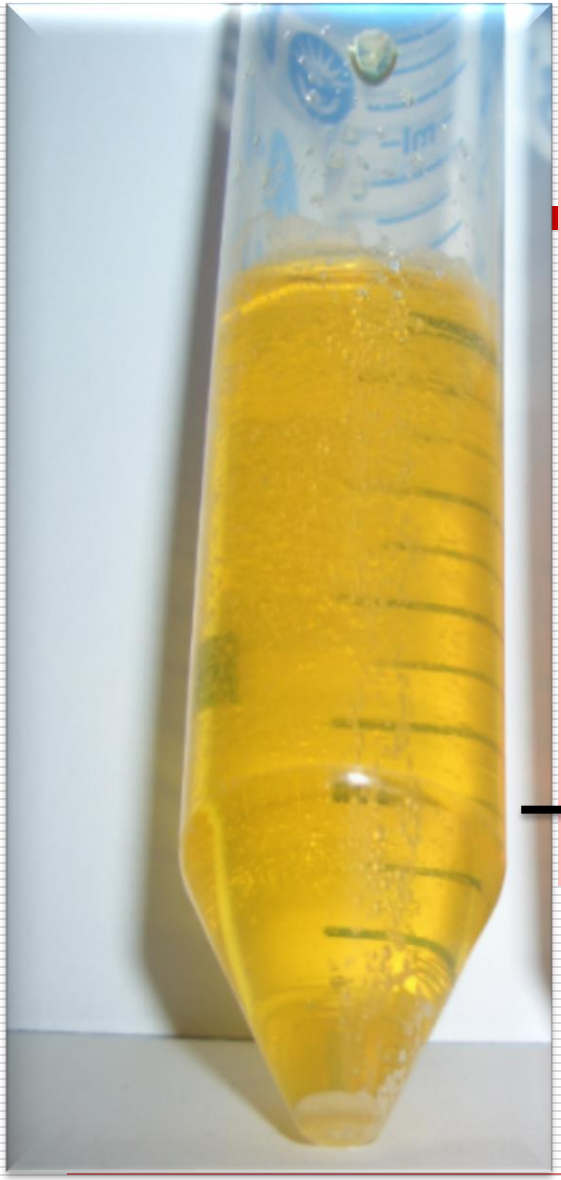
CV of 100μM CoQ-1-in pH of 7,00 (yellow native form); insensitivity to Ca^{2+}; **c(Ca^{2+})/mM = 0 (black); 1 (green); 10 (orange);50 (black) and 100 (rose)**

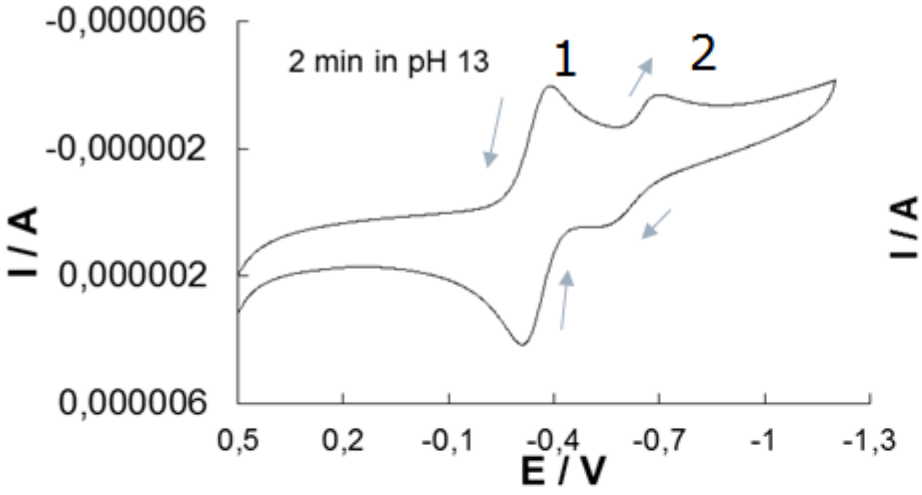
-2,4E-05
-1,6E-05
-8E-06
0
8E-06
I / A
0,8 0,6 0,4 0,2 0 -0,2 -0,4 -0,6 -0,8 -1 -1,2 -1,4
E / V

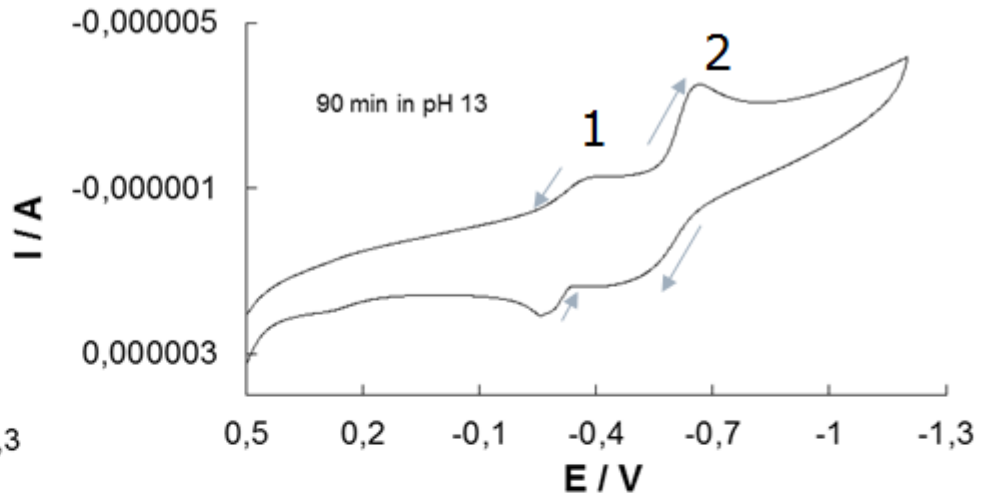
The voltammetric signal of native Coenzyme Q-0 is ***Insensitive to the concentration of Ca^{2+} ions= no complexation (same was true for other earth-alkaline cations)***

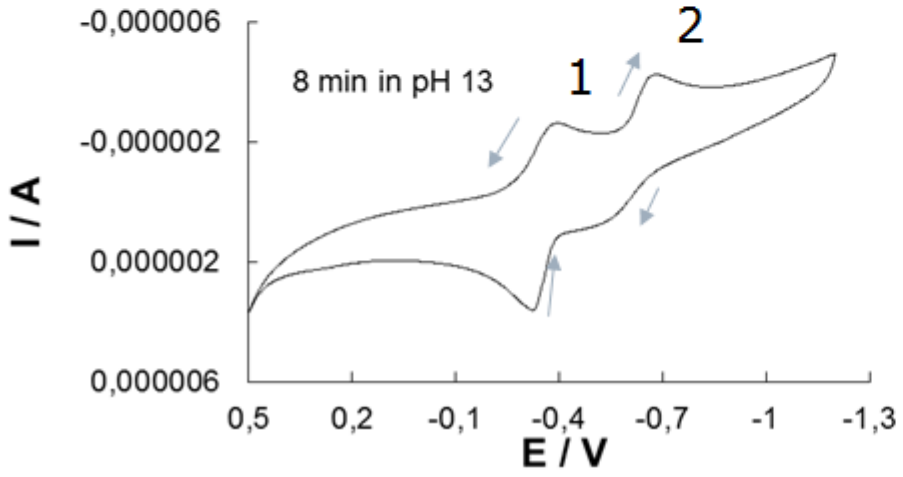
When Coenzyme Q-0
is dissolved in
in alkaline media,
there is quite
fast conversion of
the color from
yellow to intensive **red**

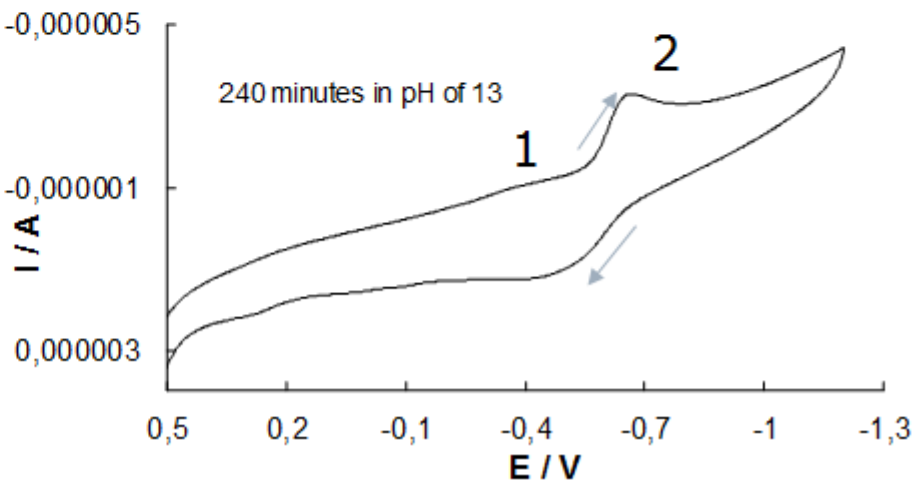
….
this is a strong indication
that chemical
reaction takes place
between Coenzyme Q-0
and the hydroxide
OH- anions



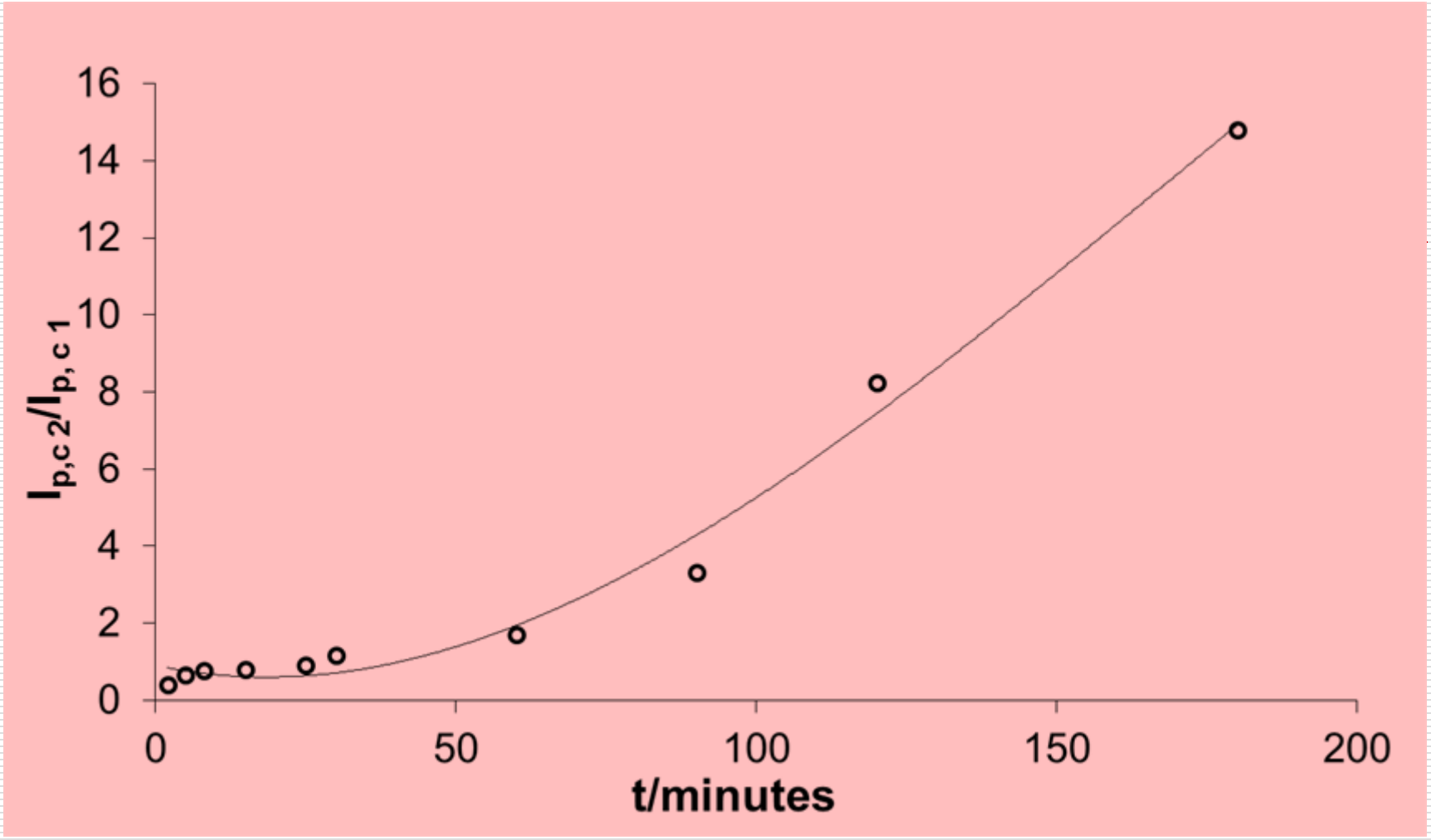






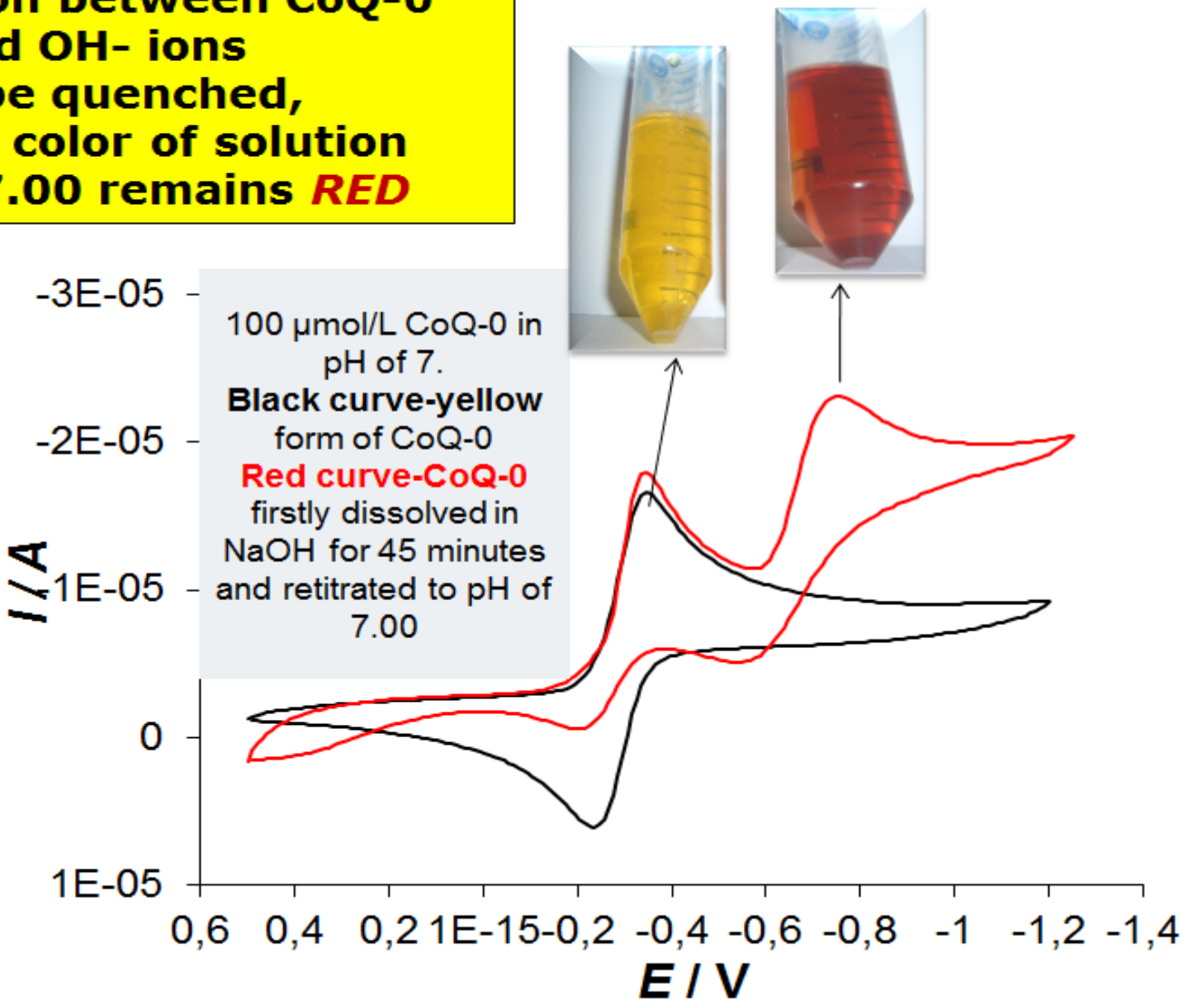


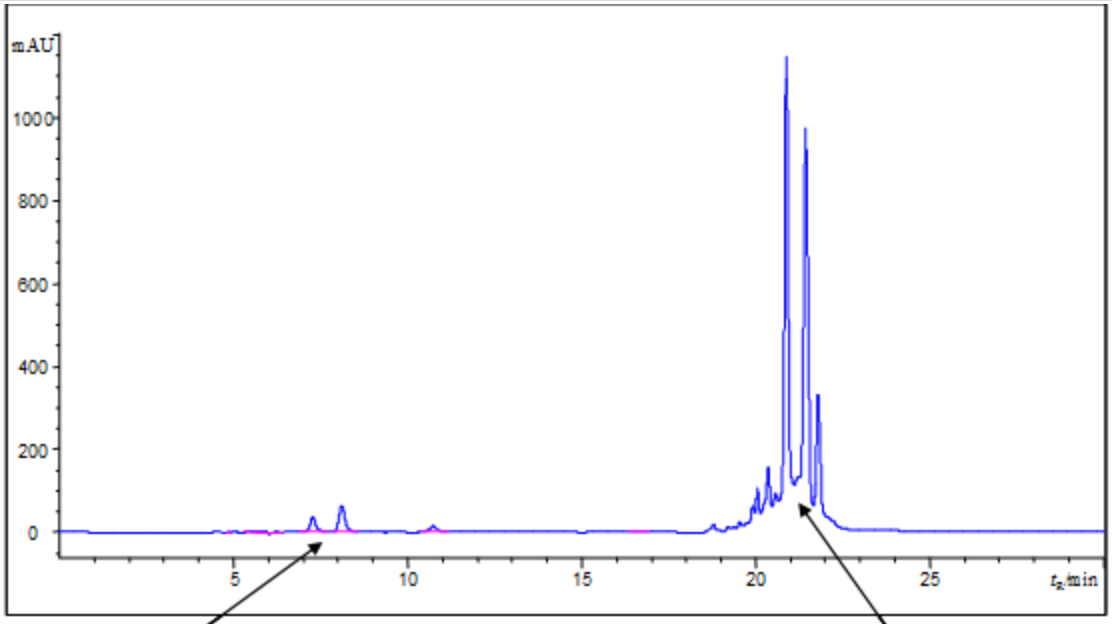
In cyclic voltammograms, one observes two signals of coenzyme Q-0 when it is dissolved in 0.1. M NaOH.
While *the signal of the native Coenzyme Q-0* (the peak assigned as "1" at more positive potentials) *decreases with the time*, *THE NEW SIGNAL* (the peak assigned as "*2*" at more negative potentials) concomitantly *gains in intensity*.

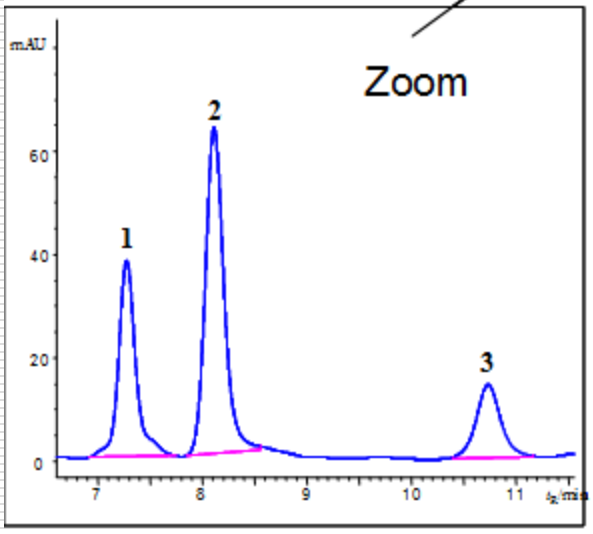


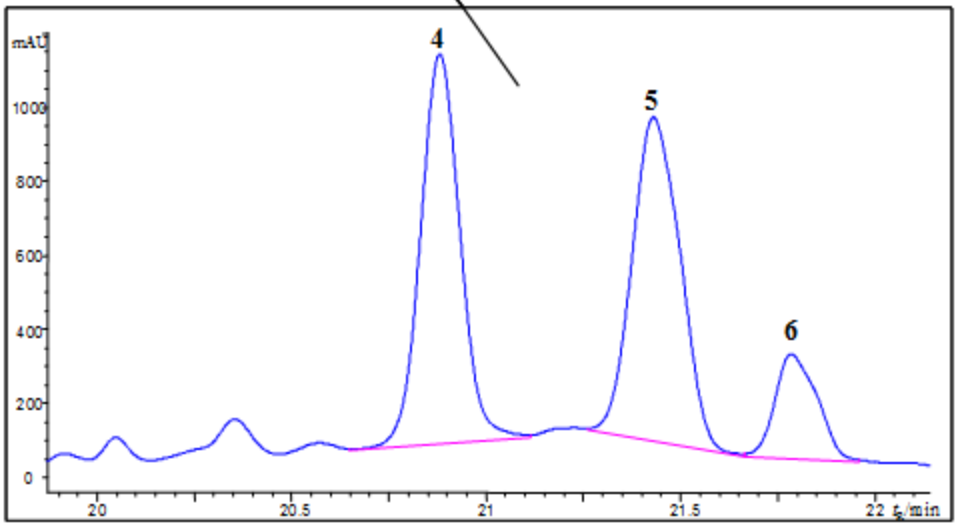
Ratio of the peak II-peak I currents vs the time from SWV experiments of CoQ-0 in pH of 13

Upon re-titration from alkaline to neutral pH, the reaction between CoQ-0 and OH- ions can be quenched, while the color of solution in pH of 7.00 remains *RED*



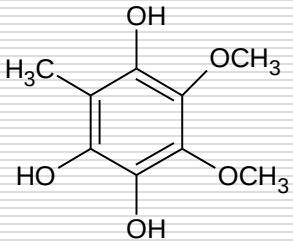






The products of the reaction of Coenzyme Q-0 and OH- anions have been identified by HPLC-MS

Compound	t_R/min	UV max/nm	MW	$[M+H]^+$	MS^2
1	7.276	266	200	201	183, 155, 127
2	**8.112**	**270**	**184**	**185**	167, 157, 143, 125
3	10.733	256	176	177	159, 131, 99
4	20.881	268	168	169	151, 123
5	21.430	268	182	183	165, 155, 137, 123, 109
6	21.78	274	272	273	240, 227



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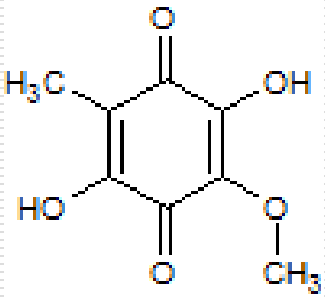
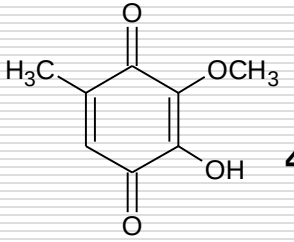


2

3???? M = 176



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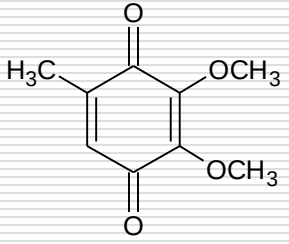

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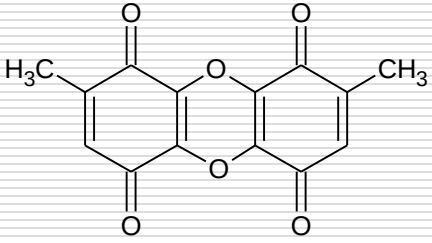

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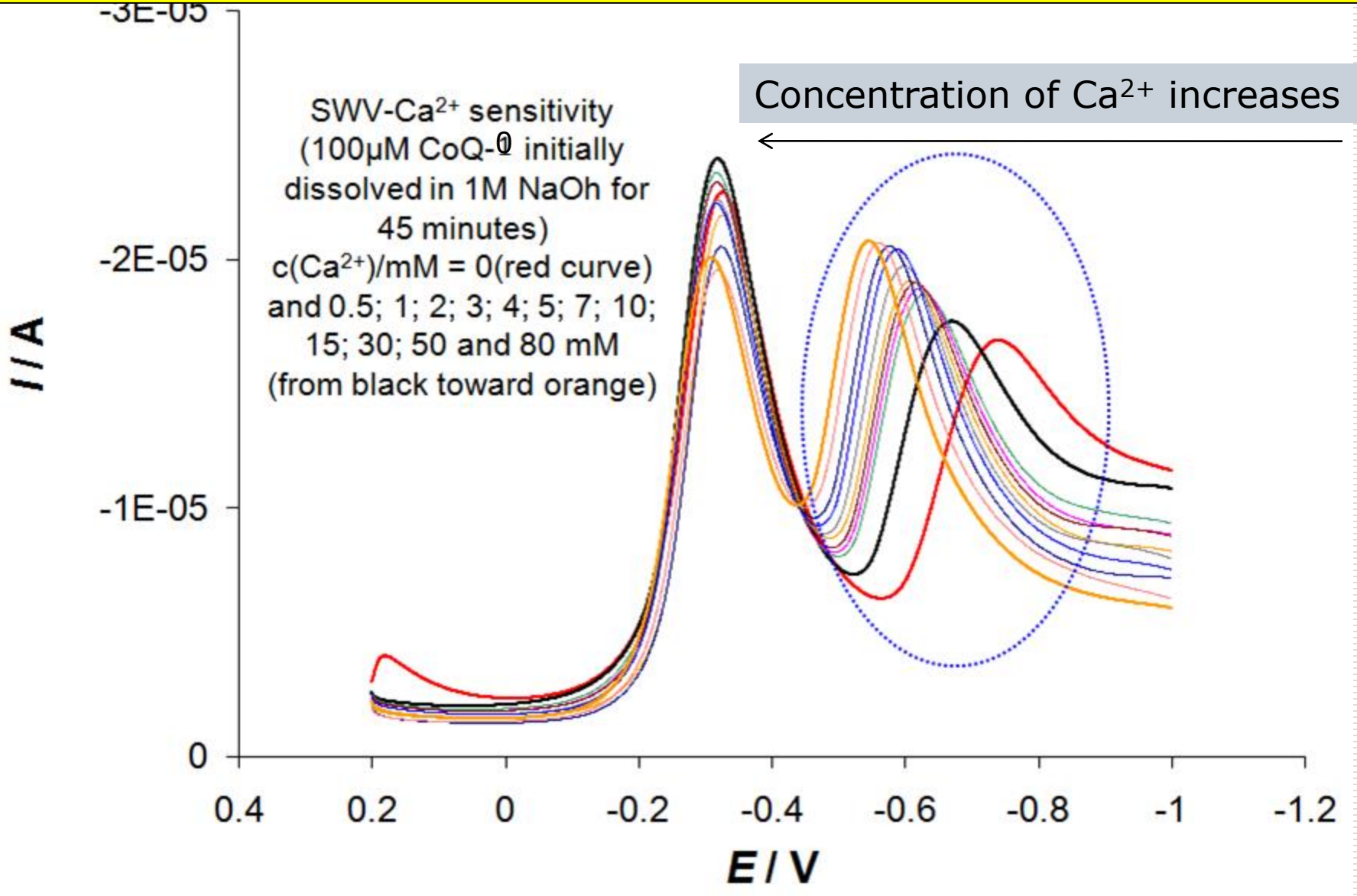
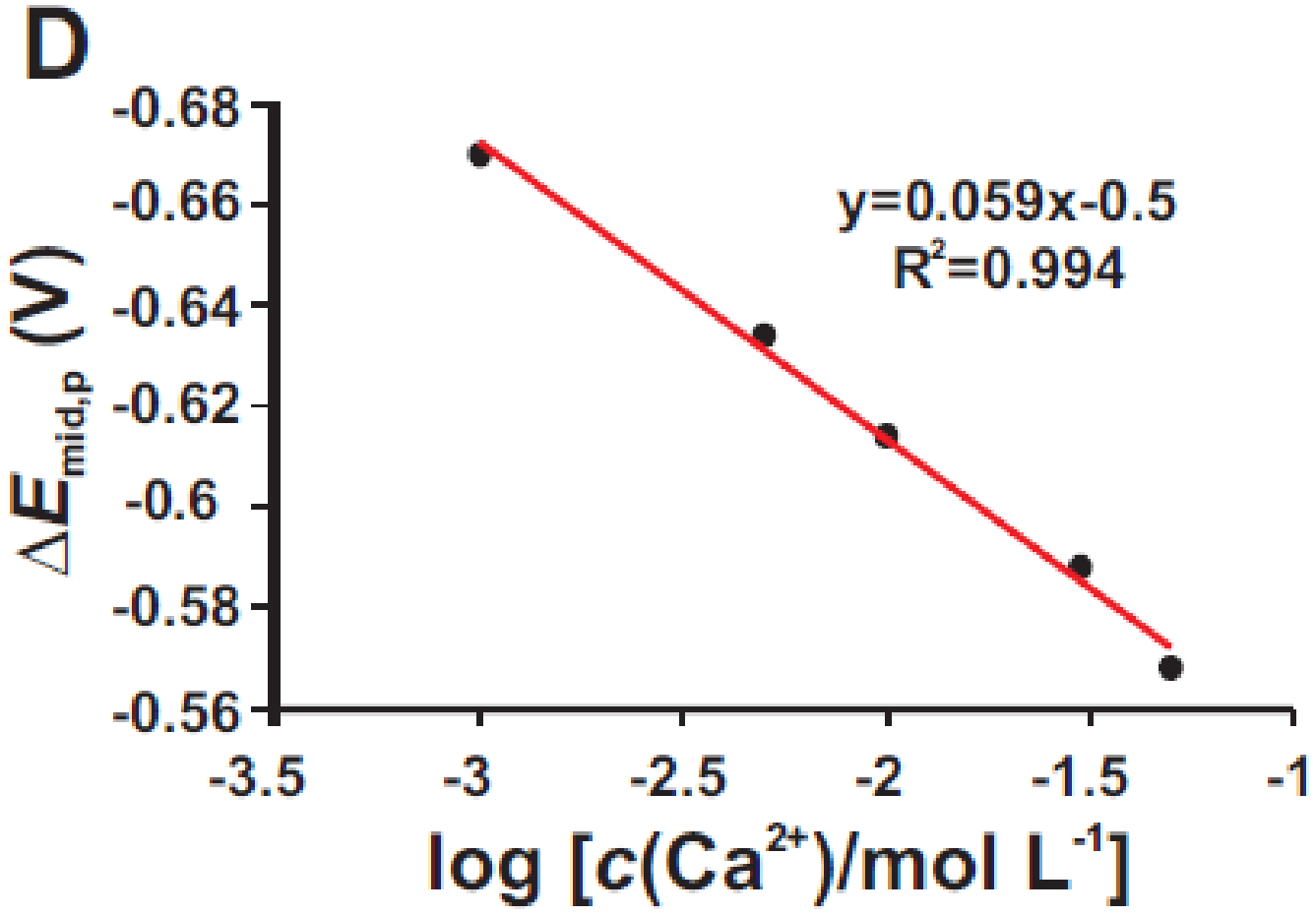
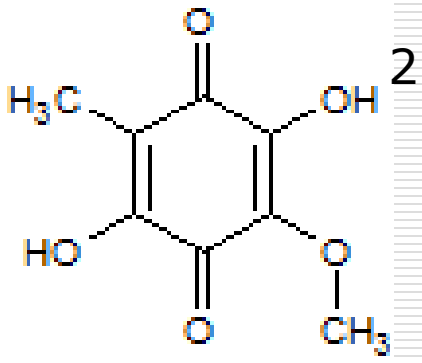
One of the derivatives of CoQ-0 obtained in alkaline media makes complex with Ca^{2+} cations in neutral solutions in stochiom. 1:2($L:M^{2+}$)

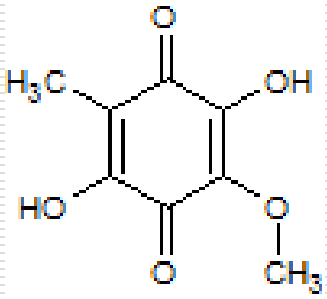


The slope of the linear dependence of $E_{p,mid}$ *vs* log[c(Ca^{2+})] of 59mV implies formation of 1:2 (Ligand to Metal) Complex between the product of the electrochemical reaction and the Ca^{2+} cations



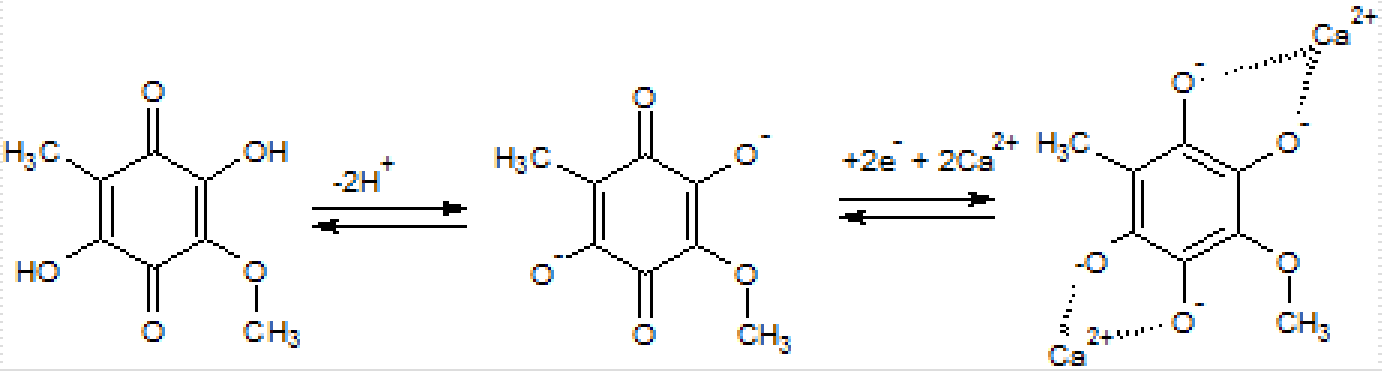


This slope implies that **compound "2"** Is most prorably The Ligand That binds Ca2+ ions



2

2,5-dihydroxy-3 methoxy-5-methyl-benzoquinone is the compound responsible for complexation with calcium cations



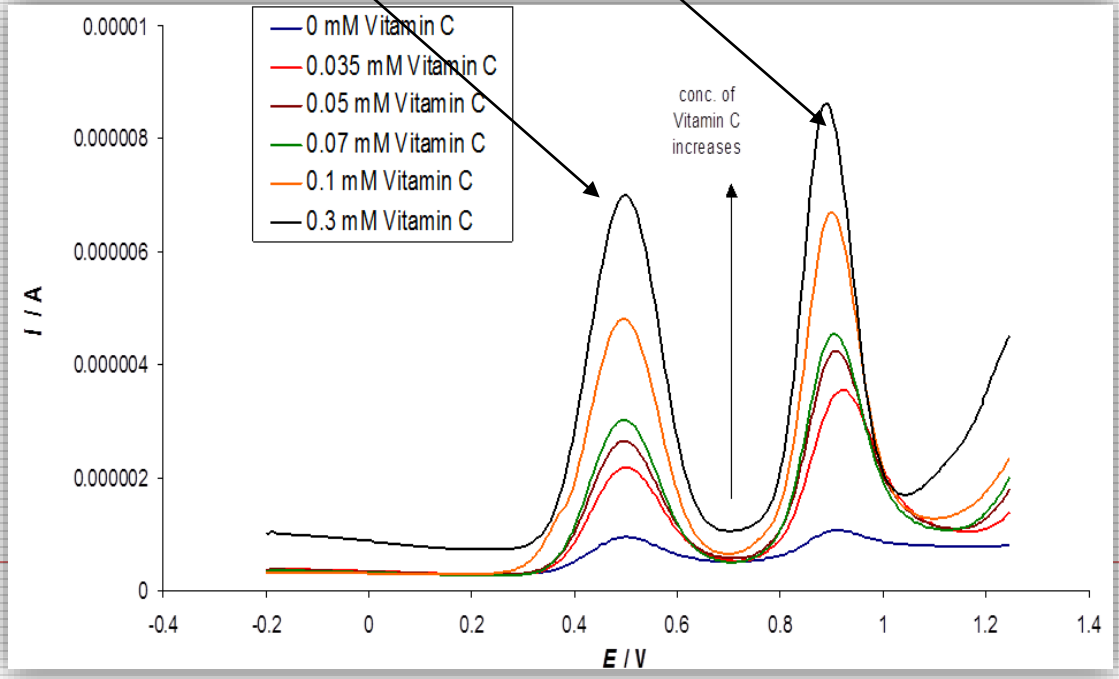
Proposed mechanism of complexation between 2,5-dihydroxy-3 methoxy-5-methyl-benzoquinone

ANTIOXIDATIVE PROPERTIES OF THE COMPOUNDS CREATED BY REACTION OF COENZYME Q-0 IN ALKALINE MEDIA

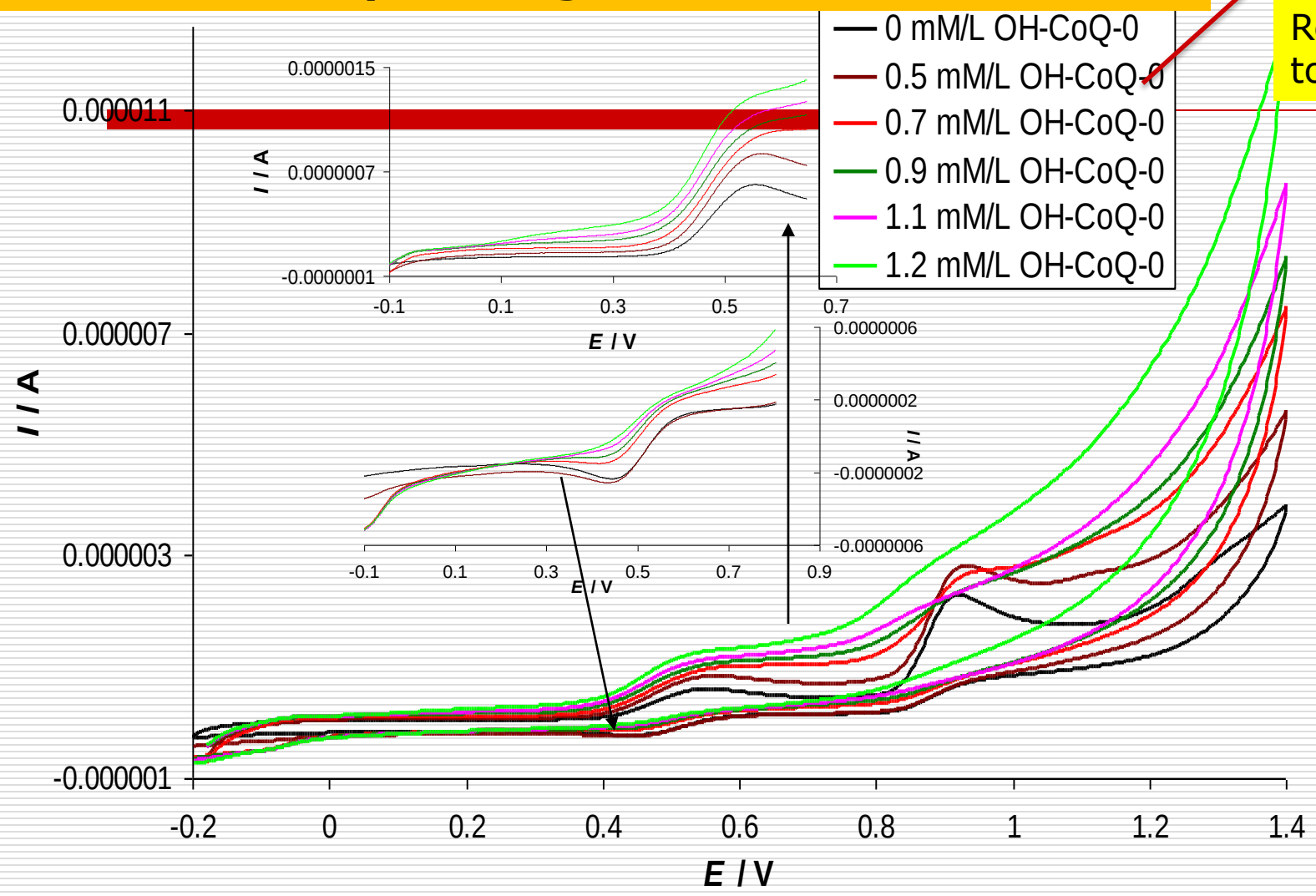
To determine the antioxidative properties of the compounds Created by reaction of Coenzyme Q-0 in alkaline media, we have used the ABTS assay as a reference standard.

ABTS undergoes stepwise two electron electrochemical oxidation while giving radical cation (in the first oxidation step), and double cation in the Second oxidation step

$$ABTS \rightleftarrows ABTS^{\bullet+} + e^- \rightleftarrows ABTS^{2+} + e^-$$



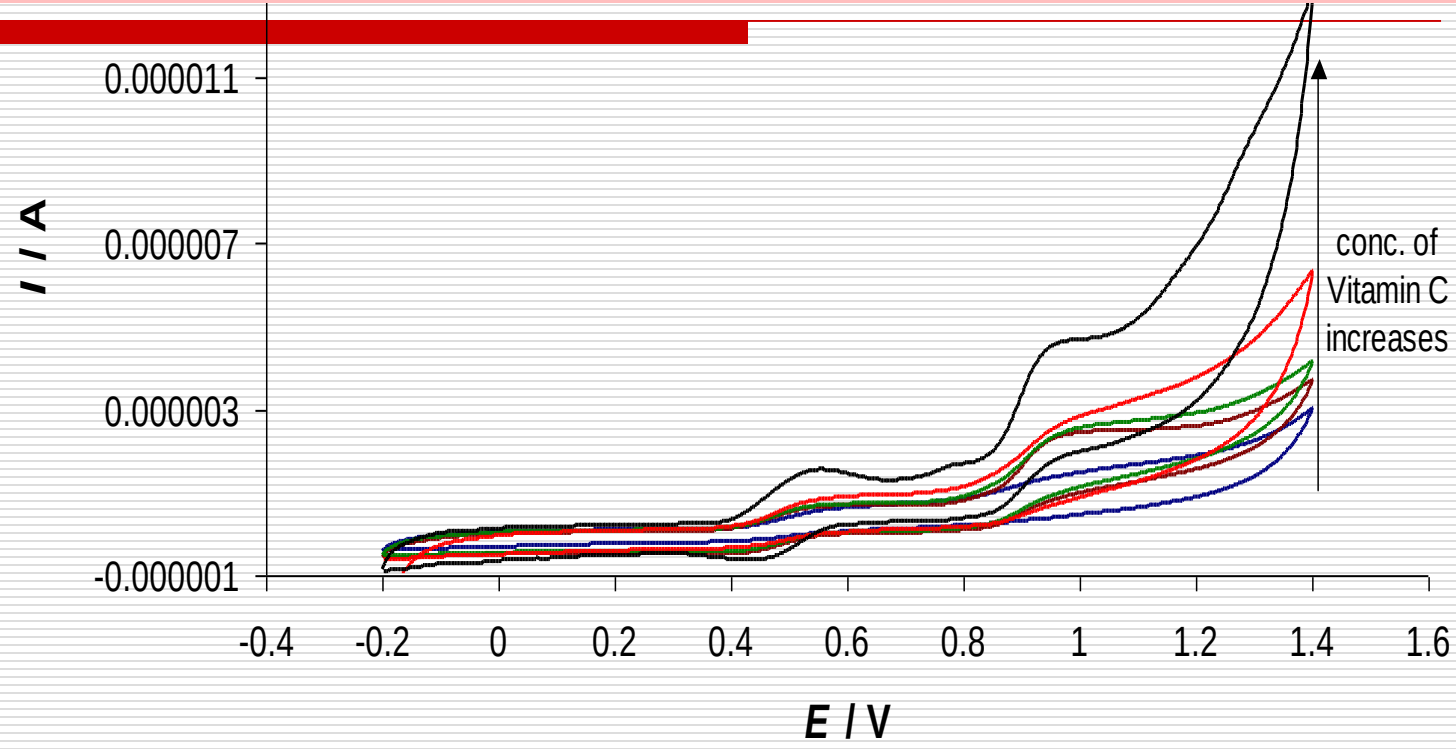
In presence of derivatives of CoQ-0 obtained in alkaline media, we observe *catalytic regenerative mechanisms* by both signals of ABTS



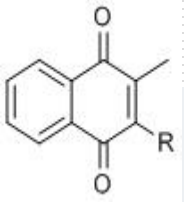
Reacted in 45 min in pH of 13, and afterwards Re-titrated to pH of 7.00

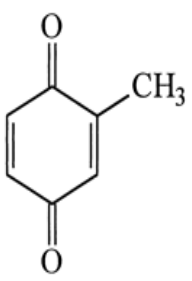
Addition of

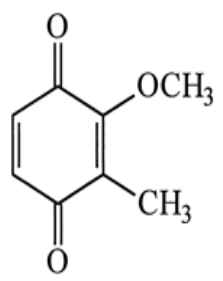
The catalytic increase of the current intensities in presence of the derivatives of Coenzyme Q-0 obtained in alkaline media is comparable to that observed of Vitamin C (same concentrations of Vit. C are used as in the experiment with Coenzyme Q-0 derivatives)



This comparison shows that the antioxidative capacity of the compounds obtained by alkaline reaction of Coenzyme Q-0 is similar to that of Vitamin C



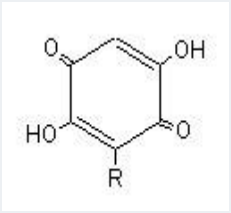




Conclusions

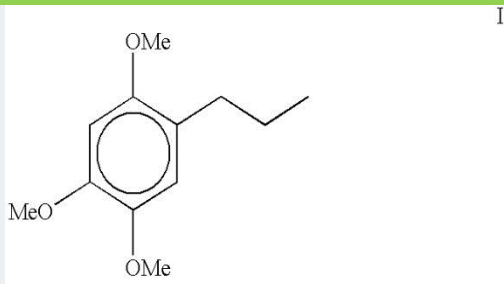
❑***There are many natural secondary metabolites with structures similar to that of Coenzyme Q-0 and its reported derivatives***

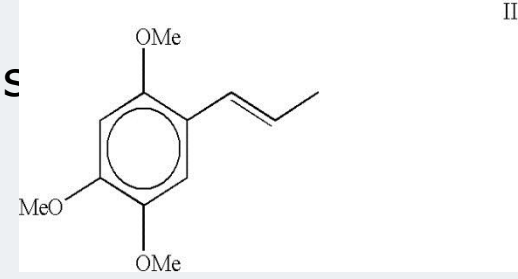
Some natural compounds with similar structure to that of CoQ-0 and its derivatives obtained in alkaline media



❑Many of them can show Similar features to those of derivatives obtained by alkaline reaction of CoQ-0

❑. Metal-binding and antioxidative features of the CoQ-0 derivatives obtained in alkaline media are of Fudnamental importance for these classes of compounds





…

Isolation of the **products** is a task currently going on.

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[2] I. Bogeski, R. Gulaboski, R. Kappl, V. Mirceski, M. Stefova, J. Petreska, M. Hoth, *J. Am. Chem. Soc*. **133** (2011) 9293-9303

[3] R. Gulaboski, V. Mirčeski, I. Bogeski, M. Hoth *J. Solid State Electrochem*.**16** (2012) 2315-2328

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[4] R. Gulaboski, P. Kokoskarova, S. Mitrev, *Electrochim. Acta* **69** (2012) 86-96