Interaction of the Quinoline Derivatives with Coenzyme Q_{10} *

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The interaction of the quinoline derivatives with CoQ_{10} is studied both experimentally, using polarographic and spectrophotometric techniques, and theoretically, applying the perturbation molecular orbital theory. The $E_{1/2}$ potentials of a series of 1:1 solution mixtures of quinoline derivatives with CoQ_{10} are measured and compared with $E_{1/2}$ of the coenzyme alone (0.52 V). An increase in the $E_{1/2}$-magnitude of the coenzyme is detected ($\Delta E_{1/2} \approx 0.03-0.13$ V). Simple perturbation molecular orbital treatment shows an increase in the energy of the lowest unoccuppied molecular orbital of the coenzyme due to the same interaction, in agreement with the polarographic results. The complexation constants of the same quinoline derivatives, as well as the antimalarials quinine, primaquine and chloroquine, with CoQ_{10} are determined spectrophotometrically and found to be in the order of 10^5. The K value for each complex is determined at 10 different wavelengths and 7 different constituent concentrations of the solution. The complexation enthalpies are all small and positive (0.98–4.53 kcal/mol), the entropies are big and positive (29–41 cal/deg.mol). The big entropy change suggests an increase in the internal motion of the complexing molecules. It is suggested that the increase in the internal motion is due to the increase in the motion of the isoprenoid side chain of the coenzyme.

Our former work [1] showed that mixing any of the antimalarials, quinine, primaquine or chloroquine with the coenzyme Q_{10} in solution, with a 1:1 molar ratio, causes an increase in the polarographic half-wave potential, $E_{1/2}$, of the coenzyme The increase in $E_{1/2}$ and consequently in the reduction potential of the coenzyme was attributed to the π-π interaction of its quinone group with the quinoline heteroaromatic ring of the drug molecule. Simple perturbation treatment confirmed this result in showing that such an interaction does increase the energy of the lowest unoccupied molecular orbital (LUMO) of the coenzyme [1]. Yet, if the actual mode of interaction were the π-π interaction then one should observe a similar increase in the $E_{1/2}$ magnitude of CoQ_{10} when mixed with other quinoline derivatives. Further, spectrophotometric studies should yield considerable values for the complexation constants of the coenzyme with these derivatives.

The measured $E_{1/2}$ of CoQ_{10} was 0.55 V (external mercurous sulfate electrode, [2]), and found to be pH dependant. Variation of the isoprenoid side chain length showed no influence on $E_{1/2}$ [2–4]. The $E_{1/2}$ values for a number of quinoline derivatives had been reported in the literature [5–11]. In most cases low lying adsorption waves as well as two reversible reduction waves could be identified. The ranges of both measured reduction waves were 1.24–1.35 V and 1.62–1.75 V, respectively [5–11]. No polarographic measurements for a mixture of a quinoline derivative with CoQ_{10} in solution were reported besides our recently published data [1].

Methods

In the present work the same perturbation molecular orbital (PMO) method as that of Ref. [1] is used to inspect the interaction energies of the substituted quinoline derivatives with CoQ_{10}. The applied Hückel α and β parameters are those recommended in the literature [12]. The HMO calculations are carried out using an IBM 1130 computer, the PMO calculations are done using a Hewlett-Packard 9810 programmable calculator with an extra 9865 A memory. Calculation of the equilibrium constant values of the formed molecular complexes are done according to Briegleb using the following Equation [13]:

$$\frac{C_A^0\, C_D^0}{{}^{c}D} + \frac{{}^{c}D}{\varepsilon^2} = \frac{1}{K\,\varepsilon} + \frac{(C_D^0 + C_A^0)}{\varepsilon} \qquad (1)$$

where C_A^0 and C_D^0 are the initial concentrations of the acceptor (CoQ_{10}) and donor (quinoline derivative) respectively. K is the equilibrium constant,

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${}^{c}D$ is the observed difference in the optical density defined as followed:

$$ {}^{c}D = D_{tot} - \varepsilon_A C_A^0 - \varepsilon_D C_D^0 \quad (2) $$

and ε the extinction coefficient of the formed complex. The values of ε_A, ε_D and D_{tot} are taken from the UV spectra of the acceptor, the donor and of their mixtures. Solutions of Eq. (1) for K and ε are obtained using a multiple variable linear regression program written for the HP-9810 [14, 15]. The number of complexes in one solution is determined according to Liptay [16] through inspection of the matrices of optical density differences ${}^{c}D_{ik}$ as defined according to Equation (2). The values of ${}^{c}D_{ik}$ are calculated for different concentrations (i) at different wave lengths (k).

$$
\begin{array}{l}
{}^{c}D_{11}\ {}^{c}D_{12}\ {}^{c}D_{13} \ldots {}^{c}D_{1m} \\
{}^{c}D_{21}\ {}^{c}D_{22}\ {}^{c}D_{23} \ldots {}^{c}D_{2m} \\
{}^{c}D_{31}\ {}^{c}D_{32}\ {}^{c}D_{33} \ldots {}^{c}D_{3m} \\
\quad \cdot \\
\quad \cdot \\
\quad \cdot \\
{}^{c}D_{n1}\ {}^{c}D_{n2}\ {}^{c}D_{n3} \ldots {}^{c}D_{nm}
\end{array}
$$

According to Liptay the rank of the matrix is equivalent to the number of complexes formed in the solution. If the rank is 1 then a 1:1 stochiometry is accepted by us, if 2 then two complexes of the stochiometries 1:1 and 1:2 are assumed. The obtained values of K at different temperatures are then used to compute the equilibrium thermodynamic data G, H and S according to the equation:

$$ \ln K = -\frac{\Delta G}{RT} \quad (3) $$

and

$$ \Delta G = \Delta H - T\,\Delta S\,. \quad (4) $$

Equation (4) is solved for the two unknowns ΔH and ΔS using a two variable linear regression program written for the HP-9810 too [15].

All polarographic measurements are done with a Cambridge Pen Recording polarograph supplied with a Uni Vector unit for alternate current polarography. Before each measurement the solution is deoxygenated by bubling N_2 through it for 20 minutes. The UV-spectra are measured using a Perkin-Elmer 402 spectrophotometer with thermostated cells. The temperatures are measured in the cell compartment. The constitutions of the solutions used for the UV spectra are similar to those applied for the polarographic measurements.

CoQ_{10} was supplied by Sigma Chemical Company, St. Louis, USA and the quinoline derivatives by Fluka AG, Buchs, Switzerland.

Results and Discussion

The measured $E_{1/2}$ values of the different quinoline derivatives are similar in magnitude to those known in the literature [5—11]. Table 1 includes these values as well as the $E_{1/2}$ of CoQ_{10} alone. It also includes the $E_{1/2}$ values of the 1:1 mixtures of CoQ_{10} with each quinoline derivative. The $E_{1/2}$ of the absorption waves are not included in the table.

The values in the second column of the table are all bigger than $E_{1/2}$ of CoQ_{10} alone (0.52 V). The increase in $E_{1/2}$ of CoQ_{10} due to the presence of a quinoline derivative is comparable to its increase due to the presence of an antimalarial [1]. The similarity justifies our assumption of a quinoline-quinone, π-π interaction between both molecules. As in the case of antimalarials [1], the $E_{1/2}$ values of the quinolines correlate well with the calculated Hückel energies of their LUMO, Figure 1. Similarly the PMO calculated energies of the lowest unoccupied molecular orbital (E_{LUMO}) of the formed

Table 1. $E_{1/2}$ values of the quinoline derivatives and of their 1:1 mixtures with CoQ_{10} measured at 22 °C, in Britton-Robinson-ethanol (1:4) mixture against saturated calomel electrode.

Quinoline Derivative	$E_{1/2}$ (V)	$E_{1/2,\,\mathrm{Deriva}+CoQ_{10}}$ (V)
—	—	0.52
2-chloro-	1.27, 1.62	0.68, 1.36, 1.76
2-hydroxy-	1.32, 1.74	0.55, 1.34, 1.76
4-hydroxy-	1.31, 1.72	0.67, 1.34
8-hydroxy-	1.28, 1.59	0.55, 1.26, 1.56
8-amino-	1.38	0.56, 1.33, 1.66
4-amino-quinaldine	1.34	0.53, 1.34
4-hydroxy-quinaldine	1.29	0.60, 1.38, 1.80
8-hydroxy-quinaldine	1.33, 1.62	0.56, 1.36

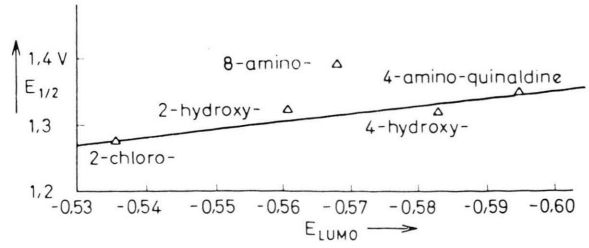


Fig. 1. Calculated Huckel LUMO energies of the quinoline derivatives as correlated to their measured $E_{1/2}$ values.

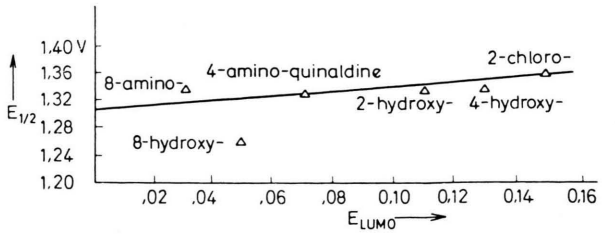
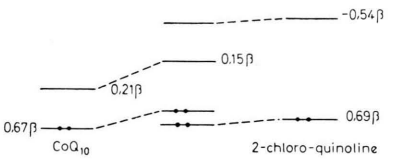


Fig. 2. Calculated Huckel LUMO energies of the formed quinoline-CoQ_{10} complexes as correlated to the $E_{1/2}$ values of their second waves.

complexes correlate well with the measured $E_{1/2}$ values of their second waves (Figure 2).

The perturbation treatment for the interaction of any of the quinoline derivatives with the coenzyme showed an increase in E_{LUMO} of the latter.

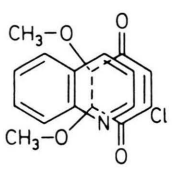


Of interest is the orientation of both cyclic compounds relative to each other in the complexes. Since the expected distances between the planes of both molecules in the complexes are large, approx. 3.3 Å [1], the repulsion terms between them should be small. The relative orientation of the molecules should then be dependant on the overlap interaction of their π-MOs. The PMO calculated orientation are pictured in Figure 3. It can be seen that on forming the complexes the quinone ring faces the part of the quinoline molecule with the bigger electron density. This is usually the ring with the heteroatom, or the ring with an electron donating substituent as in the case of 8-hydroxy- or 8-amino-quinoline.

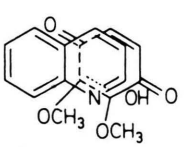
UV-Spectra and K Values

The UV spectra of the mixtures show all the bands that appear in the spectra of their constituents. No change in λ_{max} of the coenzyme or of the quinoline derivatives is noticed and no new, chargetransfer bands are observed. However a considerable change in the extinction coefficients (ε) of the component bands is detectable. Figure 4 shows the UV absorption spectra of 2-chloro-quinoline, CoQ_{10} and of their 1:1 mixture.

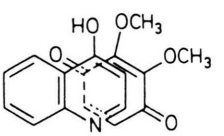
To compute the K value for each complex the absorbance values for the mixture with 7 different concentration ratios at 10 different wave lengths are recorded. In all measurements the CoQ_{10} concentration is 2×10^{-5} Mol/l, whereas the concentration of the quinoline derivative varies from 3×10^{-5} to 9×10^{-5} Mol/l. The wave lengths at which the absorbance is recorded are 220, 230, 240, ..., 320 nm. The temperatures at which the spectra are recorded are 25°, 30°, 40°, 45° and 50 °C. The computed K values are wave-length independant (Figure 5). Exceptions from the complexes of both 4-hydroxy-quinoline and 8-hydroxy-quinoline. For both complexes a slight but apparent scattering of the K values from the correlation line



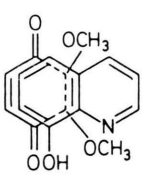
2-chloro-



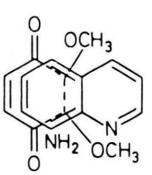
2-hydroxy-



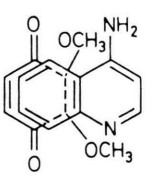
4-hydroxy-



8-hydroxy-



8-amino-



4-amino-

Fig. 3. Calculated preferred orientations of CoQ_{10} and the quinoline derivatives in their complexes.

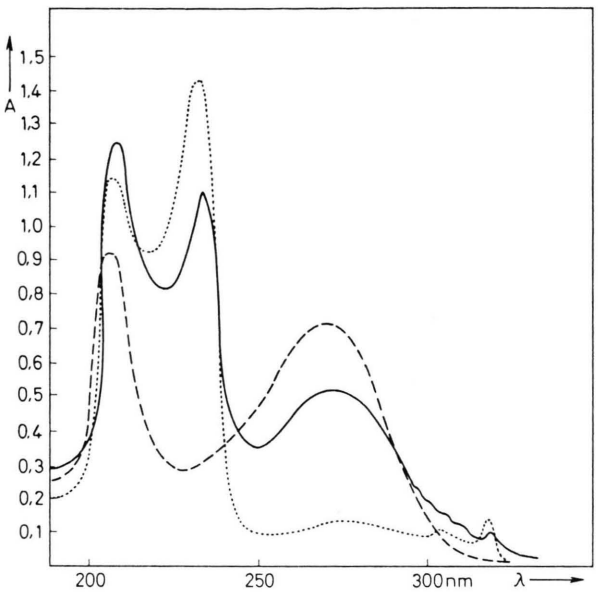


Fig. 4. UV-absorption spectra of 2-chloro-quinoline, CoQ_{10} and of their 1 : 1 mixture in a 4 : 1 ethanol-Britton-Robinson solution.
– – – – CoQ_{10} (2×10^{-2} Mol/l),
· · · · · · 2-chloro-quinoline (5×10^{-5} Mol/l),
——— 1 : 1 mixture of both solutions.

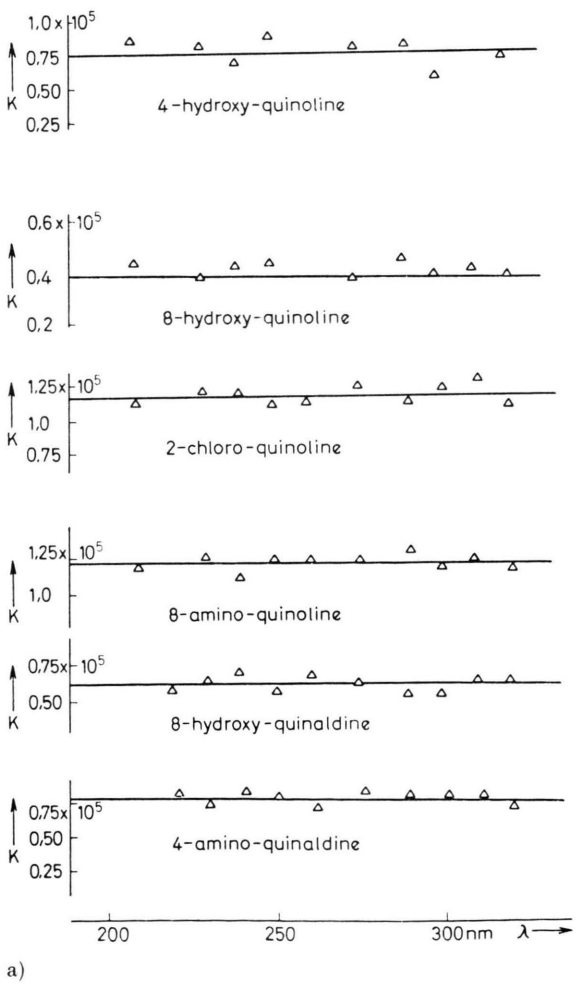
is noticed. The values of the ${}^{c}D_{ik}$ matrix elements of both complexes conform better with the rank 2 than 1. For this reason both values are written within paranthesis in Table 2. Subsequent determination of the two equilibrium constants K_1 and K_2 of each system is desired.

Table 2. UV-spectrophotometrically determined complexation constants of the quinoline derivatives with CoQ_{10} at different temperatures, in Britton-Robinson-ethanol (1 : 4) solution.

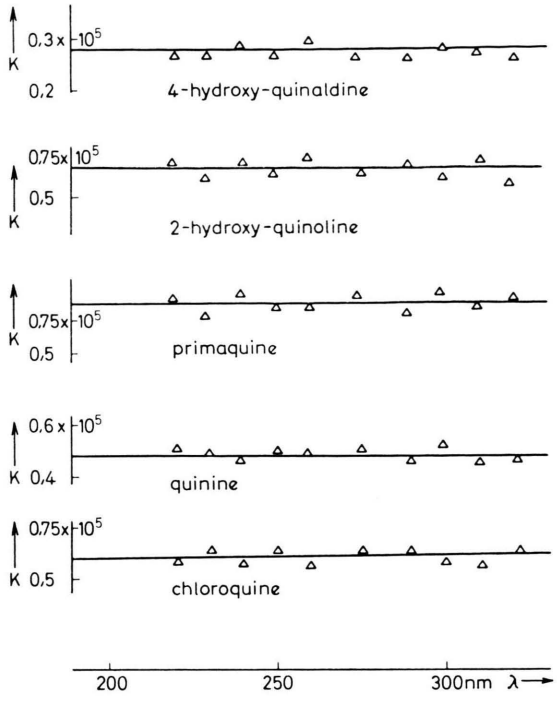
Quinoline derivative	$K \times 10^{-5}$ ($Mol^{-1} \cdot l$) 25 °C	30 °C	35 °C	40 °C	45 °C	50 °C
2-chloro-	1.172	1.172	0.956	0.956	0.913	0.913
2-hydroxy-	0.734	0.754	0.699	0.699	0.648	0.648
4-hydroxy-	(0.994)	(0.942)	(0.861)	(0.83)	(0.752)	(0.728)
8-hydroxy-	(0.407)	(0.407)	(0.350)	(0.350)	(0.293)	(0.293)
8-amino-	1.219	1.219	0.967	0.967	0.905	0.905
8-amino-quinaldine	0.773	0.773	0.714	0.714	0.673	0.673
4-hydroxy-quinaldine	0.287	0.287	0.239	0.239	0.197	0.197
8-hydroxy-quinaldine	0.639	0.639	0.601	0.601	0.548	0.548
Quinine	0.465	0.465	0.420	0.420	0.361	0.361
Chloroquine	0.549	0.549	0.501	0.501	0.471	0.471
Primaquine	0.784	0.784	0.729	0.729	0.685	0.685

Obvious are the big magnitudes of all K values. They indicate the high stabilities of the complexes and confirm our assumption that were based on polarographic measurements. The strongest formed complex is that of 8-amino-quinoline, followed by that of 2-chloroquinoline. The weakest is that of 4-hydroxy-quinaldine. The complexes of the antimalarials quinine, primaquine and chloroquine are of intermediate strength when compared with those of the measured quinoline derivatives. Comparison of the K values in the table with the $E_{1/2}$ of Table 1 shows no correlation between them. Although both 8-amino-quinoline and 2-chloro-quinoline show the highest K values and $E_{1/2}$ values at the same time, no such parallelism in the values is detected for other complexes. This noncorrelation is explained

Fig. 5. Computed K values as correlated to the measurement wave length.



a)



b)

in that the K value is a result of the perturbation of all MO energy levels in both molecules and of the entropy change, where as the $E_{1/2}$ is a result of the change in the energy of one single MO.

Table 3. ΔG, ΔH and ΔS values of the studied quinoline-CoQ_{10} complexes as calculated from the values of Table 2.

Quinoline derivative	ΔG (kcal/mol)	ΔH (kcal/mol)	ΔS (cal/deg.mol)
2-chloro-	— 6.911	3.823	36.309
2-hydroxy-	— 6.634	1.439	27.081
4-hydroxy-	(— 6.814)	(5.392)	(40.769)
8-hydroxy-	(— 6.825)	(1.367)	(23.290)
8-amino-	— 6.934	4.529	38.044
4-amino-quinaldine	— 6.665	1.918	28.749
4-hydroxy-quinaldine	— 6.078	0.938	21.561
8-hydroxy-quinaldine	— 6.552	1.220	26.069
Quinine	— 6.364	1.370	23.568
Chloroquine	— 6.462	1.175	24.937
Primaquine	— 6.673	1.945	29.864

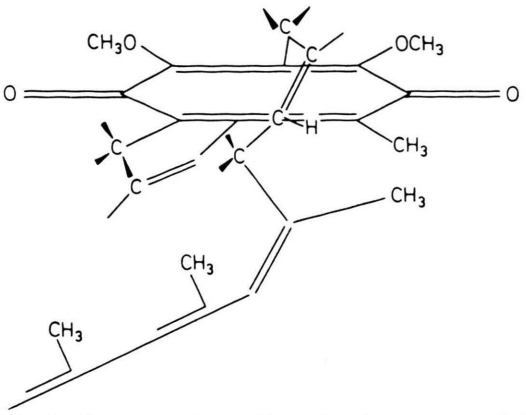


Fig. 6. Suggested three dimensional structure of CoQ_{10} in its isolated and uncomplexed state.

That the entropy change is a driving factor in the formation of these complexes may be viewed in the figures of Table 3, which include the calculated ΔG, ΔH, and ΔS values.

Of all studied complexes the change in enthalpy is small and positive, the entropy change is big and positive (21.6—40.8 e.u.). It seems that the complexation increases the degree of freedom of both molecules. Since the complex formation reduces the degree of freedom of the translational motion, the increase in entropy should then be due to an increase in the degree of freedom of internal motion. The nonrigid segment of the whole complex which may cause such a big change in entropy is the isoprenoid side chain. The positive change in entropy suggests that the motion of the side chain is more restricted in the noncomplexed state of the coenzyme. The restriction of motion might be due to a π-π interaction of the quinone ring with the olefinic side chain. Such an interaction is possible if the side chain surrounds the quinone ring. A study of the MINIT [17] molecular model of CoQ_{10} shows that such a configuration allows two of the olefinic double bonds to interact with both faces of the ring (Figure 6). The complex formation then causes a stretching of the side chain and an increase in its degree of freedom of internal motion.

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