Interaction of Antimalarials with Coenzyme Q_{10}

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Z. Naturforsch. **33 a**, 55–58 (1977) ; received August 11, 1977

Assuming face to face ($\pi-\pi$) complexation of the antimalarials, quinine, primaquine and chloroquine, with CoQ and applying Hückel MOs for their quinoline skelet and for the dimethoxybenzoquinone ring of CoQ the interaction energies are calculated using 2nd order perturbation. The perturbation treatment yielded an increase in the LUMO energy of CoQ suggesting an increase in its reduction potential due to complexation. This increase is confirmed expermentally by polarographic measurements of the $E_{1/2}$ values for the corresponding 1:1 mixtures. Similar increase is observed for the 1:1 mixture with aniline but not with cyclohexylamine. It is expected that such an increase in the reduction potential of CoQ should hinder its functioning as electron carrier in the respiratory chain.

Introduction

Antimalarials are known to inhibit the respiration process in the mitochondria of the disease causing plasmodium [1]. The inhibition can be removed through introduction of CoQ to the Plasmodium [1]. These results suggested that antimalarials interfere with the respiration process through interaction with CoQ. In the following we report a theoretical and physical study of this interaction.

Theoretical Model of Interaction

Antimalarials are mostly composed of a heteroaromatic nucleous attached to an aliphatic side chain [1]. Their interaction with the quinone ring of CoQ is expected to occur via face-face ($\pi-\pi$) orientation [2]. Such interactions are known to be favorable in the formation of molecular complexes [3]. The interaction energies may be calculated then using 2nd order perturbation theory and the Hückel molecular orbitals (HMOs) of the during and the CoQ molecules. In such a treatment the HMO energy change is calculated according to the following multicenter perturbation formula [4]:

$$\Delta E_\mu = \sum_\varrho \frac{(a_{1\mu}\, b_{1\varrho}\, \beta + a_{2\mu}\, b_{2\varrho}\, \beta + \ldots + a_{n\mu}\, b_{n\varrho}\, \beta^2)}{E_\mu - E_\varrho} \quad (1)$$

= HMOS of CoQ and antimalarial respectively,

$a_{\mu i}, b_{\varrho j}$ = HMO coefficients at the interacting atoms i and j of CoQ and the antimalarial.

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The total π-interaction energies of both systems are summed to ΔE_{tot}.

$$\Delta E_{\text{tot}} = \sum_\mu n_\mu \Delta E_\mu + \sum_\varrho n_\varrho \Delta E_\varrho . \quad (2)$$

In the present treatment the magnitude of the $\beta_{p_\sigma - p_\sigma}$ resonance parameter is defined relative to the original Hückel $\beta_{\pi-\pi}$ parameter according to the following relation:

$$\beta_{p_\tau - p_\sigma}/\beta_{\pi-\pi} = S_{p_\sigma - p_\sigma}/S_{\pi-\pi} . \quad (4)$$

$S_{p_\sigma - p_\sigma}$ $\qquad$ $S_{\pi-\pi}$

Evaluating the overlap integrals according to Roothaan [5] and using the distances 1.337 Å for the C=C bond and 3.33 Å (interplanar distance of the quinhydrone complex [6] for the $p_\sigma - p_\sigma$ interaction, one obtains the relative value 0.17 β for the $\beta_{p_\sigma - p_\sigma}$ parameter.

All possible orientations of both molecules relative to each other are considered by the calculation of each complex, orientations with opposite lone pairs are avoided due to the expected repulsion energies. The orientation with the biggest magnitude of interaction energy is accepted as the most stable orientation. The influence of the isoprenoid side chain of CoQ is neglected by the perturbation treatment. Recent polarographic measurements of CoQ molecules with different side chain lengths showed no dependancy of their $E_{1/2}$ values on the lengths [7].

All HMO calculations are carried out using a FORTRAN program run on an IBM 1130 computer at the College of Engineering, University of Baghdad. The applied h and k parameters for the hetero-

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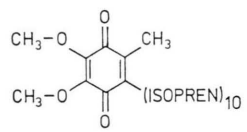
atoms are those compiled by Streitwieser [8] and have the following values:

	k	h
C=N	1	0.5
C−N	0.8	1.5
C=O	1	1
C−O	0.8	2
C−Cl	0.4	2

The perturbation calculations are carried out using a program written for the Hewlett-Packard 9810 calculator with an extra 9865 A memory. The program is written for a maximal interaction of 6 centers.

Experiments

The half wave potentials of CoQ_{10} and the antimalarials chloroquine, quinine and primaquine (Sigma Chemical Co., St. Louis, U.S.A.) as well as aniline and cyclohexylamine are measured in a 4:1 mixture of ethanol and Britton-Robinson solution ($p_H = 7.25$) using a Cambridge Pen Writing Polarograph (of Cambridge Instruments Company Ltd., London, England). The applied concentrations are 10^{-4} mol/lit for all measurements. Both mercury pool and external calomel electrodes are used as reference electrodes. The same concentrations are maintained for the 1:1 mixtures of CoQ_{10} and antimalarials. Before each measurement the solution was degased for 15 – 20 minutes with dry N_2 and then water sealed to avoid contact with the air. All measurements were done by 20 °C.



CoQ_{10}

Table 1. Measured $E_{1/2}$ values (V) and calculated HMO energies of the lowest unoccupied MOs of CoQ_{10} and the antimalarials as well as their 1 : 1 complexes *.

	$E_{1/2}$(V)	$E_{LUMO}(\beta)$	$E_{HOMO}(\beta)$
CoQ_{10}	−0.52, −1.30	+0.2	+0.67
Quinine	−1.27	−0.54	+0.57
Primaquine	−1.24, −1.66	−0.57	+0.53
Chloroquine	−1.32, −1.8	−0.6	+0.60
Aniline	−1.36	−1.0	+0.74
CoQ_{10}+Quinine	−0.6, −1,46	+0.20	+0.62
CoQ_{10}+Primaquine	−0.59, −1.38, −1.88	+0.21	+0.52
CoQ_{10}+Chloroquine	−0.6, −1.62	+0.19	+0.62
CoQ_{10}+Aniline	−0.6, −1.46	+0.18	+0.47

* Measurements done with S.C. Electrode.

Results and Discussion

Two waves are measured for CoQ_{10} with $E_{1/2}$ values −0.52 V and −1.30 V respectively. The first wave agrees well with the value −0.55 V (25 °C, external mercurous sulfate electrode) reported by Moret et al.[9] and is in the order of the reported $E_{1/2}$ values of substituted benzoquinones [10]. The calculated Hückel energy of the lowest unoccupied (LUMO) and highest occupied (HOMO) molecular orbitals of the quinone ring in CoQ_{10} are 0.21 β and 0.67 β respectively.

The positive value of the LUMO energy indicates the strong electron affinity of this molecule. On the other side, the LUMO energies of the drug heterocyclic molecules and of aniline are systematically higher than that of CoQ_{10} as shall be shown later. The higher LUMO energies are parallel to the measured $E_{1/2}$ values of the same molecules (Figure 5).

Quinine was found to yield two noncatalytic reduction waves [11]. The first wave (−1.07 V) was attributed to an adsorption-reduction process. It had more positive $E_{1/2}$ value than the original adsorption free reduction wave (−1.27 V). Our measured first wave of quinine, −0.5 V, is more positive than the recent reported value (−1.07 V). The difference may be due to different adsorption processes in different solutions. The second wave (−1.27 V) however agrees exactly with the reported $E_{1/2}$ value by Cover et al [11]. The higher $E_{1/2}$ of quinine relative to that of CoQ_{10} is in accordance to its higher LUMO energy (−0.54 β) relative to that of CoQ_{10} (+0.2 β). The 1:1 mixture of both molecules shows two waves $E_{1/2}$ = −0.6 V and −1.46 V. Both waves are more negative than those of the separate quinine and CoQ_{10} molecules. Apparently the addition of quinine tot he CoQ_{10} increases its $E_{1/2}$ value. This might be due to a molecular complex formation. The second order perturbation calculation of the complex yields the configuration shown in Fig. 1 as the most stable among the 25 different configurations considered in it.

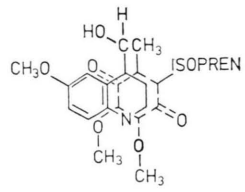
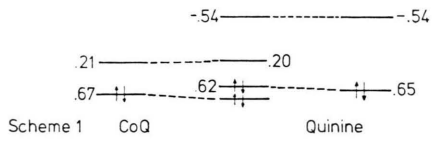


Fig. 1. The most stable configuration of the quinine-CoQ_{10} complex as calculated using 2nd order perturbation.

The increase in the reduction potential of the coenzyme is confirmed by the increase of its LUMO energy resulting from the perturbation treatment. The change in the LUMO and HOMO energies of both interacting partners is shown in scheme 1.



Scheme 1

The small magnitude of the calculated increase in the LUMO energy ($+0.01\,\beta$) might be due to the unrealistic acceptance of the quinine-CoQ_{10} distance being equivalent to that of the hydroquinone complex (3.33 Å). The increase in $E_{1/2}$ of the coenzyme is expected to hinder its biological function as electron carrier in the mitochondria of the cell.

Primaquine shows two waves with $E_{1/2}$ -1.24 V and -1.66 V, as well as a third adsorption wave having more positive $E_{1/2}$ value. Its 1:1 mixture with CoQ_{10} has three waves with $E_{1/2}$ values -0.59 V and -1.38 V as well as -1.88 V, all of which are higher in magnitude than those of the free CoQ_{10}. Purturbation treatment also shows that the interaction of both molecules increases slightly the energy of the LUMO of CoQ_{10} ($-0.002\,\beta$) and decreases that of primaquine ($+0.01\,\beta$). The calculated most stable configuration of the complex is shown in Figure 2. Totally 31 different configurations were considered by the calculation.

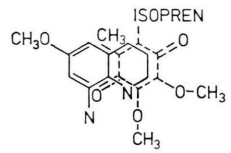


Fig. 2. Calculated most stable orientation of primaquine molecule relative to CoQ_{10} in their complex.

Polarographic measurement of chloroquine also gives two waves, besides the low adsorption wave, with $E_{1/2}$ values of -1.32 V and -1.8 V. Its 1:1 mixture with CoQ_{10} yields relatively bigger shifts in $E_{1/2}$ compared with those of the other two antimalarials. The new waves have $E_{1/2}$ values -0.6 V and -1.62 V respectively. The bigger shifts in $E_{1/2}$

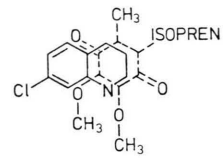


Fig. 3. Calculated most stable orientation of chloroquine relative to CoQ_{10} in their 1 : 1 complex.

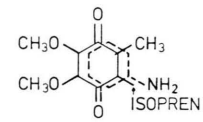


Fig. 4. Calculated most stable configuration of aniline relative to CoQ_{10} in their 1 : 1 complex.

are in agreement with the bigger LUMO energy change of CoQ_{10} as obtained through the perturbation treatment.

In addition to the three antimalaria drugs, aniline's interaction with CoQ_{10} is studied. The calculated most stable configuration of the complex corresponds to a para positioning of the amino group to one of the methoxy groups as shown in the following figure (Figure 4).

The interaction causes a destabilization of both HOMO and LUMO of CoQ_{10} and a stabilization of both MOs in aniline (Table 1). Accordingly an increase in $E_{1/2}$ values of CoQ_{10} should be noticed in the case of complexation with aniline. Polarographically, two waves with $E_{1/2}$ -0.6 V and -1.46 V are obtained for the mixture. Both waves have more negative $E_{1/2}$ values than those of the separated CoQ_{10} and aniline molecules (-0.52 V and -1.36 V respectively). To determine whether this increase in $E_{1/2}$ magnitudes is due to $\pi-\pi$ interaction alone or to a different type of interaction, e. g. $-NH_2-CoQ_{10}$ interaction, it is required to carry out the same measurements with an aliphatic amine. Cyclohexylamine is suitable for this purpose. The $E_{1/2}$ values of this amine alone are -1.42 V and -1.9 V. Its 1:1 mixture with CoQ_{10} gave two waves with $E_{1/2}$ -0.5 and -1.32 V and a third wave with $E_{1/2}$ -1.81 V. The first two waves have $E_{1/2}$ values equivalent to those of CoQ_{10} alone. Obviously the addition of the amine does not change the $E_{1/2}$ values of the coenzyme significantly. The $E_{1/2}$ increase in the case of addition of the other molecules is then due to the $\pi-\pi$ interaction with

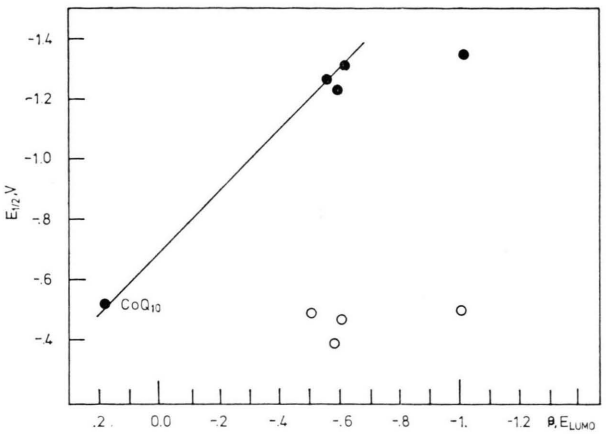


Fig. 5. Plot of the measured $E^{1/2}$ values of antimalarials and CoQ_{10} against the calculated LUMO energies, ● reduction waves, ○ adsorption waves.

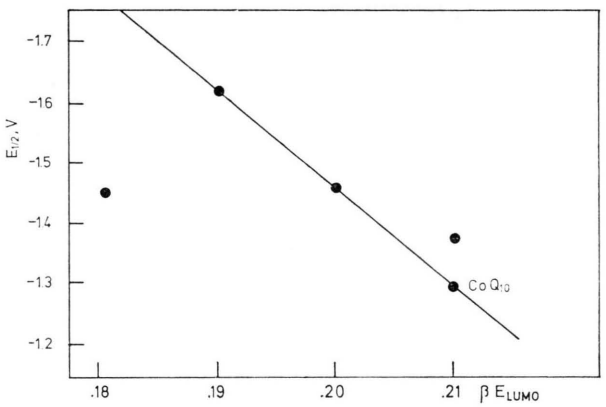


Fig. 6. Plot of the $E_{1/2}$ values of CoQ_{10} in complexes with antimalarials and aniline against its calculated LUMO energies.

the heteroaromatic rings. Figure 5 shows the measured $E_{1/2}$ values of the drugs and of CoQ_{10} plotted against their calculated LUMO energies. It is seen that where as the $E_{1/2}$ values of the reduction waves correlate well with the LUMO energies, the adsorption waves show no correlation with them. The non-correlation is probably caused by the different adsorption processes of the molecules at the Hg surface.

Figure 6 shows the calculated LUMO energies of CoQ_{10} in the complexes plotted against the measured $E_{1/2}$ values of the second waves. The correlation is obviously good. However no such correlation could be obtained for the 1st waves of the complexes, a fact that might be due to different adsorption processes of the different complexes. The relatively big deviation of aniline from the correlation line could be due to the unrealistic assumption of a constant interplanar distance (3.32 Å) by the calculation of the interaction energies for all complexes.

Conclusion

The interaction of antimalarials and of aniline with CoQ_{10} causes an increase in the magnitude of its $E_{1/2}$ values. The observation is supported by the perturbation treatment carried out for the $\pi-\pi$ interaction of CoQ_{10} with the drug molecules. The $E_{1/2}$ increase should hinder the coenzyme in its functioning as electron carrier in the biological respiratory chain and provide the physical interpretation for the recent assumption that antimalarials interact with the CoQ_{10} in the plasmodium cell [1].

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