

THE PROTONMOTIVE Q CYCLE: A GENERAL FORMULATION

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1. Introduction

A critical appraisal of the protonmotive Q^* cycle [1] in the general context of the protonmotive function of cytochrome systems [2] has suggested that the Q cycle, as originally conceived [1], lacked generality and was open to criticism because it was not yet adequately emancipated from its accidental origins. My object in this letter is to define the general principles of the protonmotive Q cycle more explicitly than before, thus facilitating either its experimental rejection or its further development and general application.

2. Fundamental principles of the Q cycle

Fig.1 represents the general flow diagram of the Q cycle, in which the functional redox group of the quinone Q (which may be ubiquinone or plastoquinone or some other analogous quinone) can diffuse only in the fully oxidised and fully reduced, unionised, states represented by Q and QH_2 respectively between redox centres c , b_L , b_R and d near the L and R sides of a lipoprotein membrane of low proton (and OH^- ion) conductance. The arrows represent the formal forward direction of the reversible processes of electron and proton flow and of translocation of Q and QH_2 ; and

* *Abbreviations:* Q , quinone; QH^* , quinone semiquinone; C side and M side, opposite sides of membrane or of respiratory chain complex corresponding to cytochrome c side and matrix side respectively; State 4, state of steady mitochondrial respiration in the presence of substrate and inorganic phosphate but in the absence of phosphate acceptor.

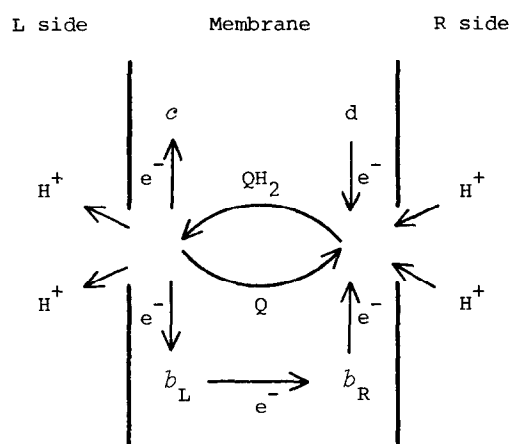


Fig.1. Flow diagram of protonmotive Q cycle in a general notation explained in the text. The arrows represent the formal forward direction of reversible transfers of electrons and protons and translocations of Q and QH_2 . No assumptions as to the sequence of electron and proton transfers in the $c-b_L$ and $d-b_R$ domains are to be inferred from the diagram. The arrows showing the electron transfers represent only the chemical flows in the $c-b_L$ and $d-b_R$ domains and should not be taken to indicate the spatial extent of these domains, either or both of which might be very compact.

the diagram shows that in one complete cycle of oxidoreduction and of translocation of Q from L to R (as Q) and back (as QH_2), one electron is transferred from d round the cycle to c , and two H^+ ions are translocated from the aqueous phase R to the aqueous phase L. The diagram should not be taken to imply any given assumptions about the spatial extents of the redox domains in which c and b_L are reactive with Q , QH_2 and other redox intermediaries near the L side of the system, and d and b_R are reactive with Q , QH_2

and other redox intermediaries near the R side of the system; nor should the diagram be taken to imply any given assumptions about the sequence of electron and proton transfers in these domains.

Investigation of the detailed (and as yet unknown or unspecified) chemical reaction and translocation mechanisms, and the topology of the catalytic components involved in the cycle, may presumably allow us to characterise the reaction domains and the sequence of the electron and proton transfers in due course. Meanwhile, it is helpful to appreciate that the general principle of the cycle represented in the flow diagram of fig.1 is dependent only upon appropriate diffusional mobilities and concentrations (or probabilities) of all the components in the cycle so as to permit the flows specified in the diagram, and that the coupling between the translocation of the two H^+ ions and the flow of the one electron from d to c will require the minimum restriction that either in the $c-b_L$ domain or in the $d-b_R$ domain one (and not both) of the two electrons must be transferred to or from each of the two centres in the domain.

This general formulation of the Q cycle is intended to be applicable to the cytochrome $b-c_1$ -dehydrogenase complexes of mitochondria, to similar cytochrome-dehydrogenase complexes and cytochrome-photosynthetic pigment complexes of bacteria, and to the cytochrome $b-f$ -photosystem complexes of chloroplasts [2].

To illustrate the general principle, it will be sufficient to consider here the cytochrome $b-c_1$ -dehydrogenase complexes of mitochondria. In this case, the L and R sides represent the C and M sides of the mitochondrial cristae membrane system, Q represents the redox functional group of ubiquinone, the centres c , b_L and b_R represent cytochrome c_1 , and electronically communicating cytochromes b that are located near the C and M sides of the membrane (possibly b_{566} and b_{562}) respectively, and d represents the respiratory chain-reactive iron-sulphur centre of the dehydrogenase. Other structural [3] and redox-functional [4] groups, not represented in fig.1, may also facilitate the redox and translocation reactions involved in the cycle.

As discussed previously [1], the rather soft information at present available about the possible redox potentials of the c and b cytochromes and of the respiratory chain-reactive iron-sulphur centre of the dehydrogen-

ases in mitochondria indicates that in State 4, $E_h(c_1)$ is around +300 mV, and $E_h(b_{566})$ and $E_h(b_{562})$ are around -100 mV and +50 mV respectively, while the E_h of the ironsulphur centre of the dehydrogenase is near 0 mV. In the general nomenclature of fig.1, this would mean that the redox potentials of c and b_L would be wide apart (i.e. around +300 and -100 mV, respectively) whereas the redox potentials of d and b_R would be close together (i.e. around 0 and +50 mV, respectively). The general implication is that the two electrons (reversibly) transferred from QH_2 in the $c-b_L$ domain cannot be in redox equilibrium with each other, and the restriction mentioned above must therefore apply here that each of the two electrons must be specifically transferred from QH_2 to its respective centre. The present redox evidence is not adequate to say whether this condition may also apply to the $d-b_R$ domain.

The type of two-equivalent redox reaction in which the two electrons transferred are each in equilibrium with separate specific centres that are at different redox potentials may be somewhat unfamiliar inasmuch as this specific type of reaction may proceed reversibly (i.e. with an appropriate concentration or probability of the intermediary, one-electron transfer state) when the stability constant of the intermediary is either greater or smaller than unity, depending on the sequence of electron transfer. The two-electron transfer process must involve the same overall free-energy change irrespective of the intermediary free-energy states, and consequently, when the two electrons are transferred reversibly at different redox potentials, these redox potentials must have the same arithmetic mean as the potential corresponding to that of the overall electron-transfer reaction. It follows that, if the first electron were transferred from QH_2 (or from its corresponding anion) in the $c-b_L$ domain at a relatively negative potential (i.e. to b_L), the stability constant of the one-electron intermediary (corresponding to the cation QH_2^+ , the semiquinone QH^\cdot or the semiquinone anion Q^-) would have to be greater than unity in this domain, whereas, if the first electron were transferred at a relatively positive potential (i.e. to c), the stability constant of the intermediary would have to be less than unity in this domain. For this reason, it is not possible to specify the sequence of the electron and proton transfers in the $c-b_L$ domain without recourse to more detailed biochemical informa-

tion concerning the one-electron transfer intermediary state or states. Similar, but quantitatively less extreme, considerations may possibly apply to the sequence of electron and proton transfers in the $d-b_R$ domain, although, as mentioned earlier, it is conceivable that both electrons may be transferred at the same potential in this case, and that both might effectively be (reversibly) transferred from either d or b_R , directly or by disproportionation of the semiquinone intermediary, under certain circumstances — notably, if the dehydrogenase (and therefore the centre d) were separate from the cytochrome $b-c_1$ complex. Thus, the QH_2 -cytochrome c oxidoreductase activity of the cytochrome $b-c_1$ complex might be due to the oxidation of QH_2 to Q via cytochromes b_{566} and c_1 , followed by the reduction of Q to a semiquinone intermediary by cytochrome b_{562} and the disproportionation of this intermediary to Q and QH_2 . In this case, the dehydrogenase might act independently as a substrate- Q oxidoreductase, reducing Q to QH_2 directly or by disproportionation of a semiquinone intermediary. A definite decision must await more detailed information about the reaction intermediaries.

The overall thermodynamic behaviour of this general formulation of the protonmotive Q cycle may be derived from the flow diagram of fig.1, by methods analogous to those outlined earlier [1].

3. Further prospect

This, more general, formulation of the fundamental principles of the protonmotive Q cycle shows how the earlier, more restrictive formulation [1] is open to criticism. In particular, the sequence of the electron and proton transfers should be regarded as a question

to be settled by future research, and the specific suggestion that QH^+ (or its anion Q^-) is the natural oxidant of the dehydrogenases [1], although obviously attractive, should not be regarded as an essential attribute of the general concept of the protonmotive Q cycle. The present, general formulation, also appears to be capable of accounting for the observed redox poises of the b and c cytochromes relative to the respiratory chain-reactive iron-sulphur centre of the dehydrogenases in mitochondria without invoking the previous ad hoc suggestion [1] of a redox bypass or pumping of QH^+ from the C to the M side of the system.

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