Biochimica et Biophysica Acta 1807 (2011) 788–802

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

Review

The Q cycle of cytochrome *bc* complexes: A structure perspective

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ARTICLE INFO

Article history:
Received 26 October 2010
Received in revised form 8 February 2011
Accepted 13 February 2011
Available online 23 February 2011

Keywords:
Cytochrome bc_1/b_6f complex
Electron transfer
Energy transduction
Plasto-/ubiquinone
Electrochemical potential

ABSTRACT

Aspects of the crystal structures of the hetero-oligomeric cytochrome bc_1 and b_6f ("bc") complexes relevant to their electron/proton transfer function and the associated redox reactions of the lipophilic quinones are discussed. Differences between the b_6f and bc_1 complexes are emphasized. The cytochrome bc_1 and b_6f dimeric complexes diverge in structure from a core of subunits that coordinate redox groups consisting of two *bis*-histidine coordinated hemes, a heme b_n and b_p on the electrochemically negative (n) and positive (p) sides of the complex, the high potential [2Fe–2S] cluster and *c*-type heme at the p-side aqueous interface and aqueous phase, respectively, and quinone/quinol binding sites on the n- and p-sides of the complex. The bc_1 and b_6f complexes diverge in subunit composition and structure away from this core. b_6f Also contains additional prosthetic groups including a *c*-type heme c_n on the n-side, and a chlorophyll *a* and β-carotene. *Common structure aspects; functions of the symmetric dimer.* (I) *Quinone exchange with the bilayer.* An inter-monomer protein-free cavity of approximately 30 Å along the membrane normal × 25 Å (central inter-monomer distance) × 15 Å (depth in the center), is common to both bc_1 and b_6f complexes, providing a niche in which the lipophilic quinone/quinol (Q/QH_2) can be exchanged with the membrane bilayer. (II) *Electron transfer.* The dimeric structure and the proximity of the two hemes b_p on the electrochemically positive side of the complex in the two monomer units allow the possibility of two alternate routes of electron transfer across the complex from heme b_p to b_n: intra-monomer and inter-monomer involving electron cross-over between the two hemes b_p. A structure-based summary of inter-heme distances in seven *bc* complexes, representing mitochondrial, chromatophore, cyanobacterial, and algal sources, indicates that, based on the distance parameter, the intra-monomer pathway would be favored kinetically. (III) *Separation of quinone binding sites.* A consequence of the dimer structure and the position of the Q/QH_2 binding sites is that the p-side QH_2 oxidation and n-side Q reduction sites are each well separated. Therefore, in the event of an overlap in residence time by QH_2 or Q molecules at the two oxidation or reduction sites, their spatial separation would result in minimal steric interference between extended Q or QH_2 isoprenoid chains. (IV) *Trans-membrane QH_2/Q transfer.* (i) n/p-side QH_2/Q transfer may be hindered by lipid acyl chains; (ii) the shorter less hindered inter-monomer pathway across the complex would not pass through the center of the cavity, as inferred from the n-side antimycin site on one monomer and the p-side stigmatellin site on the other residing on the same surface of the complex. (V) *Narrow p-side portal for QH_2/Q passage.* The [2Fe–2S] cluster that serves as oxidant, and whose histidine ligand serves as a H^+ acceptor in the oxidation of QH_2, is connected to the inter-monomer cavity by a narrow extended portal, which is also occupied in the b_6f complex by the 20 carbon phytyl chain of the bound chlorophyll.

1. Introduction

With the availability of crystal structures of the hetero-oligomeric cytochrome bc_1 [1–15] and b_6f [16–20] complexes, and of the extrinsic soluble domain of the Rieske iron–sulfur protein [21–25] from both complexes, of cytochrome *f* from the higher plant b_6f complex [26–30], pathways of electron and proton transfer and of quinone/ol entry and binding can be considered in the context of atomic structures.

Abbreviations: b_n, Q_n and b_p, Q_p, hemes, quinone/ol bound on electrochemically negative or positive sides of membrane; n-, p-side, chloroplast stroma, lumen, mitochondrial matrix, inter-membrane space, bacterial cytoplasm periplasm; CHARMM, Chemistry at Harvard Macromolecular Mechanics; CL, cardiolipin; cyt, cytochrome; DBMIB, 2,5-dibromo-3-methyl-6-isopropylbenzoquinone; EPR, electron paramagnetic resonance; E_m, E_{m7}, mid-point oxidation–reduction potential, at pH 7; FAD, flavin adenine dinucleotide; FNR, ferredoxin-$NADP^+$ reductase; *In situ*, *in vitro*, in membrane, in solution; ISP, iron–sulfur protein; MOAS, β-methacrylate stilbene; NQNO, 2*n*-nonyl-4-hydroxy-quinoline-*N*-oxide; PQ-9, UQ-10, plasto-, ubiquinone with 9, 10 isoprenoids; Q, QH_2, quinone, quinol; $Q^{\bullet-}$, semiquinone; RMSD, root mean square deviation; TMH, trans-membrane α-helix; UDM, undecyl-β-D-maltoside; UHDBT, 5-undecyl-6-hydroxy-4,7-dioxobenzothiazole; $\Delta\tilde{\mu}_H^+$, trans-membrane electrochemical proton gradient; V, volt

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[1] The theme of this manuscript was originally presented in a keynote lecture, November, 2009, for the symposium commemorating the 50th anniversary of the Institute for Protein Research, Osaka University.

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doi:10.1016/j.bbabio.2011.02.006

Properties that are common to both sets of complexes, or unique to either the bc_1 or b_6f set, can be defined. These comparisons can be used to describe the evolution of these complexes [31–37]. Recent reviews and discussions have mostly focused either on the bc_1 [38–64] or the b_6f complex [37,65–77], with some on both complexes [78–80]. It has often been assumed in discussions of the bc_1 complex that the differences in the structure and prosthetic groups of the two classes of complexes are inconsequential, and that the complexes do not differ significantly in pathways of electron and proton transfer. It will be emphasized in the present discussion that, although the bc_1 and b_6f complexes share a common evolutionary origin and many common functions, significant differences exist between the two sets of complexes with respect to details of structure, alternate electron transport pathways, and quinone-mediated redox function.

Structure-function problems discussed recently for the bc_1 complex include the role of the monomer and dimer in the electron transport pathway associated with oxidation of ubiquinol [56–58,81], the redox state of the quinone species bound to the n-side of the complex [35,53,80], inter-monomer interactions that may affect the pathway of electron transfer [45,57,82], and consideration of a stochastic approach to a description of the electron transfer reactions in the Q cycle [61].

Recent review topics on the b_6f complex have included unique aspects of structure-function: (i) The photosystem I-linked cyclic electron transport pathway [83–99], absent in mitochondria and purple photosynthetic bacteria that house the bc_1 complex. An uncertainty over the participation of the b_6f complex in the cyclic pathway of oxygenic photosynthesis is based on disagreement over whether the quinone-analogue inhibitor, antimycin A, which is a classical inhibitor of the oxidation of mitochondrial cytochrome *b* [100], and which inhibits cyclic phosphorylation [101,102], does [103] or does not [102] inhibit turnover of the chloroplast heme b_n; (ii) the additional heme c_n in the b_6f complex, which was first described by sensitive spectrophotometry [104,105], and subsequently in crystal structures [16,17]; (iii) FNR bound peripherally to the plant b_6f complex may participate along with heme b_n, in the cyclic electron transport pathway [88,106].

An understanding of intra-membrane translocation of the large lipophilic Q/QH_2 (quinone/quinol) molecules, which is coupled to electron and proton transfer, involves consideration of formidable structure problems. Charge transfer, steric, and kinetic problems associated with quinone translocation across the membrane and the *bc* complex were recognized [107–111] in the literature that preceded the emergence of crystal structures of the *bc* complexes.

2. Cytochrome bc_1 and b_6f complexes: Common and unique properties

Crystal structures of the hetero-oligomeric cytochrome *bc* complexes, which have a similar energy transducing function in respiration and photosynthesis, are summarized in Fig. 1a–c, the bc_1 complex from (A) yeast mitochondria [15] and (B) the purple photosynthetic bacterium, *Rhodobacter sphaeroides*, and (C) the b_6f complex from the cyanobacterium, *Mastigocladus laminosus* [19]. These membrane protein complexes provide the electronic connection between the reducing (dehydrogenase, bacterial photosynthetic reaction center, or photosystem II reaction center) and oxidizing (cytochrome oxidase or photosystem I) electron transport complexes in the respective electron transport chains, while coupling electron transfer within the complex to proton translocation across the membrane. Genomic and hydrophobicity [112] analysis of the cytochrome *b* subunit allowed prediction of *bis*-histidine ligation of the two trans-membrane hemes in the N-terminal heme binding domain of the cytochrome *b* polypeptide in the hydrophobic core of the complex [31,113–115], which was inferred to be identical in the b_6f and bc_1 complexes [31], and subsequently corroborated by crystal structures. The Rieske [116] iron–sulfur protein (ISP) subunit of the complex can also be considered part of its basic assembly [33,117], as

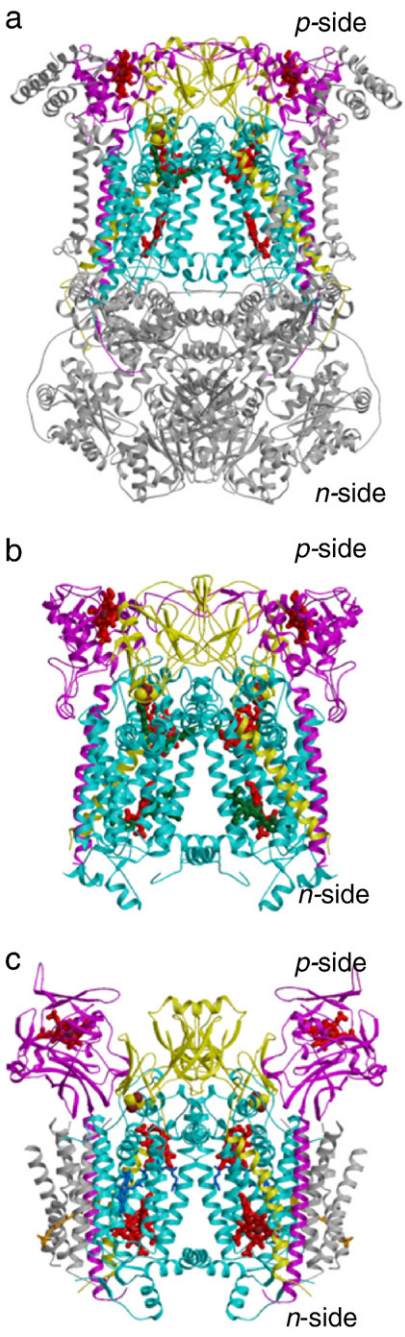

Fig. 1. Structures of the cytochrome bc_1 complex from the electron transport chain of (a) yeast mitochondria (PDB ID: 3CX5 [15]) and (b) the purple photosynthetic bacterium, *Rb. sphaeroides*, with bound antimycin and stigmatellin (2QJP, [14]); (c) native b_6f complex from the cyanobacterium, *M. laminosus* (2E74, [19]). The ribbon diagrams show the common central structure. Color code: (yellow) Rieske protein with cluster-containing peripheral domain on one monomer and its TMH spanning the width of the other; other colors: b_6f-cyt *f* and bc_1-cyt. c_1, magenta; cyt *b* and b_6f-subunit IV, cyan.

it is found in cytochrome *bc* complexes in a wide range of phylla [118], and phylogenetic reconstruction has shown significant congruence of ISP and cytochrome *b* [119] although the ISP amino acid sequences are less conserved than those of cyt *b* [23].

2.1. Structures, prosthetic groups

Cytochrome *bc* complexes contain four common redox prosthetic groups (Table 1) in their redox core: (i) two *bis*-histidine coordinated *b* hemes, b_p and b_n [31,113] whose His ligands bridge two trans-

Table 1
Subunit composition and p*I* values of the eight polypeptide subunits of the *M. laminosus* cyanobacterial cytochrome b_6f complex (PDB ID: 2E74); consensus mid-point oxidation–reduction potentials of prosthetic groups.

Subunit[a]	*M. laminosus* subunit mol. wt., kDa [241]	*C. reinhardtii* subunit mol. wt., kDa	p*I*[b] (*M. laminosus*)	p*I* (*C. reinhardtii*)[c]	E_{m7} (mV)[c]
Cyt *f* (1 heme)	32.273	31.249	6.7	8.3	+350–380
Cyt b_6 (3 hemes)	24.712	24.165	9.0	8.8	(−50 (b_n); −50 to −150 (b_p); +100 (heme c_n)[d]
ISP [2Fe–2S]	19.295	18.333	6.8	5.8	+300 (pH 6.5)–+320
suIV	17.528	17.295	8.1	6.6	–
PetG	4.058	3.984	4.5	4.4	–
PetM	3.841	4.036	10.4	4.3	–
PetL	3.530	3.436	10.2	9.5	–
PetN	3.304	3.282	5.7	6.0	–

[a] Subunits listed are the tightly bound subunits seen in the crystal structures of the b_6f complex.
[b] p*I* values include extrinsic and hydrophobic integral domains; the basic p*K*'s of suIV and cyt b_6 arise partly from an excess of basic residues on the n- or stromal side of the membrane, the side from which these subunits are predicted to be inserted into the membrane [242]; p*I* values determined for the complex in *M. laminosus* (PDB ID: 1Q90) using ExPASy [243].
[c] Redox potentials of 2 *b* hemes: in contrast to bc_1 complexes [58,190,244–250], for which the ΔE_m between hemes b_n and b_p is sufficiently resolved ($\Delta E_m \approx 125$–150 mV) to define b_h (*b*-high potential) and b_l (*b*-low potential) hemes, redox titration data do not clearly allow this inference for the b_6f complex. There is a discrepancy between titrations of the b_6f complex *in vitro*, for which a measurable $\Delta E_m \approx 100$ mV is consistently resolved [130,251–254], and a number of *in situ* (in membrane) titrations that do not show resolved b_n and b_p ($\Delta E_m \leq 50$ mV) [187,229,253,255–257]. Two studies on *in situ* titrations report two resolved *b* heme components [258,259], and a large ΔE_m has been inferred in studies on the slow electrochromic phase [79,186,192,260–262] and biphasic kinetics of heme reduction [105]. Regarding the more negative E_m values of heme b_p titrated *in-vitro*, they could result from solvent exposure [263], as shown for cytochrome *b*-559 in the PS II reaction center [264,265].
[d] For heme c_n, titration *in vitro* indicates that the ΔE_m between hemes c_n/b_n is ~150 mV [130]; *in vivo*, $\Delta E_m \approx 20$ mV [105].[e] E_{m7} for Q redox reactions: (i) $UQ + 2e^- + 2H^+ \rightarrow UQH_2$, +65 mV; (ii) $PQ + 2e^- + 2H^+ \rightarrow PQH_2$, +100 mV; (iii) $UQ + e^- \rightarrow UQ^{\bullet -}$, ~−150 mV; (iv) $PQ + e^- \rightarrow PQ^{\bullet -}$, ~−100 mV.

membrane alpha-helices, the 2nd and 4th of the cytochrome *b* polypeptide on the p- and n-sides of the complex [31,113,114]. The pattern of heme bridging two trans-membrane helices via two His residues is a frequent structure motif, as subsequently found in the crystal structures of intra-membrane electron transport proteins, such as heme *b* in fumarate reductase [120] or formate dehydrogenase-N [121] and heme *a* in cytochrome oxidase [122–125], (ii) a high potential ($E_m \approx +0.25$–0.35 V) *c*-type heme that is covalently bound in the p-side aqueous phase domain to the cytochrome *f* and c_1 polypeptides, where it serves as the electron acceptor of the [2Fe–2S] cluster. The iron–sulfur protein, through this cluster, is the electron acceptor and, through a histidine ligand, a proton acceptor of ubi- or plastoquinol at the p-side membrane interface. A newly discovered feature of *b*-heme orientation in b_6f complexes [20] is that heme b_p in *M. laminosus* (PDB ID: 2E74) is rotated 180° about the normal to the membrane plane relative to the heme orientation in *Nostoc* (PDB ID: 2ZT9) and *Chlamydomonas reinhardtii* (PDB ID: 1Q90). This heme rotation phenomenon has been noted previously and discussed in the context of *bis*-histidine coordination geometry in trans-membrane 4-helix bundles [126].

Although cytochrome bc_1 and b_6f complexes possess a common core of four redox groups consisting of the high potential [2Fe–2S] cluster, 2 trans-membrane *b* hemes, and a heme-binding protein core with a common evolutionary origin, the similarity in the structure decreases away from this core. In addition, bc_1 and b_6f complexes both contain a high potential *c*-type heme whose presence in both complexes is a result of convergent evolution [27]. There are four additional tightly bound prosthetic groups found in b_6f complexes that are not present in bc_1: (i) a 4th heme and 5th redox group, the heme c_n, also called c_i in the literature (e.g., Ref. [17]), originally described by sensitive spectrophotometric analysis of electron transport reactions of the b_6f complex *in situ* and *in vivo* [104,105]. Heme c_n was defined in the crystal structures that showed it covalently bound to the n-side of helix A of the cytochrome *b* subunit, with its heme Fe within 4 of a propionate oxygen of the adjacent heme b_n [16,17]. This proximity predicts electronic coupling between hemes b_n and c_n, which is verified by a unique EPR spectrum containing a g~12 signal [127–129]. Given this degree of electronic coupling, it is surprising that hemes b_n and c_n have been found to possess distinct redox potentials [130]. However, because heme c_n has a mid-point redox potential similar to that of heme b_n in the bc_1 complex [130], b_n–c_n could function in the Q cycle on the n-side of the b_6f complex as a two electron donor to the n-side bound quinone, Q_n (see below, Fig. 3a, b). In addition, from crystal structures [19] and redox titrations in the presence of NQNO [130], heme c_n is inferred to function as the n-side quinone binding site [19], and as a possible binding site for O_2 [129]. A mutation of interest in the heme maturation pathway of heme c_n resulted in low levels of b_6f complex [131,132], which could be overcome by a spontaneous revertant missing a protease. A double mutant made in a background of the protease-less mutant was constructed that functions at a low rate in the absence of heme c_n [133]. Three additional prosthetic groups unique to the b_6f complex are: (ii) chlorophyll *a* [134–136] (iii) β-carotene [136], and (iv) a flavin in the peripheral FNR subunit of the plant (spinach) complex [96,106,137,138].

Other unique structure features of the b_6f compared to the bc_1 complex include: (v) completely different structures of the extrinsic domain of cytochromes c_1 and *f* [26–28], except for the Cys-X-Y-Cys-His covalent heme binding sequence, and (vi) four small single trans-membrane helical subunits in a "picket-fence" arrangement at the periphery of each monomer of the b_6f complex [16–20].

2.2. Polypeptides

Of the 8 and 11 polypeptide subunits that have been defined in the crystal structures of b_6f and respiratory bc_1 complexes, respectively, 3–4 that contain the functionally essential redox groups can be considered "core" polypeptides. They contain binding sites for the redox prosthetic groups, the 2 *b* hemes, the [2Fe–2S] cluster, the high potential *c*-type heme, and the n- and p-side quinone binding sites. These subunits define the hydrophobic core that corresponds to the 3–4 subunit structure of the bc_1 complex of the purple photosynthetic bacterium, *Rb. sphaeroides* [14].

2.2.1. Additional interacting and/or bound polypeptides

A complete perspective on the atomic structure of the *bc* complexes should include the less strongly or transiently bound subunits that may be dissociated and lost from the complex during its isolation, purification, or crystallization. For the b_6f complex, these include: (i) the FNR that is found in the plant, but not the cyanobacterial or algal b_6f complex [106,137,138]; (ii) the petP polypeptide seen in cyanobacteria [139]; and (iii) the light-harvesting LHCII chlorophyll protein kinase Stt7-STN7 [140], whose presence on the n-side or stromal side of the complex may respond to quinol oxidation on the p-

side [141,142], the correlated (iv) phosphatase [143]; and (v) the petO nuclear-encoded phosphorylatable subunit [144].

2.3. The inter-monomer cavity

A prominent common feature in the structure of bc_1 and b_6f complexes is the large (30 Å×25 Å×15 Å) central cavity which, because of its presumed role in sequestering quinone from the membrane bilayer, has been termed the "quinone exchange cavity" [16]. As discussed below, the term "cavity" may be a misnomer because it is likely that it is mostly filled with lipid acyl chains. Central cavities in dimeric or pseudo-dimeric membrane proteins that sequester substrates and water are found in the structures of transport proteins such as the lac permease [145] and the glycerol-3-phosphate transporter [146].

2.4. Lipids

At least eleven lipid molecules have been defined in the 1.9 Å structure of the yeast bc_1 complex [15,50,59,62,147,148], i.e., 5 1/2 lipids per monomer. Each monomer also contains one peripheral CL, two phosphatidyl-ethanolamines, and two phosphatidic acids (Fig. 2a, b). An additional potential lipid site in each bc_1 monomer is suggested by the presence of one bound undecyl-maltoside detergent molecule. One n-side cardiolipin (CL) is shared between the N-terminal segment of the cytochrome *b* subunit in each monomer, with a proposed function of a proton antenna for H^+-coupled reduction of the n-side quinone, Q_n [59,62,149]. Considering this putative function, the distance between the quinone keto group (seen in the 1NTZ structure) and the nearest CL phosphate oxygen is 10.5 Å, a very large distance for proton transfer [150]. However, the distance for proton hopping is reduced by the presence of His202 (cyt *b*) between the CL phosphate O and the protonatable nitrogen of the cyt *b* His202.

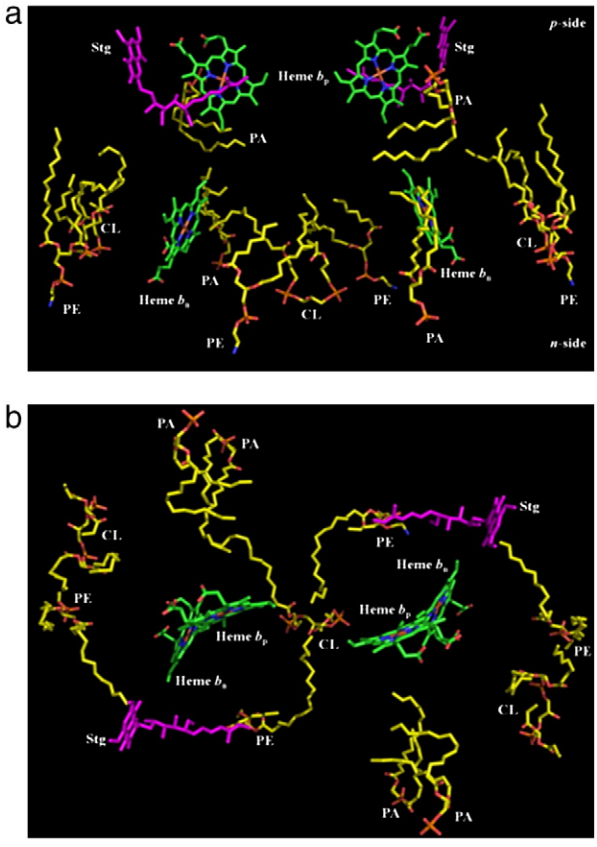

Fig. 2. Arrangement of lipids, 2 PE, 2 PA, 1.5 CL per monomer, in the yeast cytochrome bc_1 complex (PDB ID: 3CX5; [15]); (a) side and (b) top view. 1.5 molar stoichiometry of cardiolipin (CL), determined from the 3CX5 crystal structure, is a consequence of sharing one CL at the n-side interface between the two monomers.

A similar number, 7–8 lipid binding sites per monomer, is seen in b_6f complexes from the cyanobacteria, *M. laminosus* [19] and *Nostoc* sp. PCC 7120 [20]. One of these sites in the b_6f complex is occupied by a natural sulfo-lipid, first seen in the structure of the *C. reinhardtii* complex [17], whose interaction with n-side segments of the ISP and cytochrome *f* has been described [151]. The other six lipid binding sites in the monomer of the *M. laminosus* structure are occupied by four molecules of the detergent UDM and two of the lipid DOPC, whose presence greatly increased the rate of crystal formation of delipidated b_6f complex [152]. Two additional "natural" lipids, MGDG, for a total of three lipids/monomer, have been assigned in the *C. reinhardtii* b_6f complex [17]. Regarding application of the "H^+ antenna hypothesis" [59,62,149] to the b_6f complex, there are 2 UDM molecules per dimer near the position of the inter-monomer cardiolipin, CL, in the b_6f complex. These UDM detergent molecules may replace the natural lipid molecules, e.g., anionic PG, in the detergent-extracted protein complex. Of the four UDM molecules in each monomer, the head groups of three are pointing to, or are in contact with, the n-side aqueous phase. Arg207 and Lys208 intervene as possible H^+ carriers in the path between the O (OAC) of the quinone-analogue, decyl-stigmatellin, which can bind to the Q_n site in b_6f [19], and UDM as a putative substitute for CL.

2.5. Inter-monomer interactions: Conformational changes

The ability of one equivalent added per dimer of the p-side quinone-analogue inhibitor, stigmatellin, to completely inhibit electron transfer of the dimeric yeast bc_1 complex, led to the inference of inter-monomer interactions relevant to the electron transfer mechanism of the dimer [45]. A similar "half-sites" inhibition effect in the b_6f complex has been observed in photosynthetic electron transport, using the p-side inhibitor, DBMIB [153], whose structural basis could be similarly interpreted. The structural basis for inter-monomer interactions and resulting conformational changes, which could be at the root of these "half-site" effects and those observed for the bc_1 complex from yeast [45,57,154] and *Paracoccus denitrificans* [63], may be contained in the number and nature of the residues involved in close contacts between monomers in bc_1 and b_6f complexes (Table 2). The number of residues contributed to such interactions by core subunits, (i) cytochrome *b* (8 trans-membrane helices) and the ISP of the bc_1 complex, and (ii) cytochrome *b* (4 TMH), subunit IV (3 TMH), and the ISP of the b_6f complex, are similar in the two complexes. The larger number of interacting residues in the yeast (3CX5) and bovine (1NTZ) bc_1 complexes, compared to the two cytochrome b_6f complexes, is a consequence of a larger number of bc_1 TMH making inter-monomer contacts: (a) the TMH of cytochrome c_1 makes inter-monomer contact, but that of cytochrome *f* doesn't; (b) the small subunits in bc_1 make contacts, but the four small subunits in b_6f, the petG, L, M, N subunits, which are at the outside periphery of each b_6f monomer, with one TMH each, do not. One TMH in each monomer with unusual properties is that

Table 2
Number of amino acids in close contact (<4 Å) between the two monomers in the dimeric bc_1 and b_6f complexes.

Structure	3CX5	1NTZ	2Q JP	2E74	2ZT9
Close contact, aa pairs	131	120	80	65	66
Cytochrome *b*	48	44	55	39	43
b_6f-Subunit IV	–	–	–	10	8
Rieske [2Fe–2S]	23	16	25	16	15
bc_1-Subunit I	6	1	–	–	–
bc_1-Subunit II	26	24	–	–	–
bc_1-Cytochrome c_1	9	11	–	–	–
bc_1-14 kDa protein	10	14	–	–	–
Yeast-bc_1-subunit VIII	9	–	–	–	–
Bovine-bc_1-Subunit XI	–	10	–	–	–

of the Rieske ISP, whose active p-side [2Fe–2S] cluster in one monomer is connected to its TMH by a long glycine-rich disordered flexible loop that spans the trans-membrane domain of the other at a pronounced oblique angle (Fig. 1a–c; described in yellow).

Extensive conformational changes of the [2Fe–2S]-containing subdomain of the Rieske ISP are necessary to accomplish kinetically competent electron transfer from the [2Fe–2S] cluster to the heme of cytochrome c_1 or *f* [3]. For both complexes, the [2Fe–2S] donor–heme c acceptor distance, derived from structures described in PDB 3CX5 and 2E74, 22.5 and 26.1 (seen "edge–edge" in Fig. 5a, b) is too large for competent electron transfer. These distances would result in electron transfer times that are at least 1000 times larger than the ~millisecond rate-limiting step of the system [155]. Different crystal forms of bc_1 complex show conformations with shorter [2Fe–2S]–heme c_1 distances (12.8 , 3H1H, [5] and 15.5 , 1BE3, [4,156]) that would allow kinetically competent electron transfer [5]. The 15.5 distance described in PDB 1BE3, the cyt c_1-proximal conformation, is one of three crystallographically determined [2Fe–2S]–heme c_1 distances between the [2Fe–2S] cluster and the cyt c_1 heme that have been defined in the bovine complex. The others are 31.6 in the heme b_p-proximal conformation (PDB ID: 3BCC) and 27.5 in an "intermediate" conformational state (PDB ID: 1BGY [4]). These structure data imply protein conformational changes of the ISP that cause the [2Fe–2S] cluster to alternate between positions that are distal and proximal to the heme of cyt c_1, the latter allowing competent electron transfer.

The rotation-translation of the cluster-containing peripheral subdomain of the Rieske protein in the bc_1 complex is enabled by rotation-translation about the flexible linker region that connects the peripheral domain in one monomer with the trans-membrane α-helix in the other. The necessity of flexibility in this loop was demonstrated through site-directed mutations that are predicted to result in structure changes that decrease the mobility of this linker region [43,157–159]. Substitutions of multiple proline or glycine residues in the loop region of the b_6f complex, or insertions that caused loop elongation had no effect on activity [160], although these mutations are similar to those cited above that markedly decreased activity of the bc_1 complex. A crystal structure to demonstrate the cyt *f* heme-proximal state of the [2Fe–2S] cluster in the b_6f complex, which would be necessary for kinetically competent activity, has not yet been determined.

2.6. Inhibitor-induced conformational changes

(a) *p-Side quinone analogue inhibitors*. For the bc_1 complex, the inhibitor stigmatellin, which binds in the p-side entry portal close to an imidazole ligand of the ISP [2Fe–2S] cluster, is present in almost all crystal structures because its presence results in decreased mobility [160] and increased order of the ISP soluble domain, although it does not change the orientation of the cluster itself [161]. For cyt b_6f, a structure of the native complex without any bound inhibitor has been obtained [16, 19, 20]. Large conformational changes of the b_6f complex induced by stigmatellin have been reported in a study with 2D crystals [162], although such changes were not seen in a comparison of 3D crystals, native vs. b_6f with stigmatellin [19], for which the RMSD for the PDB ID: 2E74 vs. 2E76 (+tridecyl-stigmatellin) structures from *Mastigocladus laminosus* is 1.18 Å.

(b) *n-Side inhibitors*. RMSD changes of significant amplitude associated with the binding of the known specific inhibitors have not been detected: (i) the RMSD of the native (PDB ID: 1NTM) vs. antimycin A-inhibited (1NTK) bovine bc_1 complex is 0.47 Å; (ii) for *Nostoc* b_6f structures, the RMSD of PDB ID: 2E74 vs. 2E75 (+NQNO) is 0.43 Å [19]; and (iii) the RMSD for the avian bc_1 complex, stigmatellin vs. stigmatellin and antimycin is 0.36 Å (PDB ID: 3H1J vs. 3H1I). However, antimycin causes a 100–150 mV change in the E_{m7} of a mitochondrial *b* heme [163], presumably heme b_n, and a perturbation of the p-side EPR signal associated with the [2Fe–2S] cluster in the bc_1 complex of the photosynthetic bacterium, *Rhodobacter capsulatus* [64,164,165].

3. The Q cycle

The coupling of the oxidation–reduction and deprotonation–protonation of lipophilic quinone/ol (Q/QH_2) within the cytochrome *bc* complex is central to the mechanism of proton translocation in the complex. The proton/electron carriers, ubiquinone (UQ-10; [166,167]) in the respiratory bc_1 complex and plastoquinone (PQ-9) in the b_6f complex, contain 10 and 9 isoprenoid groups, respectively. In the extended state, steric problems are anticipated in translocation of these quinones in a rigid extended state across the cytochrome *bc* complex, or their reversible insertion into oxidative or reductive niches within the complex. Possible conformational transitions to folded states have been described [168–170]. Based on the observation of oxidant-induced reduction of *b*-type heme in the respiratory bc_1 complex [171], it was proposed that these quinones can cross the cytochrome *bc* complex and the membrane, as described in the "Q cycle" models proposed by Mitchell [172–174], and in subsequent discussions of this model [46,80,109,111,175,176]. Descriptions of the Q-cycle that illustrate differences between bc_1 and b_6f complexes are shown (Fig. 3a, b). Other formulations of the Q cycle are found in Refs. [51,53,80,177].

Experimental data that were fundamental to the formulation of the Q cycle models are: (a) oxidant-induced reduction of cytochrome *b* of the mitochondrial respiratory complex [171,178,179]; (b) a

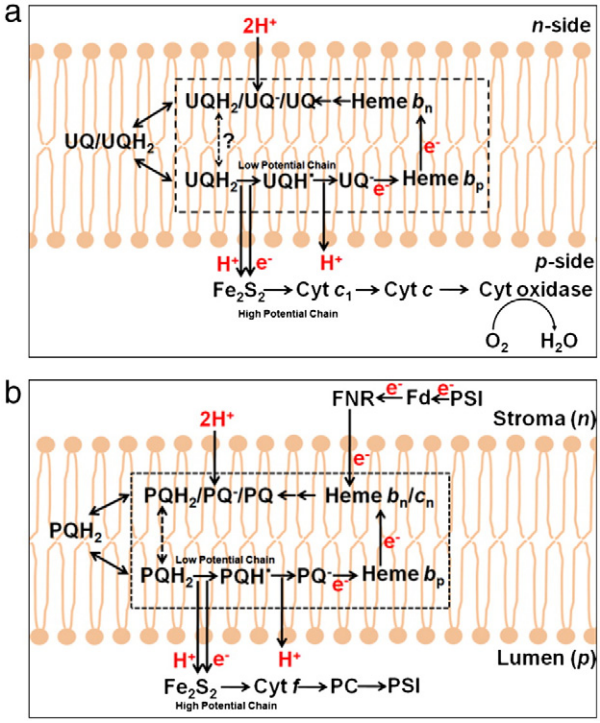

Fig. 3. Q cycle models for electron transfer and proton translocation through (A) the bc_1 complex in the respiratory chain [176] and the purple photosynthetic bacteria [48], reaction sequence (Table 3A1–3) and (B) the b_6f complex that functions in oxygenic photosynthesis (Table 3B). The original "Q cycle" model [172,174] for proton translocation, formulated in the aftermath of the experiment of the discovery of oxidant-induced reduction of heme *b* [171], focused on the mitochondrial bc_1 complex. Fundamental features of the classical Q cycle are: (i) the [2Fe–2S] complex on the p-side of the complex that functions as the one electron oxidant of the lipophilic quinol electron and proton donor, resulting in a bifurcated pathway into high and low potential chains; (ii) the high potential segment of the bifurcated pathway, initiated by electron transfer to cytochrome c_1 or *f*, which transfers one electron to the high potential electron terminal acceptor, (a) cytochrome oxidase or (b) photosystem I, while generating the semiquinone; (iii) the semiquinone donates the second electron to the two trans-membrane hemes *b*, b_p and b_n, in the low potential segment of the bifurcated chain that reduces a quinone or semiquinone [53] bound at the Q_n site.

proton:electron ratio, $H^+/e = 2$, for uncoupler-sensitive electrogenic proton translocation to the p-side aqueous phase by the bc_1 [180,181] and b_6f [182] complexes in the presence of a relatively small $\Delta\tilde{\mu}_H^+$ [183,184] (for the b_6f complex, there has been debate as to whether the extra H^+ translocation, which is electrogenic, is inhibited in the presence of a large $\Delta\tilde{\mu}_H^+$ [185], and whether it is [105,186] or isn't [187–189] specifically associated with the reduction of the hemes *b*). (c) The model is also strongly supported by the presence of specific Q binding sites of potent quinone analogue inhibitors, e.g., antimycin A and stigmatellin, on both n- and p-sides of the complexes, whose precise locations have been confirmed by: (i) crystal structures; ubiquinone (PDB ID: 3H1H) or antimycin (PDB ID: 3H1I) binding sites have been determined on the n-side of the complex adjacent to heme b_n, and the stigmatellin binding site on the p-side (PDB ID: 3H1J) within H-bond distance of the histidine ligand (His181 in yeast) to one of the Fe atoms in the [2Fe–2S] cluster. In the b_6f complex, analogous n- and p-side binding sites of NQNO and tridecyl-stigmatellin have been identified [19]; (ii) EPR detection of a ubisemiquinone free radical intermediate, in the absence, but not in the presence of antimycin [190], and an analogous oxygen-sensitive p-side signal [191].

Independent data supporting the Q cycle model for redox and H^+ transfer reactions in the b_6f complex are less complete because: (i) there is no high affinity n-side inhibitor comparable to antimycin A for the bc_1 complex, which is partly a consequence of partial occupancy in the b_6f complex of the bc_1-like Q_n site by heme c_n [19]; (ii) in contrast to the bc_1 complex, the alpha-band absorbance spectra of the two trans-membrane hemes, b_p and b_n, cannot readily be distinguished (e.g., Ref. [105]; although see Ref. [192]). Together with the fact that any ΔE_m between the two hemes is much smaller in the b_6f complex compared to bc_1, and not resolved in most *in situ* titrations, a determination of the sequence of reduction of the two hemes in b_6f, as accomplished for bc_1 in chromatophores of the photosynthetic bacteria [193,194], is precluded. (iii) From studies on the bc_1 complex in *Rb. sphaeroides*, it was inferred that transfer of the first electron in the two electron quinol oxidation to the ISP, in a proton-coupled electron transfer [195], is the rate-limiting step of the overall Q cycle [48,196] (Fig. 3a, b).

Electron and proton transfer reactions of the bc_1 and b_6f complexes in the context of a Q cycle are summarized (Table 3A1, 2). The presence of the unique heme c_n, whose covalent attachment to the cytochrome *b* polypeptide can be detected in SDS-PAGE analysis of the b_6f complex [197], and which is electronically coupled to heme b_n [127,128], makes the detailed nature of a "Q cycle" different in the b_6f complex compared to bc_1: (i) Crystal structures and spectrophotometric analysis showing quinone analogue inhibitors NQNO [19,128,130] and tridecyl-stigmatellin [19] as ligands to heme c_n imply that heme c_n is the n-side PQ binding site. The electronically coupled hemes b_n/c_n could provide a 2 electron pathway for reduction of PQ_n. The presence of NQNO and stigmatellin as ligands to heme c_n, as defined in crystal structures (2E75, 2E76; [19]), implies a role in the n-side electron transfer reactions (Table 3B, n-side reactions, ii–iv). The isolation of a plant (spinach) b_6f complex from the green alga *C. reinhardtii,* containing bound ferredoxin-$NADP^+$ reductase (FNR) [106], and of a supercomplex containing the PSI reaction center and b_6f complexes together with FNR [96], implies the possibility that PSI-linked cyclic electron transport provides an alternative source of electrons into the b_6f complex. An FNR-dependent reductive pathway to PQ_n resembles an original formulation of the Q cycle for the bc_1 complex, in which the one of the two electrons needed for reduction of UQ_n is supplied by an n-side dehydrogenase [173].

The cyclic pathway may be augmented by an NADH dehydrogenase, implied by studies on chloroplast mutants in *Arabidopsis thaliana* [97]. Regardless of the source of electrons from the cyclic pathway, it is proposed that the Q cycle in the b_6f complex could be completed on the n-side by one electron supplied by the cyclic pathway (Table 3, B3, v), which would complement the electron derived from the p-side oxidation of plastoquinol. The possibility can also be considered that two electrons stored on hemes b_n–c_n cooperatively reduce PQ (PQ_n) bound at the site proximal to heme c_n (Table 3, B3, vi) to PQH_2. A consequence of the input of one electron from cyclic electron transport to reduce Q_n is that only one p-side oxidative turnover of PQH_2 would be required to form Q_nH_2.

Another ("activated") Q cycle model [53] (Table 3, B4) proposes that the quinone species bound at the Q_n site is a semiquinone, which can form a complex and transfer an electron to the higher potential heme b_n (*b*-150; [198,199]) on the other monomer. This most recent and interesting formulation of a modified Q cycle results from consideration of a substantial number of experiments, mainly concerning the flash-induced amplitude and kinetics of the trans-complex electric field and heme *b* reduction that do not fit the models described in Table 3A1–3, 3B1, 2. The "activated" mechanism employs the dimeric *bc* complex, in which prompt oxidation of the quinol on the n-side of one monomer reduces heme b_n on the other. The mechanism then requires only one oxidation (turnover) of Q_pH_2 to provide the single electron needed to form the quinol Q_nH_2 and once primed, minimizes exchange of QH_2/Q with the membrane QH_2/Q pool. This mechanism was originally proposed for the bc_1 complex [53] and subsequently for the b_6f complex [80]. Two problems with application to the b_6f complex are: (i) the E_m of heme b_n in b_6f (Table 1) is approximately 100 mV more negative than that in bc_1 (Table 1), implying a less favorable equilibration between bound Q_n semiquinone and heme b_n than would occur in the bc_1 complex, assuming that the Q_n semiquinone has the same E_m in both

Table 3
(A1–A3) Oxidant-induced reduction, electron transfer through the high potential chain, and trans-membrane electron transfer in *bc* complexes. (B1–B4) n-side reduction of UQ_n, PQ_n.[1]

A1. p-Side quinol oxidation* (Q is PQH_2 in b_6f and UQH_2 in bc_1 complexes)
$UQ_pH_2 + FeS(o) \rightarrow UQ_p^{\bullet -} + FeS(r) + 2H^+$
$UQ_p^{\bullet -} + b_p(o) \rightarrow UQ_p + b_p(r)$
A2. High potential chain (to the soluble acceptor, cytochrome *c* or plastocyanin)
$FeS(r) + cyt\ c_1(o) \rightarrow FeS(o) + cyt\ c_1(r)$; involves rotation-translation of ISP [5];
$cyt\ c_1(r) + cyt\ c(o) \rightarrow cyt\ c_1(o) +$ "cyt *c*(r)"; cyt c_1 corresponds to cyt *f* in b_6f complex
A3. Trans-membrane p- to n-side electron transfer
Heme $b_p(r) +$ heme $b_n(o) \rightarrow b_p(o) + b_n(r)$
B1. n-Side reduction of UQ_n or PQ_n by consecutive transfer of 2 electrons (2 one-electron transfers) from the p-side;
(i) Heme $b_n(r) + UQ_n \rightarrow UQ_n^{\bullet -}$; transfer of 1 electron arising from oxidation of UQ_pH_2
(ii) Heme $b_n(r) + UQ_n^{\bullet -} + 2H^+ \rightarrow$ heme $b_n(o) + UQ_nH_2$; transfer of 2nd electron from 2nd UQ_pH_2.
B2. n-Side 2 electron reduction of PQ_n by consecutive transfer of 2 electrons from the p-side, resulting from oxidation of two PQ_pH_2 and cooperative 2 electron reduction of PQ_n transfer via hemes b_p and b_n.
$b_p(r) + b_n(r) + UQ_n + 2H^+ \rightarrow$ heme $b_n(o) +$ heme $b_n(o) + UQ_nH_2$; (2 electron reduction of ubiquinone avoids the 1 electron reduction of UQ that may be energetically uphill; [194]).
B3. n-Side 2 electron reduction of PQ by 2 electrons from p-side via heme $b_n(r)/c_n(r)$, or 1 electron from p-side and 1 from n-side (via ferredoxin/FNR) [75,76,80]
(i) Heme $b_p(r) +$ heme $b_n(o) \rightarrow b_p(o) + b_n(r)$
(ii) $b_n(r)\ /c_n(o) \rightarrow b_n(o)/c_n(r)$; the more positive potential of heme c_n relative to heme b_n [130] could facilitate this transfer; then, in a second p- to n-side transfer,
(iii) $b_p(r) +$ heme $b_n(o)/c_n(r) \rightarrow b_n(r)/c_n(r)$
(iv) $b_n(r)/c_n(r) + PQ_n + 2\ H^+ \rightarrow b_n(o)/c_n(o) + PQ_nH_2$, or via the PSI-linked cyclic pathway,
(v) $Fd/FNR(r) + b_n(o)/c_n(r)/PQ_n \rightarrow Fd/FNR(o) + b_n(r)/c_n\ (r)/PQ_n$
(vi) $b_n(r)/c_n(r)/PQ_n + 2\ H^+ \rightarrow b_n(o)/c_n(o)/PQ_nH_2$
*[o, oxidized; r, reduced];
B4. "Activated Q cycle"; *bc* complex "primed" by n-side 2 electron reduction by membrane pool quinol of Q_n to Q_nH_2 in one monomer (1) and, via inter-monomer transfer, of heme b_n to b_n (r) (2) in the other [53,80].
(i) QH_2 (pool) $+ Q_n \rightarrow$ Q (pool) $+ Q_nH_2$ [monomer 1]
(ii) Q_nH_2 [monomer 1] $+ b_n$(o) [monomer 2] $\rightarrow Q_n^-$ [monomer 1] $+ b_n$(r) [monomer 2] $+ 2H^+$
(iii) $Q_n^{\bullet -}$[1] reduction to Q_nH_2 by a single p-side turnover using reactions A1–3 and B1 above.

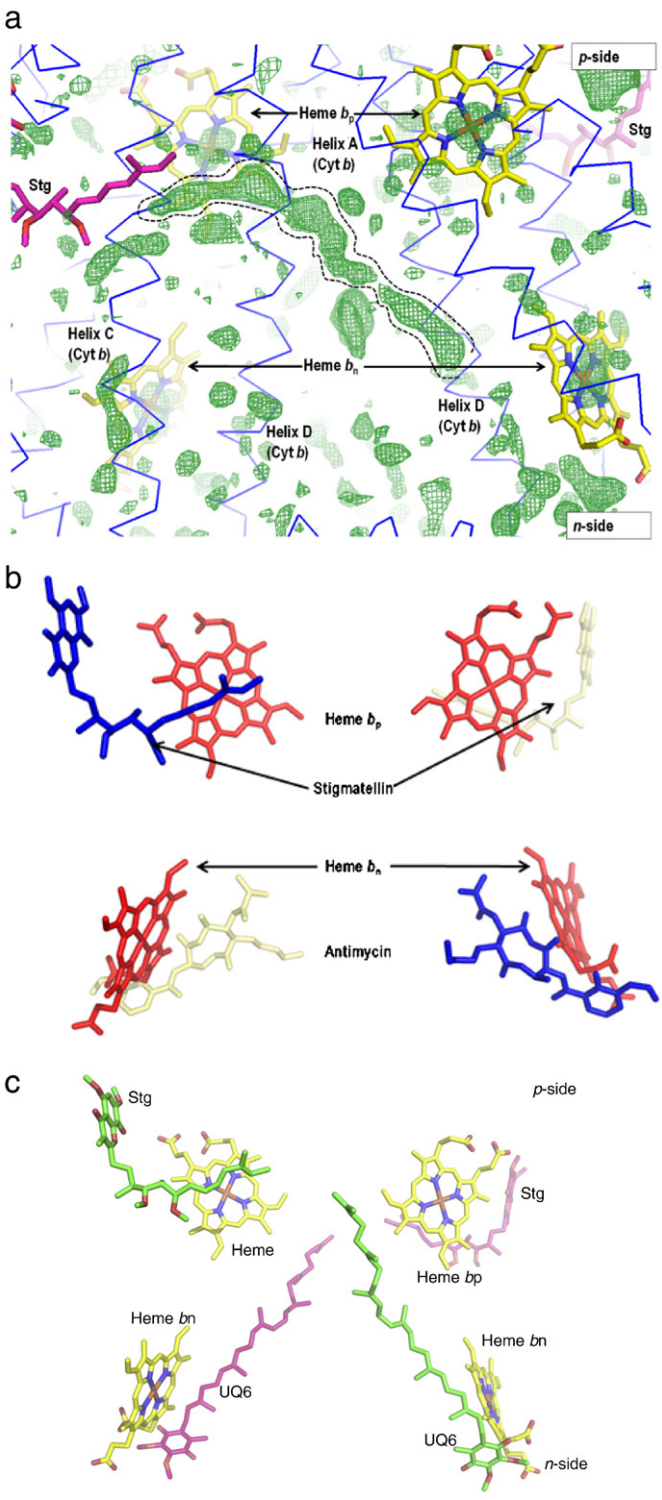

Fig. 4. (a) Presence of lipid-like molecules in the inter-monomer cavity of yeast cytochrome bc_1 complex (PDB ID: 3CX5). The outlined density may correspond to an acyl chain of a lipid or detergent molecule or it may be attributed to the isoprenoid tail of a ubiquinone molecule as found in the Q_n site of the yeast bc_1 complex (PDB ID: 1KB9). Figure generated in PyMol from PDB 3CX5 and its Fo–Fc map contoured at 3.0 sigma. Negative densities were not included in the analysis. (b) n- and p-side binding sites of quinone analogue inhibitors, antimycin A and stigmatellin (PDB ID: 1PPJ [216] or 1NTZ [10]), which are on the same side (yellow or blue) of the dimeric complex, implying that if a trans-complex quinone pathway operates for electron and proton transfer, it would be inter-monomer. (c) Yeast bc_1 complex (PDB ID: 1KB9) showing (side-view) cross-over of ubiquinone isoprenoid tail (UQ-6, bound at Q_n site) from one monomer across the inter-monomer cavity, to the Q_p site portal in the other monomer, located by presence of quinone analogue stigmatellin (Stg). The Stg and UQ-6 pair colored magenta is positioned on one face of the bc_1 dimer, while that colored green lies on the other.

systems; (ii) the large distance (PDB ID: 1NTZ [10]), 28 Å in bovine bc_1, between the ring of the quinone at the Q_n site in one monomer and heme b_n in the other would result in a very slow (time scale of seconds) electron transfer step in the cycle, suggesting a kinetic difficulty.

4. Pathways for quinone transfer: Consequences of dimer symmetry

Given the above data and logic that are consistent with, and support the Q cycle models shown in Fig. 3a, b with the electron and proton transfer reactions described in Table 3, it is noted that there are no data available on the pathway or trajectories of the lipophilic quinone/ol (Q/QH2) within the *bc* complex connecting its n- and p-sides. Then, it is important to consider in the context of the atomic structures of the *bc* complexes (Fig. 1a–c), the possible trans-membrane pathways used by the long chain lipophilic quinones/quinols to transfer electrons and protons within the *bc* complexes.

4.1. Quinone binding in the dimer: Consequences of symmetry

Although intra-complex transfer of Q, QH_2, and semiquinone has been proposed, and is implied in many models of the Q cycle [46,80,109,111,175,176], the presence of lipid acyl chains within the inter-monomer cavity is indicated by at least 11 bound lipids resolved in the yeast complex (PDB: 3CX5), and an Fo–Fc map of the inter-monomer cavity indicating additional lipid acyl chains (Fig. 4a). It is likely that the cavity is occupied by an even higher density of lipid chains than shown, but that most of this lipid is weakly bound and lost during purification and crystallization. The presence of this lipid implies that intra-complex transfer of Q/QH_2 through the inter-monomer cavity might be impeded by the lipid chains, although such obstruction would be lessened by the disorder and probable mobility of these chains. Furthermore, a consequence of the C2 symmetry is that the two monomers are arranged so that: (i) the [2Fe–2S] quinol oxidation site and the quinone reduction site (b_n in the bc_1 complex and b_n–c_n in b_6f) in the two monomers are on opposite faces of the complex (Fig. 4b); (ii) heme b_n in either monomer of the bc_1 complex, or hemes b_n–c_n in the b_6f complex, are on the same side of the complex as the 2Fe–2S cluster in the other monomer. Thus, the n-side binding site of antimycin on one monomer is on the same side of the dimeric complex as the p-side binding site of stigmatellin on the other (Fig. 4b), implying that if transfer of Q/QH_2 occurs across the *bc* complex, the transfer trajectory will be on one side of the complex [3,41]. (It is noted that the yeast 3CX5 structure does not have a true C2 symmetry because cytochrome *c* is bound to one monomer and the partly disordered cardiolipin shared on the n-side between the two monomers is asymmetrically located.)

A side-view (Fig. 4c) of the yeast bc_1 complex (PDB ID: 1KB9) shows an apparent cross-over of the ubiquinone isoprenoid tail (UQ-6) bound at the Q_n site in one monomer across the inter-monomer cavity, to the Q_p site portal in the other monomer, which is located by stigmatellin (Stg; colored magenta). The cross-over is only apparent as the Stg and UQ-6 pair colored magenta is located on one face of the bc_1 dimer, while that colored green lies on the other.

Movement and transfer of the quinone(ol) through the complex will increase efficiency. However, there must be some exchange with the Q/QH_2 pool in the bilayer because 2 QH_2 are oxidized on the p-side for every Q that is reduced on the p-side. Therefore, two electrons (i.e., 2 equivalents of reductant) are lost from the complex, and one extra Q molecule is generated in every cycle. Therefore, even if one of the 2 Q generated from the oxidation of 2 Q_pH_2 is transferred across the cavity to the Q_n site, the second Q_p must be released from the complex to the membrane bilayer, and a second Q_pH_2 supplied from the membrane bilayer to the oxidation site at the [2Fe–2S] cluster. Because the oxidation of the 2 QH_2 must occur in a few milliseconds, transfer of QH_2 from the photosystem II complex to b_6f must occur rapidly, suggesting the possibility of a supercomplex.

5. Role of the dimer in electron transfer

A dimeric or multimeric structure is a common structure motif in integral membrane proteins, prominent among which are the photosynthetic reaction centers [200–204]. The electron and proton transfer reactions described in Table 3 do not describe any special function of the dimer. They do not distinguish whether electron transfer across the complex from heme b_p to b_n is (a) intra-monomer [58,61] or (b) inter-monomer with cross-over between the two hemes b_p. The latter possibility was suggested after the appearance of the crystal structures of the bc_1 complex that defined the inter-heme distances [78] and subsequently discussed extensively [56,57,63,82,154,205–207]. A "cross-over model" suggests that a function of the dimer could be to allow a "bypass valve" for a second pathway of trans-membrane electron transfer if the pathway for trans-membrane electron transfer in one monomer is impeded by reduction of the quinone in the Q_n binding site in that monomer, or by electron equilibration in that monomer. There are different quantitative descriptions of the electronic connection between the electron donor and acceptor, e.g., whether the distance separation between electron donor and acceptor should be measured "center to center" [208,209] or "edge to edge" [155,210,211]; the electron donor-acceptor distance, in addition to the free energy change, ΔG, and reorganization energy associated with the transfer [212–215] are major determinants of the branching ratio for intra-monomer vs. inter-monomer electron transfer [213]. The crystal structures (Fig. 1a–c) provide donor-acceptor distances to an accuracy of approximately $\pm$0.3–0.5 Å (Table 4A, B) and the identity of the amino acids that bridge the potential electron transfer pathways (Fig. 5a–d). Heme edge–edge, ring–ring (bypassing side chains), and center–center (Fe:Fe) distances for seven bc_1 and b_6f structures are summarized in Table 4A and B. The seven structures include three bc_1 respiratory complexes: (i) yeast with bound stigmatellin and cytochrome *c* bound to one subunit ([15]; 3CX5), (ii) bovine mitochondria with p-side bound stigmatellin and antimycin A ([216]; 2A06), (iii) bovine complex with n-side bound ubiquinone-2 (1NTZ); (iv) 3 subunit bc_1 complex from the photosynthetic bacterium, *Rb. sphaeroides*, with p-side bound stigmatellin (2QJP); (v, vi) native b_6f complex from the filamentous cyanobacteria, *M. laminosus* and *Nostoc* PCC 7120 (2E74, 2ZT9); and (vii) b_6f complex from the green alga, *C. reinhardtii* (PDB ID: 1Q90) with the p-side bound inhibitor stigmatellin (1Q90).

Table 4
Inter- and intra-monomer distances between the two hemes b_p and b_p/b_n of the dimeric cytochrome *bc* complexes: the bc_1 complex (PDB ID: 3CX5, 2A06, yeast and bovine mitochondria with the p-side quinone-analogue inhibitor stigmatellin; 1NTZ, bovine complex with ubiquinone-2 bound at the Q_n site; 2QJP, purple photosynthetic bacterium, *Rb. sphaeroides*, with bound p-side stigmatellin and n-side antimycin); b_6f complexes (2ZT9, 2E74), native structures from two different cyanobacteria, *M. laminosus* and *Anabaena* 7120, and from the green alga, *C. reinhardtii* with tridecyl-stigmatellin (1Q90).

PDB code	3CX5	2A06	1NTZ	2QJP	2E74	2ZT9	1Q90
Resolution (Å)	1.9	2.1	2.60	2.60	3.0	3.0	3.1
R factors	0.245	0.222	0.247	0.244	0.222	0.230	0.222
	0.263	0.258	0.283	0.277	0.268	0.259	0.261
Coordinate error (Å)	0.31	0.29	0.47	0.41	0.44	0.44	0.43
A. Inter-monomer distances (Å)							
Heme b_p–heme b_p (edge–edge)	10.0	10.5	10.9	10.6	12.9	12.7	12.7
Heme b_p–heme b_p (ring–ring)	13.7	14.3	13.8	13.4	15.2	15.1	15.1
Heme b_p–heme b_p (center–center)	21.2	21.4	20.7	20.7	22.0	22.1	22.0
B. Intra-monomer distances (Å)							
Heme b_p–heme b_n (edge–edge)	7.2	7.0	8.6	7.9	7.4	8.2	8.9
Heme b_p–heme b_n (ring–ring)	12.2	12.0	12.3	11.9	12.2	12.0	12.2
Heme b_p–heme b_n (center–center)	20.7	20.4	20.6	20.4	20.6	20.7	20.8

Split Soret band circular dichroism spectra of the mitochondrial bc_1 [217–219] and b_6f complex from *C. reinhardtii* b_6f [220], cyanobacteria and spinach chloroplasts [221], are diagnostic of heme–heme excitonic interactions that arise from the small inter-heme distances required for such interactions. For inter-monomer electron transfer, the only pathway considered is that between the two b_p hemes because of the large distance (~30 Å) in all cytochrome *bc* structures between the two hemes b_n and between heme b_n and b_p in different monomers. The pathway between the two b_p hemes, bridged by two Tyr residues and two Phe residues, respectively, in the bc_1 and b_6f complexes, approximately 10 Å in the yeast bc_1 complex and 13 Å in the *M. laminosus* b_6f complex is shown (Fig. 6c, d). For inter-monomer electron transfer, i.e., "cross-over," differences in edge–edge and ring–ring distances, distance for closest contact between the two hemes b_p, relative to that between b_p and b_n, are (10.0–7.2) = 2.8 Å and (13.7–12.2) = 1.5 Å, respectively, for the yeast respiratory bc_1 complex, which has the best resolution in the set (Fig. 1a, 6a [15]; Table 4A, B). This comparison implies that the intra-monomer b_p–b_n pathway would be favored. The b_p–b_p edge–edge and ring–ring inter-monomer distances are also greater than the intra-monomer b_p–b_n distances for all six of the other representative bc_1 and b_6f complexes considered in Table 4A and B. The difference in the inter- vs. intra-monomer distances (determined edge–edge, ring–ring) is (2.7 Å, 1.5 Å) and (2.3 Å, 1.5 Å) for the bc_1 complexes described in 2QJP and 1NTZ, and (4.5 Å, 3.1 Å), (5.5 Å, 3.0 Å), and (3.8 Å, 2.9 Å) for the b_6f complexes described in 2ZT9, 2E74, and 1Q90. Thus, for all seven cytochrome *bc* complexes, the intra-monomer distances, edge–edge and ring–ring, are clearly smaller than the inter-monomer distances. The differences for center–center distances show the same tendency, but are smaller and in some cases do not exceed experimental uncertainty. It is of interest that these inter-heme distances are the same for *bc* complexes from different sources and are not changed by the presence of n- or p-side quinol analogue inhibitors.

Considering only the distance dependence of the electron transfer rate, the difference in edge–edge and ring–ring distances would predict [155,208–211,222–227] a branching ratio for electron transfer from heme b_p that would significantly favor the intra-monomer pathway. This logic is similar to that used previously to predict a branching ratio that favors the intra-monomer pathway by two orders of magnitude [215]. The latter reference provides an extensive discussion of the intra/inter-monomer electron transfer problem, including the effect of the trans-membrane electric field generated by intra-monomer electron transfer that would inhibit the transfer. Recent studies using *b* heme knock-out mutants and splicing of the cytochrome *b* gene have demonstrated that the inter-monomer cross-over branching ratio is >1 [81], and has been estimated to be 2–10 to 1 [228]. Special functions associated with the inter-monomer cross-over pathway, discussed elsewhere for the bc_1 complex, have been mentioned above. For the b_6f complex, a selective pathway for electron transfer is implied from the observation that FNR, in the presence of the "artificial" electron donor NADPH, reduces no more than half of the *b* heme in the b_6f complex [19,229,230]. This half could be the heme b_n in the two monomers [229] or hemes b_n and b_p in one. Selection of the one monomer may result from interaction via n-side docking of an electron donating protein such as FNR [106] (Fig. 3b). In this case, because the chemical reduction is so slow (> seconds) and the half-reduction is an equilibrium level, an explanation solely in terms of differential kinetics of reduction based on differences in inter-heme distances is not adequate.

6. The problem of the p-side portal

Passage of the lipophilic quinol to its oxidation and deprotonation site at the [2Fe–2S] cluster requires that after its entry into the inter-monomer cavity, or transfer from its n-side reduction site, it must pass through a narrow 15 Å long portal that is 10–12 Å and 13–14 Å wide at the cavity-side entrance in bc_1 and b_6f complexes. The nature of this portal for stigmatellin has been described for the yeast bc_1 complex [7].

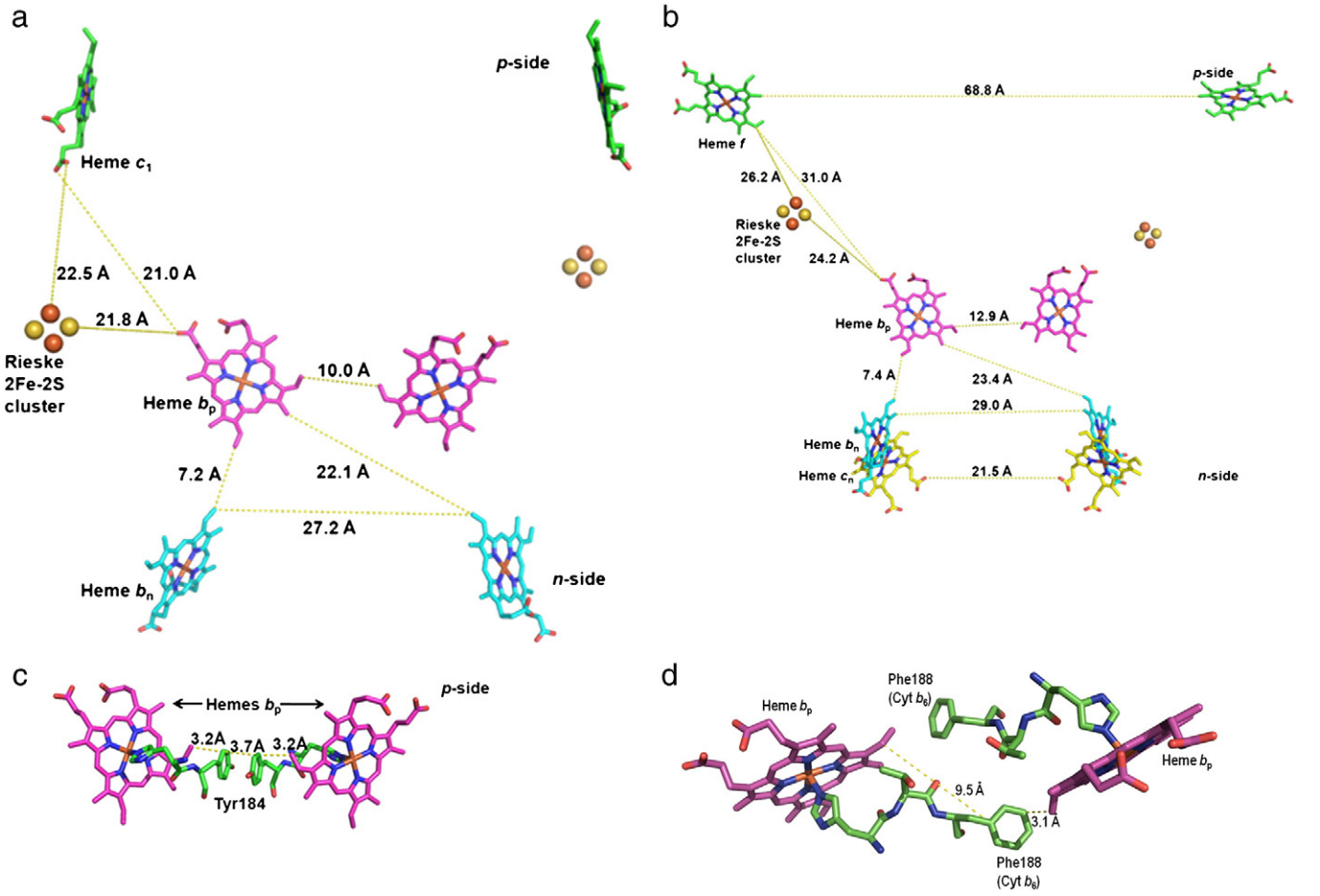

Fig. 5. Possible pathways for electron transfer. Intra-and inter-monomer edge–edge distances for: (a) yeast bc_1 (PDB ID: 3CX5); (b) cyanobacterial b_6f (PDB ID: 2E74) complex. (c, d) Center–center (Fe–Fe) connection via histidine ligands, and (c) an intra-monomer Tyr184–Tyr184 bridge in yeast bc_1 (PDB ID: 3CX5), and (d) a Phe188–Phe188 bridge in the *M. laminosus* b_6f complex.

The portal is shown with an inserted p-side quinone analogue inhibitor, tri-decyl stigmatellin or stigmatellin (in green) in Fig. 6a, b for the cytochrome b_6f and bc_1 complexes, respectively. Such portals are also present in the Q_B quinone binding site of the bacterial [231,232] and photosystem II photosynthetic reaction centers [204,233]. The overlap of tridecyl-stigmatellin and the phytyl chain of chlorophyll *a* also passing through the portal in the b_6f complex (*M. laminosus*; PDB ID: 2E76) is shown (Fig. 6c). An expanded view of the Q/QH_2 entry/exit portal showing residues within 4 Å of stigmatellin is shown in (Fig. 6d) for the yeast bc_1 complex. Stigmatellin, possessing a chromone ring that forms an H-bond with the His181 (bc_1; PDB ID: 3CX5) or His129 (b_6f; PDB ID: 2E76) ligand of the Rieske [2Fe–2S] cluster, and inhibits electron transfer from the cluster to the heme of cytochrome c_1 or *f*, was defined as a "class Ib" inhibitor [12]. UHDBT is another inhibitor in this class. Myxothiazol and MOAS, which contain a β-methoxyacrylate ring, were classified as "1a" inhibitors [12]; the binding of myxothiazol in the p-side portal is shown (Fig. 6e).

A better understanding of the insertion and passage of the lipophilic Q/QH2 through the portal could be gained through molecular dynamics analysis, as studied in the passage of ubiquinone through a defect in the ring of light-harvesting (LHI) bacteriochlorophyll molecules surrounding the photosynthetic reaction center [234], and the insertion of a drug molecule into a virus capsid protein [235], which has a formal resemblance to quinol insertion into the p-side entry portal to the [2Fe–2S] cluster. The combination of kinetic and steric constraints of portal entry-extrusion of quinol/quinone in the most frequent description of the Q cycle, described symbolically in Fig. 3a, creates a unique sequence of intra-membrane transfer events that occur twice in the millisecond turnover time of the bc_1 and b_6f complexes: (i) QH_2 with its isoprenoid chain of 45–50 carbons must find the narrow portal entry; (ii) traverse its narrow aperture; (iii) transfer 2 electrons and 2 protons; (iv) Q is extruded from the portal after oxidation and deprotonation. As the problem of entry into and from the portal is dynamic, different folded conformations [168,169,234] of the quinone may be relevant to the Q/QH_2 passage through the portal. As an indicator of the conformational flexibility of the portal, the average *B* factors (^{2}) of (i) portal residues and (ii) residues in neighboring trans-membrane helices are 27.2 and 25.8 for the 1.9 yeast bc_1 complex with stigmatellin bound in the portal (3CX5), implying that the portal is relatively ordered in the presence of stigmatellin, an inference previously made for the yeast 2.3 structure (PDB ID: 1EZV), with *B* factors (measures of disordered regions in the structure) of 37.0 and 35.2 ^{2}, respectively, for the bound stigmatellin and neighboring portal residues [7]. In contrast, for native b_6f complex solved in the absence of any quinone analogue inhibitor (2E74), the *B* factor (60.6 ^{2}) for the residues lining the p-side portal is substantially larger than that, 44.7 ^{2}, of residues in the neighboring trans-membrane helices, indicative of greater flexibility or disorder in the structure of the portal, which would facilitate passage of quinol/quinone or the analogue inhibitor. The greater order upon insertion of the quinone analogue inhibitor suggests that entry of the quinone or analogue requires interaction with the walls of the portal, which is reflected in the decreased *B* values.

In addition to the binding sites of stigmatellin [17,19] and NQNO [19] defined in crystal structures of the b_6f complex, the high affinity binding site of the p-side quinone analogue inhibitor DBMIB [236] was found near the p-side aqueous interface, 19 from its site of inhibition

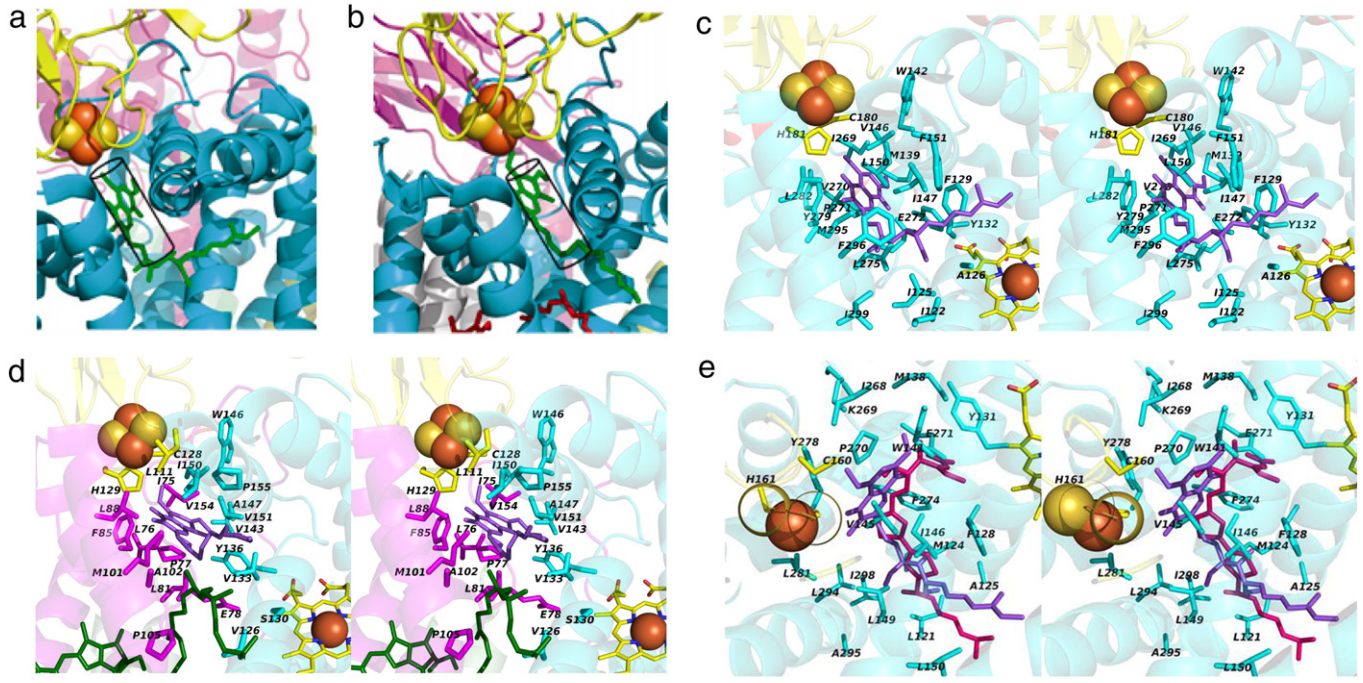

Fig. 6. Narrow p-side quinol/quinone binding niche to access/exit the p-side [2Fe–2S] electron/proton acceptor in cytochrome *bc* complexes: (a): Stigmatellin (green) in a p-side portal in cytochrome bc_1 complex (PDB ID: 3CX5); (b) Tridecyl-stigmatellin (green) in a narrow portal near the p-side of the *M. laminosus* cyt b_6f complex (PDB ID: 2E76); chlorophyll *a* shown in red, partly occluding the portal; (c, d) Expanded views (stereo) of p-side Q/QH_2 entry/exit portal showing all residues within 4 Å of stigmatellin (colored violet, as in panels a, b) in (c) the yeast bc_1 (PDB ID: 3CX5) complex, and (d) the *M. laminosus* b_6f complex (PDB ID: 2E76), showing the residues around tridecyl-stigmatellin (colored violet); the chlorophyll *a* phytyl chain (colored green) is shown occupying a portion of the portal. (e) Overlap (stereo) of p-side stigmatellin (PDB ID: 1SQX) and myxothiazol (1SQP) sites in the bovine mitochondrial bc_1 complex.

at the [2Fe–2S] cluster [18]. However, EPR analysis showed one high affinity site for DBMIB to be proximal to the [2Fe–2S] cluster [237,238], and a second low affinity site further away from the cluster. DBMIB inhibition activated by light flashes implies that there is light-activated movement of DBMIB from the distal peripheral site to the inhibitory site proximal to the [2Fe–2S] cluster [239,240]. Thus, from its high affinity binding site determined in the crystal structure, DBMIB traverses a long and labyrinthine pathway to the [2Fe–2S] cluster where it exerts its inhibitory effect.

Acknowledgments

We thank H. Huang and C.B. Post for discussions on molecular dynamics of the quinone isoprenoid chain, and D. Baniulis, D. Beratan, F. Daldal, J. Hempel, G. Kurisu, F. Rappaport, S. Savikhin, S.D. Zakharov, and H. Zhang for helpful discussions. Studies of the authors related to this article were supported by U.S. NIH GM-38323. Diffraction measurements associated with crystal structures of the b_6f complex were carried out with advice from S. Ginell, J. Lanarz, and F. Rotella at Beam-Line19-ID of the Structural Biology Center, Advanced Photon Source, Argonne National Laboratory, operated by the University of Chicago (contract DE-AC02-06CH11357, U.S. Department of Energy, Office of Biological and Environmental Research).

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