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Interactions of quinone with the iron–sulfur protein of the bc_1 complex: is the mechanism spring-loaded?

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Abstract

Since available structures of native bc_1 complexes show a vacant Q_o-site, occupancy by substrate and product must be investigated by kinetic and spectroscopic approaches. In this brief review, we discuss recent advances using these approaches that throw new light on the mechanism. The rate-limiting reaction is the first electron transfer after formation of the enzyme–substrate complex at the Q_o-site. This is formed by binding of both ubiquinol (QH_2) and the dissociated oxidized iron–sulfur protein (ISP_{ox}). A binding constant of ~ 14 can be estimated from the displacement of E_m or pK for quinone or ISP_{ox}, respectively. The binding likely involves a hydrogen bond, through which a proton-coupled electron transfer occurs. An enzyme–product complex is also formed at the Q_o-site, in which ubiquinone (Q) hydrogen bonds with the reduced ISP (ISPH). The complex has been characterized in ESEEM experiments, which detect a histidine ligand, likely His-161 of ISP (in mitochondrial numbering), with a configuration similar to that in the complex of ISPH with stigmatellin. This special configuration is lost on binding of myxothiazol. Formation of the H-bond has been explored through the redox dependence of cytochrome c oxidation. We confirm previous reports of a decrease in E_m of ISP on addition of myxothiazol, and show that this change can be detected kinetically. We suggest that the myxothiazol-induced change reflects loss of the interaction of ISPH with Q, and that the change in E_m reflects a binding constant of ~ 4. We discuss previous data in the light of this new hypothesis, and suggest that the native structure might involve a less than optimal configuration that lowers the binding energy of complexes formed at the Q_o-site so as to favor dissociation. We also discuss recent results from studies of the bypass reactions at the site, which lead to superoxide (SO) production under aerobic conditions, and provide additional information about intermediate states.
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1. Introduction

The availability of structures for the complete bc_1 complex has stimulated a renewed interest in these central components of the main energy transduction pathways [1–7]. The structures have been invaluable in providing new mechanistic insights, and, quite gratifyingly, they confirmed features expected from an extensive prior period of research on the biochemistry and mechanism of the complex, and from structural prediction.

One surprise from the structures was the disposition of the extrinsic head domain of the Rieske iron–sulfur protein (ISP), found in at least eight different positions in structures reported to date [2–7], and the recognition that in none of these positions would a static structure be competent in catalysis [3]. The explanation in terms of a requirement for movement between catalytic interfaces on cytochrome (cyt) b and cyt c_1 [3,8–10] is now generally accepted. The structures have encouraged new studies of mechanistic aspects. Much of this work has been directed to understanding the role of the ISP movement [11–16]. Movement of the ISP during catalysis has also focused attention on the role of this group as a substrate, and its participation in formation of the intermediate complexes at the Q_o-site of the bc_1 complex [8–10,16–20]. The structures have provided a

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detailed picture of the binding of inhibitors at the site, but no direct information on the configuration of the substrate quinol, intermediate semiquinone or product quinone [1–7]. The structures showed weaker electron density for the extrinsic domain of the ISP than for the remainder of the protein, and quantitative analysis of this phenomenon gave ranges for the binding constants for ISP at the cyt *b* interface (ISP_B) in the crystals, all of which (with the exception of the stigmatellin- or UHDBT-containing complexes) were around 1 or less [9]. Larger values for binding constants involving transient states could be derived from thermodynamic and kinetic studies of the partial reactions leading to turnover of the Q_o-site [18].

Several aspects of the mechanism are controversial, particularly the question of whether or not the reaction requires participation of two quinones in double-occupancy [10,17,21–23]. As in the past, the heat of controversy is inversely proportional to the hardness of the data, which in this case reflects the lack of information on occupancy by the quinone species under functional conditions. In this paper, we review the evidence available on the nature of the liganding between the ISP and different occupants of Q_o-site.

1.1. Substrate binding

The change in rate of a reaction on varying substrate concentration is determined by the consequent change in concentration of the enzyme–substrate (ES)-complex. Crofts and colleagues have used this to explore the binding constants associated with formation of the ES-complex at the Q_o-site. From the movement of ISP seen in the structures, it is clear that two substrates are involved—QH_2 and ISP_{ox}, likely in its dissociated form [18–20]. The concentration of these could be varied independently by redox or pH titration, respectively. Formation of the ES-complex was reflected in the differential binding of quinol when the ISP is oxidized, and in the preferential binding of the dissociated form of ISP_{ox}. By observing the displacement of the kinetically determined values of E_m (for the Q/QH_2 couple) or pK (of ISP_{ox}) from the values in the absence of interaction, we could estimate relative binding constants for QH_2 and ISP_{ox}, both of which showed values ~ 14 [10,17,18,20].

1.2. Kinetics of QH_2 oxidation

The bifurcated reaction delivers the two electrons from QH_2 to two separate chains. From detailed kinetic studies following flash-activation in *Rb. sphaeroides*, including the temperature dependence of partial reactions, Hong et al. [18] showed that the oxidation of bound QH_2 was rate-determining, and the partial reaction with the highest activation energy. The rate was dependent on the driving force for the first electron transfer to ISP_{ox}, since mutations leading to changes in E_m or pK of ISP gave rise to changes in rate consistent with Marcus theory [18,19]. However, the rate appears not to depend on the E_m for the acceptor of the second electron, heme b_L. From this it seems clear that the first electron transfer is the limiting step. At saturating substrate concentrations and ambient temperature, the turnover time is about 0.75 ms. From the structures and the relatively short reaction pathway, the slow rate of the reaction is anomalous, but can be explained in terms of a coupled proton and electron transfer. It seems likely that this is along the H-bond between QH_2 and His-161 of the oxidized ISP. If so, the energy of activation would be given by the sum of positive contributions from two improbable processes:

$$E.b_L.QH_2.ISP_{ox} \overset{\Delta G_{proton}}{\leftrightarrows} E.b_L.QH^-.H^+ISP_{ox} \overset{\Delta G^{\#}_{electron}}{\leftrightarrows} ES^{\#} \rightarrow E.b_L.QH\cdot.ISPH$$

However, because H^+ transfer along H-bonds is very rapid, the constraints of Marcus theory might apply only to the electron transfer part. Crofts et al. [24] suggested that the treatment of Moser et al. [25] could be adapted by including an additional Brönsted term, given by the difference between the pK values of the participating groups, QH_2 (pK>11.3) and ISP_{ox} (p$K \sim 7.6$), to describe the probability of proton transfer:

$$\log_{10}k = 13 - 0.6(R - 3.6) - 3.1(\Delta G^\circ + \lambda)^2/\lambda - (pK_{QH2} - pK_{ISPox}).$$

This gave a good fit to the observed rates using values for λ and intrinsic rate constant in the range expected for electron transfer over the $\sim$ 7-Å distance of the bridging histidine. It should be noted that this treatment is appropriate only if the form of the ISP_{ox} participating in the reaction is the dissociated species, so that the reaction is constrained to a proton-coupled electron transfer.

1.3. The quinone–ISPH complex

Binding of Q to the reduced ISP (ISPH) can be studied through the effects on the rhombic EPR spectrum [21,22,26,27]. There are changes throughout but those in the g_x region are most prominent, becoming sharper on interaction with quinone ($g_x = 1.80$), stigmatellin or UHDBT ($g_x = 1.78$). Bertrand et al. [28] and Link [29] have previously discussed the EPR spectroscopic characteristics of reduced Rieske-type centers, and noted the changes in rhombicity associated with the modification of energies for electron spin transitions with magnetic field along the g_x, g_y and g_z directions under different conditions of ligation.

Increasing differences between g_x and g_y reflect increasing asymmetry of the cluster. Interestingly, the variation in rhombicity induced in the ISP of the bc_1 complexes of *Rb. sphaeroides* and *Rb. capsulatus* by mutation, or by variation in occupancy of the Q_o-site, shows a similar pattern (Fig. 1).

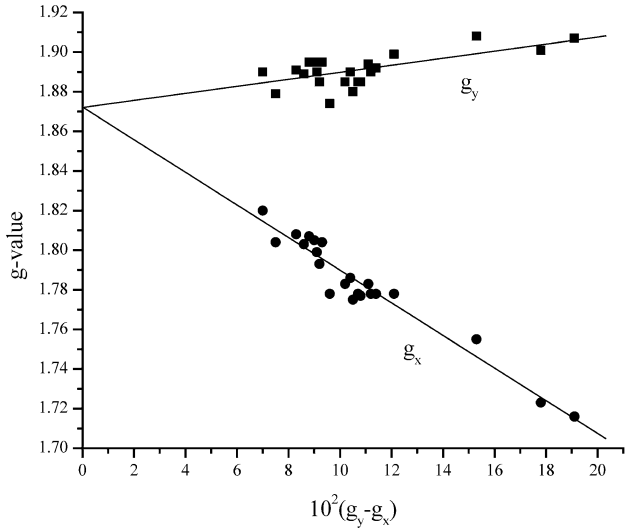

Fig. 1. Rhombicity of the [2Fe–2S] cluster in terms of linear variation of g_x and g_y components in the EPR spectra of the Rieske cluster in the bc_1 complex, plotted against $(g_x - g_y)$. The different pairs of points were taken from published spectra of the ISP from *Rb. sphaeroides* and *Rb. capsulatus* for different mutant strains [19,20,43,44], and different occupancies of the Q_o-site. The linear relationship is predicted by a phenomenological theory based on the distortion of Fe^{2+} ligand field [28]. Increasing difference between g_x and g_y reflects increased asymmetry.

An alternative approach is to score the rhombicity according to an R factor, comparing the anisotropies of $g_y - g_z$ and $g_y - g_x$ in the EPR spectrum [29,30]:

$$R_{z(x)} = \frac{300(g_y - g_{x(z)})}{(2g_{z(x)} - g_y - g_{x(z)})} \quad [\%]$$

Using this approach, Samoilova et al. [31] noted that the quinone complex and the stigmatellin complex had a similar rhombicity, with $R_z < R_x$, which was different from the $R_z > R_x$ seen after binding of myxothiazol, when the mobile domain is rotated away from the Q_o-site, and has no contact with the occupant. Pulsed EPR experiments (1D and 2D ESEEM) were used to investigate the interaction between the paramagnetic reduced Rieske cluster and the nuclear spins of the immediate environment. Because the spectrum is rhombic, the different orientations of the cluster could be probed by selection of g_x, g_y or g_z lines. It was found that the complex between quinone and ISPH, detected through hyperfine and quadrupole couplings with $^{14}N_\delta$ from one of the histidine ligands, was similar to that seen with stigmatellin. From the structures, the histidine involved was likely His-161 (in chicken numbering, 3), which forms a H-bond with stigmatellin through $N_\varepsilon H$. This strongly supports the suggestion that ISPH forms a similar H-bond with quinone [9,10,17,21,22].

1.4. Kinetic aspects

From the redox dependence of the appearance of the g_x line, Ding et al. [21,22] concluded that Q and QH_2 interacted with the site (when ISP is reduced) with a similar binding coefficient. They ascribed a $g_x = 1.783$ line, seen after partial extraction of quinone, to interaction of a tightly bound species with ISPH, and the $g_x = 1.80$ signal to further interaction with an exchangeable quinone, to give a double-occupancy model. However, from the movement of the ISP, it is clear that its interaction cannot reflect any complex longer lived than the turnover time of the high potential chain [10]. From the kinetics of reduction of cyt c_1 under conditions in which a fraction of the ISPH is initially tied up in the $g_x = 1.80$ complex (Fig. 2), Crofts et al. [9] suggested limits for the release rate, with $t_{1/2}$ between < 30 μs and 3 ms. Analysis of the kinetics is complicated by the fact that the observed oxidation represents only about half of the total oxidizing equivalents

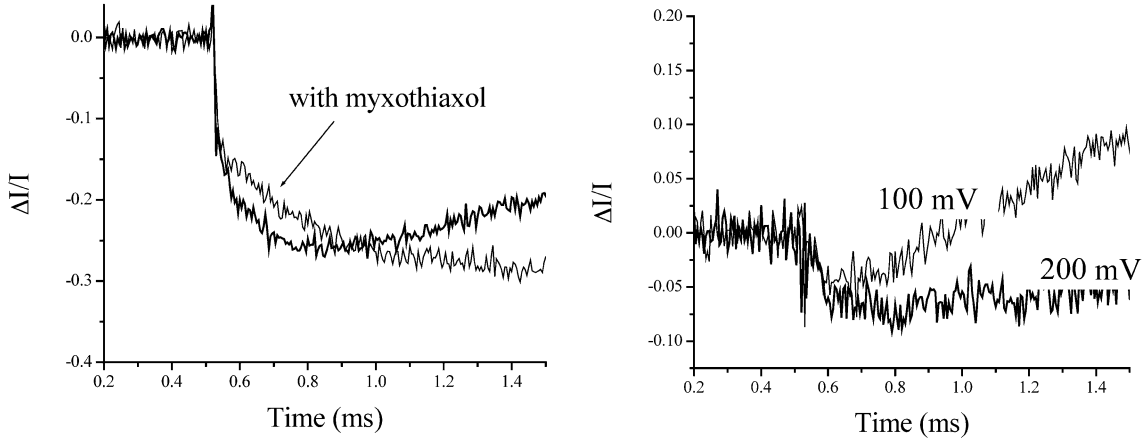

Fig. 2. Kinetic traces showing cyt c_t (c_1 plus c_2) oxidation (measured from $\Delta A_{551} - \Delta A_{542}$) following flash activation of chromatophores poised with the ubiquinone pool ~ 30% reduced (left, ~ 100 mV), in the presence and absence of myxothiazol, as indicated. The difference kinetics (right) show the phase of oxidation slowed in the presence of myxothiazol, due to more rapid reduction of cyt c_1 by ISPH in the ISP_C position. Difference traces when the quinone pool was oxidized (200 mV) or partly reduced (100 mV).

available, and includes rise and decay phases for cyt c_2 and c_1 and the unseen oxidation of ISPH [9,18,32]:

$$2P^+ + c_2 + ISPH.c_1 \leftrightarrows 2P + c_2^+ + ISPH.c_1^+ \leftrightarrows 2P + c_2 + ISP_{ox}.c_1^+ + H^+$$

The ISPH component includes forms in both ISP_B and ISP_C positions, and the broad range reflected uncertainty as to the fraction in these states.

1.5. Thermodynamic aspects

The results of our ESEEM studies provide strong evidence that a H-bonded complex is formed between quinone and ISPH similar to that seen with stigmatellin. What are the thermodynamic consequences of this binding? Values for E_m from titrations of the complete bc_1 complex with and without inhibitors are variable, but a number of studies have been reported in which a change in E_m value was measured on addition of myxothiazol, MOA-stilbene or simple alcohols [14,15,33]. In general, for the native bc_1 complex, changes in the range ΔE_m 30–45 mV have been observed, from $E_{m,7} \sim 265$ mV, in the presence, to ~ 300 mV in the absence of reagent.

An alternative approach to assaying the E_m change on interaction between quinone and ISPH is through kinetics. When the ambient redox potential is around the mid-point for the ISP, the decrease in $E_{m,\ ISP}$ on addition of myxothiazol is expected to lead to a decrease in the fraction of the reduced ISP, and hence to an increase in amplitude of cytochrome oxidation as its reductant is lost from the equilibrium mix. This effect is readily detectable, with an amplitude consistent with the changes in equilibrium constant calculated from E_m values (Fig. 3).

Previous authors have interpreted the change in E_m as reflecting an interaction between the ISP and either the inhibitor or the protein. However, the structures strongly suggest that no complex is formed between the ISPH and myxothiazol or similar inhibitors [2,5,10]; after addition of inhibitor, almost all ISP initially close to cyt b and the Q_o-site had changed to a position close to cyt c_1. In light of the ESEEM evidence for formation of a H-bonded complex between quinone and ISPH [31], we propose an alternative explanation for the E_m change. On formation of the complex with quinone, the E_m value of ISP is shifted to a more positive value by an amount reflecting the binding constant for the interaction with quinone. This is similar to the change observed in the complexes of ISPH with UHDBT or stigmatellin. On addition of myxothiazol, this interaction is lost, and the ISP shows a lower E_m value. If the binding constant between ISP_{ox} and quinone is $\ll 1$, then the change in E_m gives the binding constant for formation of the ISPH.Q complex ($K_{binding} = \exp(\Delta E_m/RT) - 1$), with a value in the range 3–5. From this, the fraction of ISPH complexed will be in the range 75–85%, consistent with the integrated area of the g_x line, which is similar in the presence of quinone or stigmatellin (100% occupancy). In relation to the kinetic data, translation from ISP_B to ISP_C positions must be in the range < 30 μs, as expected if the reactions of the high potential chain are much faster than the rate-limiting step [18]. However, it should be recognized that the kinetic differences of Fig. 2 also reflect a change in equilibrium constant for electron transfer from ISPH to cyt c_1.

This new interpretation of the myxothiazol-induced change in apparent E_m of ISP is relevant to two recent reports in the literature.

(i) The E_m change induced by alcohols is of interest, because these reagents also eliminated the sharp $g_x = 1.80$ line characteristic of the H-bond interaction between ISPH and quinone [33]. An explanation that would account for

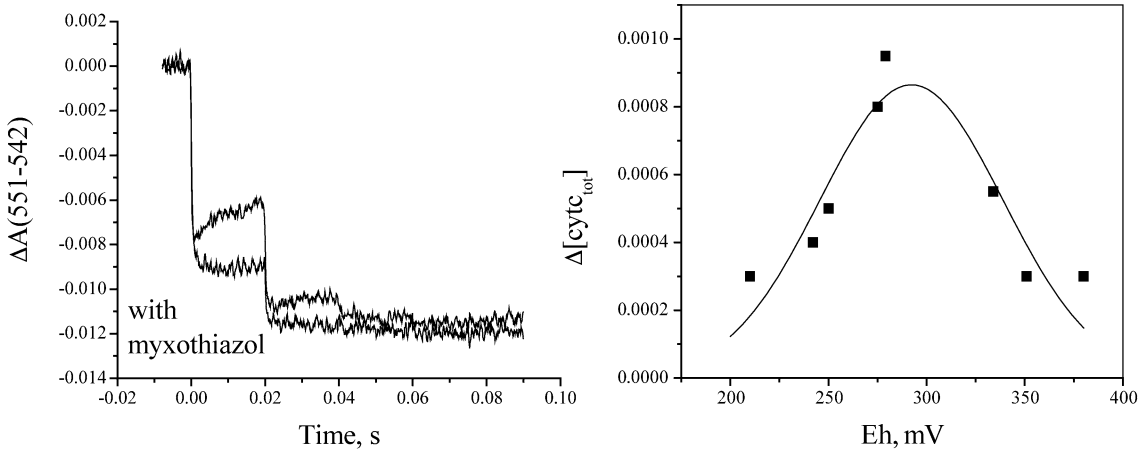

Fig. 3. The change in amplitude of cyt c_{tot} oxidation after a single saturating flash following addition of myxothiazol. Left: the kinetics observed at 285 mV with and without myxothiazol. Right: the dependence of the amplitude of the extra cyt c oxidation as a function of E_h. The data are fit by assuming that the apparent E_m of ISP is 305 ± 5 mV before and 260 ± 5 mV after addition of myxothiazol.

both these effects is that the alcohols compete with ISPH as H-bond donor to the Q_o-site quinone, and thus release the ISP in its low potential form.

(ii) Darrouzet et al. [15] reported a set of mutants in which changes in E_m of ISP were observed when the linker region connecting the ISP extrinsic head group to its anchoring N-terminal segment was changed in length. Several of these showed quite large changes in apparent E_m ($E_{m,app}$ 355–460 mV) compared to wild-type (~ 320 mV), but this effect largely disappeared on addition of myxothiazol (E_m 295 ± 25 mV for all strains); the myxothiazol-induced change was therefore much greater than the ~ 40 mV effect discussed above. If the myxothiazol-induced change reflected only the loss of interaction with the resident quinone, then a simple interpretation would be that the linker-length determined the strength of interaction.

The range for ΔE_m values ($E_{m,app} - E_m$ for the unliganded (myxothiazol) complex) lies between that of the native complex (~ 40 mV), and that of the complex with stigmatellin (~ 240 mV or 23 kJ mol^{-1}), the latter value being appropriate for the buried H-bond seen in the structures (bond energies of 20–25 kJ mol^{1}). Since it is relatively easy to weaken bond strength, but difficult to increase it, these results suggest the possibility that the native configuration is designed to weaken the interaction; the ISP might be spring-loaded so as to favor the dissociation reaction. Such a spring-loaded interaction could also apply to the ES-complex, with obvious mechanistic implications.

1.6. Bypass reactions at the Q_o-site in the presence and absence of oxygen

The reaction of the Q_o-site with O_2 to produce superoxide (SO) has been much studied, and is generally attributed to one-electron reduction by the intermediate semiquinone species generated at the site when transfer of the second electron to the low potential chain is blocked [33–37]. This occurs on antimycin inhibition or on development of a large back-pressure from Δp, with a maximal rate ~ 2% of the normal turnover. Several recent observations have provided new insights to the nature of the reaction.

In mitochondrial complexes, myxothiazol inhibits the maximal SO production in the presence of antimycin, but only by about 70%. In the absence of antimycin, production of SO is stimulated by addition of myxothiazol to give a similar rate (~ 0.6% full turnover) [38,39]. Several groups have argued convincingly that the reaction involves formation of semiquinone at the Q_o-site [36,39,40]. Since formation of semiquinone depends on oxidation of quinol, this could occur only if an ES-complex was formed in the presence of myxothiazol, with occupation of the distal domain of the site by ubiquinol and reaction with ISP_{ox}. Such a double-occupancy is quite unexpected, since most data seem to indicate that myxothiazol eliminates all quinone species from the site [2,10,41]. Muller et al. [39] found that, also surprisingly, if the rate of quinol oxidation was assayed by reduction of cyt *c*, the bypass rates observed under anaerobic conditions in the presence of either antimycin or myxothiazol were the same as under aerobic conditions. This could be explained if generation of semiquinone under all conditions was rate-limiting, and independent of [O_2], and that two pathways competed for the semiquinone, both with much higher rate constant, one to O_2 and the other indirectly to cyt *c*. Under aerobic conditions, O_2 out-competes the alternative pathway as acceptor for the second electron. Two plausible candidates for the alternative pathway were suggested. Most obviously, the returning ISP_{ox} could oxidize the semiquinone after it had donated the first electron to cyt *c* via cyt c_1. However, another possibility would involve migration of the semiquinone out of the Q_o-site to find an adventitious site for direct reduction of cyt *c* at the membrane–water interface. In either case, since the distance from the [2Fe–2S] cluster in the ISP_B position to cyt c_1 would preclude direct transfer from the complexed state [9], the reaction could occur only if the intermediate ISPH.SQ state dissociated to products. This shows that the ISPH.SQ state is not so tightly bonded as to preclude dissociation. A third observation of interest was that increasing the [O_2] fivefold above ambient had no effect on the rate of SO generation in the presence of myxothiazol, but stimulated the rate in the presence of antimycin by ~ 25%. The saturation at ambient O_2 in the presence of myxothiazol indicates a K_m in the range < 20 μM. The relatively high affinity compared to that in the absence of myxothiazol shows that at least a fraction of the semiquinone was in a less reactive configuration when the Q_o-site was free of inhibitor.

These observations are open to a number of interpretations. Although the myxothiazol-insensitive SO production must indicate some double-occupancy, it is difficult to extend this to a justification of such a mechanism under normal turnover. Two features suggest that the 70% inhibition in the mitochondrial complex must represent a minimal value for displacement of the distal domain occupant. (i) The [O_2] dependence shows that at least a fraction of the semiquinone is in a less reactive state in the unoccupied Q_o-site. Since the observed rate will depend on the product of occupancy and rate constant, if the SQ in the presence of myxothiazol is hyper-reactive, the occupancy must be proportionately less. (ii) In *Rb. sphaeroides*, the antimycin-resistant bypass under anaerobic conditions was completely inhibited by myxothiazol, indicating that the weak double-occupancy is not a common property of all bc_1 complexes (Chen, Y. and Crofts, A.R., unpublished, and Ref. [42]). A question that must remain open is the nature of the less reactive SQ species responsible for the fraction of SO production stimulated by increasing [O_2]. In single occupancy models, this would be well explained by movement of the SQ deeper into the site to occupy the myxothiazol-binding domain. In double occupancy models, it would represent distribution of the electron to a second, less accessible quinone species. The data did not allow discrimination between these possibilities.

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