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Anomalous Distance Dependence of Electron Transfer across Peptide Bridges

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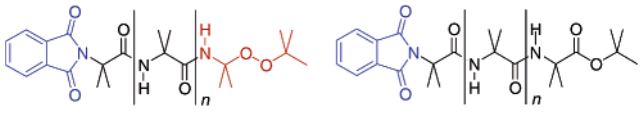
The peptide backbone is essential in assisting long-range electron transfer (ET) in proteins.[1,2] Rather than just separating the donor (D) and the acceptor (A), the role of the peptide spacer is to provide a framework in which electronic states are available to support the actual electron tunneling between the D and A electronic states. Several data on the distance dependence of the ET across peptide systems have been reported.[2−5] In this regard, various results, obtained by using oligoproline bridges, pointed to a mild exponential dependence for not-too-short bridges.[2,3] The possible mechanisms responsible for this type of outcome have been discussed.[2,6] Besides the specific α-amino acids composing the bridge, hydrogen bonds also have been recognized to increase the electronic coupling and thus the ET rate between D and A.[1b,c,7] This is a feature of which oligoprolines are obviously lacking. Very recently, Sisido et al. reported interesting results on the photoinduced ET between chromophores embedded, as pendant groups, along α-helical polyglutamate peptides.[5] In contrast with oligoproline bridges, the ET rate exhibited a complex dependence on the number of residues. However, when the actual edge-to-edge D/A distance, d_{ee}, was taken into account, the ET rate was found to obey a simple exponential distance dependence. The participation of the α-helix H-bonds was also discussed.

To investigate systematically how distance increase *and* concomitant intramolecular H-bond formation impact the electron tunneling, we devised a series of structurally well-defined peptide systems. The peptides of choice were α-aminoisobutyric acid (Aib) homooligomers, which are known for their propensity to form rigid 3_{10}-helices because of steric hindrance at the α-carbon and the resulting restricted torsional freedom.[8,9] We report here the results obtained on the electrochemically induced ET from a phthalimide radical-anion donor to a peroxide acceptor. Our data reveal that not only intramolecular H-bonds are important but also that they may even counteract efficiently the d_{ee} increase.

We studied molecules $\mathbf{1}_n$ ($n = 0-6$) in comparison with the corresponding esters $\mathbf{2}_n$, in which the peroxide acceptor is absent.

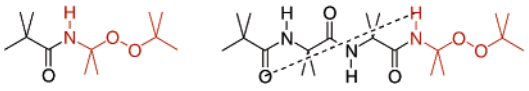


1, $n = 0$ - 6 **2**, $n = 0$ - 6

The syntheses and characterization of compounds $\mathbf{1}_n$ and $\mathbf{2}_n$ have been described in detail elsewhere.[10] The IR absorption data indicated that the tendency to form turns and helices in solution shows up even with the shortest compounds, starting from $n = 1$. In addition, the X-ray diffraction analysis of crystals of $\mathbf{1}_0$, $\mathbf{1}_1$, and $\mathbf{1}_5$ pointed to the incipient formation of a 3_{10}-helix even for $n = 1$.[10] The key motif of the peptide systems investigated is thus that the increase of n does not solely result in a larger D/A separation but it is also accompanied by a concomitant increase in the number of H-bonds ($n \equiv n_H$) and, consequently, in the peptide stiffness.

To study the intramolecular ET in compounds $\mathbf{1}_n$, we followed a previously established approach.[11] The $E°$'s of both A and D were obtained, independently, by using model molecules. The $E°$'s for the reversible reduction of the phthalimido end of compounds $\mathbf{2}_n$ were determined by cyclic voltammetry (CV)[12] to be (from $n = 0$ to 6) −1.478, −1.378, −1.354, −1.334, −1.327, −1.327, and −1.328 V. The positive $E°$ shift corresponding to formation of the first intramolecular H-bond, 0.10 V, is particularly large. For longer peptides, the bridge dependence of $E°$ diminishes and then vanishes for $n \geq 4$. This striking bridge-length effect is attributed to the formation and progressive increase of the number of intramolecular H-bonds, which lowers the energy of the LUMO of the phthalimido group significantly.[13]

We studied also the model acceptors **3** and **4**.[10] Whereas the first was prepared to simulate the A end of $\mathbf{1}_0$, the second was meant to provide the A model for the other molecules, in which the NH adjacent to the peroxide functional group is H-bonded.



3 **4**

For both acceptors, the CV peak is irreversible, broad, and located at very negative potentials (at 0.2 V s^{-1}, the peak potentials are −2.26 and −2.54 V, respectively). The main features of these peaks are thus the same as those observed for the dissociative ET (DET) to other dialkyl peroxides.[14−16] We could estimate the $E°$'s of **3** and **4** by studying the DET from a series of electrogenerated radical-anion donors. For both acceptors, the rate was determined as a function of the donor $E°$. By comparing the data with those pertaining to di-*tert*-butyl peroxide, a DET acceptor having $E° = -1.48$ V,[15b] we calculated the reactivity difference and, from it, estimated the acceptor $E°$. For **3** and **4**, we obtained −1.12 and −1.22 V, respectively. Therefore, also for the peroxide acceptor, H-bond formation affects the $E°$ significantly. In contrast with the D models, the $E°$ shift is negative because H-bonding develops a partial negative charge in proximity of the A group.

The CV curves for the reduction of $\mathbf{1}_n$ are compared in Figure 1. The reduction of $\mathbf{1}_0$ is irreversible even at high scan rates and −40 °C. As for similar dissociative-type D−bridge−A systems,[11] the CV analysis clearly shows that the electron is first injected into the kinetically fast D moiety and only subsequently is transferred from the ET antenna to the peroxide end. For $\mathbf{1}_1$, the CV is partially

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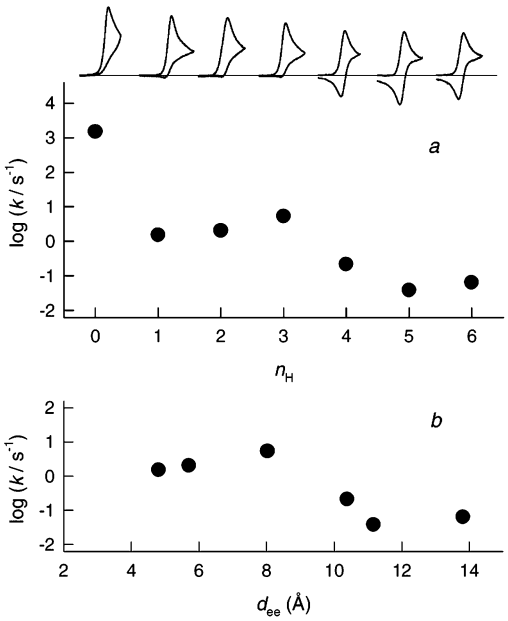
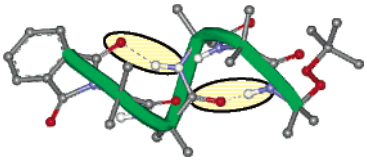


Figure 1. Dependence of the $\Delta G°$-corrected rate constants for DET in compounds $\mathbf{1}_n$ on (a) the number of Aib units ($\mathbf{1_0}-\mathbf{1_6}$) and (b) the D/A edge-to-edge distance ($\mathbf{1_1}-\mathbf{1_6}$). The CV curves were obtained at 0.1 V s^{-1}.

reversible, which means that the electrogenerated phthalimide radical anion releases the electron at a much lower rate. However, the apparent rates observed with the longer peptides $\mathbf{1_2}$ and $\mathbf{1_3}$ are essentially identical to that of $\mathbf{1_1}$. These results are not due to the competitive intermolecular DET, as checked by carrying out concentration studies and digital simulation of the experimental CV curves. Only for $n = 4$ was a net decrease of the ET rate observed. Finally, a perceptible increase of the ET rate on going from $\mathbf{1_5}$ to $\mathbf{1_6}$ was measured.

To compare the kinetic results, the data were corrected for the $\Delta G°$ differences.[17] Figure 1a illustrates the *n*-dependence of the ensuing ET rate constant, *k*. On going from $\mathbf{1_0}$ to $\mathbf{1_1}$, the steep decrease of the rate can be attributed to the flexibility (no H-bonds) of $\mathbf{1_0}$, which may result in quite small D/A distances. Afterward, the onset of a mild dependence of *k* on *n* emerges. In particular, the observed *n*-dependence shows that for $n = 1-3$ the disadvantage of increasing the bridge length is efficiently matched by the benefit of increasing the number of intramolecular H-bonds. Interestingly, the data appear to display some periodicity, which would be in keeping with the fact that a full turn of the 3_{10}-helix requires 3.24 Aib residues.[8b] We calculated also the d_{ee} values, using the structural parameters of Aib peptides.[8b,10] As shown in Figure 1b, however, we found that log $k - d_{ee}$ displays the same peculiar trend as that of log $k - n_H$.[18] This outcome is thus quite different from the exponential dependence on d_{ee} observed with other, not-too-short peptide bridges.[2,3,5] Overall, our results indicate that increasing the number of Aib units and thus the stability of the secondary structure results in a better D/A electronic coupling. The trend observed is thus ascribed to an active role played by the intramolecular H-bonds on the ET process. The case of $\mathbf{1_3}$ nicely exemplifies this conclusion because the ET rate increases with respect to those of $\mathbf{1_2}$ and $\mathbf{1_1}$, although d_{ee} is larger by 2.3 and 3.2 Å, respectively. In fact, as highlighted in the model below, a peculiar situation develops for $\mathbf{1_3}$ because the same residue is H-bonded to both D and A, thereby establishing a particularly efficient ET shortcut.

The main ingredient that contributed to showing the important effect of the intramolecular H-bonds on the ET rate is the propensity of Aib peptides to form a well-defined and rigid structure, a property that is maintained even in aqueous solution.[19] Our study is the first



electrochemical investigation of D−(peptide bridge)−A systems in solution and also the first investigation of a DET across peptides. We now are working to alter the energies of the D, bridge, and A components.

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