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Neighboring Pyrrolidine Amide Participation in Thioether Oxidation. Methionine as a "Hopping" Site

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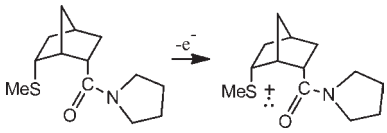
ABSTRACT



Methionine residues have been shown to function as efficient "hopping" sites in long-range electron transfer in model polyprolyl peptides. We suggest that a key to this ability of methionine is stabilization of the transient sulfur radical cation by neighboring proline amide participation. That is, in a model system a neighboring pyrrolidine amide lowers the oxidation potential of the thioether by over 0.5 V by formation of a two-center three-electron SO bond.

Biological electron transfer occurs over prodigious distances with high rates. Both electron tunneling and "hopping" models have been studied to account for biological electron transfer.[1,2] In the "hopping" model an electron or hole transiently resides at intermediary sites. In this model the rate of electron transfer depends on the number of "hopping" sites and their redox potentials. Giese and co-workers[3,4] designed a peptide system in which amino acid side chains could be evaluated as "hopping" sites and, in which, polyproline runs favored adoption of a PPII helical conformation[5] which fixed the distance between redox centers.

Methionine proved to be especially efficient as a "hopping" site. This was unexpected because the thioether side chain of methionine is relatively difficult to oxidize to the corresponding radical cation.[6] However, it has been reported[7] that the peak potential of endoamide **1a** was lowered by 550 mV by comparison with the corresponding exoamide **2a** owing to neighboring group participation to give **3a** in which there is a two-center three-electron (2c-3e) SO bond. We recently reinvestigated this system and found that **3a** is indeed formed upon a one-electron oxidation of endo-**1a**[8] but its oxidation potential is lowered by only

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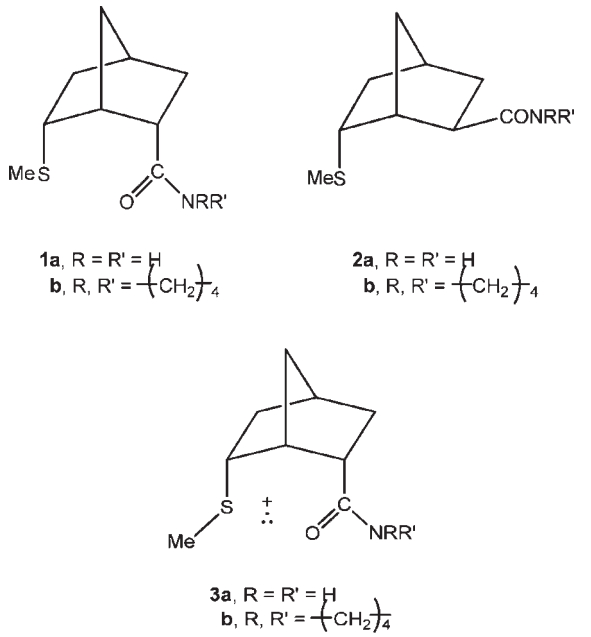
330 mV[9] relative to exo-**2a**. This lowering in oxidation potential is probably insufficient to account for the remarkable ability of methionine to function as a "hopping" site. However, in the peptides studied by Giese and coworkers[2] the methionine residue is flanked by proline residues. Furthermore, it is known[10] that amide resonance increases in pyrrolidine amides relative to primary amides rendering the oxygen of pyrrolidine amides more electron rich which is expected to favor 2c-3e SO bond formation. Consequently, pyrrolidine amide **1b** was synthesized and its redox chemistry studied.



The structure of endopyrrolidine amide **1b** was unequivocally established by an X-ray crystallographic structure

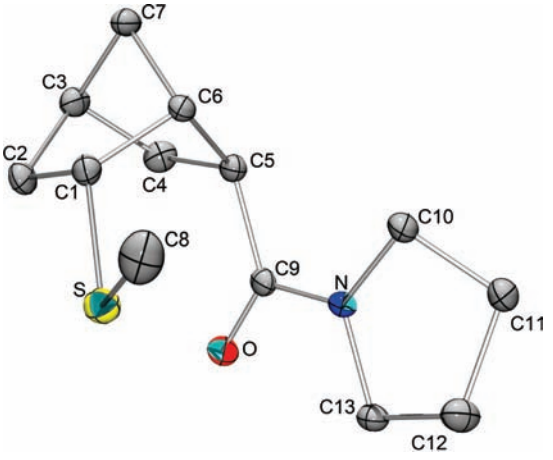


Figure 1. ORTEP drawing of endopyrrolidine amide **1b**.

study, and an ORTEP drawing of the molecule is shown in Figure 1. This amide undergoes irreversible oxidation in acetonitrile with a voltammetric anodic peak potential of +0.74 V versus Ag/0.1 M $AgNO_3$ in CH_3CN at a scan rate of 0.10 V/s. Under these conditions exoamides **2a** and **2b** undergo irreversible oxidation with peak potentials of 1.40 and 1.27 V, respectively. Thus oxidation of endopyrrolidine amide **1b** occurs at a potential 660 and 530 mV less positive than that for exoamide **2a** and exopyrrolidine amide **2b**, respectively.

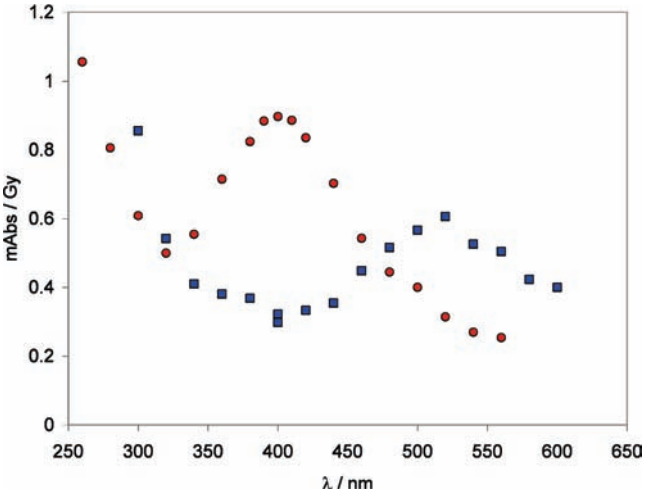


Figure 2. Experimental spectrum of 1.0 mM endo-**1b** (red circle) and 1.0 mM exo-**2b** (blue square) at pH 4 in N_2O-saturated aqueous solution 0.6 μs after pulse irradiation with a dose of 40 Gy.

Pulse radiolysis studies[11] were undertaken to gain more insight into the reason for the facilitated oxidation of endo-**1b**. One-electron oxidation of endo-**1b**, in contrast to such oxidation of its exo isomer **2b**, with $^{\bullet}OH$ under pulse radiolytic conditions produced a short-lived transient with a maximal molar absorptivity of 1.4×10^3 M^{-1} cm^{-1} at 390−400 nm as shown in Figure 2. This absorption is ascribed to the 2c-3e SO bonded radical cation **3b** by analogy to our previous work.[8] In contrast, no intermediate absorbing at 390−400 nm was detectable during pulse radiolysis of the exopyrrolidine amide **2b**, consistent with the geometric exclusion of an intramolecular 2c-3e SO bond. Instead, pulse irradiation of **2b** yielded an intermediate absorbing at 525 nm, which, by analogy to published data,[8] is assigned to an intermolecular 2c-3e SS bond formed via association of one-electron oxidized **2b** with a second nonoxidized molecule **2b**. To further support our assignments, calculations were done. With PM3[12] two conformers of endo-**1b** were identified which differed in energy by about 1 kcal/mol and were significantly more stable than the other conformers; neither of

(9) The initially reported value for the electrode potential of endo-**1a** reflected the value due to Br^- redox catalysis. The redetermined value reflects oxidation in the absence of Br^-.

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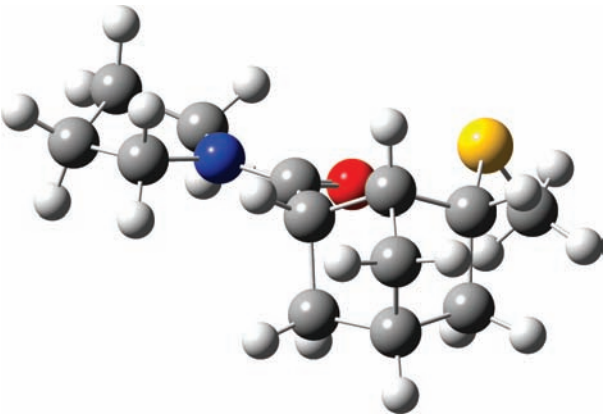

Figure 3. Drawing of calculated energy minimum structure for radical cation **3b**.

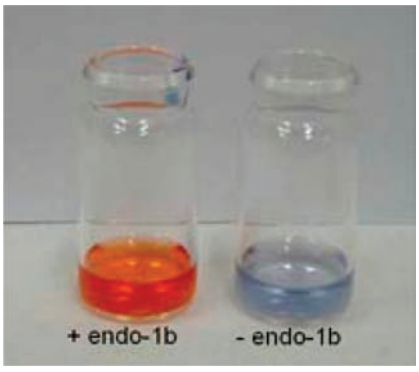

Figure 4. The redox indicator $[Fe(phen)_3]^{3+}$ ($E° = 1.1$ V, blue, reduced form red) is instantaneously reduced by endopyrrolidine amide **1b**.

these corresponded to the structure determined by X-ray crystallography, but when this structure was tested as an optimization starting point, a new conformer of essentially the same energy was found. Calculations were done on the radical cations of these three low energy conformers using DFT.[13] After geometry optimization[14] the radical cation of lowest energy obtained is shown in Figure 3. The S···O distance for the radical cation shown in Figure 3 is 2.35 Å, and it can be described in terms of a 2c-3e SO bond.

Furthermore, in keeping with the anomalously low oxidation potential of endo-**1b**, preliminary experiments with $N_3^{\bullet}$ which is a much weaker[15] one-electron oxidant than $^{\bullet}OH$[16] produce a species absorbing at $\lambda = 390$ nm in our pulse radiolysis studies.

Reactions of endopyrrolidine amide **1b** and exopyrrolidine amide **2b** with the redox indicators ferroin $[Fe(phen)_3]^{3+}/[Fe(phen)_3]^{2+}$ and $[IrCl_6]^{2-}/[IrCl_6]^{3-}$ were then studied.[17] The color change of ferroin from blue to red on addition of endopyrrolidine amide **1b** was instantaneous (Figure 4), but no change in color was observed in control experiments with exopyrrolidine amide **2b**. The reaction of hexachloridoiridate(2−) with endopyrrolidine amide **1b** was slower ($t_{1/2} \approx 30$ min) than that with ferroin. Such a difference can be expected based on the 0.2 V lower oxidation potential[17] of $[IrCl_6]^{2-}/[IrCl_6]^{3-}$ compared to $[Fe(phen)_3]^{3+}/[Fe(phen)_3]^{2+}$.

We have shown that the neighboring pyrrolidine amide in **1b** lowers the oxidation potential of a thioether by over 0.5 V, in acetonitrile. This shift is substantially larger than that observed with the primary neighboring amide in **1a**. Neighboring pyrrolidine amide participation in the oxidation of methionyl residues may be key to the exceptional ability of methionine as a "hopping" site. Indeed methionine residues in proteins in which the sulfur is juxtaposed to a proline amide moiety might be expected to be especially susceptible to oxidation.

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Supporting Information Available. Experimental procedures, X-ray crystallographic parameters for **1b**, computational results including absolute energies and geometries for **1b** and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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