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Neighboring π-Amide Participation in Thioether Oxidation: Conformational Control

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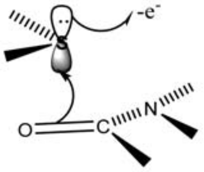
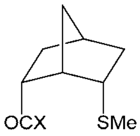
Ⓢ *Supporting Information*

ABSTRACT: The electrochemical oxidation of thioethers is shown to be facilitated by neighboring amide participation. ^{1}H NMR spectroscopic analysis in acetonitrile solution of two conformationally constrained compounds with such facilitation shows that two-electron participation by the amide π_2 orbital can occur to stabilize the developing sulfur radical cation.



One-electron oxidation of thioethers with neighboring amide groups in peptides results in the intramolecular formation of transients with two-center three-electron (2c, 3e) S−O or S−N bonds.[1] Since the electrochemical oxidation potentials of thioethers with neighboring amide moieties, such as **1a** and **1b** (1.07[2] and 0.74[3] V, respectively), are less anodic than those of the corresponding isomers **2a** and **2b** (1.40[2] and 1.27[3] V, respectively) in which intramolecular bond formation is precluded, the facilitation of the electrochemical oxidation of **1a** and **1b** has been ascribed to 2c, 3e S−O bond formation in their oxidation. Such lowering of the oxidation potentials of thioethers may account for the efficiency of methionine as a "hopping site" for electron transfer in proteins as suggested by Giese and co-workers.[4] Two-electron donation by the neighboring amide to the developing sulfur radical cation can occur from the in-plane nonbonding n_o orbital or the perpendicular (with respect to the amide plane) π_2 orbital, which by photoelectron spectroscopic studies are of comparable energy.[5] Without geometrical constraints, it is expected that the more localized n_o orbital would preferentially participate.[5,6] Conformationally constrained compound **3** was previously reported,[2] in which constraints favor an in-plane approach that results in interaction of n_o with sulfur (see Figures S9 and S10), and its electrochemical oxidation potential was reported to be 1.16 V (less anodic than **2a** or **2b**). This paper presents evidence that out-of-plane approach also results in facilitated oxidation.



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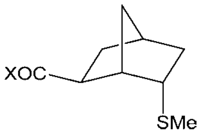
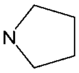
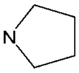


2a, X = NH$_2$

b, X = N



b, X = N



Diketopiperazine **4** was reported previously,[2] and its structure was unequivocally determined in the solid state by X-ray crystallography. The structural analysis shows that the sulfur is positioned almost perpendicular to the neighboring amide plane (see Figures S11 and S12 for views of this geometry). The amide is incorporated into a diketopiperazine ring in a boatlike conformation[7] in which one of the attached methyl groups is 2.609 Å from the bridgehead hydrogen at C(1) of the bridged bicyclic ring (see Figure 1). Interestingly, molecular models show that the boat can undergo ring inversion to the alternative boat conformation, which results in the sulfur being positioned in the plane of the neighboring amide moiety *and* the methyl groups on the piperazine ring being far removed from H(1).

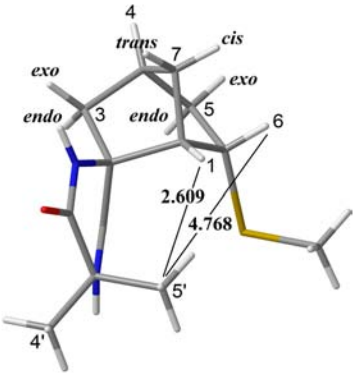


Figure 1. Numbering and key distances[8] in diketopiperazine **4**.

To determine the conformation of diketopiperazine **4** in acetonitrile (the solvent used for electrochemical studies), it

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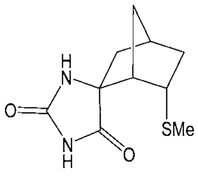

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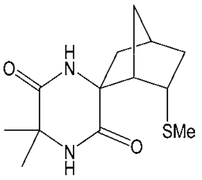

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was analyzed by NMR spectroscopy. The ^{1}H NMR spectrum of **4**, shown in the Supporting Information (SI), depicts only one detectable conformation, and its NOESY spectrum, shown in Figure 2, displays a strong cross-peak (circled in the figure) between diketopiperazine methyl group 5′ and H(1) as required for the solid-state conformation (see Figure S3 for the full NOESY spectrum). This confirms that the conformation in acetonitrile solution is the same as that in the solid state. The electrochemical oxidation potential of **4** is 1.08 V (comparable to that of **1a** and lower than that of **2a** and **2b**). The latter suggests that an amide group can facilitate thioether oxidation through π_2 participation.

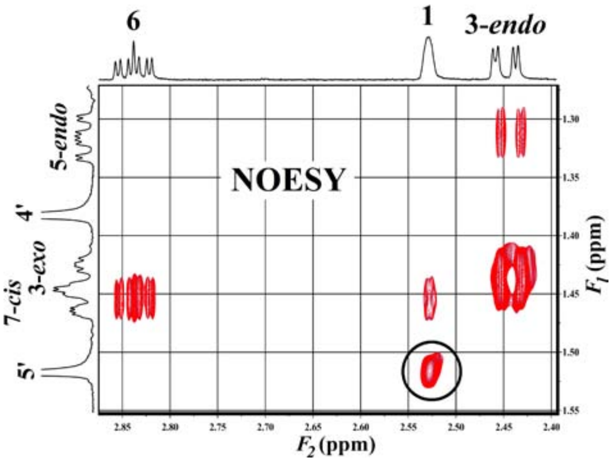


Figure 2. Expanded region of the 2D NOESY spectrum of compound **4** in CD$_3$CN (τ_m = 0.9 s). Negative cross-peak intensity is indicated in red. The circle highlights the NOE correlation between the diketopiperazine methyl group 5′ and H(1) of the bicyclic moiety. See Figure S3 for the full NOESY spectrum.

Another example is L-proline amide **5**, synthesized from the previously reported[9] enantiomerically pure unsaturated carboxylic acid **6** via (methylthio)carboxylic acid **7** (conversion of racemic **6** to racemic **7** was previously reported).[10] However, enantiomerically pure **7** was more expediently obtained by resolution of racemic **7** as reported in the SI. The structure of **5** was unequivocally determined in the solid-state by X-ray crystallographic analysis, and the ORTEP drawing is shown in Figure S1. Examination of the solid-state structure of **5** shows that the proline amide adopts a trans conformation, which is common for proline amides because of steric effects.[11] In addition, this conformation is favored by a weak n → π* interaction[12] (also important in oligoprolines[13]) where the amide carbonyl oxygen is the n donor and the ester carbonyl is the π* acceptor. The signatures of the n → π* interaction are a short O···C distance and pyramidalization of the carbonyl moiety.[14] The distance between the amide O and ester carbonyl carbon is 2.944(1) Å, which is less than the sum of their van der Waals radii (3.22 Å).[15] In addition, the Bürgi−Dunitz angle θ is 94.46(6)°, and the pyramidalization parameters Δ and Θ, which reflect the nonplanarity of the ester moiety, are 0.023(1) Å and 2.7(1)°, respectively.[7b,16] It should be noted that in this solid-state structure of **5** the sulfur is located above the plane of the amide moiety (see Figures S13 and S14 for views of this geometry). To determine the conformation of **5** in acetonitrile solution, it was analyzed by NMR spectroscopy. Its ^{1}H NMR spectrum, shown in the SI, reveals only one detectable conformation, and its NOESY spectrum (Figure 3) displays strong cross-peaks (circled in the figure).

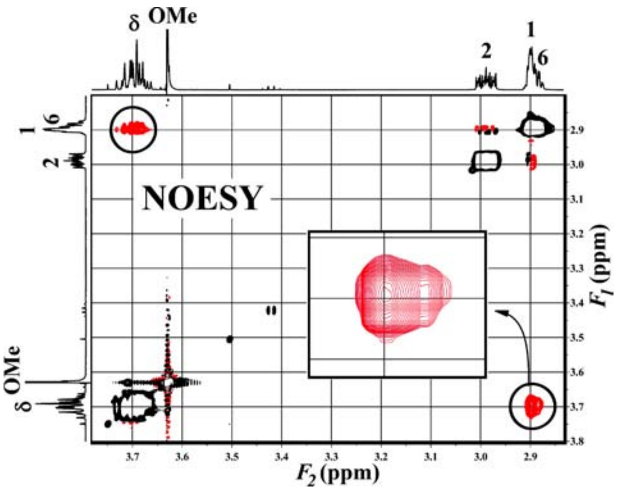
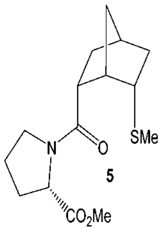


Figure 3. Expanded region of the 2D NOESY spectrum of **5** in CD$_3$CN (τ_m = 0.9 s). Negative cross-peak intensity is indicated in red. The circles highlight the NOE correlations between NCH$_2$ hydrogens of the proline ring and both H(1) and H(6) of the bicyclic moiety. The inset is an expansion of the lower-right cross-peak. See Figure S5 for the full NOESY spectrum.



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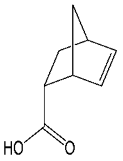

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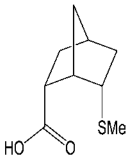

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In the solid-state structure, the distance between these hydrogens is short (2.30 and 2.27 Å, respectively; see Figure 4). Furthermore, rotation of the amide carbonyl group to obtain the cis conformation substantially increases the distance between these hydrogens. Thus, it can be concluded that the solid-state conformation is maintained in acetonitrile solution. The electrochemical oxidation potential of **5** in acetonitrile is 0.819 ± 0.063 V, which is close to that of **1b**, whose oxidation potential was redetermined to be 0.750 ± 0.003 V under the same conditions as for **5**. Unlike **1b**, however, **5** showed very complicated electrochemistry. The much larger standard deviation for the oxidation potential of **5** compared with **1b** is attributable to several reactions occurring simultaneously. The much larger standard deviation for the oxidation potential of **5** compared with **1b** should be noted, and addition of 2,6-di-*tert*-butylpyridine did not alleviate this problem. Consequently, a controlled-potential electrolysis of **5** was carried out at a potential of 1.0 V. The reaction stoichiometry in electrons of *n* = 2.5 indicates that additional oxidation beyond the formation

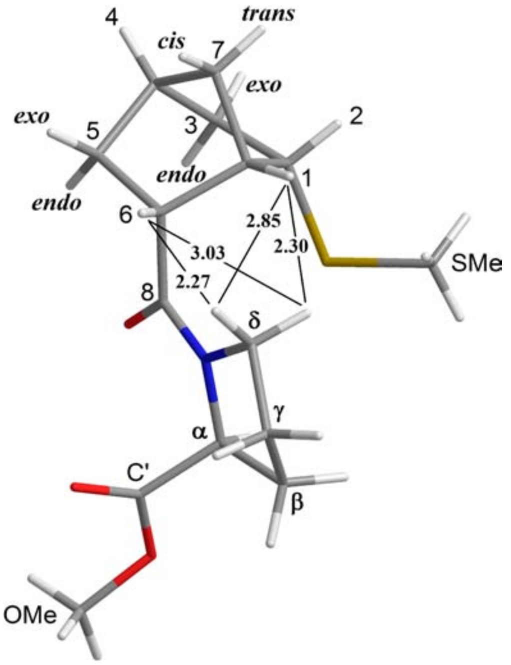

Figure 4. Numbering and key distances in proline amide **5**.

of the sulfoxide occurred. On the basis of the decrease in current with time, the electrolysis achieved an approximately 74% yield. The products of the electrolysis were analyzed by HPLC-MS. The major product corresponds to sulfoxide, as shown in the SI. Thus, it can be concluded that the oxidation process of **5** proceeds by electron transfer from sulfur, since the major product is the expected sulfoxide. In addition, the lowest ionization energies obtained by photoelectron spectroscopy (see the SI) assigned to the sulfur lone-pair ionizations[17] of **1b** and **5** are comparable. Consequently, proline ester **5** provides a second example in which a neighboring amide group can facilitate electrochemical thioether oxidation by π_2 participation.

In sum, the present evidence supports the notion that neighboring amide participation can facilitate thioether oxidation by electron donation from the π_2 orbital as well as from the n_o orbital. However, the bonding in 2c, 3e S–O methionine radical cations in dipeptides has been suggested to be predominantly electrostatic rather than covalent.[18] Furthermore, on the basis of calculations it has been opined[19] that 2c, 3e bonds are not formed in cation radical methionine analogues but rather that indirect multicenter interactions and electrostatic repulsion in the neutral species account for the lowered oxidation potentials. Calculations may resolve these interesting issues and the structures of the corresponding radical cations in the cases reported here.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01309.

> Experimental procedures, ORTEP of **5**, tables of crystallographic and atomic parameters for **5**, full NOESY spectra for **4** and **5**, views of **3**–**5**, CV of **5**, peak potentials for **5** and **1b**, HPLC-MS of the controlled-potential electrolysis of **5**, ^{1}H NMR spectra of **4** and diastereomerically pure **5**, and photoelectron spectra of **1a** and **5** (PDF)

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Notes

The authors declare no competing financial interest.

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