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Oxidative Induction of β-Turn Conformations in Cyclic Peptidomimetics: Conformational Analyses As Indicators of Configuration

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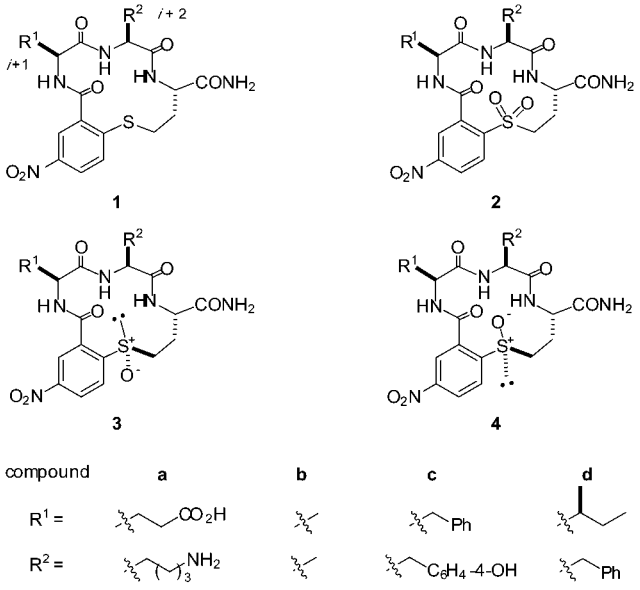
Oxidation of methionine to methionine oxide can perturb peptide conformations. For instance, this type of transformation may establish an intramolecular hydrogen bond to a main-chain amide-NH that disrupts helicity,[1] or decrease hydrophobicities in amphiphilic helices causing them to revert to β-sheet conformations.[2] Reported here is a case where oxidation of a sulfide causes a cyclic peptidomimetic to adopt a β-turn conformation. Moreover, it emerged that occurrence of the β-turn conformation is so closely correlated to only one of the two sulfoxide epimers that conformational studies can be used to predict absolute configurations at sulfur.



This project arose from a modest set of objectives. Previous work had shown that cyclic amine and ether analogues of **1** (where the sulfur atom is substituted with NH or O) tend to adopt β-turn conformations in DMSO.[3] These conformations were desired for preparations of libraries of molecules that might mimic or disrupt certain protein−protein interactions.[4] To expand the series, we decided to make the cyclic thioether **1a** and study its preferred conformation in solution.

Thioether **1a** was prepared via methods analogous to those previously reported,[5] and its conformation in solution was studied by a combination of experiments as already outlined for the cyclic amine and ether analogues.[4] The syntheses gave good purities and yields of the desired products. However, unlike its NH- and O-analogues, the preferred conformations of thioether **1a** do not include β-turn structures. The minimum energy conformation

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Table 1. Key NMR Parameters for Compounds **1a**−**4a**

parameter	compound 1a	3a	2a	4a	ideal type-I
NH_{i+2} H/D exchange[b]	fast	fast	slow	slow	slow
$NH_{i+3}T_c$ (-ppb/K)[a]	6.37	1.26	0.60	1.70	<3.0
NH_{i+3} H/D exchange[b]	medium	slow	slow	slow	slow
^3J $Glu_{\alpha,NH}$ (Hz)[a]	8.5	5.0	4.5	5.5	4.0
^3J $Lys_{\alpha,NH}$ (Hz)[a]	8.0	7.5	8.5	9.0	9.0
NH(Glu)-NH(Lys)[a,c]	M	W	M	M	M
NH(Lys)-NH(hCys)[a,c]	M	M	M	M	M
NH(Glu)-H(Aryl)[a,c]	S	S	W	none	n/a

[a] In DMSO-d_6. [b] In CD_3OD; rates are classified as "fast", "medium", or "slow" as compared with other NH in the same molecule. [c] Classified as relatively "weak", "medium", or "strong" cross-peaks.

located in quenched molecular dynamics studies (QMD, Supporting Information) is consistent with the NMR data (Table 1), but it does not closely resemble any identifiable secondary structure. It is difficult to identify the reasons for this difference, but they are probably related to the larger van der Waals radius of sulfur compared with those of nitrogen and oxygen, and the fact that S−C bonds are longer than N−C and O−C.[6]

The failure of **1a** to rest in β-turn conformations motivated us to explore oxidized derivatives of this thioether. Initially, the corresponding sulfoxides (**3a** and **4a**) were avoided because of the difficulties that would be encountered determining the relative configuration of the stereocenter at sulfur. Consequently, the sulfone **2a** was prepared next.

NMR, CD, and QMD analyses of compound **2a** led to a surprising and welcome conclusion: this compound has a preference for type-I β-turn conformational states. The temperature coefficient for the NH_{i+3} was low, indicative of H-bonding or solvent shielding[7] or both and that same NH exchanged slowly with CD_3OD; the $C_\alpha H$ to NH coupling constants were very near to the ideal values expected for type-I turns, and the close contacts observed from ROESY studies were also consistent. A representative low-energy conformation simulated from QMD studies (*i.e., without applying spectroscopic constraints*) is shown in Figure 1.

Why should the sulfone **2a** have a preference for a β-turn conformation if the thioether **1a** does not? A clue for the origin of the conformational switch to β-turn conformations upon oxidation was found in the 1D NMR studies. Those experiments revealed that, unexpectedly, there were *two* NH protons that were relatively slow to exchange when the molecule was placed in CD_3OD. It was the NH_{i+2} residue that had these unexpected spectroscopic characteristics, and this led us to propose that the β-turn in compound **2a** was stabilized by an NH_{i+2} to OS hydrogen bond. Consistent with this, one of the NH_{i+2} to OSO distances in a representative low-energy conformer was only 2.38 Å (Figure 1).

Only one of the diastereotopic sulfone oxygens participates in the unusual transannular H-bond postulated for compound **2a**.

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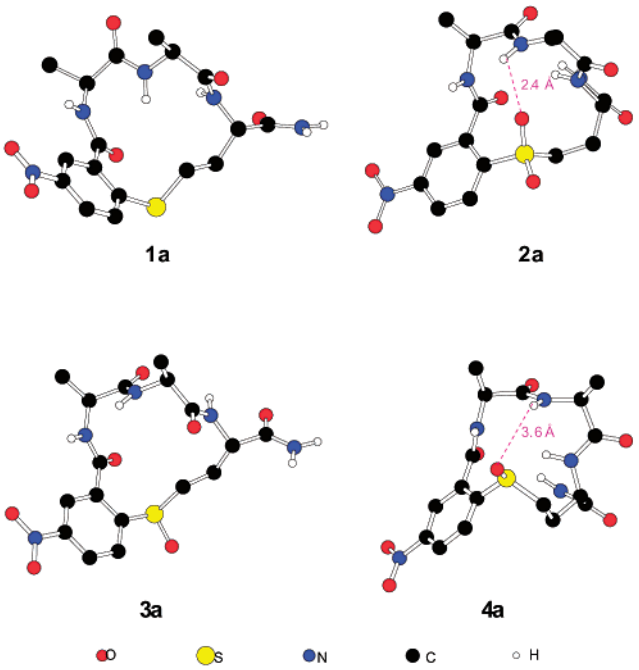

Figure 1. Simulated low-energy conformers for compounds **1a**−**4a**.

Therefore it seemed logical that only one of the corresponding sulfoxides would display a similar interaction.

Oxidation of the thioether **1a** with sodium periodate gave a 1:2 mixture of sulfoxides that were separable by preparative HPLC. There was no immediate basis for a stereochemical assignment of the sulfur configuration, but QMD simulations of these two diastereomers (*without any spectroscopic constraints*), indicated that only the (*S*)-isomer **4a** could adopt a type-I β-turn conformation with an extra transannular H-bond, whereas β-turn conformers did not feature prominently for the (*R*)-sulfoxide **3a**. Spectroscopic analyses showed that the major stereoisomer had a preferred β-turn conformer (Table 1); hence, it appeared likely that this compound had the (*S*)-sulfoxide configuration, that is, it was compound **4a**. Consistent with this assignment, the spectroscopic studies gave data for the minor stereoisomer that matched the preferred conformation simulated for sulfoxide **3a**, whereas the virtual preferred β-turn conformation for **4a** matched the spectroscopic data for the major isomer nearly perfectly. Moreover, exchange of the $\underline{\mathrm{NH}}_{i+2}$ proton in CD_3OD was slow for compound **4a** relative to that for **3a**.

Glu-Lys side chains are polar and capable of H-bonding, and thus it was important to explore whether the trends outlined for compounds **1**−**4** were unique to this particular substitution pattern. Consequently, a similar approach was used to study the compounds **1b**−**d** to **4b**−**d**. The NMR and CD data accumulated show that the sulfones **2** and one of the sulfoxide epimers **4**, adopt β-turn conformations, whereas the sulfides **1** and the sulfoxides **3** have no similar conformational biases. The trends in the NMR data that are implied in Table 1 are much clearer when the whole data set for all the compounds **1**−**4** are plotted together (Table S1, Supporting Information).

Circular dichroism (CD) studies support the assertion that unusual transannular H-bonds stabilize the β-turn conformations in compounds **2a** and **4a**, and also provide further evidence for their stereochemical assignments (Figure 2). Compounds **1a**, **2a**, and **4a** give an ellipticity minimum at approximately 205 nm characteristic of a type-I β-turn,[8] whereas compound **3a** does not.

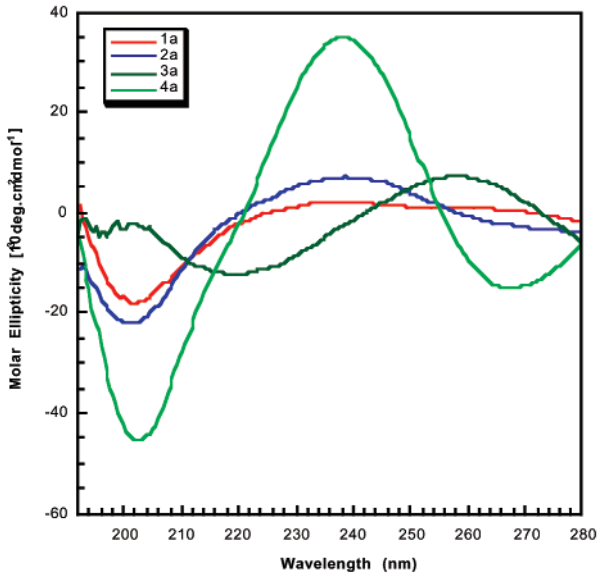

Figure 2. CD spectra for compounds **1a**−**4a**.

The conformational biases simulated by QMD are consistent with β-turn conformations for the (*S*)-sulfoxides, and not the (*R*)-isomers. These observations do not provide incontrovertible assignments of the absolute configurations at the sulfoxide *S*-atoms; this would almost certainly require crystallographic analyses, and we were unable to form suitable crystals from these peptidomimetics. Nevertheless, the weight of evidence presented in favor of the proposed assignments is substantial.

This work demonstrates that unusual transannular H-bonds for peptidomimetics containing sulfone or sulfoxide functionalities can profoundly effect their preferred conformational states in solution. It is also highlights a rare situation in which conformational analyses can be used to infer stereochemical configurations.

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Supporting Information Available: Details of the syntheses, spectroscopic data for characterization and conformational studies, results from the QMD calculations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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