

SHORT COMMUNICATION

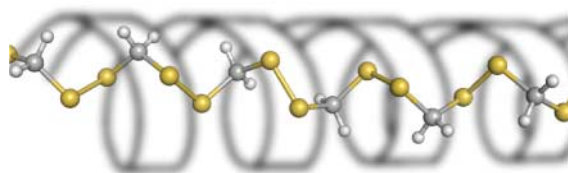
Theoretical study of a nonpeptidic polydisulfide α -helix[†]

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A carbon–sulfur molecule has been designed as a mimic of peptides. Density functional theory calculations showed that the oxidation of 10 moles of methanedithiol led to a polydisulfide oligomer, $\text{HS}(\text{CH}_2\text{SS})_9\text{CH}_2\text{SH}$. The polydisulfide can adopt an α -helix type of secondary structure, where the chain is coiled. Unlike proteins, the S–S bonds in the polydisulfide function as secondary rather than tertiary structural elements. The helix contains 8 non-hydrogen atoms per turn, 2.7 Å methylenes per turn, a pitch distance of 8.6 Å, and a radius of 1.00 Å. The methylene sites could carry R group residues similar to amino acids.



Keywords: peptide mimics; carbon–sulfur polymers; α -helices; disulfides; secondary structure

A challenging endeavor is the design of carbon–sulfur molecules as mimics of peptides. Secondary structural details of rubbery C–S polymers including helices, turns, and folds are often difficult to detect spectroscopically. For example, the elastic Thiokol polymer $(\text{CH}_2\text{CH}_2\text{SSSS})_n$ formed from the condensation of Na_2S_4 and 1,2-dichloroethane has many possible conformations (1). On the other hand, π -conjugated carbon–sulfur $[n]$ helicenes are rigid due to the fused connections of the thiophene rings (2).

We report here on computations of polydisulfide oligomers (**1** and **2**) bearing 1,3-SCH₂S type bonding (Figures 1 and 2). This type of bonding is quite common. It is found in 1,3,6-trithiane arising from $\text{CH}_2=\text{S}$ trimerization (3), in dithiane bridging groups holding together supramolecular fragments (4), and in volatile *bis*-disulfides from Welsh onions and scallions (5). $\text{HS}(\text{CH}_2\text{SS})_9\text{CH}_2\text{SH}$ was predicted to form helix and non-helix structures upon the end-group oxidation of 10 HSCH₂SH molecules with the formal the loss of 20 protons and 20 electrons. The helix form of **1** seemingly mimicked the structure of peptides.

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[†]This paper is dedicated to Professor Eric Block

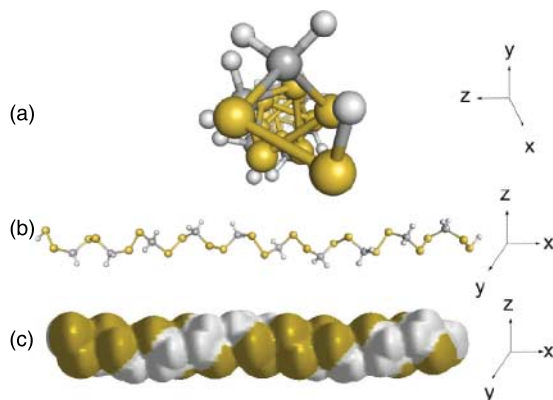


Figure 1. B3LYP/6-31G(d) optimized structure of the HS(CH₂SS)₉CH₂SH helix **1** looking down the axis of the tube (a), and showing the side view with a ball-and-stick model (b), and the van der Waals surface generated with a solvent accessible atomic radius of 1.4 Å (c).

Note: The grey atoms are carbons, the yellow atoms are sulfur, and the white atoms are hydrogen.

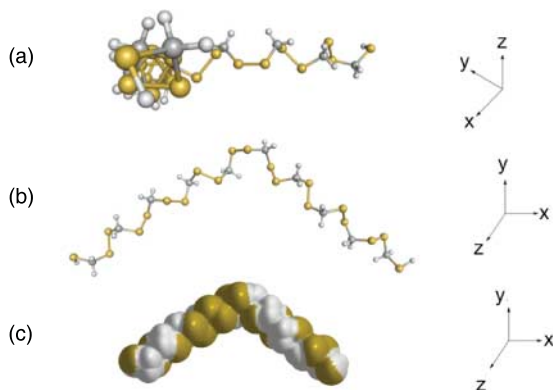


Figure 2. B3LYP/6-31G(d) optimized structure of the P P P P M M M M HS(CH₂SS)₉CH₂SH **2** diastereomer looking down the axis of the P P P P portion of the tube (a), and showing the side view with a ball-and-stick model (b), and the Van der Waals surface generated with a solvent accessible atomic radius of 1.4 Å (c).

The calculation results were obtained for a right-handed helix of HS(CH₂SS)₉CH₂SH **1** (all *P* enantiomer). It adopts an α -helix type of secondary structure, where the polymer chain is coiled into a spiral structure. The HS(CH₂SS)₉CH₂SH helix contained 8 non-hydrogen atoms per turn, 2.7 Å methylene residues per turn, a pitch distance of 8.6 Å, a tube length of 35.6 Å, S–S bond distances of 2.08 Å, C–S–S bond angles of 103.6°, through-space S–S bond distances of 3.16 Å, and a radius of 1.00 Å. There is a clear disulfide *gauche* influence in the helix, where the ϕ (C–S–S–C) dihedral angles ranged from 88.3° to 90.0°. For organic disulfides, a 90° dihedral angle is preferred (6). In comparison, helical elemental sulfur stretched from hot liquid sulfur contains 3.3 sulfur atoms per turn, a pitch distance of 4.6 Å, S–S bond distances of 2.07 Å, bond angles of 106.0°, torsion angles of 85.3°, and a radius of 0.95 Å (7).

Conformational information was provided by calculations. Diastereomer P P P P M M M M **2** bearing a “kink” in the center disulfide was more stable than helix **1** by ~1 kcal/mol (Figure 2). A few non-helical conformations were found that were more stable than helix **1** by ~6 kcal/mol. On the other hand, several unwound starting geometries, when optimized, reverted back to helix **1**. Increases in energy in the tens of kcal/mol range were also found in some conformations compared to the helical conformation. Thus, it is difficult to conclude whether helix **1** is kinetically

stable and persistent based on the small survey of the conformational space conducted here and the errors associated with the density functional theory calculations. B3LYP calculations are not without their shortcomings and carry some errors in accuracy. We know that B3LYP/6-31G(d) underestimates disulfide bond dissociation energies by ~ 11 kcal/mol (8). For HSSH, the 55 kcal/mol computed value is lower than the 66 ± 2 kcal/mol experimental value (8). CBS-QB3 calculations bring the computed value closer with 62 kcal/mol, but due to computational cost it cannot be used with helix **1** unless months of computer time are invested. Worse yet, semi-empirical and molecular mechanics calculations provide inaccurate energetics since they are not parameterized for polysulfide or through-space S–S interactions, and even produce unreliable geometries.

Our computations support the idea that oxidatively polymerized methanedithiol yields helical and non-helical polydisulfides, such as **1**. Interestingly enough, in **1** the disulfide groups serve as secondary rather than tertiary structural elements. Needless to say, tertiary structures of proteins involve thiol/disulfide equilibria (9). Biochemical research has focused much more attention on protein disulfide formation than it has on helices resulting from dithiols although a study has recently shown a self-replication process in the oligomerization of aromatic dithiols (10). The methylene linker in helix **1** could serve as a residue site to carry information if contemplating a hypothetical information carrier (11). If we wish to make peptide mimics of sulfur polymers, which might be an interesting notion, attention could be paid to R group substitutions $\text{HS}[\text{CR}(\text{H})\text{SS}]_n\text{CH}_2\text{SH}$ (R = amino acid type residues) and their resultant chiral topologies, S–S and C–S bond rotation energies, and helix dimensions.

Theoretical methods

Calculations were conducted using the Gaussian 09 program package (12), and the structures were viewed with the GaussView 5 program (13). Standard theoretical chemistry notations were used (14). B3LYP/6-31G(d) calculations were used for **1**. The stationary points of optimized minima structures were examined by frequency calculations and showed zero or very near zero negative frequencies. Standard convergence criteria were met $<10^{-4}$ for the forces. However, due to flexibility of the chain, minima were obtained at $<10^{-2}$ for the displacements, which is less stringent than the default convergence criteria. CBS-QB3 was used for the bond dissociation energy calculations of HSSH with standard convergence criteria.

Acknowledgements

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