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Title
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Permalink
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Journal
Chemical Communications, 50(31)

ISSN
1359-7345

Author
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Publication Date
2014-04-21

DOI
10.1039/c4cc00925h

Supplemental Material
https://escholarship.org/uc/item/5qr4c7sm#supplemental

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Mechanism of the cysteine sulfenic acid *O*-sulfenylation of 1,3-cyclohexanedione†

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Cite this: *Chem. Commun.*, 2014, **50**, 4102

Received 9th February 2014,
Accepted 4th March 2014

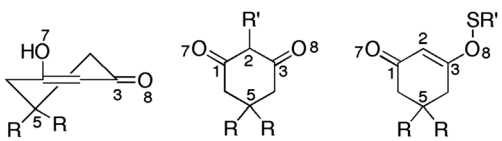
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The density functionals B3LYP, B3PW91, M062X, and CAM-B3LYP with the 6-311+G(d,p) basis set predict the cysteine sulfenic acid *O*-sulfenylation of the *s-cis*-ketoenol tautomer of 1,3-cyclohexanedione proceeds through a cyclic 14-membered transition state structure containing three water molecules.

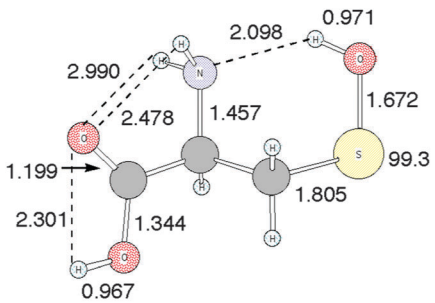
Protein sulfenylation is a post-translational modification of emerging importance in eukaryotes and 1,3-cyclohexanedione (**1**, Fig. S1 in the ESI†) and 5,5-dimethyl-1,3-cyclohexanedione (dimedone, **2**) based chemoselective probes represent important tools for its detection.[1] Generally, the covalent modification of the cysteine sulfenic acid is considered to take place through the *C*-sulfenylation on carbon 2 of the 1,3-cyclic diketones (**1**, **2**, Fig. 1) to form sulfides (thioethers).[1–3] In this manuscript, the investigation of an alternative reaction that leads to sulfenic ester formation through *O*-sulfenylation is presented and supported (Fig. 1).

The presence of the conjugated system in cyclic 1,3-diketones suggest that *O*-sulfenylation to form unstable sulfenate esters (**4**, Fig. 1) is reasonable.[2] It is known that electrophilic sulfenyl sulfur reacts with nucleophiles such as alkenes, enamines, and enols. Owing to the vital importance and significance of the chemoselectivity of 1,3-cyclohexanedione (**1**) and 5,5-dimethyl-1,3-cyclohexanedione (**2**) in detecting protein sulfenic acids, it is important to understand the fundamental mechanisms and products of the sulfenylation reactions. We are using computational quantum chemistry (see ESI†) to investigate the fundamental chemistry, properties, and structures of sulfenic acids and their reactions with (**1**) and (**2**) in order to acquire data and information to assist in elucidating the nature of the chemistry of protein thiols and protein sulfenic acids.[2,4,5]



1b R = R = H
2b R = R = CH_3 **3** **4**

Fig. 1 Enol tautomers of 1,3-cyclohexanedione (**1b**) and 5,5-dimethyl-1,3-cydohexanedione (**2b**) and the *C*-sulfenylated (**3**) and *O*-sulfenylated (**4**) products from R'SOH.



5

Fig. 2 M062X/6-311+G(d,p) geometry optimized structure of the sulfenyl tautomer of cysteine sulfenic acid (Cys–SOH, **5**).

Amino acids exist as zwitterions in aqueous solution and in the crystalline state and in the neutral (nonionized) forms in the gas phase. In the gas phase, the lowest energy conformer of cysteine sulfenic acid (Cys–SOH, **5**, Fig. 2) is stabilized by strong intramolecular hydrogen bonds, dispersive and steric interactions, and electrostatic, exchange, and hyperconjugative electronic effects owing in part to the polar functional groups (amino, carbonyl, hydroxyl, hydroxysulfanyl) which possess acceptor and donor properties.[6] One of the objectives of this study is to utilize specific cysteine–water complexes that maintain the conformation and nonbonding interactions of the water free lowest energy conformer of cysteine sulfenic acid (**5**, Fig. 2).[2]

The energy barriers for the *O*-sulfenylation reaction of cysteine sulfenic acid (**5**) with the *s-cis*-ketoenol (**1b**) tautomer

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc00925h

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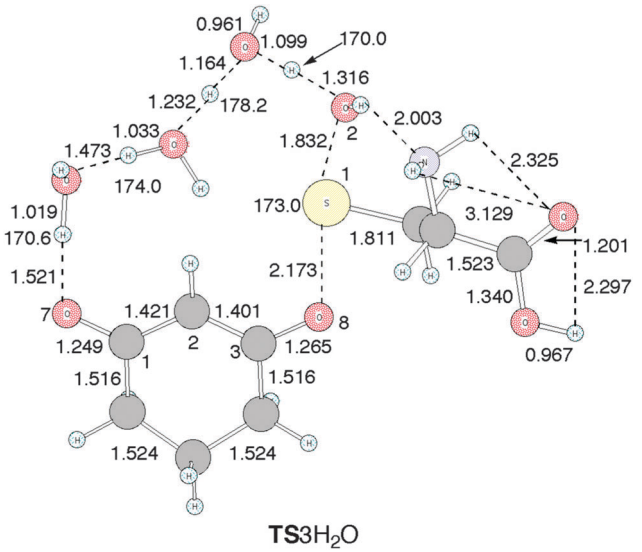


Fig. 3 M062X/6-311+G(d,p) geometry optimized structure of the three waters transition state (**TS**3H_2O) for the cysteine sulfenic acid (Cys–SOH, **5**) *O*-sulfenylation of the *s-cis*-ketoenol tautomer (**1b**) of 1,3-cyclohexanedione (**1**).

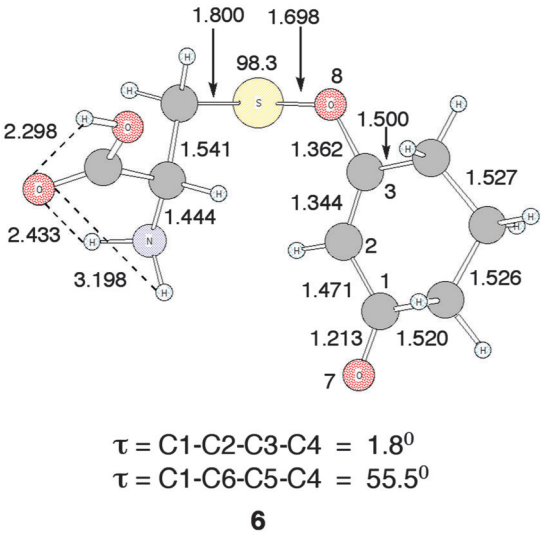


Fig. 4 M062X/6-311+G(d,p) geometry optimized structure of sulfenate ester (**6**).

through cyclic transition states **TS**H_2O (10-membered ring, boat or sofa conformation), **TS**2H_2O (12-membered ring, boat or sofa conformation), and **TS**3H_2O (14-membered ring, sofa conformation, τ = C1–C2–C3–C4 = −1.3°; C1–C6–C4–C3 = −0.8°; C3–C2–C1–C6 = 0.4°) are shown in Table S2 in the ESI.† It is seen that the inclusion of water molecules in the transition state structures lowers the activation barrier. The inclusion of water molecules in the transition state structures helps to relieve strain, helps to stabilize charges, and helps to set up a system to facilitate proton transfer from O7 in *s-cis*-ketoenol (**1b**) through a hydrogen-bonded network of water molecules in a Grotthuss-type mechanism.[7] The geometry-optimized structure of transition state **TS**3H_2O is shown in Fig. 3 and the structures of transition states **TS**H_2O and **TS**2H_2O are given in Fig. S2 in the ESI.† The geometry-optimized structure of the *O*-sulfenylation product (**6**) is given in Fig. 3 and 4. Sulfenate esters are known to be unstable and sulfenate anions, which are also unstable, may be oxidized sulfinate anions and may disproportionate to the corresponding sulfinate and thiolate anions.[8]

The cysteine sulfenic acid (**5**) *O*-sulfenylation of the *s-cis*-ketoenol tautomer (**1b**) of 1,3-cyclohexanedione (**1**) to afford the sulfenate ester (**6**) proceeds through a cyclic 14-membered transition state structure containing three water molecules (**TS**3H_2O, Fig. 3). The half-chair conformation of *s-cis*-ketoenol (**1b**) becomes a sofa conformation (τ = C1–C2–C3–C4 = −1.3°; C1–C6–C4–C3 = −0.8°; C3–C2–C1–C6 = 0.4°) along the reaction path from ground state to transition state **TS**3H_2O. B3LYP, B3PW91, M062X, and CAM-B3LYP predict the energy barrier for the *O*-sulfenylation reaction of the three-water complex of cysteine sulfenic acid (**5**–3H_2O) with the *s-cis*-ketoenol (**1b**) to be 7.4, 5.3, 6.6, and 7.1 kcal mol^{-1}, respectively. The small energy barrier of only 2 kcal mol^{-1} between the two waters and three waters transition states may be due to entropic and other environmental effects. Larger energy barriers are predicted for transition state structures involving one water molecule **TS**H_2O (10-membered ring) and two waters (**TS**2H_2O, 12-membered ring, Fig. S2 in the ESI†).

The mechanism for the formation of the *O*-sulfenylated product (**6**) involves attack of O8 in the enol or enolate form of the *s-cis*-ketoenol tautomer (**1b**) on the sulfur atom in cysteine sulfenic acid (**5**). The inclusion of water molecules assists in orienting the structure of the transition state in order to facilitate the proton transfer process. There is electron delocalization involving O7–C1–C2–C2–O8 in transition state **TS**3H_2O as evidenced by the equal C1–C2 and C2–C3 bond lengths and by the similar C1–O7 and C3–O8 bond lengths. In contrast, the C1–O7, C1–C2, C2–C3, and C3–O8 bond lengths in the half-chair ground state conformation of *s-cis*-ketoenol (**1b**) are 1.355 Å, 1.350 Å, 1.464 Å and 1.221 Å, respectively.

The results of this computational quantum chemistry study are consistent with the half-chair *s-cis*-ketoenol tautomer (**1b**) of 1,3-cyclohexanedione (**1**) reacting with the three water complex of the lowest energy conformer of cysteine sulfenic acid (**5**–3H_2O) through a cyclic 14-membered transition state structure **TS**3H_2O to afford the sulfenate ester (**6**).

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