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Computational Studies of the Tropone Natural Products, Thiotropocin, Tropodithietic Acid, and Troposulfenin. Significance of Thiocarbonyl−Enol Tautomerism

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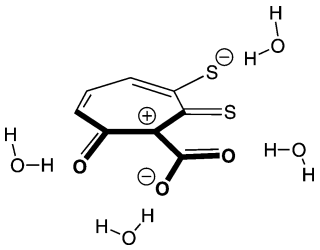
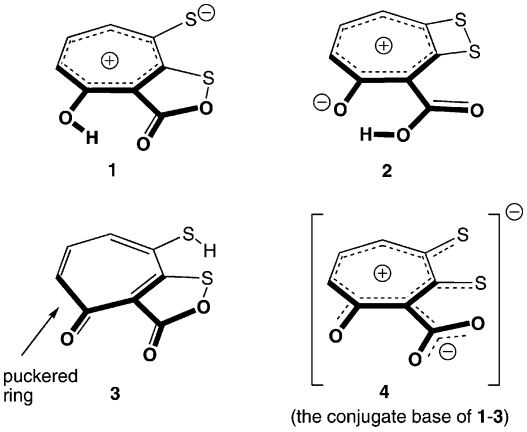


Computations provide insight to the stability and isomeric possibilities of thiotropocin, tropodithietic acid, and troposulfenin. Thiotropocin and tropodithietic acid contain a flat 7-membered ring and delocalized π-bonds similar to those of tropylium ion ($C_7H_7^+$). Troposulfenin is far less stable; it contains a puckered tropone ring and localized bonds similar to 1,3,5-cycloheptatriene. A facile 1,5-hydrogen shift suggests that thiotropocin and tropodithietic acid exist as a pair of interconverting tautomers. Loss of an acidic proton from these three tautomers produces the same conjugate base structure.

The computational studies presented here indicate partial tropylium ion character in thiotropocin (**1**), tropodithietic acid (**2**), and the conjugate base (**4**), but not troposulfenin (**3**) (Scheme 1). Our interest in the subject was sparked due to the debate surrounding the structural identity of the natural tropones **1**−**3**.[2−16] After a 23-year period, questions remain about the viability of **1**−**3**.[2−16] To take an example, in 2005, an antibiotic substance was described imprecisely as "the sulfur containing compound thiotropocin or tropodithietic acid produced by *Roseobacter* strain 27-4...".[10] In 2006, Laatsch[16] cited unpublished work suggesting that previous structural assignments of **1** and **3**[2−15] were incorrect and that they should instead be **2**.[16] The X-ray structure has been obtained for **2**,[8] although Cane provided evidence for the detection of **1** from ^{13}C-labeling experiments in DMSO and $CDCl_3$ solution.[12]

SCHEME 1



One problem is that it is unclear whether **1**−**3** rearrange with each other in solution. Compounds **1**−**3** can be regarded as tautomers and may possess dynamic behavior, possibly influenced by solvent proticity and pH. However, no spectroscopic evidence exists for the conjugate base. No previous study postulated a role of the conjugate base **4** in the equilibration of **1**−**3**. Our computed data show that, aside from isomer **3** being considerably higher in energy than **1** or **2**, the rearrangement between **1** and **2** is facile.

Computed Structures. Compounds **1**−**4** optimize to minima at the B3LYP/6-31+G(d) level of theory (Table 1). Compounds

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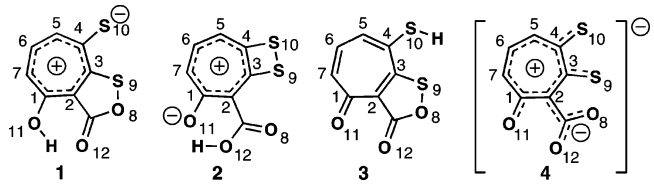
TABLE 1. Calculated Stuctural Parameters of 1−4[a]



	formally single bonds				formally double bonds							
	C1−C2[b]	C1−C7[b]	C3−C4[b]	C5−C6[b]	C2−C3[b]	C4−C5[b]	C6−C7[b]	O8−S9[b]	S9−S10[b]	O11−O12[b]	C4−C3−S9	θ[c]
1	1.42	1.41	1.44	1.41	1.38	1.39	1.39	1.94	1.51	2.58	108.7	0.0
2	1.46	1.46	1.44	1.43	1.38	1.37	1.37	2.34	2.23	2.53	103.9	0.0
3	1.48	1.48	1.44	1.44	1.38	1.36	1.36	1.69	3.04	2.89	117.0	27.6
4	1.48	1.46	1.48	1.42	1.38	1.38	1.37	1.79	2.69	2.82	109.8	0.0

[a] Structures optimized at the B3LYP/6-31+G(d) level. [b] Distances in Å, angles in deg. [c] The dihedral angle is θ = C6−C7−C1−C2.

1, **2**, and **4** each contain a flat 7-membered ring and delocalized π-bonds. Troposulfenin **3**, on the other hand, shows puckering of its 7-membered ring with distortion away from planarity. The dihedral angle of four carbon atoms (θ = C6−C7−C1−C2) in **1**, **2**, and **4** is equal to 0.0° but in **3** equals 27.6°. The calculated geometry of **3** shows greater bond alternation with more distinct single and double bonds in the 7-membered ring (e.g., the C4−C5 and C1−C7 bond distances are different from each other, 1.36 and 1.48 Å). The bond alternation pattern of **3** bears a resemblance to 1,3,5-cycloheptatriene, in which the computed C1−C2 bond is 1.35 Å, the C2−C3 bond is 1.45 Å, and the C3−C4 bond is 1.37 Å. By comparison, the formal single bonds become shorter and the formal double bonds become longer in **1**, **2**, and **4** [cf. calculated C4−C5 bond lengths of 1.39 Å (**1**), 1.37 Å (**2**), and 1.38 Å (**4**); also compare C1−C7 bond lengths of 1.41 Å (**1**), 1.46 Å (**2**), and 1.46 Å (**4**)]. The formal double bond C4−C5 distance is 0.01−0.03 Å shorter and the formal double C1−C7 bond 0.01−0.05 Å longer in **1**, **2**, and **4** compared to C−C bond of tropylium ion itself (i.e., $C_7H_7^+$) (1.40 Å). Thus, tropylium ion character in **1**, **2**, and **4** is not complete. Additionally, judging whether delocalized π-bonds and bond alternation exist near the site of the ring fusion (e.g., the C2−C3 bond in **1** and **3**; and the C3−C4 bond in **2**) cannot be done easily because the accuracy of the calculations are in hundredths not thousandths of angstroms. The above analysis of computed bond alternation is similar to the method used by Katritzky et al. to estimate aromatic content in carbocycles and heterocycles.[17,18]

We also discovered that the HOMO of **3** differs significantly from the HOMO of **1**, **2**, and **4** (Figure 1). Unlike **1**, **2**, and **4**, the π orbital of the tropone ring does not contribute significantly to the HOMO of **3**. The HOMO of **1** contains a delocalized π orbital on the tropone ring that interacts with a π-type lone pair molecular orbital on S9. An antibonding interaction also exists between the tropone ring and π-type lone pair MOs on S10 and O11. The HOMOs of **2** and **4** are similar and contain a delocalized π orbital on the tropone ring (with a nodal plane that bisects the C2−C3 bond and C6) that mixes with the π* of S9−S10. The HOMOs of **2** and **4** also contain antibonding interactions between the delocalized π orbital of the tropone ring and π-type lone pair MOs on S10 and O11. A difference between the HOMO of **1** and that of **2** and **4** is the lack of mixing of the tropone ring with π* of COO in **1**. In contrast to **1**, **2**, and **4**, the HOMO of **3** contains overlapping orbitals localized onto the oxathiolane heterocycle.

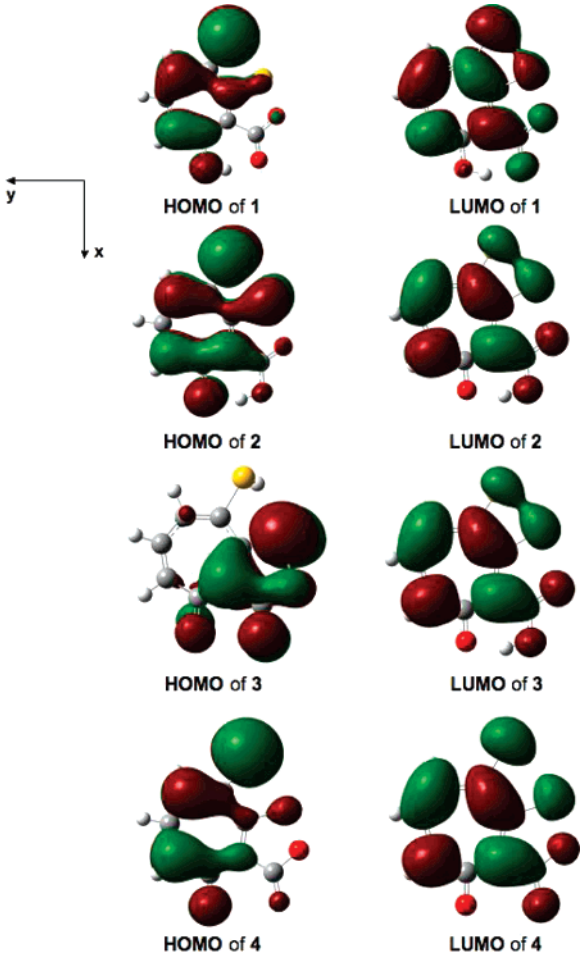


FIGURE 1. HOMO and LUMO orbitals of **1**−**4**. The molecular orbitals were obtained from B3LYP/6-31+G(d)-optimized structures with isovalues of surfaces set at 0.02.

The Conjugate Base 4. The formation of a conjugate base was implicated in the reaction of sodium bicarbonate with thiotropocin,[3,12] but its structure was not examined. Further experiments to probe the nature of the conjugate base have not been conducted. Our computational results suggest that loss of

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TABLE 2. Calculated Proton Affinities (PA)[a]

compd	acidic site	PA (kcal/mol)
1	O11	327.7
2	O12[b]	332.0
3	S10	315.0

[a] Calculations at the QCISD(T)/6-31G(d)//B3LYP/6-31+G(d) level. [b] Not examined for O8.

an acidic proton from **1**, **2**, or **3** leads to the same conjugate base structure, **4**. Conjugate base **4** shares its negative charge via heteroatom resonance. It is a unique structure that contains many resonance contributors. As noted above, our computations identify some tropylium ion character in **4**, but unlike **1**−**3**, **4** contains neither a strained 4-membered dithiete ring[19,20] nor an unstable electrophilic oxathiolane ring.[21] Conjugate base **4** possesses bond distances of S9−S10 (2.69 Å) and O8−S9 (1.79 Å) that are within the sum of the van der Waals radius for S−S (3.60 Å) and for S−O (3.32 Å).[22]

Computed Energetics. There are a number of structures located near the energy minima with different conformations of the acidic hydrogens in **1**−**3**. In each case, the lowest energy conformer was used. According to QCISD(T)/6-31G(d)//B3LYP/6-31+G(d) calculations with zero-point energy (ZPE) corrections, the relative energy of **1** is 4.4 kcal/mol, **2** is 0.0 kcal/mol, and **3** is 14.6 kcal/mol. Tropodithietic acid **2** is the most stable of the three structural isomers. No longer destabilized by an adjacent thione or thiolate ion group (S10 in **1**), the oxathiolane can open up by formation of the S9−S10 bond in **2**. Troposulfenin **3** is far less stable than **1** and **2** because of energy that can be released upon tautomerization in a process in which the tropone ring becomes planar.

Proton Affinities. The proton affinities (PA) for **1**−**3** were calculated (Table 2). Some authors suggest the existence of **3**,[14] although calculations predict that it contains the most acidic site among the three structural isomers (315.0 kcal/mol, S10 of **3**). Protonation of **4** at S10 is not favored. Instead, protonation of **4** at O8, O11, or O12 is favored and leads to the formation of **1** and **2**. An assessment of the activation barriers for tautomerizations of **1**−**3** was conducted to further help understand the isomeric possibilities.

Tautomerization. We examined the hydrogen shift pathways among **1**−**3**. At the QCISD(T)/6-31G(d)//B3LYP/6-31+G(d) level, a 2.6 kcal/mol saddle point (**TS12**) connects **1** and **2**, which represents a proton shift from O11 to O12 in a concerted unimolecular reaction (reaction A, Figure 2). Inclusion of zero-point energy correction reduces this barrier to 0.0 kcal/mol, suggesting a barrierless process in the gas phase. We anticipate that in aqueous solution **1** and **2** will be stabilized relative to

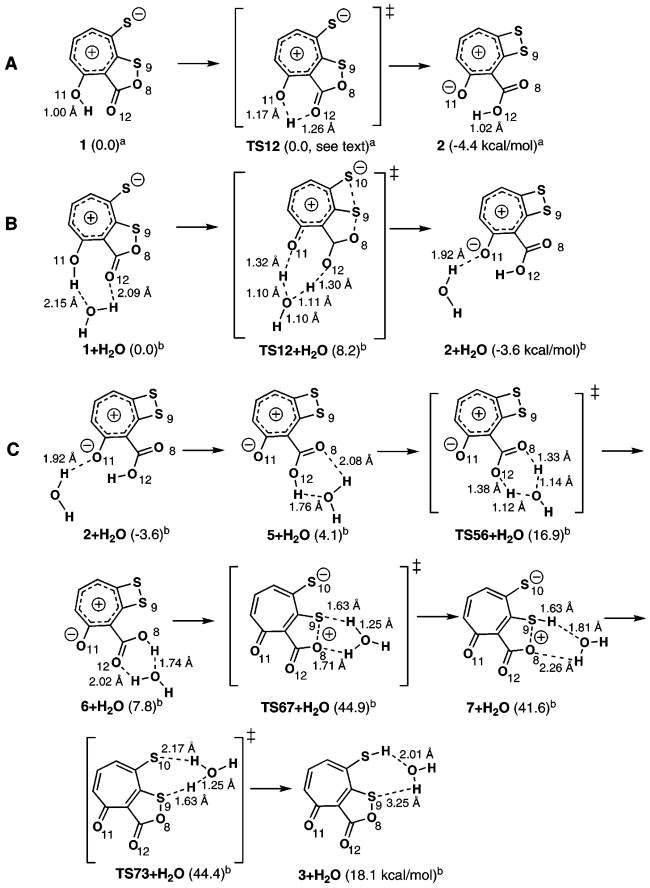

FIGURE 2. Computed hydrogen shifts among the natural product tautomers. Bond distances are given in Å; energetics (in parentheses) are in kcal/mol. Compounds in reaction C are relative to **1**+H_2O in reaction B. [a]QCISD(T)/6-31G(d)//B3LYP/6-31+G(d) with ZPE corrections. [b]B3LYP/6-31+G(d) with ZPE corrections.

TS12 to produce a small barrier.[23] Next, we examined a water-assisted proton transfer connecting thiotropocin to tropodithietic acid [noted as **1**+H_2O and **2**+H_2O (reaction B, Figure 2)] with B3LYP/6-31+G(d) calculations with ZPE corrections. Here, the specific water interaction for conversion of thiotropocin to tropodithietic acid led to **TS12**+H_2O with a barrier height of 8.2 kcal/mol. **TS12**+H_2O has a slightly longer O11−H (1.32 Å) and O12−H bond (1.30 Å) compared to **TS12** [O11−H (1.17 Å) and O12−H (1.26 Å)]. A path was computed for converting tropodithietic acid **2** to troposulfenin **3** (reaction C, Figure 2). Reaction C is high in energy compared to reactions A and B. The reorientation of water from **2**+H_2O to **5**+H_2O is endothermic by 7.7 kcal/mol. The barrier height of **TS56**+H_2O is 12.8 kcal/mol and connects **5**+H_2O with **6**+H_2O. The barrier height of **TS67**+H_2O is 37.1 kcal/mol and reaches **7**+H_2O in a reaction that is endothermic by 33.8 kcal/mol. Transition state **TS73**+H_2O is 2.8 kcal/mol above **7**+H_2O, and transfers a proton in the water-assisted reaction from S9 to S10 to reach **3**+H_2O in an exothermic process (−23.6 kcal/mol). Here, **TS73**+H_2O has S9-H and S10-H bond distances of 1.63 Å and 2.17 Å, respectively. We sought, but were unable to find a

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(20) Ishii, A.; Nakayama, J. *Rev. Heteroatom Chem.* **1998**, *19*, 1−34.

(21) Considering the literature on oxathiolane intermediates in biological reactions, surprisingly little is known about the possible chemical reactions of the oxathiolane in **1**. For example, oxathiolanes react rapidly with thiol given the electrophilic sulfur atom within the ring, e.g.: Breydo, L.; Gates, K. S. *J. Org. Chem.* **2002**, *67*, 9054−9060; Gates, K. S. *Chem. Res. Toxicol.* **2000**, *13*, 953−956.

(22) (a) Rašović, A.; Steel, P. J.; Kleinpeter, E.; Marković, R. *Tetrahedron* **2007**, *63*, 1937−1945. (b) Iwaoka, M.; Takemoto, S.; Tomoda, S. *J. Am. Chem. Soc.* **2002**, *124*, 10613.

(23) Gilli et al. described a β-diketone enol system, in which the ZPE is near the top of the TS barrier for an intramolecular H-transfer in the gas-phase, but in aqueous solution a small barrier emerges: Gilli, P.; Bertolasi, V.; Pretto, L.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **2004**, *126*, 3845−3855.

concerted H-transfer route from S9 to S10 (to convert **7** to **3**) in the absence of a water molecule; we believe that this is because the C3−C4−S10−H torsion angle of **3** is 71.4°, and the proton is situated out of plane. We note that reaction C (as written) may not represent the sequence of proton transfer to reach **3** in solution; instead, protonation−deprotonation of the intermediates with solvent can take place.

Considering the mechanisms for the hydrogen migration in reactions A−C (Figure 2), it is possible the unimolecular reaction, reaction A, is responsible for the facile conversion of **1** to **2** in a slightly exothermic reaction (−4.4 kcal/mol). Tautomers **1** and **2** have similar energetics and PAs, and the rearrangement of **1** and **2** is easy. Thus, calculations suggest that they are essentially one and the same compound, and probably should never have been named as two separate compounds. By analogy, the keto−enol forms of acetoacetic ester do not receive different names. We have resisted terming tropodithietic acid to thiotropocin a tautomerase activity. However, in a complex fashion **1** and **2** could be a keto−enol situation of a type that opens the dithiete ring and produces a thiocarbonyl-enol. In this way, we prefer the term "structural isomerism". Proton exchange and matters regarding the symmetry of hydrogen bonds have been of immense interest in physical organic chemistry.[24] Our calculations predict that **1** and **2** exist as isomers rather than a single structure with a symmetric hydrogen bond (OHO species). Similarly, we did not find evidence for a symmetric hydrogen-bonded SHS species in probing the structure of **3**.

A problem that is still awaiting exploration is the determination of the chemistry underlying biological activity. The natural material shows a wide range of potentially useful, pH dependent,[3] biological activities (antifungal, antimicrobial, antitumor, etc.).[2−16] Bimolecular reactions could be examined in future work, such as a nucleophilic attack that may favor the electrophilic oxathiolane (S9) position of **1**.

Computational Methods

Density function theoretical (DFT) calculations were conducted by the exchange-correlation of B3LYP along with Pople basis set 6-31+G(d) with the use of the Gaussian 03 program package.[25] Transition structures have been confirmed by frequency calculations, and by tracing the IRCs. Since DFT does not account for long-range correlation effects, single point QCISD(T)/6-31G(d) calculations have been conducted on B3LYP/6-31+G(d) optimized structures for **1**−**3**. Vibrational frequencies have been calculated in order to include ZPE corrections. The molecular orbitals were viewed with the GaussView program.[26] Standard computational notations were used.[27,28] Previous B3LYP studies have been successful in predicting experimental thiocarbonyl-thiol tautomerisms.[29−31] Our B3LYP/6-31+G(d) computations performed well in predicting the relative energetics of dithiete (c-$C_2H_2S_2$) and dithione ($C_2H_2S_2$), which is an important indicator regarding the quality of the calcualtions.[32−34] The compounds optimize to minima or maxima on the potential energy surface. The calculations of the compounds with a coordinated water molecule were not very prone to basis set superposition errors (BSSE). We observed BSSEs of ∼1.5 kcal/mol in the water assisted reactions (reactions B and C, Figure 2).

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Supporting Information Available: Total energies and Cartesian coordinates of the calculated structures. Computed entropies, enthalpies, and free energies for **1**, **2**, and **TS12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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