Attractive Through-Space S−O Interaction in the DNA-Cleaving Antitumor Antibiotic Leinamycin

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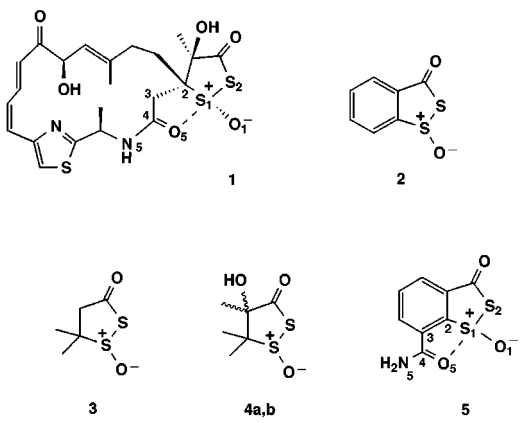
We describe here a study on the intramolecular nonbonded 1,5-sulfur−oxygen (S−O) interaction in the antitumor antibiotic leinamycin **1**. The results from density-functional theoretical and semiempirical calculations on leinamycin **1** and model systems **2**−**5** provide evidence for the 1,5-S−O nonbonded interaction. Our results are used to explain previous experimental data on the X-ray structure of leinamycin **1** (Hirayama, N.; Matsuzawa, E. S. *Chem. Lett.* **1993**, 1957). The amide oxygen (O5) alters the thiosulfinate ester conformation and stabilizes the 1,2-dithiolan-3-one 1-oxide heterocycle. The attractive interaction induces S1 of leinamycin to adopt a distorted trigonal bipyramidal geometry. The magnitude of this stabilizing interaction is ∼6 kcal/mol.

Introduction

The DNA-cleaving properties of the natural product leinamycin (**1**) and simple 1,2-dithiolan-3-one 1-oxides (**2**−**4**) have been recently observed (Scheme 1).[1] The mechanism of **1**−**4** utilizes thiol for DNA damage.[2,3] The groups of Gates[1,4] and Asai[5] have laid the groundwork for understanding the intermediates involved in these reactions. Strong evidence has implicated polysulfide (RSS_xSR) and oxygen radical intermediates in the DNA damage; the assignments of sulfenic acid (**B**), oxathiolane (**C**), hydrodisulfide (**D**), and episulfonium ion (**E**) intermediates are more tentative (Scheme 2). Products formed in the DNA reactions can be envisioned to arise from intermediates **B**−**E**. Kanda and co-workers very recently suggested that the amide nitrogen (N5) of leinamycin **1** may be responsible for the rapid decomposition of the drug in vivo.[6,7]

The role of the adjacent amide group and the influence it imparts on leinamycin **1** is of obvious importance. *We describe here the first study on the intramolecular nonbonded 1,5-sulfur−oxygen (S−O) interaction in leinamycin **1***. B3LYP/6-31G* and PM3 calculations are used to explain the previous X-ray data on leinamycin **1**.[9] Our theoretical study of the 1,2-dithiolan-3-one 1-oxides **1**−**5** was designed to assess the role of the amide oxygen on the geometry and stability of the drug, leinamycin **1**.

Scheme 1



Compound **5** is a simple model of the DNA-cleaving core of leinamycin **1**. We find the nonbonded 1,5-S−O interaction alters the thiosulfinate ester conformation of **1** and **5** and stabilizes the sulfur heterocycle. The calculated geometries are shown in Tables 1-4 and will be discussed first, followed by the energetic results.

Geometries

Many X-ray structures possess the 1,5-intramolecular S−O interaction,[8] of which the structure of leinamycin **1** is included.[9] B3LYP/6-31G* theoretical calculations reproduce X-ray structures of molecules with 1,5-S−O interactions. Table 1 shows that the B3LYP/6-31G* level describes well the 1,5-S−O interaction of 1,3-dioxo-3*H*-2,1λ^4-benzoxathiol-7-carboxylic acid methylester (**6**) when compared to the X-ray crystal data[10] and a B3LYP calculation with a triple-ζ (6-311G**) basis set.

Ab initio or density-functional theoretical calculations are required to adequately describe the 1,5-S−O interaction. To our knowledge, semiempirical and empirical computational methods are not parametrized for in-

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Scheme 2

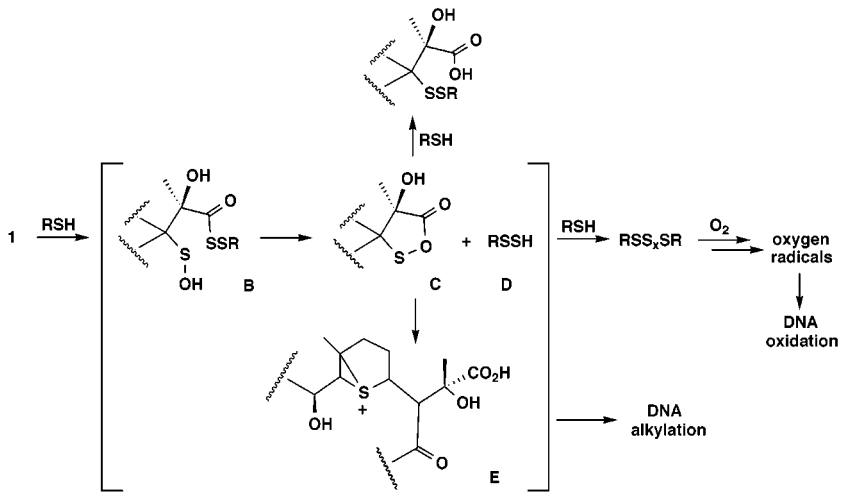
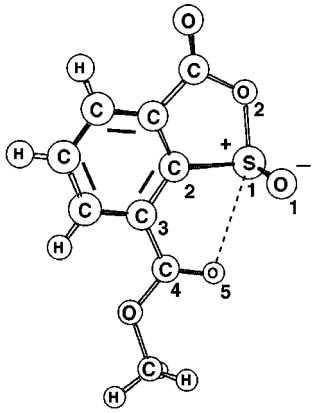


Table 1. Selected Structural Parameters of 1,3-dioxo-3*H*-2, 1λ^4-benzoxathiol-7-carboxylic Acid Methylester 6[a]



	X-ray[a]	B3LYP/6-31G*[c]	B3LYP/6-311G**[d]
	Atomic Distances (Å)		
S1−O1	1.437	1.479	1.473
S1−O2	1.684	1.773	1.786
S1−O5	2.813	2.810	2.806
	Bond Angles (deg)		
O2−S1−O1	104.5	107.7	107.5
O2−S1−C2	89.8	88.0	87.6
O2−S1−O5	164.5	157.5	156.3
	Dihedral Angle (deg)[b]		
S1−C2−C4−O5	−1.6	10.0	10.8

[a] Reference 10. [b] The dihedral angle θ = S1−C2−C4−O5 is positive for a counterclockwise movement from S1 to O5 as you look from C2 to C4. [c,d] Optimized geometries.

tramolecular nonbonded 1,5-S−O interactions. B3LYP/6-31G* calculations on the natural product leinamcyin **1** are prohibitively long. We chose to optimize the sulfur heterocycle of **1** at the B3LYP/6-31G* level and then transpose the structure into the macrocycle followed by a constrained optimization at the PM3 level.[11] Compounds **2**−**5** optimize to well-defined minima at the B3LYP/6-31G* level. Compound **4** is calculated as diasteromers **a** and **b** with the hydroxyl group positioned anti and syn to the sulfoxide oxygen O1, respectively. Compound **5** optimizes to a minimum where the S1 and O5 atoms are chelated.

Table 2. Calculated and Experimental Values of 1,2-Dithiolan-3-one 1-Oxide Structural Parameters[a]

compd.	S1−S2	S1−O1	S1−O5	S2−S1−O1	S1−S2−O5
1	2.143	1.528	(2.800)[c]	109.4	(165.0)[c]
2	2.215	1.497		113.2	
	(2.130)[b]	(1.471)[b]		(109.6)[b]	
3	2.193	1.500		110.6	
4a	2.219	1.501		111.2	
4b	2.251	1.497		110.0	
5	2.237	1.494	2.780	110.0	159.3

[a] Distances in Å; angles in deg. [b] Experimental values in parentheses; ref 12. [c] Experimental values estimated from ref 9.

The calculated features indicate the nonbonding 1,5-S−O interaction plays an important role in determining the structure of 1,2-dithiolan-3-one 1-oxide **1** and **5**. The calculated S2−S1−O1 bond angles in **1** (109.4°) and **5** (110.0°) are either equal to or less than those of the synthetic analogues **2** (113.2°), **3** (110.6°), **4a** (111.2°), and **4b** (110.0°) (Table 2). The X-ray structure of **2** has been reported.[12] The calculated S1−S2 bond length of **2** (2.215 Å) compares well with the X-ray value (2.130 Å), as do the calculated S1−O1 bond length (1.497 Å) and the X-ray value (1.471 Å). The calculated S2−S1−O1 angle (113.2°) of **2** is overestimated compared to the X-ray structure (109.6°); however, a reduced S2−S1−O1 bond angle from the 1,5-S−O interaction in **1** and **5** is apparent (vide infra). The X-ray structure of leinamycin **1** is published;[9] however, the coordinates are not available for comparison with our calculations.

The 1,5-S−O interaction plays a major role in determining the electronic and structural character of leinamycin **1**. B3LYP/6-31G* calculations revealed the leinamycin core **1** (R,R′,R″ = H) with the dihedral angle θ (S1−C2−C4−O5) equal to 40° is most stable (Table 3). Five conformations were optimized at the PM3 level with constrained B3LYP/6-31G* geometries imposed in the drug **1** (R = macrocycle, R′ = OH, R″ = CH_3). The effect

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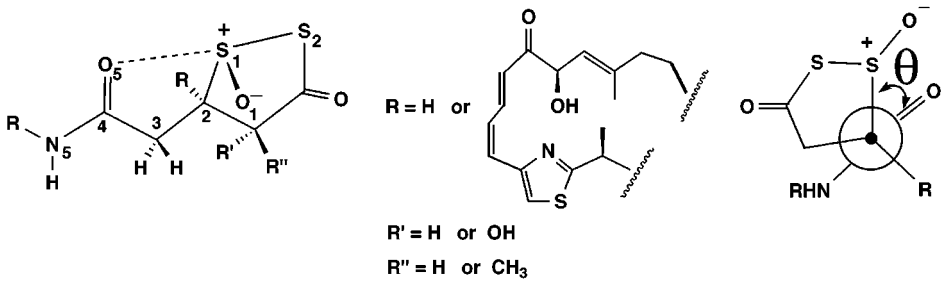
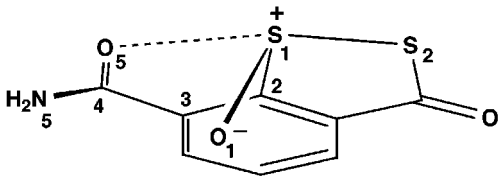
Table 3. Selected Structural Parameters of Leinamycin, 1[a]



	PM3 geometries[b]				NBO charges				
θ[c]	S1−S2	S1−O1	S1−O5	S2−S1−O1	S1	S2	O1	O5	ΔE[d]
−40°	2.132	1.515	3.638	110.7	1.131	−0.008	−0.873	−0.592	6.2
−20°	2.137	1.512	3.382	109.4	1.137	−0.012	−0.873	−0.598	5.2
0°	2.147	1.508	3.223	108.4	1.151	−0.019	−0.881	−0.610	3.2
40°	2.143	1.528	2.800	109.4	1.168	−0.027	−0.899	−0.620	0
80°	2.117	1.543	4.080	113.8	1.139	−0.008	−0.895	−0.620	1.0

[a] Distances in Å; angles in deg. [b] Geometries were first claculated at the B3LYP/6-31G* level for **1** (R, R′, R″ = H). DFT geometries were transposed into **1** (R = macrocycle, R′ = OH, R″ = CH_3) and then optimized at the PM3 level with the S1- -O5 bond distance, S2−S1- -O5 bond angle, and the dihedral angle θ = S1−C2−C4−O5 frozen. [c] θ is positive for a clockwise movement from S1 to O5 as you look down from C2 to C4. [d] B3LYP/6-31G* energies (kcal/mol), **1** (R, R′, R″ = H).

Table 4. Selected Structural Parameters of the Amide Containing Benzodithiolanone-oxide, 5[a]



	B3LYP/6-31G* geometries				NBO charges				
θ[c,d]	S1−S2	S1−O1	S1−O5	S2−S1−O1	S1	S2	O1	O5	ΔE[e]
−60°	2.214	1.491	3.404	110.0	1.141	0.012	−0.840	−0.564	6.4 (6.2)[f]
−35°	2.224	1.489	2.955	108.0	1.159	0.006	−0.842	−0.581	4.1
0°	2.245	1.490	2.626	107.7	1.191	−0.001	−0.855	−0.597	1.6
29.9°	2.237	1.494	2.780	110.0	1.188	0.006	−0.865	−0.594	0
45°	2.225	1.496	2.963	111.5	1.179	0.008	−0.869	−0.591	0.5
60°	2.215	1.498	3.216	112.6	1.168	0.011	−0.874	−0.583	1.6

[a] Distances in Å; angles in deg. [b] The dihedral angle θ = S1−C2−C4−O5, is positive for a clockwise movement from S1 to O5 as you look down from C2 to C4. [c] Optimized structure θ = 29.9°. [d] Optimized structure with θ constrained at 60°, 35°, 0°, −45°, and −60°. [e] B3LYP/6-31G* energies. [f] B3LYP/6-311G**//B3LYP/6-31G* energy in parentheses.

of the 1,5-S−O interaction is observed to a reduced extent when θ = −40°, −20°, 0°, and 80° as compared with θ = 40°. As the torsion angle θ is decreased from 40° to −40°, we observe a small increase in the S2−S1−O1 bond angle (from 109.4° to 110.7°), a decrease in the sulfur−sulfur (S1−S2) bond distance (from 2.143 to 2.132 Å), and a decrease in the S1−O1 bond distance (from 1.528 to 1.515 Å). Similar structural changes are observed when θ is increased from 40° to 80° with the exception of an increase in the S1−O1 bond distance (from 1.528 to 1.543 Å). Accompanying the geometrical changes is a transfer of electron density from S1 to the axial ligands as revealed by increases in the natural bond order (NBO)[13] positive charge at S1 and negative charges at S2 and O5, respectively, when comparing **1**, θ = 40° with θ = −40° and 80°. The S−O interaction in leinamycin **1** is a direct result of the proximity of the heterocycle S1 and the amide oxygen O5.

To provide further evidence for the potential of the 1,5-S−O interaction in 1,2-dithiolan-3-one 1-oxide, we conducted a detailed study on compound **5**. Six conformers for **5** are identified. We compared the B3LYP/6-31G* optimized structure of **5** (θ = S1−C2−C4−O5 = 29.9°) with those from optimizations where the dihedral angle θ is frozen at 60°, 35°, 0°, −45°, and −60° (Table 4). The favorable interaction between S1 and O5 influences the electronic and structural character of **5**. As the torsion angle θ of **5** is increased from 29.9° to 60°, we observe an increase in the S2−S1−O1 bond angle (from 110.0° to 112.6°), a decrease in the sulfur−sulfur (S1−S2) bond distance (from 2.237 to 2.215 Å), and a small increase of the S1−O1 bond distance (from 1.494 to 1.498 Å). Except for the destabilizing oxygen−oxygen interaction of O1 and O5 similar results are observed upon decreasing θ from 29.9° to −60°. We believe the destabilizing O1−O5 interaction accounts for the decrease in the S1−O1 bond distance (from 1.494 to 1.491 Å) and the undetectable change in the S2−S1−O1 bond angle (110.0°). It is clear that accompanying the geometrical changes is a transfer of electron density from S1 to the axial ligands as revealed by increases in the NBO positive charge at S1 and negative charges at S2 and O5, respectively, when comparing **5**, θ = 29.9° with 60° and −60°. The effect of

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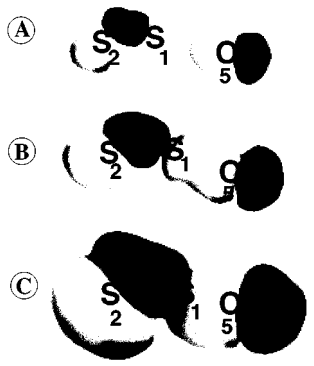


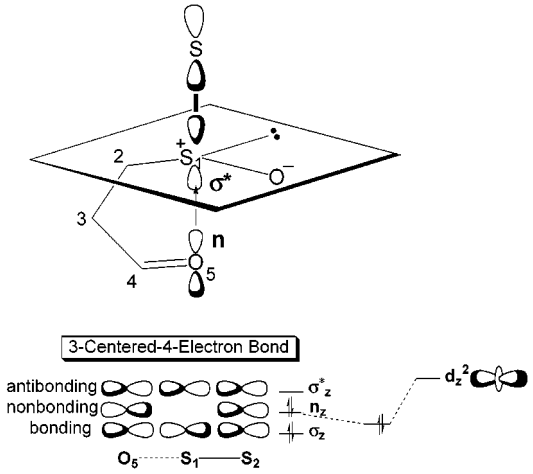
Figure 1. Extended-Hückel molecular orbital picture of the 1,5-sulfur−oxygen interaction. Three different electron-density isosurface values are shown: A = 0.01 au; B = 0.004 au; C = 0.0004 au.

the 1,5-S−O interaction in **5** is observed to a reduced extent when $\theta = 60°$ or $-60°$ as compared with $\theta = 29.9°$.

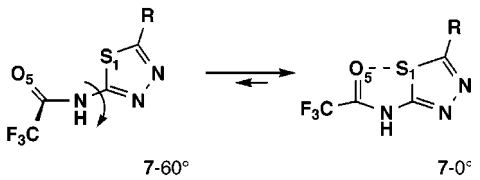
The covalent contact for a sulfur−oxygen bond is 1.8 Å[14] and the van der Waals contact is 3.3 Å.[15] Compounds **1** and **5** are asymmetric with two nonequivalent sulfur−oxygen bonds. The S1−O1 bond distance is 1.528 Å for **1** and 1.494 Å for **5** and the S1−O5 bond distance is 2.800 Å for **1** and 2.780 Å for **5**. The calculated S1−S2 bond distances of **1** (2.143 Å) and **5** (2.237 Å) are substantially longer than common S−S bond distances;[12,16] for example, the S−S bond distance of the thiosulfinate ester *syn*-7,8-dithiabicyclo[4.2.1]nonan-9-ol S-oxide is 2.079 Å.[17]

From the data above it is apparent the 1,5-S−O interaction induces a geometry at S1 best described as distorted trigonal bipyramidal. Atoms S2 and O5 occupy the axial positions while atoms C2 and O1 occupy the equatorial positions. The apical bonds are longer than the equatorial bonds, as observed in a large number of X-ray structures which contain 1,5-S−O interactions.[8,16] To investigate the source of the attractive S1−O5 interaction in leinamycin, we calculated the extended-Hückel molecular orbital of the sulfur−oxygen interaction with 3 different electron-density isosurface values (Figure 1A−C). With "appropriate" values for the isosurface, one can infer whether the S−O interaction is dominated by lone-pair $n_{(O)}$ to $\sigma^*_{(S)}$ interactions or intramolecular electrostatic effects. The S−O interaction of leinamycin **1** has a minimum electron density around 0.01 au (Figure 1A) consistent with weakly interacting sulfur and oxygen atoms.[18,19] The elegant studies of Wiberg and co-workers indicate a value of 0.0004 au is a better choice for isodensity-polarizable continuum model (IPCM) calculations based on the molecular volume of solutes.[20−23]

Scheme 3



Scheme 4



Sequential decreases in the value of the isosurface, from 0.004 au (Figure 1B) to the recommended 0.0004 au value (Figure 1C) indicate significant orbital overlap between sulfur and oxygen. This provides merit for a discussion of an $n_{(O)}$ to $\sigma^*_{(S)}$ interaction in leinamycin **1** via a 3-centered-4-electron (3c-4e) bond (Scheme 3). Unfortunately, the evidence collected cannot rule out whether the S−O stabilization is simply a matter of electrostatics. However, the NBO analyses reinforce the notion of a molecular orbital description that places a deficiency of electron density on S1 in a 3c-4e bond[24,25] because the positive charge at S1 is enhanced in **1**, $\theta = 40°$ (+1.168) compared to $\theta = -40°$ (+1.131) and $\theta = 80.0°$ (+1.139).

Energetics

The same through-space 1,5-S−O interaction that influences the geometry of 1,2-dithiolan-3-one 1-oxide also affects its energetics. The results indicate the conformers of **1** and **5** which possess 1,5-S−O interactions are ~6 kcal/mol below conformers with separated S1 and O5 atoms (Tables 3 and 4). Compare **1**, $\theta = 40°$ with $\theta = -40°$ and 80° and compare **5**, $\theta = 29.9°$ with $\theta = -60°$ and 60°. Similar energetic stabilizations have been found previously for compounds with 1,5-S−O interactions. Upon rotation about the torsion angle C=N−C=O5 of 5-propyl-2-(trifluoroacetamido)-1,3,4-thiadiazole (**7**) a 6.7 kcal/mol stabilization was observed at the HF/3-21G* level (60° to 0°, Scheme 4).[26]

Conclusion

The results from density-functional theoretical and semiempirical calculations on leinamycin **1** and model

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systems **2**−**5** provide evidence for the 1,5-S−O nonbonded interaction. The computed results shed new light on the previous X-ray data of leinamycin **1**[9] and indicate the adjacent amide oxygen (O5) participates in an apical-directed stabilization of the 1,2-dithiolan-3-one 1-oxide heterocycle indicative of a through-space sulfur−oxygen interaction. The 1,5-S−O interaction induces S1 of leinamycin to adopt a distorted trigonal bipyramidal geometry. The heterocycle is stabilized by ∼6 kcal/mol. It will be important to determine the potential for nonbonding interactions between the amide nitrogen (N5) and S1. In light of Kanda's recent work, it appears the amide nitrogen N5 plays a role in the decomposition of the drug in vivo.[6,7] We provide evidence the amide oxygen (O5) stabilizes the ground-state structure of leinamycin **1**. How these interactions might affect the bioactivity of the drug remain to be seen. The relevant transition state and rate-determining step for these reactions are not known; however, an enhanced DNA-cleaving efficiency is observed for leinamycin **1** compared to **2**−**4**.[3] Of all the variables that control biochemical reactivity, the attractive through-space 1,5-S−O interaction has received little attention. These interactions are well established in organic sulfur chemistry,[8] e.g., Kuczman and co-workers demonstrated that the 1,5-S−O interaction in *ortho*-carboxyl aryl methyl sulfide provided dramatic rate enhancements for chlorination with chloramine-T (TsNHCl) compared to the *para*-substituted compound where no such S−O interactions are possible.[27] The syntheses of dithiolanone-oxides capable of nonbonding interactions are currently being pursued to investigate this mechanism.

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