Ab initio investigation of reaction between 1,2-dithiolan-3-one 1-oxide and thiol: studies related to the mechanism of action of antitumor antibiotic leinamycin.

proposed by

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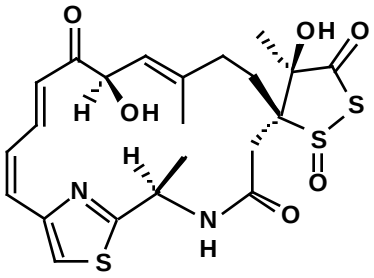
Introduction

Leinamycin (**1**) was isolated from an unnamed strain of *Streptomyces* in 1989[1] and its structure was elucidated by NMR spectroscopy[1], X-Ray crystallography[2] and chemical synthesis.[3] It contains an unusual 1,2-dithiolan-3-one 1-oxide heterocycle. Leinamycin exhibits antitumor activity and is also effective against gram-positive bacteria.[2] Early experiments indicated that leinamycin probably derives its antitumor, antibacterial activity through cleavage of DNA, and that the 1,2-dithiolan-3-one 1-oxide heterocycle is essential for this activity.[5] It has now been shown that leinamycin possesses at least two modes of thiol-mediated DNA damage: oxidative DNA damage and DNA alkylation. Thiol appears to be required for efficient action of antibiotic.



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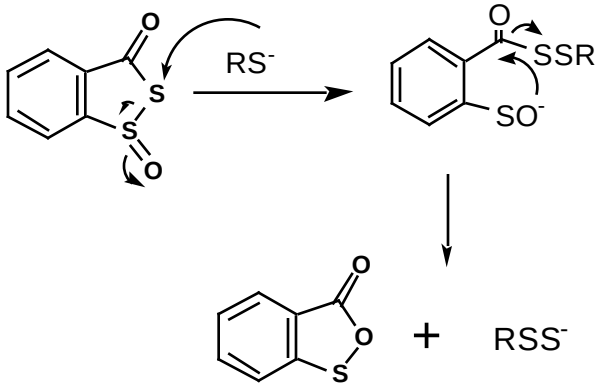


Mechanism of the reaction of thiol with 1,2-dithiolan-3-one 1-oxides has been elucidated[6] (scheme 1). It involves attack of thiol of the central sulfur with ring opening. It is followed by ring closing to form hydrodisulfide **2** and oxathiolanone **3**. Both of these products play important role in DNA damage by leinamycin[5,7]. Minor product (~10% yield) presumably resulting for attack of thiol on sulfoxide sulfur is also observed in the reaction[6].

Interestingly, reactions of of 1,2-dithiolan-3-one 1-oxides with amines[8] and alcohols[9] have been shown to proceed via attack of nucleophile on carbonyl carbon. Though this type of reactivity is intuitively understandable (soft/hard nucleophile principle), more quantitative explanation of it would be desirable.

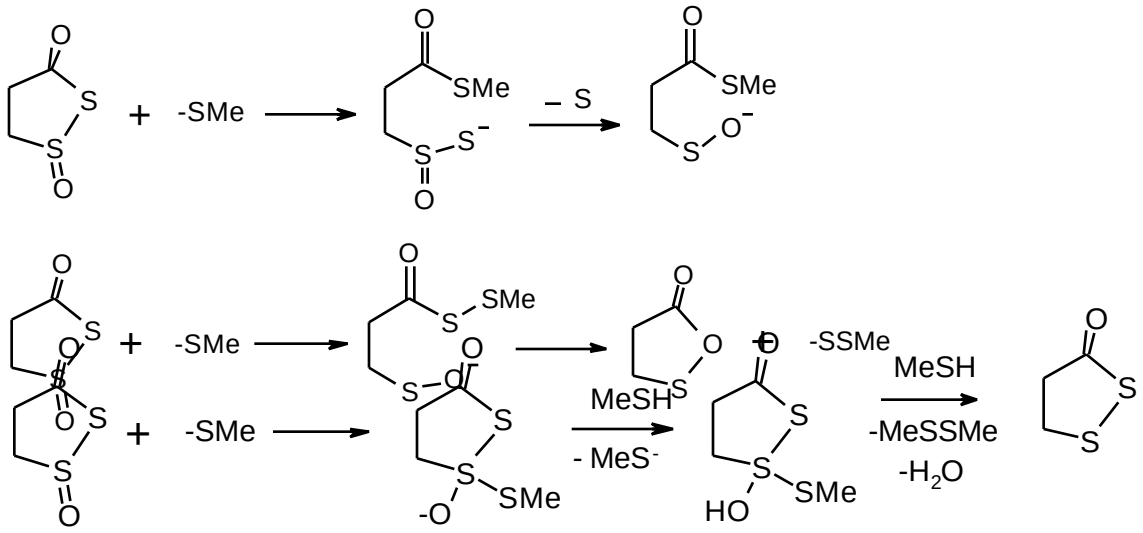
Goals and objectives

In order to obtain some quantitative data on reactions of 3 different nucleophiles (thiols, amines and alcohols) with all 3 electrophilic sites of 1,2-dithiolan-3-one 1-oxide heterocycle (sulfoxide and sulfinyl sulfurs and carbonyl carbon) we decided to investigate this system using computational methods. If the results of computations will confirm the observed reactivity patterns, they can provide an additional insight to the reactivity of this heterocycle. Initially these reactions will be modeled in the gas phase though inclusion of solvent model in calculations is possible at the later stage.

In this project we will focus on the nucleophile required for biological activity of leinamycin - thiol. The unsubstituted 1,2-dithiolan-3-one 1-oxide and methylthiolate anion will be used.

We think that assumptions that we made to reduce the size of the system wonít affect the results. It is known[6] that substituents don't have major influence on the reactivity of 1,2-dithiolan-3-one 1-oxides. Nature of thiol also doesnít seem to play any significant role in the reaction. Usage of thiolate anion instead of thiol is reasonable because in aprotic solvent thiols react with 1,2-dithiolan-3-one 1-oxides only in the presence of base.

Ab initio studies of nucleophilic substitutions were performed earlier on the variety of systems (see refs. 10, 11 for examples) and gave satisfactory results. Exact reactions that we are going to study in this project are presented below:



Proposed research

We decided to use RHF/3-21+G* level for geometry optimizations. In case of transition states, initial guess of geometry will be provided by finding transition state on PM3 level. This geometry will be further optimized on RHF/3-21+G* level. Frequencies for each optimized structure will be calculated on the same level of theory. Single point calculations will be performed on B3LYP/6-311+G** level using optimized geometries.

Our system is relatively large and floppy so small basis set and Hartree-Fock theory has to be used for geometry optimisation. Semiempirical methods don't perform well for transition states but can serve to provide an initial guess because they are extremely fast. Presence of negative charge forces us to include diffuse functions into the basis set. Inclusion of d orbitals, especially on S, is also useful. Note that in the optimization we include d orbitals only on S (3-21G* set). It helps to account for their possible participation in bonding and for high polarizability of S. Very large basis set in the single point calculation should increase accuracy of final energy without having major effect on overall computation time. Density functional theory (particularly B3LYP) is used because

it is known to produce good results within reasonable amount of computer time. Hartree-Fock methods don't perform satisfactory in the systems of this type (S-S and especially S=O bonds). MP4 should perform well but is extremely slow. MP2 generally performs somewhat worse than B3LYP and it's also somewhat slower (especially for large systems and large basis sets)[12].

The reactions that we are going to study in this project are presented above. From each of these reactions we need 2 pieces of data: 1) activation energy; 2) energy difference between reagents and products. In order to get this data we need to optimize geometry of all minima and transition states. Frequency calculation for every structure must also be performed and will provide us with ZPE and thermal corrections to energy. It will also confirm the identity of the structure. IRC calculations may be performed on some transition states to find the minima that they connect. PES scans may be also performed to help locate transition states.

After applying zero-point and thermal corrections, activation energies and reaction enthalpies will be used which reaction is preferred in this system. Low activation barrier and/or large gain in energy will serve as criteria for preferred reaction.

We are going to use Shiva (SGI Power Challenge L) for our computations. If somebody gives me a couple of thousands hours of computer time on Cray, I'll use it instead. But Shiva will work fine, too. PC will be too slow for this task (it will take at least several days to run the optimization).

Our estimate is that it will take 1-2 days to optimize every transition state structure on Shiva and 4-8 hours for a ground state. Single point calculations should take less than 8 hours each. IRC calculation may take a day or two. Given that we have about 10 transition states and 6 minima, a month will be a reasonable estimate.

Group actions

Most of this project was done by Leonid because it is related to his research. Lixin provided some advice and helped with illustrations. Group met a couple of times for about an hour.

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