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Ab Initio Investigation of the Fragmentation of 5,5-Diamino-Substituted 1,4,2-Oxathiazoles

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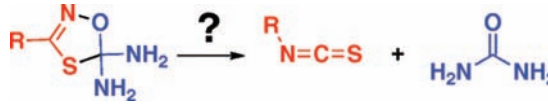
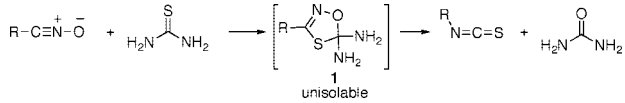
ABSTRACT



The mechanism for the fragmentation of 5,5-diamino-1,4,2-oxathiazole derivatives has been studied at the CCSD(T)/6-311+G(3df,2p)//MP2/6-31+G(2df,p) level of theory. The calculations suggest that the fragmentation occurs via a stepwise process involving the formation of polar intermediates that lie in shallow potential wells. We find a large thermodynamic driving force for fragmentation, which together with a weakening of the C−S bond through electron donation by the amino substituents provides the impetus for a low-barrier fragmentation.

The reactions of nitrile oxides with thiourea provide an efficient low-temperature route to the production of isothiocyanates and urea.[1] The reactions presumably proceed via transient 5,5-diamino-1,4,2-oxathiazole derivatives (e.g., **1**, Scheme 1), which are formed through a 1,3-dipolar cycloaddition reaction. This class of heterocycles could have use as prodrugs, as the isothiocyanates that are produced upon fragmentation are known to possess useful anticancer activities. These include the ability to inhibit the processes of carcinogenesis[2] and tumorigenesis[3] and advantageously do not appear to result in side effects typical of many currently used chemotherapeutic drugs. Furthermore, there is considerable evidence suggesting that urea and a number of its derivatives also possess useful biological activity.[4] The fact

Scheme 1. Isothiocyanate Preparation via the Formation and Decomposition of 5,5-Diamino-1,4,2-Oxathiazoles (**1**)



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that these molecules could give rise to dual biological activity may be an attractive feature in the treatment of a number of cancers. Unfortunately, to the best of our knowledge there exist no examples of such heterocycles that have been isolated under standard laboratory conditions, thus precluding investigations into their use as prodrugs.

Experimental studies suggest that the electronic nature of the migrating group (R) at the 3-position, i.e., whether it is electron-rich or electron-deficient, has little effect on the stability of the diamino-oxathiazoles.[5] However, the facile fragmentation of these diamino-substituted derivatives contrasts with the behavior of systems substituted by two alkyl (or aryl) substituents at the 5-position, in which case fragmentation temperatures in excess of 150 °C are required.[6] Indeed, a recently reported polymer-supported synthesis of isothiocyanates, based on the fragmentation of 1,4,2-oxathiazole derivatives bound to a polystyrene support, was found to require high-temperature thermolysis (in excess of 160 °C), although the temperature could be reduced somewhat through the use of a solvent with increased polarity.[7]

The observation that the presence of two amino groups lowers the temperature required to induce fragmentation to such an extent that the heterocycles are not isolable at room temperature is intriguing. Driven by a curiosity to rationalize these experimental findings, our initial interest has been focused on using high-level quantum chemistry computations to help unravel the mechanism by which the fragmentation of 5,5-diamino-1,4,2-oxathiazole derivatives occurs. To this end, fragmentation of the prototypical 5,5-diamino system **Oxa1** (Figure 1), in which migration of a methyl group occurs, i.e., **1** with R = CH_3, has been investigated. In addition, to put these results into context and to fully appreciate the effect of diamino-substitution at the C5-position, fragmentation of the corresponding 5,5-dimethyl system **Oxa2** has also been examined.

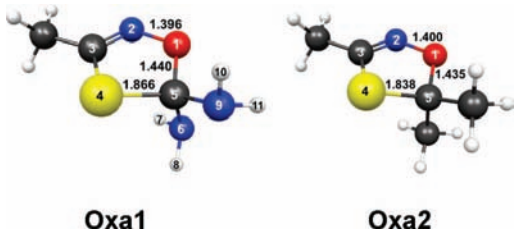

Figure 1. Global minimum structures of **Oxa1** and **Oxa2**.

To investigate the mechanism of the fragmentation, calculations have been performed at the CCSD(T)/6-311+G(3df,2p)//MP2/6-31+G(2df,p) level of theory.[8] Unless otherwise stated, all energies in this paper refer to free energies calculated at 298 K using zero-point vibrational energy and thermal corrections obtained from scaled[9] MP2/6-31+G(2df,p) harmonic vibrational frequency calculations. The vibrational frequencies were also used to characterize structures as equilibrium structures (all real frequencies) or transition structures (one imaginary frequency). Intrinsic reaction coordinate (IRC) calculations were used to confirm the two equilibrium structures to which each transition structure is linked. Finally, as the experimental studies of **Oxa1** have been performed in tetrahydrofuran (THF), corrections to energies and barriers using free energies of solvation (ΔG_{solv}) obtained at the HF/6-31+G(d) level with the IEFPCM model and UFF radii have been included where appropriate.

The global minimum structures of **Oxa1** and **Oxa2** are shown in Figure 1. There are no qualitative structural differences between the two heterocycles. Regarding the critical bond lengths, i.e., those bonds that need to be cleaved to produce the two products, it can be seen that the C−S bond length in **Oxa1** is calculated to be 1.866 Å, which is longer than the 1.838 Å calculated for **Oxa2**. This increase in bond length can be attributed to electron donation from the lone pair of the *axial* amino group into the C−S σ^* orbital, an interaction that is consistent with the results of natural bond orbital (NBO) calculations. A smaller increase in the C−O bond length in **Oxa1** relative to **Oxa2** is also observed, which is attributed in this case to electron donation from the lone pair of the *equatorial* amino group into the C−O σ^* orbital. There is also a small decrease of 0.004 Å in the O−N bond length of **Oxa1** compared with **Oxa2**.

We begin our energy considerations by noting that the thermodynamics for the formation and fragmentation of **Oxa1** and **Oxa2** suggest **Oxa1** to be relatively less stable than **Oxa2** (Figure 2). In this regard, *formation* of **Oxa1** is less thermodynamically favorable than **Oxa2** on account of the loss of the conjugative stabilization provided by the

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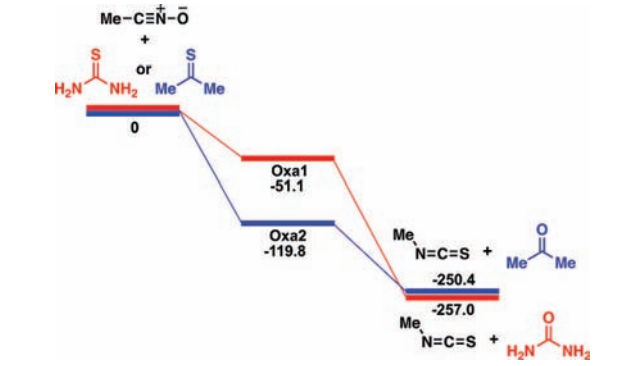

Figure 2. Gas-phase free energy profile for the formation and fragmentation of **Oxa1** and **Oxa2** (298 K, kJ mol^{-1}).

amino lone pairs in the thiourea reactant in the former case. On the other hand, *fragmentation* of **Oxa1** proceeds with an exothermicity significantly greater than that of **Oxa2**, a result that can be attributed to the formation of the conjugatively stabilized urea as a product in the former case. It is likely that this substantial thermodynamic driving force for the fragmentation of **Oxa1** provides, in part, an impetus for the greater facility by which fragmentation occurs.

Regarding the mechanism for fragmentation of **Oxa1**, it has been proposed that the reaction may proceed either via a concerted pathway or via a stepwise pathway involving the intermediacy of a thioacyl nitrene intermediate.[5,10] However, the barrier to the formation of the isothiocyanate via such a nitrene has been previously calculated using high-level ab initio methods to be in excess of 250 kJ mol^{-1}.[11] Such a barrier is clearly not compatible with a reaction that proceeds with great facility at room temperature.

We have not found evidence for a formally concerted mechanism in the course of the present investigation. However, two polar intermediate structures (**INT1** and **INT2**) lying in shallow wells were located that are formed as a result of cleavage of the C−S bond (Figures 4 and 5, respectively). The free energy profile for the fragmentation of **Oxa1** via such intermediates is shown in Figure 3.

Heterolysis of the C−S bond results in the formation of **INT1** (Figure 4), lying 41.1 kJ mol^{-1} higher in free energy

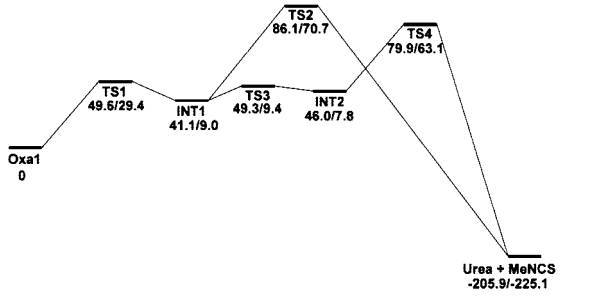

Figure 3. Free energy profile (gas-phase/THF, 298 K, kJ mol^{-1}) for the fragmentation of **Oxa1**.

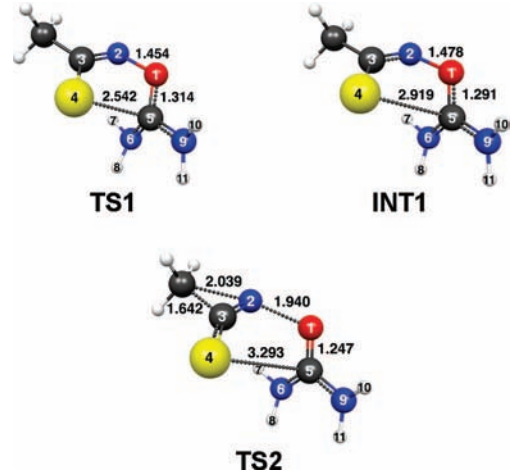

Figure 4. Fragmentation of **Oxa1** via **INT1**.

than **Oxa1** (Figure 3). This energy difference is reduced to just 9.0 kJ mol^{-1} in THF. We find that **INT1** can be obtained from **Oxa1** via **TS1** with a free energy barrier of 49.6 kJ mol^{-1}, which is reduced to 29.4 kJ mol^{-1} in THF. **INT1** has a substantially cleaved C−S bond, with a C···S distance of 2.919 Å, whereas the O−N distance is increased from 1.396 Å in **Oxa1** to 1.478 Å in **INT1**.

Fragmentation of **INT1** can occur in a direct manner through **TS2**, in which migration of the methyl substituent occurs with concomitant cleavage of the O−N bond. **TS2** lies 86.1 kJ mol^{-1} above **Oxa1** in the gas phase or 70.7 kJ mol^{-1} in THF (Figure 3).

The fragmentation pathway (Figure 3) can alternatively include a second intermediate **INT2** (Figure 5), which lies 4.9 kJ mol^{-1} higher in energy than **INT1**. However, when solvation corrections are included it becomes 1.2 kJ mol^{-1} lower in energy. This increased stabilization in THF can be attributed in part to the larger dipole moment of **INT2** (7.49

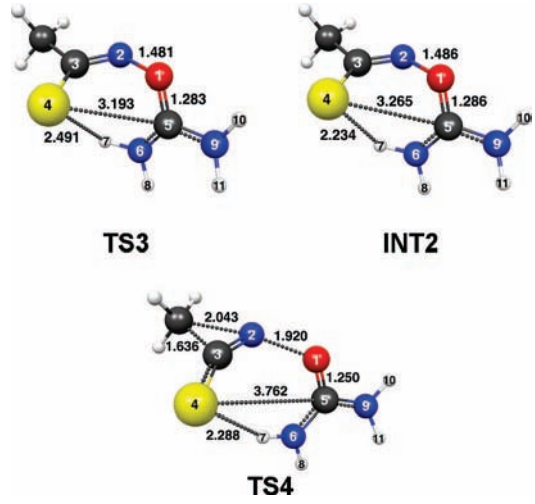

Figure 5. Fragmentation of **Oxa1** via **INT2**.

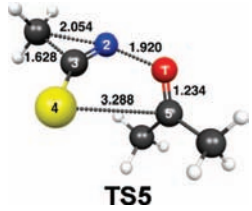

Figure 6. Fragmentation of **Oxa2** via **TS5**.

D) relative to that of **INT1** (6.14 D), though the main conclusion here is that this part of the potential energy surface is quite flat. We find that **INT2** may be obtained from **INT1** via **TS3** with a barrier of just 8.2 kJ mol^{-1}, which is reduced to just 0.4 kJ mol^{-1} in THF.

The C···S distance in **INT2** is increased substantially to 3.265 Å from that found in **INT1**. Hydrogen bonding between H(7) and S is observed, which results in an increase in the N(6)−H(7) bond length from 1.015 Å in **Oxa1** to 1.032 Å. Fragmentation of **INT2** can occur via **TS4**, which lies 79.9 kJ mol^{-1} higher than **Oxa1**, whereas in THF this energy is reduced to 63.1 kJ mol^{-1}. It can be seen that fragmentation via **TS4** provides a slightly lower free energy pathway, relative to direct fragmentation via **TS2** (Figure 3).

With these gas-phase and solution-phase free energy barriers in hand for the minimum energy pathway, approximate calculations using the Eyring−Polanyi equation suggest that the half-life of **Oxa1** is in the order of 1−10 s. Our proposed mechanism is thus consistent with the inability to isolate such structures under standard laboratory conditions.[1,5]

The influence of diamino-substitution can be put into context by considering the corresponding fragmentation of the dimethyl-substituted species **Oxa2**, which occurs via **TS5** (Figure 6). The key distinction between fragmentation of **Oxa1** via **TS2** and fragmentation of **Oxa2** via **TS5** is that the overall barrier in the latter case is much higher: 169.7 vs 86.1 kJ mol^{-1}. **TS5** actually resembles **TS2** quite closely, but we were unable to locate any intermediate analogous to **INT1** in this case. This can be attributed to the lack of an adequate stabilization of such an intermediate by the two methyl (as opposed to two amino) substituents. The overall barrier for fragmentation via **TS5** is reduced to 161.0 kJ mol^{-1} in THF, consistent with experimental solvent effect findings for the related 5,5-diaryl 1,4,2-oxathiazole systems.[7]

In summary, we can see that there is a large thermodynamic driving force associated with the fragmentation of **Oxa1** relative to **Oxa2**, with the former producing a significantly more stable carbonyl product: urea versus acetone. This results in a gas-phase exothermicity of 205.9 kJ mol^{-1} for the **Oxa1** fragmentation compared with 130.6 kJ mol^{-1} for **Oxa2**. In addition, electron donation from the axial amino substituent of **Oxa1** into the C−S σ^* orbital, which leads to a lengthening of this bond, can be expected to assist the fragmentation. Both these effects lead to **Oxa1** fragmenting via a significantly reduced barrier. Two pathways for the fragmentation of **Oxa1** have been identified, both involving polar intermediates. Solvation in THF is found to reduce the barriers associated with the fragmentation reactions of both **Oxa1** and **Oxa2**, consistent with experimental findings.

Looking further ahead, it is possible that appropriately substituted amino groups in which the electron-donating capacity of the amino substituent(s) is reduced could lead to a larger barrier for the fragmentation process and result in isolable structures. To that end, investigations are currently under way to investigate the influence of amino-group substitution on fragmentation barriers. This may lead to the identification of structures that could be isolated under standard laboratory conditions.

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Supporting Information Available: MP2/6-31+G(2df,p)-optimized geometries of all structures in Cartesian coordinates and CCSD(T)/6-311+G(3df,2p)//MP2/6-31+G(2df,p) energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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