Ab initial Investigation of Intermediate Dissociation Modes in Nitrosation of Imidazoline and Oxazoline

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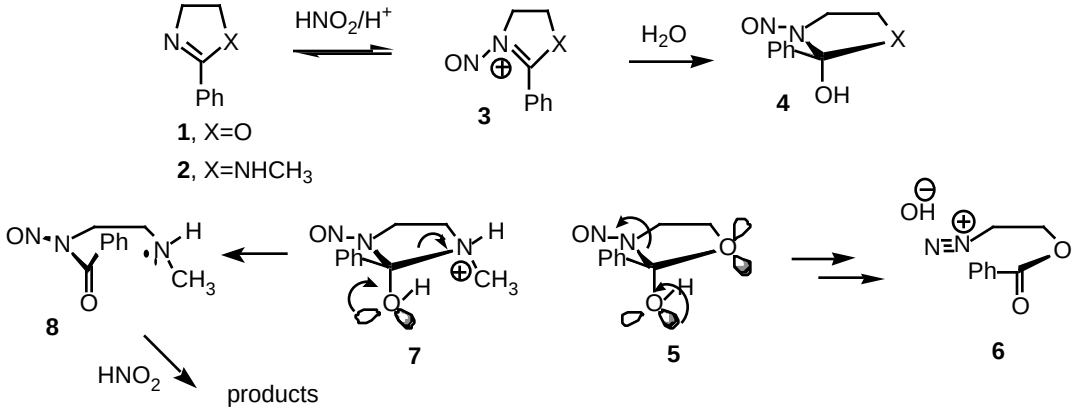
Introduction

One of our research goals is to identify structural features of consumed or natural compounds which have high reactivity toward nitrosating agents. We have found oxazoline **1** and imidazoline **2** react very rapidly with sodium nitrite in glycial acetic acid at ambient temperature.[1]

Through analysis of the reaction products, we found nitrosation of **1** and **2** involving different pathways. The key steps in our proposed mechanisms are shown below.



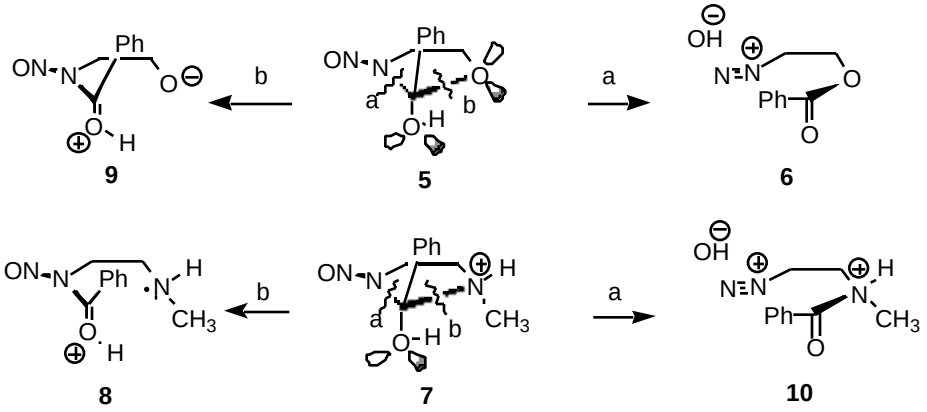
Scheme1. Mechanism for nitrosation of oxazoline and imidazoline

Either **1** or **2** generates nitroimminium ion **3** in nitrosating conditions. Addition of **3** by water will form the tetrahedral intermediate **4**. When X = O and $NHCH_3$, **4** is shown as **5** and **7** respectively. The factors controlling the bond cleavage modes in **5** and **7** may contribute to: 1) the nature of leaving group; 2) stereoelectronic factors. In case of **5**, unshared pairs (the darker) from both the ring O and the OH can be oriented anti-periplanar to the C-N bond and facilitate its breaking; so cleavage of C-N bond and thereafter isomerization gives dizonium ion **6**. In case of **7**, however, products are formed from cleaving the bond of C and CH_3 bearing N in intermediate **7**. Since the stereoelectronic effects on bonds of C-N(CH_3) and C-N(NO) are almost equal, we contribute the bond cleavage preference of C-N(CH_3) to that the methyl ammonium ion must be a better leaving group than N(R)NO.

In this proposal, we seek to verify the nitrosation mechanism of **1** and **2** from computational point of view. Once the calculation results are consistent with our mechanism, where N(R)NO as a leaving group is ranked could be estimated.

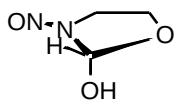
Goals and Objectives Section

Both of the intermediate **5** and **7** have two possible dissociation pathways shown as below.

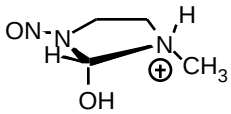


Scheme 2. Two pathways for nitrosation reactions

Cleavage of bond **a** produces a dizonium ion (**6** or **10**), whereas scission of bond **b** gives a nitrosoamide (**8** or **9**). Our major goals in this proposal are pursuing evidence from ab initio calculations in support energetically that 1) Cleavage of bond **a** is major pathway in case of **5**; 2) bond **b** cleaves dominantly in case of **7**. Presumably these bond dissociation is irreversible. The key issue for achieving the goal is to compare the activation energies E_a for pathway **a** and **b** in both cases. Since the complexity of nitrosation reaction cause the kinetic data can not be fit into any order of reaction, theoretical calculation is the only way to achieve our goal.



11



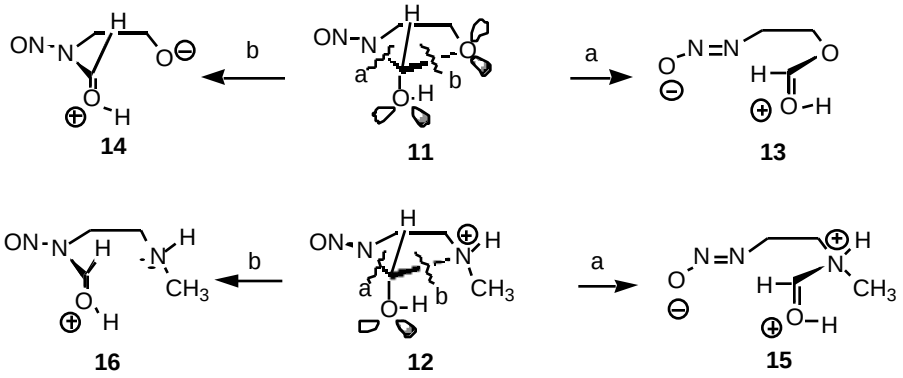
12

Simpler model species **11** and **12** are chosen for studying in the gas-phase and in solution. The gas-phase reaction potential energy surfaces for dissociation of **11** and **12** via either **a** pathway or **b** pathway to corresponding products are going to be determined by using ab initio molecular orbital calculations. To simulate the real nitrosation reaction, the influence of solvation will also be taken into account.

Proposed Research Section

Methodology:

Hartree-Fock theory is good at computing geometry of molecules. To save CPU time, full geometry optimizations at RHF/3-21G level will be performed for the ring intermediates **11**, **12**, open-ring intermediates **13**, **14**, **15**, **16,** and transition states.



Scheme 3. Postulated intermediates for the two gas-phase reactions

However, Hartree-Fock theory is insufficient for accurate modeling of the energetics of reactions and bond dissocition.[2] Usually running a high-level single point energy calculation at a geometry computed with a cheaper method is as good as performing all calculations at the higher level of theroy.[2] So energies will be evaluated with B3LYP hybrid functional[3,4] with the 6-31+G* basis set in Gaussian94.[5] This is one of the most accurate methods. The average error for B3LYP/6-31+G*// RHF/3-21G is about 8.0 kcal/mol.[2] ZPE (zero point energy) will be calculated B3LYP/6-31+G* level.

Solvation effect of glycial acetic acid will be estimated for gas-phase using the continuum solvation method PCM/DIR, developed by Tomasi and coworkers,[6] with the B3LYP/6-31+G* wave function. This continum solvation model includes not only electrostatic but also cavitation effects, generally yield accurate results for the free energy of solvation.[7]

Scope:

Stationary points for 6 ground states and 4 transition states will be calculated at B3LYP/6-31+G*// RHF/3-21G level. ZPE calculations will be done for all these 10 structures. Then the energies of all the stationary points will be corrected with their ZPE via equation $E_0 = E_{elec} + ZPE$. Solvation contributions of glycial acetic acid for all 10 stationary points will also be calculated. The energy will be expressed as equation $E = E_0 + E_{sol}$

Interpretation:

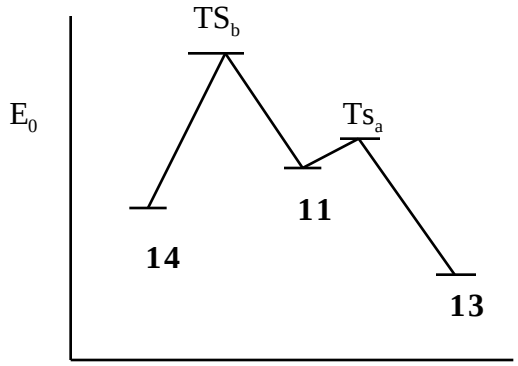


Figure 1. Assumed gas-phase reaction of **11** energy profile

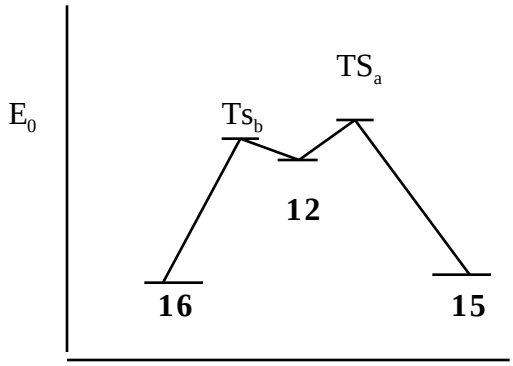


Figure 2. Assumed gas-phase reaction of **12** energy profile.

Once all these calculations described above are done, the energy profiles in gas-phase reactions will be plotted like **Figure 1** and **2**. Energy profiles containing solvation effect may be obtained similarly. In **Figure 1**, if E_0 (TS_a) < E_0 (TS_b), the energy barrier for pathway **a** is lower than that of pathway **b**, so bond **a** will cleave. In **Figure 2**, if E_0 (TS_a) > E_0 (TS_b), the pathway b is dominated. The results expected above are consistent with our experimental results.

Energy profiles containing solvation effect are expected to be similar to **Figure 1** and **2**. They are more reliable to verify our nitrosation mechanisms.

Facilities and feasibility:

All these calculation will be done on Supercluster computer on MU compus by shiva account (SGI power challenge) .

Timeline:

Gas phase reaction:

we need to compute 6 ground state energies and 4 transition state energies for two gas phase reactions. Structure **12** was slected to test calculation time. Geometry optimization of **12** with 3-21G basis set requires 46.3 minutes CPU time. For this optimized structure, the single point energy computated by B3LYP/6-31+G* requires 12.1 minutes. So the estimated CPU time for each ground state requires about 1 hour. The CPU time for locating transition state is approximately 4 or 5 times more than that of ground states. Based on this, CPU time for each transition state is about 5 hours. Totally, we need 6 hours CPU time for ground states and 20 hours CPU time for transition states.

We still need to compute the zero point energy of each ground states and transition states. This requires another 26 hours CPU time.

We assign six days for gas phase reaction.

	1	2	3	4	5	6
Daytime	3 ground states	3 ground states	one transition states	ZPE of 3 ground states	ZPE of 3 ground states	ZPE of one transition state
Overnight	one transition states	one transition states	one transition states	ZPE of one transition state	ZPE of one transition state	ZPE of one transition state

Solvent Effect:

Energy of ground states and transition with solvent effect will also be computed in 6 days.

By this assumption, the whole project will take 3-4 weeks for computation and data interpretation. If we put several jobs to the queue at the same time and do it by two persons, this project could be finished in two weeks.

References

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Group Action and Dynamics:

We have group meeting twice a week in GC-MS room or in our lab. One is on Friday afternoon, the other is on Monday morning after class. Each meeting lasted from 40 minutes to one hour.

Working in a group for this project was really a positive experience. we can help each other for the difficult point in computational chemistry. Since we are students of organic chemistry, lots of concepts in quantum chemistry are not familiar to us at the beginning. By forming a group, we can help each other to understand these concepts which are essential to project #2. Another advantage is that we can search large amount of source to get a appropriate topic. We have looked through about 20 papers in two journals (journal of the American Chemical Society, journal of organic chemistry) in order to find an interesting topic which is related to our research project. However, we considered a topic related to our own research may be interesting. At this time, Wenge has some experimental data published in Tetrahedron Letters. In that paper, the explanation for the nitrosation pathways came only from analysis of products. The unpublished kinetic study results indicat those two nitrosation reactions can not be fit into any order of reaction. This reminds us why not interpret the reaction pathway by computational chemistry. So we decide to work on this topic for project #2.

By working on this project, we learn lots of theory beyond the course 433. For example, how to select an appropriate basis set and how to calculate the solvent effect. Both of us benefited from cooperation in this project. Also, our further study on computational chemistry may start from this point. We hope we can engage in this kind of activities again.