Reaction Mechanism study of Cyanide Catalyzed Synthesis of Benzoxazole using Reaction IR Spectroscopy

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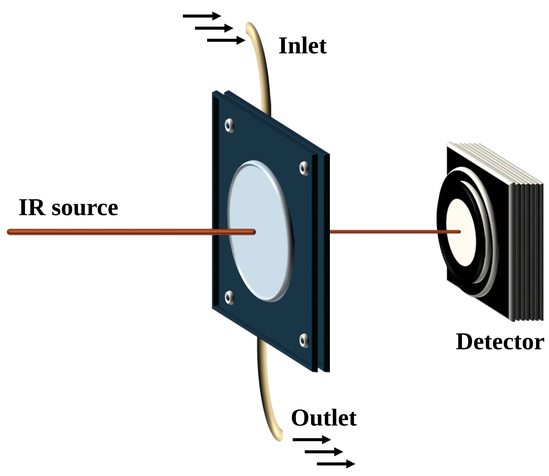
Abstract

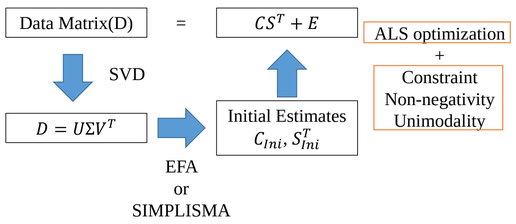
Benzofused heteroaromatic compounds are used as building blocks for therapeutically active compounds, natural products, and functional materials. Prof. Cheon's group in Korea University successfully developed the methods for the synthesis of benzofused heteroaromatic compound using cyanide catalyst.1 They proposed the reaction mechanism which utilized the 5-exo-tet cyclization by Baldwin's rule and aerobic oxidation. However, Prof. Yu's group recently proposed different mechanism of the reaction based on the computational method.2 They suggested that the reaction will go through stepwise oxidative dehydrogenation and cyclization. To resolve this controversy, we kept track of the real–time variation of IR spectrum from reactant, various intermediates, and product using the home-built reaction IR spectroscopy. With the help of Multi Curve Resolution-Alternating Least Square method, the kinetics of each compound including intermediates are resolved, which enabled us to investigate the reaction mechanism of cyanide catalyzed synthesis of benzoxazole.

Introduction

1. Flow type Reaction IR Cell

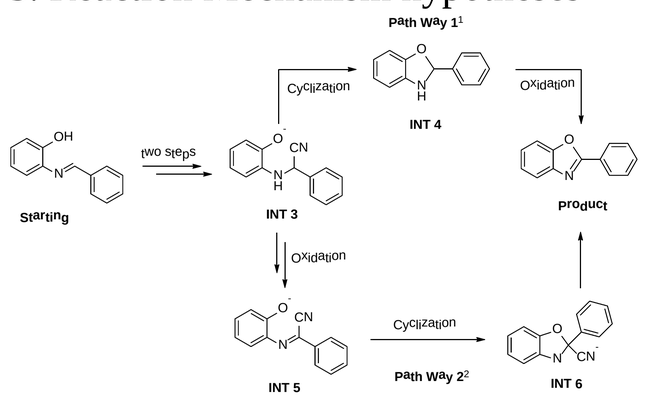


2. MCR-ALS method



SVD : Singular Value Decomposition
EFA : Evolving Factor Analysis
ALS : Alternating Least Square
$\chi = \xi c$ (ξ; *molecular specific coefficient*)
$A = \varepsilon bc$ (*Beer-Lambert Law*)

3. Reaction Mechanism hypotheses



[1] Y. H. Cho, et. al. *Adv. Synth. Catal.*, 2012, 354, 2992-2996
[2] W. Chen, et. al. *J. Org. Chem.*, 2016, 81, 10857–10862

Computational Method

All the computations reported in this work were carried out using **Gaussian 09** program package. All structures were optimized using the **M06-2X** functional method with **6-31+G(d)** basis level. The **UM06-2X** functional method was used for the molecules that has doublet and triplet spin states structures as oxygen (O_2) molecule, and radical intermediate states. Frequency calculations were implemented at the same functional to confirm the optimized structures but the basis set was used higher level, as **6-311++G(3df,2pd)**. Solvation model was implemented **CPCM model** with **DMF** solvent(ε=36.7) All the spectroscopic intensity in this work are reported in atomic unit (a.u.), and peak position are scaled by 0.943.

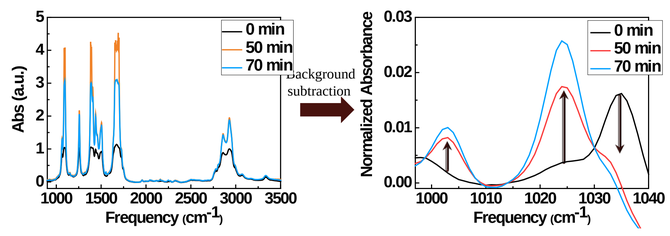
Experimental Method

Experiment was performed in the same condition which was performed previously by Y. H. Cho, et. al. in Korea University[3]. An open test tube were added a **phenolic imine (0.25 mmol: 1.0 equiv)** and **NaCN (12.2 mg; 0.25 mmol; 100 mol%)** were dissolved in **DMF** (1.0 mL). The reaction mixture was stirred at room temperature in an open flask and monitored by FT-IR every 5 min. The complete termination of the reaction was convinced by the peak of the product in the FT-IR. We tried the MCR-ALS analysis to obtain a time profile of reaction components.

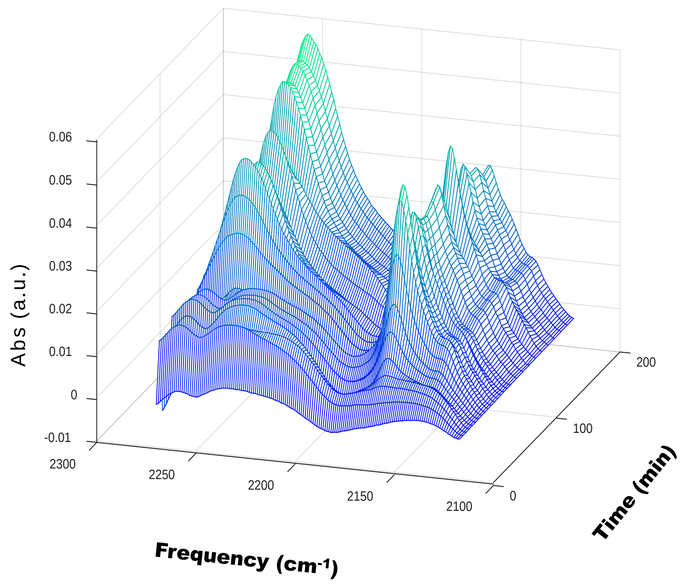
[4] Y. H. Cho, et. al. *Adv. Synth. Catal.*, 2012, 354, 2992-2996

Results

1. Reaction IR Spectra

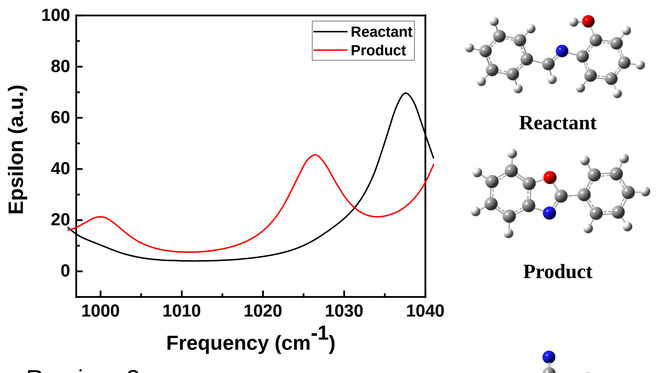


Vibrational Probe
Region 1: 1000~1040 cm^{-1} reactant and product (aromatic C-H bending modes)
Region 2: 2000~2300 cm^{-1} intermediate molecules (-C≡N stretching modes)

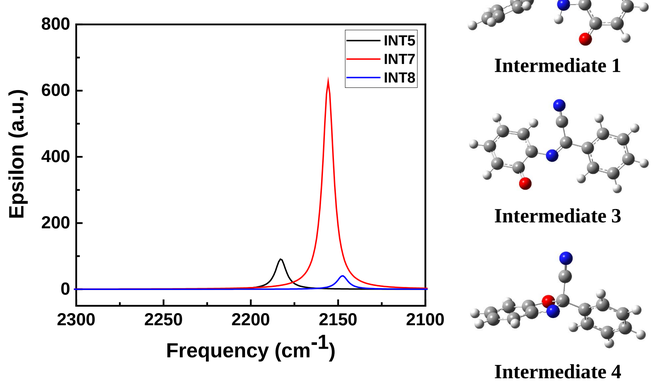


2. Quantum Calculations`

Region 1



Region 2



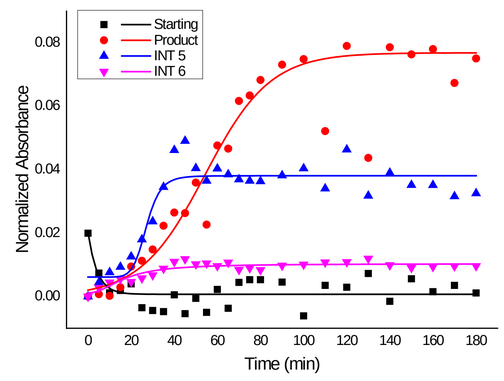
3. Mode Assign of Experimental Data

Molecule	Calulation (cm^{-1})	Peak Postion (cm^{-1})	Vibrational Mode
Reactant	1038	1035	Aromatic C-H bending
Intermediate 3	2183	~2200	-C≡N stretching
Intermediate 5	2157	2160	-C≡N stretching
Intermediate 6	2147	2150	-C≡N stretching
Product	1000	1003	Aromatic C-H bending
Product	1026	1024	Aromatic C-H bending

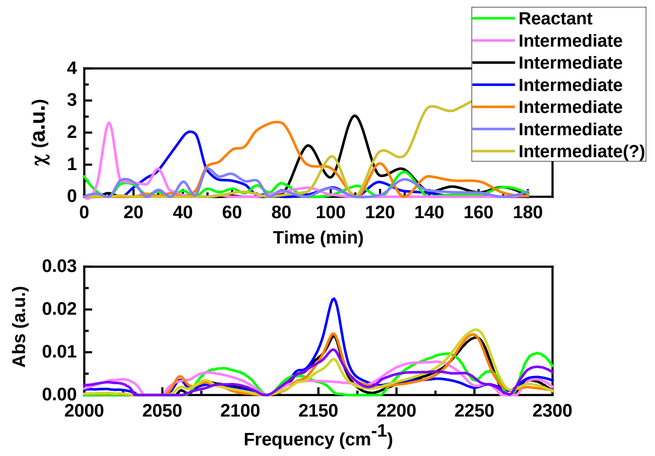
*** Scaling factor**: calculated peak position × 0.943
* molecules are estimated.

Discussions

1. Time profile of Reaction components

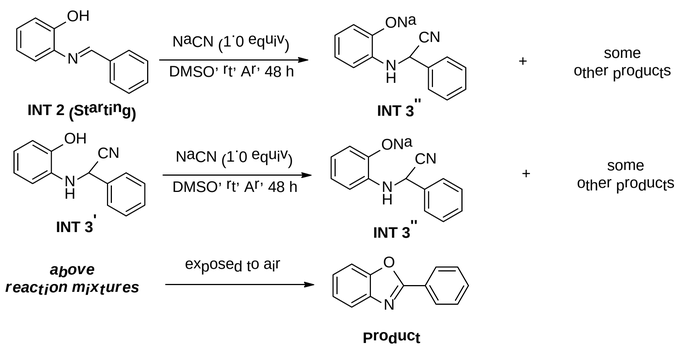


Without knowing the shapes of the spectra and the concentration profile, we can decompose the spectroscopic data into the spectra and the concentration profile by using MCR-ALS. Since during the reaction the acquisition of concentration profile is hard, this method will suggest a new way to obtain the concentration information of reaction components. By using this concentration data, we could find the clues to the mechanism.



2. Analysis of the results

Computational result about path way 2 and IR result almost perfectly coincide with each other. Besides, IR results shows that there are at least 3 CN stretching mode which can not be explained by the path way 1. Even after the reaction, it is able to observe the peak from the intermediate which could be understand by there are some kind of equilibrium between product and intermediate. If product and intermediate are in equilibrium, the final step should be obviously reversible which is irreversible step in path way 1. All of the result are more reasonable to explain by the path way 2.



[4] Y. H. Cho et. al. *Tetrahedron..*, 2013, 69, 6565–6573

Under argon atmosphere, reaction stopped at INT 3'' and when reaction mixtures were exposed to air, benzoxazoles were formed. This can be explained by path way 2. That is under argon atmosphere, reaction is unable to process the oxidation step so that reaction stopped at INT 3.

Conc. & Ack.

Conclusion

It was possible to trace the reaction components through above time profile and decomposed IR spectrum. Reaction IR spectroscopy, quantum chemical calculation, and MCR-ALS analysis can provide hints of reaction mechanism.

Acknowledgement

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