論文の内容の要旨

論文題目： Studies on Utilization of Unique Properties and Reactivities of Azulene Derivatives
（アズレン誘導体のユニークな物性と反応性の利用に関する研究）

氏名： ジン ユウ

Azulene (AZ) is a ten carbon, non-alternant, aromatic hydrocarbon, comprising a fused 5,7-bicyclic system. This compound has been attracted chemists due to its blue color and a high dipole moment of 1.08 D. The latter character is attributable to one electron transfer from the seven-membered ring to the five-membered one resulting in 6π aromatization of each ring. As a consequence, the five membered ring of AZ has cyclopentadienyl-anion-like character and the seven membered ring is tropylium cation. Interestingly, this molecular skeleton is also found in nature as a sesquiterpene compound guaiazulene (GA), or 1,4-dimethyl-7-isopropylazulene. AZ and its derivatives have high reactivity toward various electrophiles. Because HOMO of AZ has the large coefficient at the 1- and 3-positions, electrophilic aromatic substitution of AZ occurs at these sites. In addition, this compound also undergoes metal catalyzed C-H activation exclusively at 2-positon, which enables the synthesis of various 2-substituted azulenes. Due to highly polarized character of AZ, this compound also shows very high 1-methyl-cation-stabilizing effect. AZ and its derivatives have been applied in diverse area including pharmaceuticals, photo- or electrofunctional materials. However, application of AZ-derivatives utilizing its reactivity is quite limited.

In Chapter 1, general introduction of the thesis is given. It includes a basic properties/reactivities of AZ, and an application of AZ-containing molecules/polymers as functional materials.

In Chapter 2, a peptide library screening method utilizing reactivity and colored nature of AZ derivatives was mentioned. Peptide catalysts represents a unique class of catalyst but it is difficult to find a good peptide catalyst because of large number of possible sequences. In order to overcome such a problem, a peptide library screening method has been developed. However, this methodology was limited to a specific reaction. Based on this background, I tried to utilize AZ as reactive and visualizing unit for peptide library screening. After trying several reaction systems, I finally found that azulene-2-ylboronic acid behaves as catalyst activity marker for the Michael reaction to 4-hydroxybut-2-enal. This reaction could be applied to the library screening of resin-bound 7-residue random peptide of which N-terminal was fixed to D-Pro. Some resin beads turned blue upon mixing with reagents, and the peptides bound on those beads could be cleaved from the resin and analyzed by MS/MS. Several consensus sequence were found in the catalytically active peptides.

In Chapter 3, a facile reaction between guaiazulene-3-methanol derivatives and thiols was introduced. In the studies of Chapter 2, it was noticed that guaiazulene-3-methanol was highly reactive to nucleophilic GA. Accordingly, its reactivity was tested with mixing other types of nucleophiles. Among all of those tested nucleophiles, guaiazulene-3-methanol only reacted with thiols spontaneously under room temperature. This thiol-preference can be explained by weak acidity and high nucleophilicity of thiols. The reactivity was not affected by substituents on GA-derived alcohol, but depended on types of thiols.

As the color of GA-derived alcohol was blue, this led the further application of this reaction on detection of biothiols. By mixing guaiazulene-3-methanol and Ac-Cys-OH, the reaction proceeded spontaneously and completed in 5 min to give the thiol-labelled product in 89% yield. Accordingly, the guaiazulene-3-methanol was used as a labelling agent to achieve the naked-eye visualizations of biothiols including amino acids, peptides and proteins on filter paper. When GSH was employed as a test molecule, semi-quantitative nature of this staining could be confirmed.

From other viewpoint, this reaction is considered to be a protection of thiol group. Through screening of various deprotecting agents, it was noticed that the removal of the S-bound azulenylmethyl group can be realized by the treatment with tris(2-carboxyethyl)phosphine (TCEP) in MeOH. *S*-azulenylmethyl-protected cysteine was useful for the solution phase synthesis of peptides because the peptide containing such unit is blue and this made the chromatographic separation of the product easier. A demonstrating experiment utilizing such an advantageous character of the labelled Cys was carried out. Orthogonally protected two Cys were connected to give a dipeptide. First deprotection with dithiothreitol (DTT) successfully underwent disulfide bond cleavage, and the subsequent treatment with TCEP gave fully protected dipeptide.

In Chapter 4, synthesis and successful isolation of calix[5]azulene was discussed. During the studies mentioned in previous chapters, I had happened to find that the GA works as not only a nucleophile, but also as a leaving group. Treatment of bis(guaiazulen-3-yl)methane with 4-methoxybenzenethiol in the presence of TFA resulted in the substitution of GA by the thiol. Changing the nucleophile into bi-nucleophilic AZ, it is expected to form linear polymer containing AZ part in the main chain. A polymer with alternating 1,3-azulenediyl and methylene units should have an intermediate rigidity and is expected to show unique properties, but such a polymer has not been reported so far.

Firstly, I tried a polymerization using bis(guaiazulen-3-yl)methane and AZ in the presence of TFA. From the analysis of the product, it was supposed that 3 to 8-mer having GA in one terminus was mainly formed. Besides them, cyclic tetramer (calix[4]azulene) and pentamer (calix[5]azulene) were also observed in a 40:60 ratio. To date, synthesis of such calixazulenes has been reported starting from azulene and formaldehyde. In that case, only calix[4]azulene could be isolated. Then I focused on the synthesis and isolation of calix[5]azulene. This was achieved with using H_2SO_4 as a catalyst in xylene, where the pentamer was formed as a main product. The desired pentamer was successfully isolated by repetitive washing with chloroform.

In Chapter 5, the summary and the perspective were given. Throughout this thesis, I am expecting broaden understanding of AZ chemistry and its applications in diverse area.