

博士論文の要旨

専攻名 **Department of Science and Advanced Technology**

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博士論文題名 **Applications of Cucurbiturils for Supramolecular Catalysis in Organic Chemistry**

(超分子触媒ククルビットウリルの有機化学への応用に関する研究)

要旨 (2, 000字程度にまとめること。)

Cucurbit[n]uril (Q[n], n=5~8 or 10) is a family of cage-like host molecules oligomerized between glycoluril and formaldehyde, and the enclosed hydrophobic cavity, with two identical portal regions laced by carbonyl oxygen, is always able to bond non-covalently to organic and inorganic guests with weak ion-dipole, hydrogen binding, hydrophobic or hydrophilic properties. Depending on the host-guest chemistry, cucurbituril-induced supramolecular catalysis has made a significant contribution to organic synthesis including photodimerization, hydrolysis, and oxidation so on.

The cucurbit[8]uril-catalytic oxidation of alcohols by IBX (*o*-iodoxybenzoic acid) has been explored in pioneering work, but the mechanism was unclear. To get the foundation information of this supramolecular catalysis, veratryl alcohol was employed as a model substrate, which was the first case subjected to this catalytic oxidation, to investigate the host-guest interaction with Q[8]. The evidences of both fluorescence spectrometry and electrochemical analysis suggested a ternary complex formed between IBX, veratryl alcohol and Q[8] in a molar ratio of 1 : 1 : 1. Quantum chemistry was

carried out according to above experimental results, and revealed the presence of Q[8] was in favor of the formation of the iodoester intermediate in the process of IBX oxidizing veratryl alcohol due to the encapsulation in the cavity of Q[8]. Two series of aryl alcohol substrates, 2,3,4-methoxybenzyl alcohol and 2,3,4-pyridinemethanol hydrochlorides, were subjected to this Q[8]-catalytic oxidation, and the results of kinetic and thermodynamic analysis revealed that the electronic property of the substituent affected significantly the supramolecular catalysis, that is, the conversion of aryl alcohol was seriously dependent on substituent structure of substrate, which indicated that electron distribution on the α -carbon was mechanistically connected to the IBX oxidation procedure. In the absence of Q[8], the α -carbon could be stabilized by with conjugated electron-rich substituent and easily oxidized, while the presence of Q[8] improved the oxidation of alcohols with negative inductive effect substituent.

The applications of cucurbituril family have been limited in aqueous solution due to their insolubility in any organic solvent. The appearance of hemicucurbit[n, n = 6 or 12]uril (HemiQ[n]) and their unique solubility in chloroform or alcohol afforded a new opportunity to develop the platform of the supramolecular chemistry of cucurbiturils, sequentially, a few applications of HemiQ[n] for supramolecular catalysis have been developed.

The chemo-selective oxidation of bifunctional substrates *via* a supramolecular strategy was achieved. IBX oxidation of hydroxybenzyl alcohols produced the corresponding aldehyde and quinones, while the presence of HemiQ[6] was able to restrain the IBX oxidation of phenolic hydroxyl groups to afford the aldehyde as the only product. 2,3,4-Hydroxybenzyl alcohols are a kind of bifunctional substrates

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embracing synchronously phenolic and alcoholic hydroxyl groups, both which could be carried out the IBX oxidation to provide a mixture of both aldehyde and quinone products. With the participation of 50 mol% hemicucurbit[6]uril, phenolic hydroxyl groups were able to be protected against oxidation by IBX to realize the chemo-selective oxidation reaction, and the corresponding aldehydes were observed as the only product species. The conversion and reaction rates were greatly affected by the structures of substrates, and the stereo effect and electronic effect played very important role in this selective oxidation system. The kinetics in the presence of HemiQ[6] revealed that the oxidation depended on both the steric effects and electronic effects of the substrates, namely, the reactivity of 2-hydroxyl alcohol was thermodynamically the lowest, as the two hydroxyl groups were very close to each other. The oxidation of 3-hydroxybenzyl alcohol was faster than the others as the result of inductive effect of its phenolic hydroxyl group.

Various spectroscopies, including ^1H NMR, IR, and UV-vis were employed to confirm the formation of 1 : 1 host-guest interactions of HemiQ[6] with hydroxybenzyl alcohols, which were stabilized by the formation of hydrogen bonds between HemiQ[6] and the benzyl alcohol guests through the binding of active hydrogen by the macrocyclic compound. And the host-guest interactions were also evaluated by calculation chemistry, and the results afforded the

exclusion complexes of HemiQ[6] with 2,3,4-hydroxybenzyl alcohols in the ratio of 1 : 1, respectively. The calculated binding energies were sequentially consistent with the association constants fitted by UV-vis titrations. The energy-minimized optimization suggested the host-guest interactions were stabilized by the formation of hydrogen bonding between the carbonyl groups on the macrocycle and the phenolic hydroxyl groups on substrates.

The esterification of carboxylic compounds in the presence of hemicucurbit[6]uril *via* a supramolecular strategy was discovered. Esterification of the model substrate MA (4-methoxy-4-oxobut-2-enoic acid) in the presence of different amounts of HemiQ[6] (0.5, 1.0, and 2.0 equiv., respectively) had reaction rate constants of $k_{0.5} = 0.18 \text{ h}^{-1}$, $k_{1.0} = 0.36 \text{ h}^{-1}$ and $k_{2.0} = 0.52 \text{ h}^{-1}$. These results confirmed that the reaction rate increased with the ratio of catalyst to substrate. Ineffective catalysis of MA esterification with a stoichiometric amount of CH_3OH suggested that the essence for the HemiQ[6]-catalyzed reaction was solvolysis. Compare the kinetics of substrate MA with AA (acrylic acid) and BA (benzoic acid) shown that the catalytic activities should bear relation to the dimension of substrates. The different conversion of sorts of substrates in the presence of HemiQ[6] revealed that the supramolecular catalysis was favor in the conjugated structures. The inefficacy of HemiQ[12] demonstrated that the catalytic capability depended on the structure of the macrocyclic compound used.

A novel aerobic oxidation system catalyzed by HemiQ[6] in water was explored. The aerobic oxidation of furan in aqueous solution in the presence of HemiQ[6] to produce furan-2,5-diol, which was stabilized by encapsulation of HemiQ[6], which could be transformed to the dione confirmation in acidic

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solution and escaped from the macrocyclic compound. The ^1H NMR titration experiments of the host-guest interaction at different pH values suggested protonation should improve the encapsulation, and therefore a unique property that HemiQ[6] can be protonated was revealed. The oxidizing kinetics suggested that the procedure was a consecutive reaction with a series of constants $k_1 = 2.9 \times 10^{-2} \text{ min}^{-1}$, $k_2 = 2.7 \times 10^{-2} \text{ min}^{-1}$, and $k_3 = 5.7 \times 10^{-3} \text{ min}^{-1}$, respectively. The kinetic investigation at $\text{pD} = 2.0$ indicated the HemiQ[6]-catalytic oxidation of furan could be accelerated by acidification of solution. As a consequence, a plausible mechanism was established on the above evidences, which was supported by the calculation results of quantum chemistry. 2-Methylfuran was employed to give the product 2-methylfuran-5-ol exhibiting a satisfied activity in this aerobic oxidation with the supramolecular catalysis of HemiQ[6], but the oxidation of thiophene was very slow in either neutral or acidic condition.

In summary, a few supramolecular catalysis systems of cucurbiturils were developed, and afforded new applications in cucurbituril chemistry. The investigations on host-guest interaction between IBX, veratryl alcohol and Q[8], as well as IBX oxidation of aryl alcohols in the presence of cucurbit[8]uril, provided fundamental evidences to establish the mechanism of Q[8]-improved oxidation. The application of hemicucurbit[6]uril for IBX oxidation of hydroxylbenzyl alcohols realized a chemo-selective

reaction. HemiQ[6]-induced esterification offered an alternative manner to produce ester without participation by any acid. The protonation of HemiQ[6] can catalyze the aerobic oxidation of heterocyclic compounds.