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Short Communication

Rapid regio- and enantioselectivities and kinetic resolution of DL-lysine by an effective supramolecular system in water☆

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ABSTRACT

Herein we reported an example of chiral recognition, regioselective and kinetic resolution of DL-lysine by supramolecular interactions in aqueous solution of β-cyclodextrin. High regio- (>99%) and enantioselectivies (>99%) are achieved in a short time (<10 min) under mild conditions.

1. Introduction

Selectivity and velocity are the critical issues in the chemical reaction. In order to observe high selectivity and velocity, many methods like harsh conditions (relative high or low temperature), extra reagents, and complicated steps are applied [1–4]. Among all the methods, catalyst is one of the most common ways to achieve high selectivity and velocity. But very few catalysts can realize high selectivity (region and enantio) and velocity at the same time. In human body, high selectivity (region and enantio) and velocity can be achieved in the presence of enzyme. No harsh conditions are needed in the process. To mimic the function of enzyme is still a goal for the chemists. Supramolecular chemistry, which focuses on van der Waals' force, hydrogen bond, and other reversible bonds, has attracted more attention [5–9]. A broad range of organic chemistry subdisciplines has been affected by the principles of supramolecular chemistry. The interplay of multiple intermolecular interactions is the key point of molecular recognition and self-assembly processes [10]. The concept like hydrogen bond donors has been used in the organocatalyst design with increasing sophistication [11–16]. Furthermore, enzymes are considered as the best-understood catalyst system involving hydrogen bonding at this stage [17].

In supramolecular chemistry, the inner hydrogen bonds in the cavity of cyclodextrins (CDs) make CDs unique materials compared with other aromatic rings (Fig. 1) [18]. These hydrogen bonds are the critical forces in the hydrophobic molecules in polar solvents. The weak interactions can generate significantly different results in chemical reactions [19]. CD is a class of α-1,4-linked cyclic oligosaccharides, can be divided into α-, β-, γ-CD, according to the repeating glucose unit numbers, six, seven and eight, respectively [20,21]. β-CD, with a hydrophobic cavity and hydrophilic outside surface, is widely used as the host molecule in supramolecular chemistry for its low price, water-solubility and biocompatibility. CDs and their derivatives had attracted much interest in the enzyme mimics [22–24].

Very recently, Akashi et al. reported the first example of chiral recognition and kinetic resolution of aromatic amine guests using supramolecular nanocapsules assembled from CD derivatives in nonpolar media [25]. For the limit reports on chiral recognition [26–28] and enantioselective reactions [29] with supramolecular chiral nanocapsules, this observation is remarkable and should be applicable as a powerful chiral selector and a potent reaction tool for various enantioselective reactions.

Amino acids, as the basic building concept of peptides, play important roles in many fields like drugs and functional materials [30,31]. Chiral is one of the most important properties of amino acid. Only L-amino acid can form peptides in human body. Meanwhile, most drugs contain the special fragments of chiral amino acids [32]. In order to obtain the optical pure amino acids, many methods are invented. The strategy of isolating the racemization amino acid is still an important way.

L-Lysine is an essential amino acid in human body. It plays an important role in drug synthesis, functional material preparation and so on [33]. It should be noted that the two amino groups of lysine have almost

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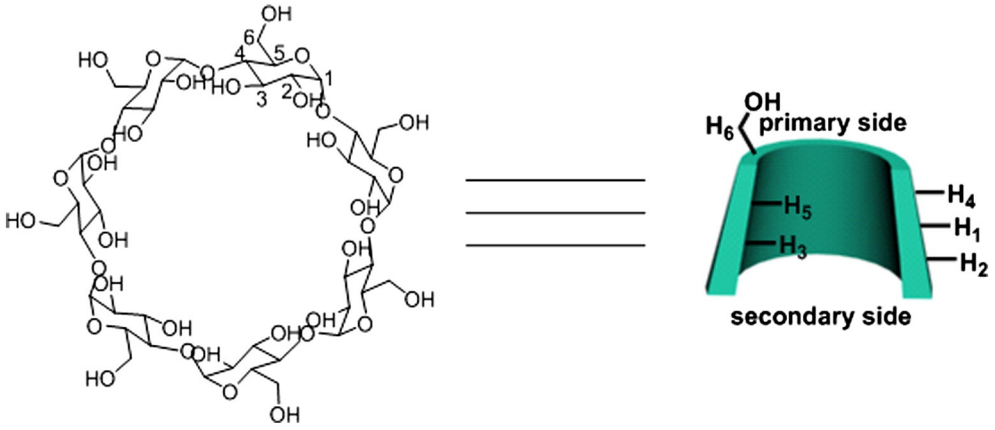


Fig. 1. Sketch of the proton positions in a β-CD molecule.

the same chemical activity under normal conditions [34]. As an amino protecting group, benzyloxycarbonyl (Cbz) is widely used for the high stability and could be removed easily under hydrogen [35]. Normally, optical pure lysine is essential to obtain the optical pure mono-Cbz protected lysine. To the best of our knowledge, pure optical mono-protected lysine from racemization lysine has not been reported.

In preliminary experiments, we evaluated the regioselectivity of L-lysine in the presence of β-CD and its derivatives [36,37]. Opposite regioselectivity can be achieved by modifying the structure of β-CD. The special inclusion orientation of the amino acid in the cavity of β-CD is proved by the NMR spectrum and theoretical calculations. In theory, the inclusion between chiral molecules and CDs is different [38]. These properties have been used in the separation of drug stereoisomers; chiral selector, etc [39–41]. We proposed that the inclusion of L- or D-lysine with β-CD is different. This can be used for the chiral recognition and kinetic resolution.

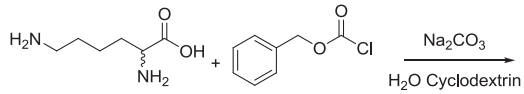
The result is exciting. We observed high regio- (>99%) and enantiomeric excess (ee >99%) product in short times (<10 min). No product is observed in the absence of β-CD in the same time (Table 1 entry 2). This proved that β-CD plays the key role in the reaction. Long reaction time and decreased yield are observed when pH decreased (Table 1 entries 4, 5). We propose that base neutralizes hydrogen chloride generated in the reaction. Through changes in the chemical shifts of guest and host protons, ^{1}H NMR spectroscopy can be used to prove the existence of inclusion complexes and provide information about the geometrical orientation of the guests with their hosts [42]. We therefore undertook a ^{1}H NMR study to investigate the inclusion complex formed between β-CD and lysine using different mole ratios between the host and guest to probe the inclusion effect. From the overlaid spectra provided in Fig. 2, it can be seen that the chemical shifts (Table 2) of protons α and β in lysine in D_2O changed by −0.0380 and −0.0100 ppm respectively in the presence of 1 mol equivalent of β-CD, as compared to lysine alone. By contrast, no chemical shift change was observed for protons γ, δ, and ε which taken together implies that the α-amino group was positioned inside the cavity of the cyclodextrin whilst the terminal amino group was exposed where it is able to react with Cbz-Cl to form the observed carbamates. 2D NMR ROSEY spectrum, which can provide more direct evidence for the inclusion complex, was used in our study [43]. The correlations between H_α of lysine and H_3, H_5 of β-CD inner cavity can be observed obviously from 2D NMR ROSEY result (Fig. S1), meaning that the α-amino group of lysine is recognized and included by the cavity of β-CD to form supramolecular complex. This result is in line with the ^{1}H NMR analysis.

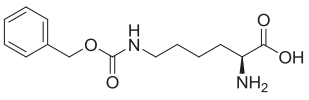
Density functional theory (DFT) calculations have been carried out to study the complexation thermodynamics of CDs [44,45]. The calculated relative energies using polarizable-continuum model (PCM) can indicate the stability of the inclusions. All calculations presented here were performed by using hybrid density functional theory method implemented in Gaussian 09 program package [46]. To provide realistic pictures of the interaction between lysine and β-CD, we calculated the energies of β-CD/D-lysine and β-CD/L-lysine inclusions in solvent phase using PCM (ε = 80) (see the ESI† for details) [47–49]. It has been noted by Knowles that 95% ee only involves energy differences of about 8 kJ/mol, which is approximately the strength of one hydrogen bond [50]. The calculated energies of α-NH_2 secondary face D-lysine inclusion is 13.36 kJ/mol higher than those of α-NH_2 secondary face L-lysine inclusion. Therefore, the β-CD/L-lysine inclusion has a higher enantioselectivity, which is consistent with our experimental results (Fig. 3).

2. Conclusions

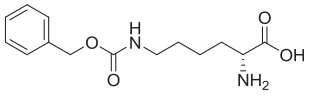
In summary, we have demonstrated that high regio- and enantioselectivities of lysine can be achieved in a short time. ^{1}H NMR

Table 1
Optimization of reaction conditions [a].

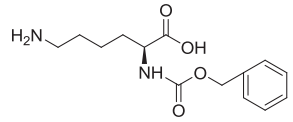




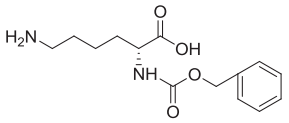
a L-ε -protected lysine



b D-ε -protected lysine



c L-α-protected lysine



d D-α-protected lysine

Entry	Catalyst	pH	Temp (°C)	Time (min)	Yield (%)[b]				ee (%)[c]
					a	b	c	d	
1	β-CD	8	25	10	45%	–	–	–	>99%
2	None	8	25	10	–	–	–	–	–
3	None	8	25	60	–	–	–	–	–
4	β-CD	7	25	10	–	–	–	–	–
5	β-CD	7	25	30	20%	–	–	–	>99%
6	β-CD	9	25	10	45%	–	–	–	>99%

[a] All reactions were carried out with DL-lysine (1.0 mmol), β-CD (10 mol%), Cbz-Cl (0.05 mmol) and H_2O (10 ml).
[b] Isolated yield.
[c] Enantioselectivities were determined by chiral HPLC.