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Kinetic resolution of primary amines via enantioselective N-acylation with acyl chlorides in the presence of supramolecular cyclodextrin nanocapsules

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ABSTRACT

The non-enzymatic kinetic resolution of primary amines via enantioselective N-acylation with acyl chlorides was accomplished for the first time by using the selective sequestration of one enantiomer within a supramolecular cyclodextrin (CD) nanocapsule in nonpolar solvents. In addition, the first example of a crystalline structure for an inclusion complex between an acyl chloride and a CD derivative is reported.

1. Introduction

Enantiomerically pure amines and amides are ubiquitous substructures in biologically active compounds, pharmaceuticals, and chiral catalysts.[1] The kinetic resolution (KR) of a racemic amine is one of the most useful methods to access optically pure amines. Since the first report by Fu's group,[2] a great deal of attention has been paid to non-enzymatic acylation processes for the KR of racemic amines.[2,3] In most cases, less reactive acylation reagents and considerably lower temperatures were needed for the KR of amines due to their high reactivity.

Supramolecular nanocapsules formed by the self-assembly of molecular building blocks have attracted considerable attention due to their ability to act as reaction vessels and confinement containers.[4] Recently, Gibb et al. reported the KR of constitutional isomers of long-chain esters utilizing a self-assembled supramolecular nanocapsule as a means for selective protection.[5] In this system, one isomer was selectively encapsulated into the supramolecular nanocapsule cavity, and thus its hydrolysis was remarkably inhibited. More recently, we reported the high chiral recognition and KR of primary amines utilizing a supramolecular chiral nanocapsule assembled by 6-*O*-triisopropylsilylated β-cyclodextrin (TIPS-β-CD) in nonpolar solvents.[6] In particular, the KR of racemic 1-(1-naphthyl) ethylamine (1-NEA) was achieved via enantioselective N-acylation with benzoic anhydride in the presence of this supramolecular chiral nanocapsule with an enantiomeric excess of up to 91%. This result implies that the supramolecular cyclodextrin nanocapsule can potentially function as a powerful tool for the KR of highly reactive chemical species including primary amines. The application of this supramolecular chiral nanocapsule to the KR of racemic amines with commonly used acylation reagents, such as acyl chlorides, will greatly increase its synthetic utility. In general, it has been considered that the reactivity of acyl chlorides is too high to use as acylation reagents in KR,[7] although acyl chlorides are the most useful acylation reagents from the viewpoints of accessibility and reactivity. Herein, we report the first example of the KR of primary amines through enantioselective N-acylation with acyl chlorides utilizing the selective sequestration of one enantiomer within the supramolecular CD nanocapsule.

2. Results and discussion

2.1. The formation of inclusion complexes between 6-*O*-modified CDs and primary amines

Based on our recent finding,[6] (*R*)- and (*S*)-1-(1-naphthyl)ethylamine [(*R*)- and (*S*)-**1**], (*R*)- and (*S*)-1-(2-naphthyl)ethylamine [(*R*)- and (*S*)-**2**], and (*R*)- and (*S*)-1-(1-phenyl)ethylamine [(*R*)- and (*S*)-**3**]

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(Fig. 1) were chosen as primary amine substrates. 6-*O*-*tert*-Butyldimethylsilylated β-cyclodextrin (TBDMS-β-CD) and TIPS-β-CD (Fig. 1) were used as components of supramolecular CD capsules. Table 1 summarizes the association constants (K) between these 6-*O*-silylated β-CDs and the chiral amines in benzene-d_6 or cyclohexane-d_{12}, and the chiral selectivity (K_S/K_R). In this study, we newly determined the association constants between TBDMS-β-CD and (*R*)- or (*S*)-**1** and between TIPS-β-CD and (*R*)- or (*S*)-**3** by an NMR titration method. Shifts of the H_3 and H_5 proton signals of TBDMS-β-CD upon the addition of (*R*)- or (*S*)-**1** were observed in cyclohexane-d_{12} (Fig. S1, Supplementary data), suggesting the formation of a TBDMS-β-CD–(*R*)- or (*S*)-**1** complex. Job plots using an NMR method showed a maximum at a [TBDMS-β-CD]/[(*R*)- or (*S*)-**1**] molar ratio of 2:1 (Fig. S5, Supplementary data), indicating that TBDMS-β-CD formed a 2:1 complex with (*R*)- or (*S*)-**1**. This result demonstrates that a supramolecular dimer capsule of TBDMS-β-CD incorporates these chiral guests inside the cavity. The chiral recognition ability of the supramolecular TBDMS-β-CD nanocapsule towards **1** was lower than that of the supramolecular nanocapsule derived from TIPS-β-CD (Table 1, entries 2 and 4), showing that a difference in the substituents on the Si atom between TBDMS-β-CD and TIPS-β-CD has large effect on the chiral recognition in nonpolar solvents. On the other hand, when (*R*)- or (*S*)-**3** bearing a phenyl group was used as a guest, Job plots showed the formation of a 1:1 complex with TIPS-β-CD (Fig. S6, Supplementary data), in contrast to the complexes between TIPS-β-CD and other chiral guests bearing a naphthyl group with 2:1 molar ratios. Even when the supramolecular TIPS-β-CD nanocapsule was used, little chiral selectivity for **3** (K_S/K_R=1.0) was observed. This result indicates that the presence of the supramolecular dimer capsule plays a crucial role for the high chiral recognition.

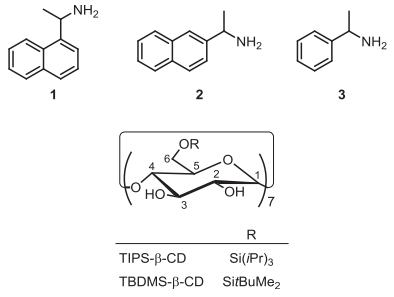
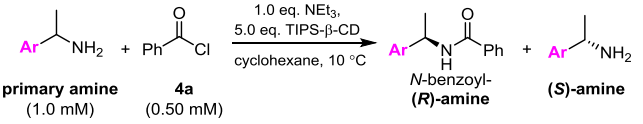


Fig. 1. Primary amines **1**–**3** and 6-*O*-silylated CDs used in this study.

chloride **4a** in the presence of the supramolecular TIPS-β-CD nanocapsule was examined. Similar to our recent study using acid anhydride as an acylation reagent,[6] cyclohexane was chosen as the solvent, in which the supramolecular TIPS-β-CD nanocapsule showed high chiral recognition towards **1** (Table 1, entry 1). A mixture of primary amines **1**–**3**, TIPS-β-CD (5.0 equiv), and triethylamine (1.0 equiv) in cyclohexane was stirred for 1 h to reach complexation equilibrium. Then benzoyl chloride **4a** (0.5 equiv) was added at 10 °C, and the mixture was stirred at 10 °C for 6 h. Table 2 shows the conversion of **1**–**3**, the enantiomeric excess (ee, %) of the resulting *N*-benzoyl-(*R*)-amines, and the *s*-factor (s).[8] The enantioselective N-acylation of **1** with **4a** exceeded 77% ee (Table 2, entry 1). As expected from the lower chiral recognition capability of the supramolecular TIPS-β-CD nanocapsule towards **2** and **3** as compared to **1** (Table 1), the reactions of these amines with **4a** proceeded with lower enantioselectivity (Table 2, entries 2 and 3). These results confirm that the origin of the enantioselectivity in this reaction system should be the selective sequestration of one isomer of the amines within the supramolecular CD nanocapsule. The ^{1}H NMR spectra of the products showed that no reaction occurred between the free OH group of TIPS-β-CD and **4a** under these conditions.[9]

Table 2
Enantioselective N-acylation of primary amines **1**, **2**, and **3** with benzoyl chloride **4a** in the presence of TIPS-β-CD in cyclohexane at 10 °C[a]



Entry	Primary amine	Conv.[b] (%)	ee[b] (%)	s
1	**1**	44	77	14
2	**2**	44	11	1.3
3	**3**	45	2	1.0

[a] N-acylation of **1**, **2**, and **3** (1.0 mM) was carried out with benzoyl chloride **4a** in nonpolar solvents (0.6 mL) at 10 °C for 12 h in the presence of TIPS-β-CD (5.0 equiv) and triethylamine (1.0 equiv).
[b] Conversion of **1**, **2**, and **3** and enantiomeric excess of *N*-benzoyl-(*R*)- amines were determined by HPLC.

A larger scale reaction of racemic amine **1** (0.1 mmol) with **4a** (0.05 mmol) proceeded with the almost same conversion and selectivity (conv.=46%, ee=76%, s=14) as those of the above-mentioned micromole scale reaction (Table 2, entry 1). This result indicates that the enantioselective N-acylation of the primary

Table 1
Association constants between 6-*O*-silylated β-CD and (*R*)- or (*S*)-**1**, **2**, and **3** in nonpolar solvents at 10 or 25 °C

Entry	CDs	Solvent	T (°C)	Association constant		Selectivity
				K_R	K_S	K_S/K_R
(*R*)- or (*S*)-**1**/M^{-2}						
1[a]	TIPS-β-CD	Cyclohexane-d_{12}	10	$(1.5\pm0.52)\times10^6$	$(6.1\pm2.1)\times10^9$	41±13
2[a]	TIPS-β-CD	Cyclohexane-d_{12}	25	$(4.2\pm0.96)\times10^6$	$(1.3\pm0.20)\times10^8$	31±6.1
3[a]	TIPS-β-CD	Benzene-d_6	25	$(1.5\pm0.31)\times10^6$	$(1.8\pm0.41)\times10^7$	12±2.6
4	TBDMS-β-CD	Cyclohexane-d_{12}	25	$(1.8\pm0.40)\times10^5$	$(1.2\pm0.33)\times10^6$	6.1±1.6
(*R*)- or (*S*)-**2**/M^{-2}						
5[a]	TIPS-β-CD	Cyclohexane-d_{12}	25	$(1.2\pm0.12)\times10^7$	$(2.7\pm0.18)\times10^7$	2.3±0.21
(*R*)- or (*S*)-**3**/M^{-1}						
6	TIPS-β-CD	Cyclohexane-d_{12}	25	$(2.2\pm0.49)\times10^2$	$(2.3\pm0.40)\times10^2$	1.0 ±0.22

[a] Ref. 6.

2.2. Enantioselective N-acylation of primary amines in the presence of supramolecular 6-*O*-modified CDs nanocapsules

On the basis of the results mentioned in Section 2.1, the enantioselective N-acylation of racemic amines **1**–**3** with benzoyl amines with acyl chlorides in the presence of the supramolecular TIPS-β-CD nanocapsule is little affected by the reaction scale.

Using **1** and **4a** as an amine substrate and an acylation reagent, respectively, we examined the effect of the reaction conditions, such as the amount of CD, the solvent type, temperature, and the CD type,