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Chiral Recognition and Kinetic Resolution of Aromatic Amines via Supramolecular Chiral Nanocapsules in Nonpolar Solvents

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Supporting Information

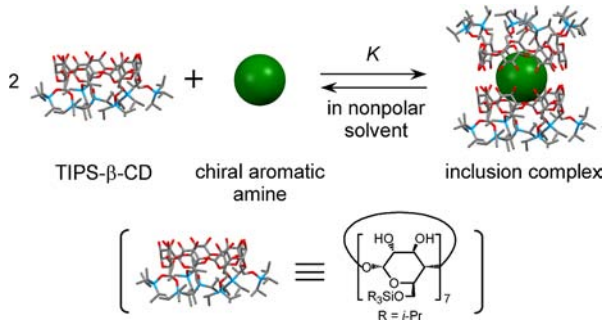
ABSTRACT: Herein we report the first example of chiral recognition and kinetic resolution of aromatic amine guests using supramolecular nanocapsules assembled from cyclodextrin derivatives in nonpolar media. With these nanocapsules, an extremely high chiral recognition of 1-(1-naphthyl)ethylamine (**1**) in cyclohexane was achieved, with a binding selectivity of up to 41 for (*S*)-**1** over (*R*)-**1**. In addition, kinetic resolution of **1** through enantioselective N-acylation was accomplished with an enantiomeric excess of up to 91%.

Supramolecular nanocapsules constructed by the self-assembly of molecular building blocks have attracted considerable attention in the fields of supramolecular and synthetic chemistry[1] because they exhibit unique guest discrimination properties[2] as well as a high stabilization effect toward reactive intermediates[3] by utilizing their isolated nanocavity from the bulk solution. To date, a variety of supramolecular nanocapsules have been employed as molecular selectors[4] and reaction vessels.[5] However, reports on chiral recognition[6] and enantioselective reactions[7] with supramolecular chiral nanocapsules bearing asymmetric cavities are limited, even though well-designed supramolecular chiral nanocapsules should effectively recognize chiral guests because of the confined chiral environment and also should function as potent reaction tools for enantioselective reactions via the selective sequestration of one enantiomer.

We recently reported that a supramolecular nanocapsule formed by self-assembly of 6-*O*-triisopropylsilyl-*β*-cyclodextrin (TIPS-*β*-CD) exhibited a high affinity for pyrene in benzene or cyclohexane.[8] Because this nanocapsule possesses an asymmetric cavity derived from the constituent D-glucose units, it has potential for enantioselective recognition of specific chiral guests (e.g., chiral aromatic amines and chiral aromatic alcohols) in nonpolar solvents through multipoint interactions, including hydrogen bonding between the CD hydroxyl groups and the guest polar groups as well as inclusion of the guest aromatic moiety into the CD cavity. Herein we report the extremely high chiral recognition of an aromatic amine by a supramolecular chiral nanocaspsule assembled from TIPS-*β*-CD in a nonpolar solvent. In addition, the selective sequestration of one enantiomer by the supramolecular chiral nanocapsule in the nonpolar solvent enabled the successful kinetic resolution of racemic aromatic amines. To the best of our knowledge, this is the first example of chiral recognition by a supramolecular CD nanocapsule in a nonpolar medium and kinetic resolution of racemic compounds utilizing selective sequestration of one enantiomer within the supramolecular CD nanocapsule.

(*R*)- and (*S*)-1-(1-naphthyl)ethylamine [(*R*)- and (*S*)-**1**] and (*R*)- and (*S*)-1-(2-naphthyl)ethylamine [(*R*)- and (*S*)-**2**] were used as chiral guests to examine the effect of the guest structure on the binding and chiral recognition by the supramolecular TIPS-*β*-CD capsule in nonpolar media. The chiral recognition ability of the supramolecular TIPS-*β*-CD capsule toward these aromatic amine guests was evaluated on the basis of the association constants (*K*) between two TIPS-*β*-CD molecules and one molecule of the chiral guests in benzene-d_6 and cyclohexane-d_{12} (Scheme 1), which were determined by the ^{1}H

Scheme 1. Formation of an Inclusion Complex between a Supramolecular TIPS-*β*-CD Nanocapsule and a Chiral Aromatic Amine in a Nonpolar Solvent



NMR method. Figure 1 shows the changes in the ^{1}H NMR signals of TIPS-*β*-CD induced by the addition of (*R*)- or (*S*)-**1** in benzene-d_6 at 25 °C. Upon the addition of (*R*)- or (*S*)-**1**, new signals appeared at 4.1 and 5.2 ppm. As the ratio of (*R*)- or (*S*)-**1** to TIPS-*β*-CD increased, the intensities of these new signals increased, while the original proton signals of TIPS-*β*-CD decreased. These observations suggest that complexation between TIPS-*β*-CD and (*R*)- or (*S*)-**1** occurs in benzene-d_6 and that the complexation equilibrium at 25 °C is slow on the NMR time scale. When the (*S*)-**1**/TIPS-*β*-CD ratio reached 2:1, the original proton signals of TIPS-*β*-CD almost disappeared (Figure 1b). On the other hand, in the case of the (*R*)-**1** guest, the original signals of TIPS-*β*-CD remained visible even with a (*R*)-**1**/TIPS-*β*-CD ratio of 2:1. These results suggest that TIPS-*β*-CD binds (*S*)-**1** with a higher association

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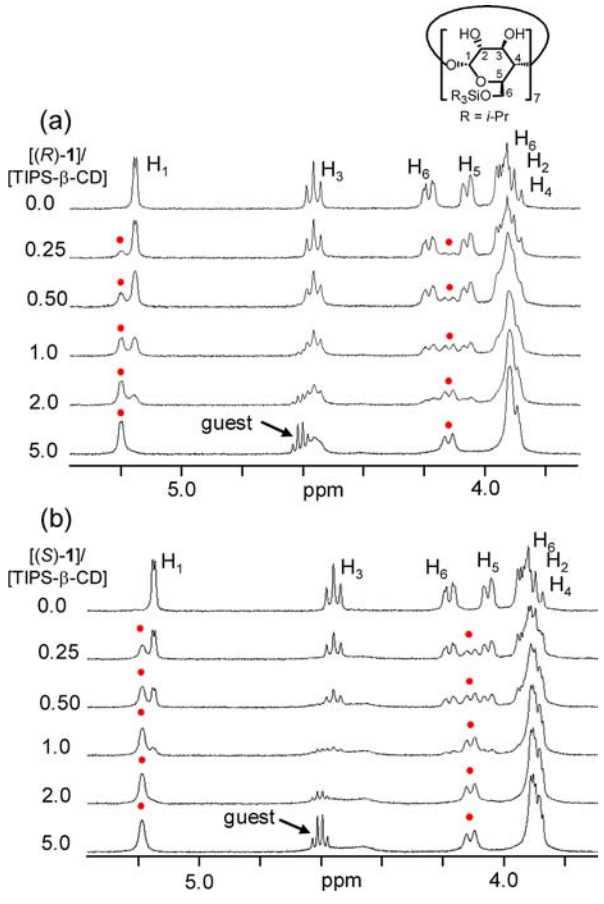

Figure 1. ^{1}H NMR spectral changes observed for TIPS-β-CD (1.0×10^{-3} M) upon addition of (a) (*R*)-**1** and (b) (*S*)-**1** in benzene-d_6 at 25 °C. Red circles denote new signals that appeared upon addition of **1**.

constant than for (*R*)-**1**. The Job plots using an NMR method showed a maximum at a [TIPS-β-CD]/[(*R*)- or (*S*)-**1**] molar ratio of 2:1 [Figure S4 in the Supporting Information (SI)], clearly indicating that TIPS-β-CD forms a 2:1 complex with (*R*)- or (*S*)-**1** in benzene-d_6. This result also suggests that a supramolecular dimer capsule of TIPS-β-CD incorporates these chiral guests inside the cavity. In the case of cyclohexane-d_{12} as the solvent, similar ^{1}H NMR spectral changes occurred upon the addition of (*R*)- or (*S*)-**1** (Figure S1). Additionally, the Job plots (Figure S5) confirmed the complexation between the supramolecular dimer capsule of TIPS-β-CD and (*R*)- or (*S*)-**1**.

Table 1 shows the *K* values for association of two TIPS-β-CD host molecules and one (*R*)- or (*S*)-**1** guest molecule (K_R or K_S, respectively) in benzene-d_6 and cyclohexane-d_{12} at 25 or 10 °C as estimated from the ^{1}H NMR spectral changes of TIPS-β-CD upon the addition of (*R*)- or (*S*)-**1**. In these solvents, the supramolecular TIPS-β-CD capsule shows a clear binding selectivity for (*S*)-**1**. It is noteworthy that an extremely high chiral selectivity (K_S/K_R) of up to 31 was achieved. Decreasing the temperature to 10 °C further enhanced the chiral selectivity in cyclohexane-d_{12} to 41, which is much higher than the chiral selectivities of CDs and CD derivatives toward racemic aromatic guests in aqueous media.[9] These results demonstrate that the supramolecular capsule assembled from TIPS-β-CD in a nonpolar solvent is highly effective for the chiral recognition of **1**. The thermodynamic parameters for complexation of TIPS-β-CD with (*R*)- and (*S*)-**1** in benzene-d_6 and cyclohexane-d_{12}, which were calculated from the association constants at different temperatures (see Tables S1−S3 in the SI), reveal that the complexation is enthalpy-driven. When (*R*)- or (*S*)-**2** was used as the guest, an inclusion complex with TIPS-β-CD was not formed in benzene-d_6. On the other hand, clear associations between TIPS-β-CD and those guests were observed in cyclohexane-d_{12}, although the chiral selectivity was lower than in the case of **1**. These results reveal that the substitution position of the 1-aminoethyl group on the naphthalene ring of the guest significantly influences the guest inclusion within the supramolecular capsule cavity in nonpolar solvents.

Two-dimensional NMR spectroscopy effectively provides information about the structure of the inclusion complex in solution. The resonances of the protons of (*R*)- and (*S*)-**1** and the H_3 and/or H_5 protons of TIPS-β-CD in the nuclear Overhauser effect spectroscopy (NOESY) spectra of the inclusion complexes in benzene-d_6 or cyclohexane-d_{12} (Figures S7−10) are clearly correlated, confirming that (*R*)- and (*S*)-**1** are incorporated within the cavity of the supramolecular TIPS-β-CD capsule in these solvents. In benzene-d_6, the cross-peaks between the H_3 protons of the host and all of the naphthalene protons of (*R*)- or (*S*)-**1** were clearly observed, whereas the cross-peaks between the H_5 protons of the host and the protons of the (*R*)- or (*S*)-**1** were much weaker. This result indicates that an (*R*)- or (*S*)-**1** molecule is included in the TIPS-β-CD capsule cavity with the long axis of the naphthalene ring almost perpendicular to the cavity axis, which is similar to the case for pyrene inclusion.[8] On the other hand, in cyclohexane-d_{12}, stronger cross-peaks were observed between the H_5 protons as well as the H_3 protons of the host and almost all of the naphthalene protons of (*R*)- and (*S*)-**1**, suggesting that the long axis of the incorporated (*R*)- or (*S*)-**1** molecule is tilted toward the axis of the TIPS-β-CD capsule cavity. Consequently, the (*R*)- or (*S*)-**1** molecule penetrates deeper into the CD cavity compared with the case of benzene-d_6 as a solvent. The calculated ratios of the volume integrals of the correlation peaks between the host H_5 protons and the guest

Table 1. Association Constants for TIPS-β-CD and Chiral Aromatic Amines in Benzene-d_6 and Cyclohexane-d_{12} at 25 or 10 °C

		association constant (L^2 mol^{-2})		selectivity
solvent	*T* (°C)	K_R	K_S	K_S/K_R
		(*R*)- or (*S*)-**1**		
C_6D_6	25	$(1.5 \pm 0.31) \times 10^6$	$(1.8 \pm 0.41) \times 10^7$	12 ± 2.6
c-C_6D_{12}	25	$(4.2 \pm 0.96) \times 10^6$	$(1.3 \pm 0.20) \times 10^8$	31 ± 6.1
c-C_6D_{12}	10	$(1.5 \pm 0.52) \times 10^8$	$(6.1 \pm 2.1) \times 10^9$	41 ± 13
		(*R*)- or (*S*)-**2**		
C_6D_6	25	~0	~0	–
c-C_6D_{12}	25	$(1.2 \pm 0.12) \times 10^7$	$(2.7 \pm 0.18) \times 10^7$	2.3 ± 0.21

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naphthalene protons to those between the host H_3 protons and the guest naphthalene protons were 0.42 and 0.22 for the TIPS-β-CD−(*S*)-**1** and TIPS-β-CD−(*R*)-**1** complexes, respectively, in cyclohexane-d_{12}. Because the ratio indicates how deep the naphthalene ring penetrates into the CD cavity, these values show that the naphthalene ring of (*S*)-**1** penetrates deeper into the CD cavity than the naphthalene ring of (*R*)-**1**. Additionally, the higher chiral selectivity in cyclohexane-d_{12} can be explained in terms of the larger difference in the extents of penetration of (*R*)- and (S)-**1** into the CD cavity in cyclohexane-d_{12} compared with benzene-d_6.

The X-ray crystal structure of the inclusion complex between a supramolecular TIPS-β-CD capsule and (*S*)-**1** in benzene solution (Figure 2) shows that the (*S*)-**1** molecule is

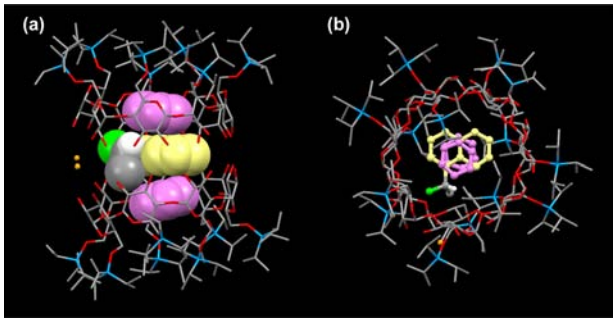


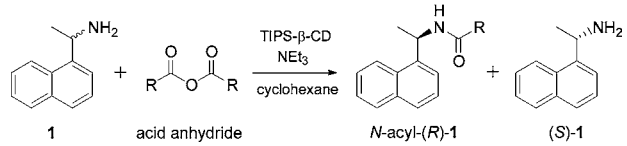
Figure 2. Crystal structure of the supramolecular TIPS-β-CD capsule−(*S*)-**1** inclusion complex. (a) Side view. TIPS-β-CD is shown with a cylinder representation, whereas (*S*)-**1** and benzene are shown with space-filling representations. The O atoms in H_2O are shown as orange balls. H atoms except for the α-methine hydrogen of (*S*)-**1** have been omitted for clarity. (b) Top view. TIPS-β-CD is shown with a cylinder representation, whereas (*S*)-**1** and benzene are shown with ball-and-stick representations. O atoms in H_2O are shown as orange balls. Color labels: gray, carbon in TIPS-β-CD and aliphatic carbon in (*S*)-**1**; cyan, silicon; red, oxygen in TIPS-β-CD; yellow, naphthalene ring; violet, benzene molecule; orange, oxygen in H_2O.

incorporated within the supramolecular capsule cavity formed by the two TIPS-β-CD molecules through hydrogen bonding between the secondary hydroxyl groups. Interestingly, as in the case of a pyrene guest,[8] the (*S*)-**1** molecule forms a sandwich-type complex with two benzene molecules through $\pi-\pi$ interactions and is located at the center of the capsule cavity. Hydrogen bonding between the NH_2 group of (*S*)-**1** and the 3-OH group of TIPS-β-CD with a N···O distance of 2.88 Å also occurs (Figure S13). Unlike the case of a pyrene guest,[8] two H_2O molecules, which are possibly originated from TIPS-β-CD−bound water or a trace amount of water in the solvent, are present between the two TIPS-β-CD molecules, acting as connecting linkers through hydrogen bonding. This difference is probably due to the steric effect of the aminoethyl group of (*S*)-**1**. The location of (*S*)-**1** in the crystalline state reasonably agrees with the proposed location of (*S*)-**1** in the benzene solution. Although X-ray analysis of a crystal of the inclusion complex between a supramolecular TIPS-β-CD capsule and (*R*)-**1** in benzene has not yet been successful, the interactions between the guest and the solvent molecules inside the supramolecular capsule cavity as well as hydrogen bonding between the NH_2 group of the guest and the OH group of TIPS-β-CD appear to affect the inclusion mode of the guest molecule within the capsule cavity, resulting in the high chiral selectivity in the guest inclusion.

In view of the high chiral recognition ability of the supramolecular TIPS-β-CD capsule toward **1** in nonpolar solvents, a nonenzymatic kinetic resolution of **1** via enantioselective N-acylation was expected to proceed. The selective inclusion of (*S*)-**1** over (*R*)-**1** within the supramolecular capsule cavity should predominantly shield the *S* isomer from the acylation reagents in the bulk solution, resulting in the kinetically preferential N-acylation of the *R* isomer over the *S* isomer.

On the basis of this hypothesis, we examined the enantioselective N-acylation of racemic **1** with acetic anhydride or benzoic anhydride in the presence of TIPS-β-CD in cyclohexane. A mixture of racemic **1** and TIPS-β-CD in cyclohexane was stirred for 1 h to reach complexation equilibrium. The acid anhydride was then added at 10 °C, and the mixture was stirred at 10 °C for 1 h (for acetic anhydride) or 40 h (for benzoic anhydride). Table 2

Table 2. Kinetic Resolution of 1 via Enantioselective N-Acylation with Acid Anhydride in the Presence of TIPS-β-CD in Cyclohexane[a]



1 acid anhydride *N*-acyl-(*R*)-**1** (*S*)-**1**

		acid anhydride				
entry	equiv of TIPS-β-CD	R	equiv	conv. (%)[b]	ee (%)[b]	*s*
1	none	CH_3	0.50	48	–	–
2	1.0	CH_3	0.10	10	50	3.2
3	2.0	CH_3	0.10	9	72	6.7
4	5.0	CH_3	0.10	7	83	11
5	5.0	CH_3	0.35	29	70	7.5
6	5.0	CH_3	0.50	42	59	5.7
7	none	Ph	0.50	48	–	–
8	5.0	Ph	0.10	7	91	23
9	5.0	Ph	0.20	18	87	17
10	5.0	Ph	0.50	49	75	15

[a]Acylation of **1** (6.0×10^{-4} mmol) was carried out with acid anhydride in cyclohexane (0.6 mL) at 10 °C for 1 h (R = CH_3) or 40 h (R = Ph) in the presence of triethylamine (1.0 equiv) and TIPS-β-CD. [b]The conversion of **1** and enantiomeric excess of *N*-acyl-(*R*)-**1** were determined by HPLC.

summarizes the conversion of **1**, the enantiomeric excess (% ee) of the resulting *N*-acyl-(*R*)-**1**, and the *s* factor[10] as functions of the amount of TIPS-β-CD and acid anhydride added. In all cases, enantioselective N-acetylation of (*R*)-**1** exceeded 50% ee in the presence of TIPS-β-CD. The enantioselectivity was enhanced as the amount of TIPS-β-CD increased (entries 2−4), confirming that the selective inclusion of (*S*)-**1** within the TIPS-β-CD capsule cavity is responsible for the enantioselective N-acetylation. On the other hand, increasing the amount of acetic anhydride lowered the enantioselectivity (entries 4−6). With benzoic anhydride, which possesses a bulkier acyl group than acetic anhydride, N-acylation proceeded with higher enantioselectivity. In particular, the highest enantioselectivity for N-benzoylation of (*R*)-**1** occurred with a combination of 5.0 equiv of TIPS-β-CD and 0.10 equiv of benzoic anhydride (91% ee, s = 23). Generally, it is considered that nonenzymatic kinetic resolution of racemic primary amino compounds is

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difficult because of the higher reactivity of primary amino groups.[11] Thus, this supramolecular capsule should be a powerful tool for nonenzymatic kinetic resolution of racemic amino compounds.

In conclusion, we have demonstrated that high chiral recognition of aromatic amines can be realized by using inclusion within the cavity of a supramolecular CD nanocapsule in nonpolar solvents. In particular, an extremely high binding selectivity for (*S*)-1-(1-naphthyl)ethylamine [(*S*)-**1**] over the corresponding *R* isomer was achieved. A crystallographic study of the complex between the supramolecular nanocapsule and (*S*)-**1** obtained from benzene solution showed that hydrogen bonding between the guest and the CD host as well as the interactions between the guest and the solvent molecules inside the capsule cavity play crucial roles in the enantioselective guest inclusion. Moreover, through chiral recognition with the supramolecular nanocapsule in cyclohexane, a nonenzymatic kinetic resolution of racemic **1** via enantioselective N-benzoylation is attained with up to 91% ee and an *s* factor of 23. This supramolecular nanocapsule should be applicable as a powerful chiral selector and a potent reaction tool for various enantioselective reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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