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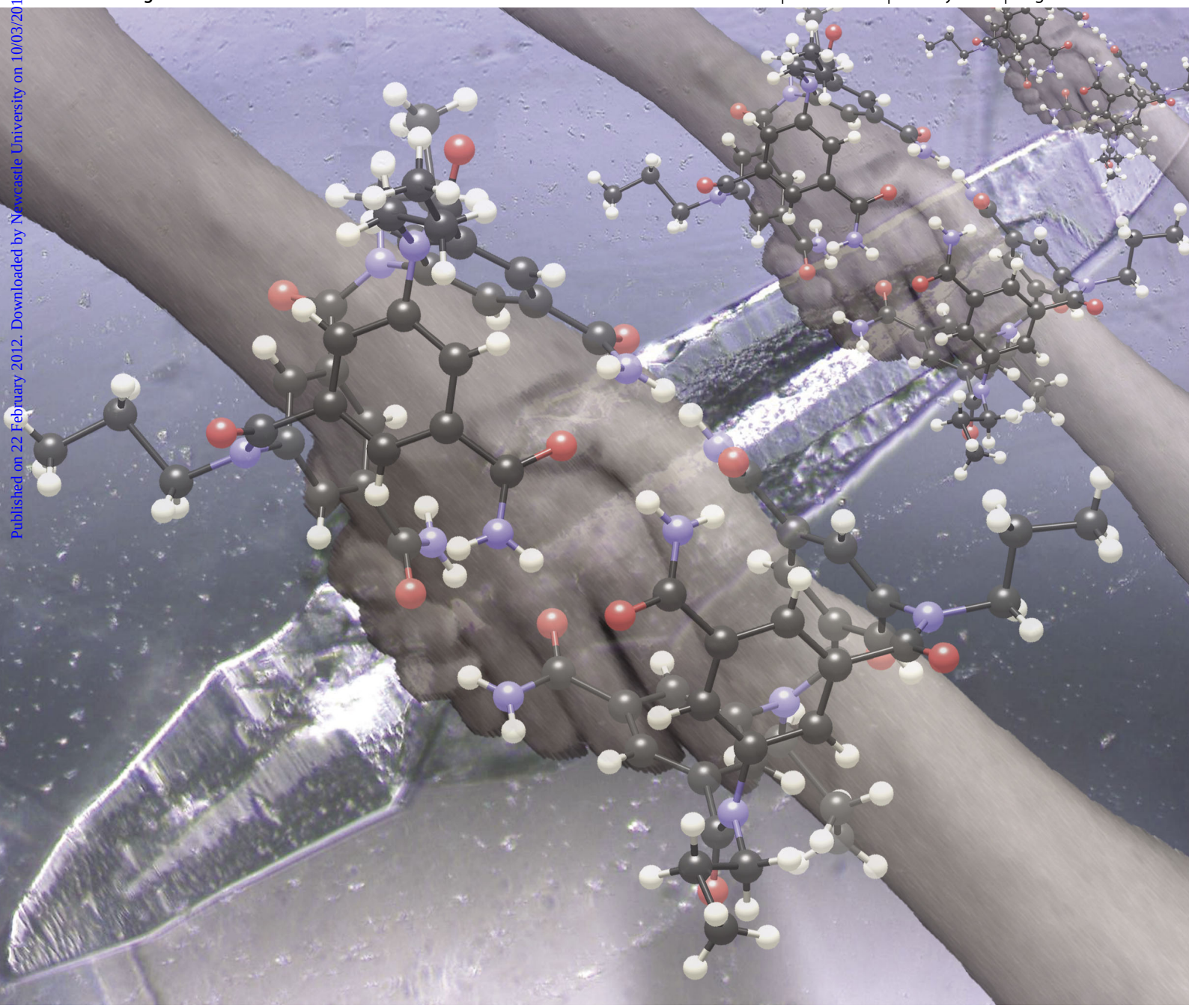

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COMMUNICATION

Molecular chirality and chiral capsule-type dimer formation of cyclic triamides *via* hydrogen-bonding interactions†‡

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Chiral properties of bowl-shaped cyclic triamides bearing functional groups with hydrogen-bonding ability were examined. Chiral induction of cyclic triamide 3a was observed by addition of chiral amine in solution, and chiral separation was achieved by simple crystallization to afford chiral capsule-type dimer structure of 4a.

Molecular tectonics using weak intermolecular interactions,[1] such as hydrogen bonding,[2] has attracted much attention for the development of functional organic materials with well-ordered three-dimensional structures.[3] For example, bowl-shaped macrocyclic molecules, such as calixarenes,[4] with multiple hydrogen bonds are useful templates for construction of various functional molecules, including specific receptors[5] and capsule-type supramolecules.[6,7] We have synthesized cyclic tris(*N*-methyl-*m*-benzamide) **1**[8] by condensation reaction of *m*-methylaminobenzoic acid and examined its conformational properties.[9] Cyclic triamide **1** has a bowl-shaped *syn* crystal structure, in which the three phenyl groups are directed to the same side. In solution, it exists in rapid equilibrium between the *syn* conformer (major) and the *anti* conformer, in which one phenyl group is flipped in the opposite direction to the other two (Fig. 1). Although the size of the cavity in *syn*-**1** is rather small, it plays a significant role in dimer formation of the cyclic triamide bearing substituents at the 5-positions in the crystalline state, because the substituent of one molecule

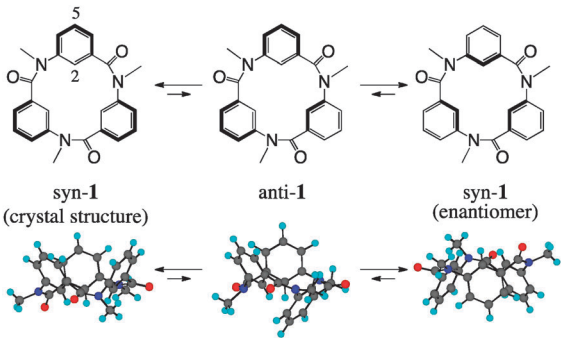

Fig. 1 Structure and conformations of cyclic triamide **1**.

resides in the cavity of the other molecule.[10] Further, *syn*-**1** has conformational chirality based on the direction of the amide bond. At present, the enantiomers of *syn*-**1** have not been separated, and only racemic crystals have been obtained by crystallization of **1** and its derivatives. In this study, we examined the chiral properties in solution and the formation of the capsule-type dimer in the crystal state for cyclic triamides bearing functional groups at the 5-positions. Chiral separation of one derivative was achieved by simple crystallization.

In the bowl-shaped *syn* structure, functional groups with hydrogen-bonding ability at the 5-positions would lie in the same direction, and might interact with other molecules *via* a unique hydrogen-bond network structure. Such functionalization might also affect the chiral properties of cyclic triamides. Therefore, we designed cyclic triamides **2–5**, bearing 5-carboxyl groups or derivatives (ester or amide). The substituents on the amide nitrogen atoms were chosen to be *n*-propyl or *n*-pentyl, on the basis of solubility considerations (Scheme 1). The cyclic triamides **2** with 5-ester groups were prepared by the condensation of monomethyl 5-(*n*-alkylamino)isophthalate in the presence of dichlorotriphenylphosphorane.[9] Hydrolysis or amidation of **2** afforded the acid (**3**) or amide (**4** and **5**) derivatives, respectively.

The conformations of the cyclic triamides were determined by temperature-dependent ^{1}H NMR spectroscopy. Cyclic triamide **1** showed a broad spectrum at room temperature, and two sets of signals corresponding to the *syn* and *anti* conformers were observed at lower temperature.[8–10] The conformers could be assigned based on the observation of H^2 protons of the *anti* conformer at higher field (6.35 ppm for **1**).

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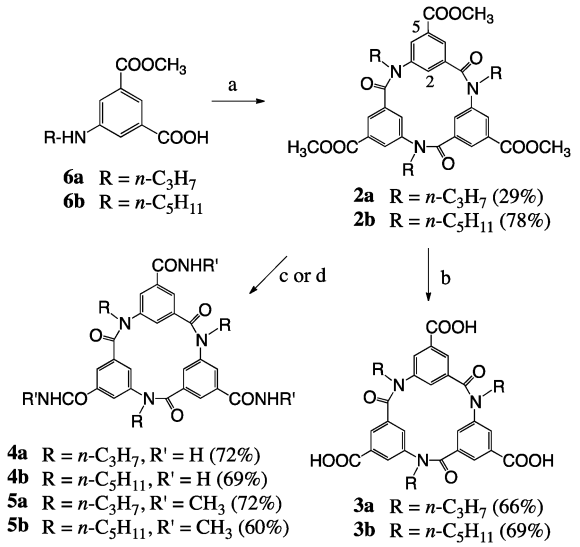

Scheme 1 Structures and synthetic schemes of cyclic triamides **2–5**. (a) Ph_3PCl_2, $(CHCl_2)_2$, 120 °C; (b) 2 M NaOH, EtOH, rt; (c) 7 M NH_3, MeOH, rt; (d) 40% CH_3NH_2, CH_3OH, rt.

In all compounds examined, the *syn* conformer is the major species ($\Delta G^0 < 0$). In the case of **1**, the ratio of the *syn* conformer was increased in more polar solvents, being 85% and 97% in CD_2Cl_2 and CD_3OD, respectively. A similar tendency was observed for compounds **2** with 5-ester groups, as well as in other cyclic triamides bearing alkyl, phenyl, bromo, or amino groups at the 5-positions.[10] Interestingly, the cyclic triamides bearing 5-carboxyl (**3**) or 5-carboxamide groups (**5**) did not show this tendency. The ratio of the *syn* conformer was 94% for **5a** and 95% for **5b** in CD_2Cl_2, while it was 97% for both in CD_3OD. Further, among the cyclic triamides **3** bearing 5-carboxyl groups, only the *syn* conformer was observed in CD_2Cl_2, while the ratio of the *syn* conformer in CD_3OD was similar to those of other cyclic trimers. This result suggests that hydrogen-bonding networks stabilize the *syn* conformers of cyclic triamides **3** and **5** (Table 1).

Then, we examined the chiral properties of the cyclic triamides in solution by examining the interaction with chiral additives.[11] Significant CD signals of **3a** were induced in the presence of (*R*)-(+)-bornylamine (Fig. 2). Interestingly, the CD intensity was maximum in the presence of three

Table 1 *Syn*/*anti* equilibrium of cyclic triamides

	In CD_2Cl_2		In CD_3OD	
Compound	Ratio[a] (*syn* : *anti*)	ΔG^{0b}/kcal mol^{-1}	Ratio[a] (*syn* : *anti*)	ΔG^{0b}/kcal mol^{-1}
1	77 : 23	−0.6	97 : 3	−1.8
2a	79 : 21	−0.7	95 : 5	−1.5
2b	79 : 21	−0.7	94 : 6	−1.4
3a	>99 : <1	<−2.3	93 : 7	−1.3
3b	>99 : <1	<−2.4	91 : 9	−1.2
4a	Not soluble		96 : 4	−1.6
4b	Not soluble		94 : 6	−1.4
5a	94 : 6	−1.4	97 : 3	−1.8
5b	95 : 5	−1.5	97 : 3	−1.8

[a] Temperature is 263 K for *N*-methyl (**1**) and *N*-*n*-pentyl derivatives (series **b**), or 253 K for *N*-*n*-propyl derivatives (series **a**). [b] ΔG^0 (kcal mol^{-1}) = ΔG^0 (*syn*) − ΔG^0 (*anti*).

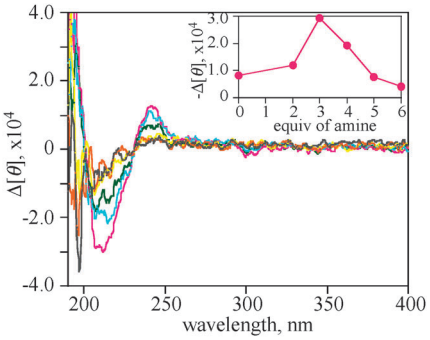

Fig. 2 CD spectra of **3a** (5.2×10^{-4} M) in the presence of various concentrations of (*R*)-(+)-bornylamine in acetonitrile (20 °C). $\Delta[\theta]$ represents the difference from the corresponding value of the amine only. Inset: plot of $-\Delta[\theta]$ values at 212 nm *vs.* equivalents of amine with respect to **3a**.

equivalents of bornylamine, and further additions decreased the intensity. Thus, although the nature of the interaction between **3a** and bornylamine and the structure of the complex were not established, chiral induction of *syn*-**3a** bearing carboxyl groups occurred in the presence of chiral amine.

X-Ray crystallographic analysis indicated that the crystal of **3b** recrystallized from acetonitrile corresponded to a head-to-head dimer of *syn*-**3b**, in which the three carboxyl groups in one molecule form double hydrogen bonds with those in the other molecule (Fig. 3a and b). The two molecules of *syn*-**3b** in the dimer are enantiomeric, and the crystal is racemic (space group: $P6_3/m$). The dimer contains a capsule-like inner space surrounded by six phenyl rings. The longest diameter of the inner space based on the van der Waals radius is *ca.* 3.2 Å. The hydrogen-bonded dimers are laminated along the *c* axis of the unit cell to form a columnar packing structure (Fig. 3c and d). The columns are ordered along the *ab* plane of the unit cell.

In the crystal of **4b** obtained from methanolic solution, the enantiomeric pair of *syn*-**4b** formed a similar capsule-type dimer structure (space group: $P2_1/c$) (Fig. 4). In this case, the 5-carboxamide group of one molecule forms hydrogen bonds with two adjacent carboxamide groups of the other molecule.

Interestingly, the cyclic triamide **4a** formed chiral crystals from acetonitrile (space group: $P4_32_12$ or $P4_12_12$), in which the head-to-head capsule-type dimers consist of a single enantiomer of *syn*-**4a** (Fig. 5). Two enantiomeric chiral crystals were obtained, and could be distinguished by their CD spectra in KBr.

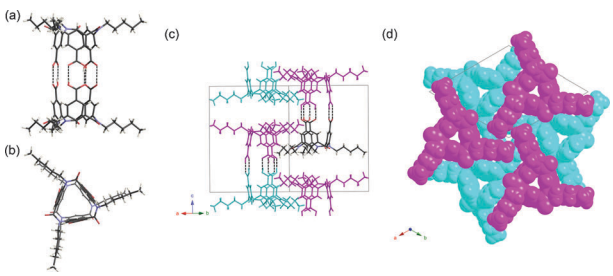

Fig. 3 Crystal structure of **3b**. (a) Side view and (b) top view of the dimeric structure. (c) Packing structure and (d) space-filling model along the *c* axis. Magenta- and cyan-colored molecules are enantiomers of each other. Hydrogen bonds are shown as black dotted lines. Included solvent molecules are omitted for clarity.

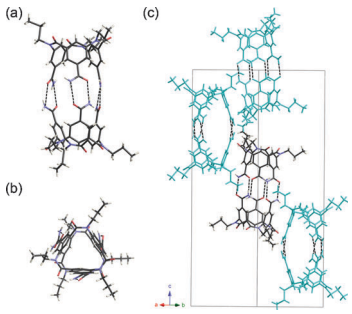

Fig. 4 Crystal structure of **4b**. (a) Side view and (b) top view of the dimeric structure. (c) Packing structure. Magenta- and cyan-colored molecules are enantiomers of each other. Hydrogen bonds are shown as black dotted lines. Included solvent molecules are omitted for clarity.

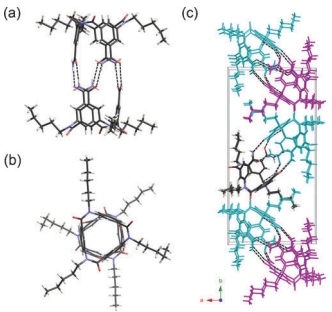

Fig. 5 Crystal structure of **4a**. (a) Side view and (b) top view of the dimeric structure. (c) Packing structure. Hydrogen bonds are shown as black dotted lines. Included solvent molecules are omitted for clarity.

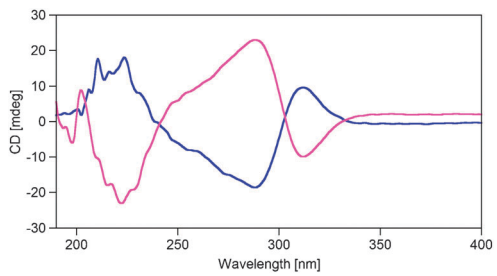

Fig. 6 CD spectra of enantiomeric chiral crystals of **4a** in KBr.

The mirror-image CD spectra are shown in Fig. 6. This is the first report of the separation of chiral cyclic triamides without the use of any chiral factor other than the chiral cyclic skeleton of the *syn* molecule.

We have synthesized cyclic triamides bearing functional groups with hydrogen-bonding ability. Interaction of the carboxyl groups of **3** with chiral amine resulted in chiral induction of *syn*-**3** in solution, and interaction between the carboxyl groups or carboxamide groups of two molecules afforded capsule-type dimer structures in the crystal state. Chiral crystals of the chiral capsule-type dimer of **4a** were obtained, and their CD spectra were determined. ^{1}H NMR study suggested that such hydrogen-bonding interactions including capsule-type dimer formation would occur in the solution of **3–5**, and the detailed analysis of the solution structure is ongoing. These cyclic triamides have simple structures with chirality in the skeleton, exhibit unique dynamic behaviors, and can be easily synthesized. The triamides bearing hydrogen-bonding functional groups form interesting bowl-shaped monomeric and capsule-type dimeric structures, which may have application as molecular tectons, like other functional macrocycles.

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