A Chiral Tweezers-Type Dicarboxylic Acid: Studies on Its Complexation with Amines Utilizing CD Spectrum

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Complexation of a tweezers-type dicarboxylic acid (**1**) having an optically active π-system at its center with tertiary amines (triethylamine and DABCO) and secondary amines (piperidine and 4,4′-bipiperidine) was investigated under highly dilute conditions (about 6×10^{-5} mol dm^{-3}) in $CHCl_3$. The complex formation could be pursued with the CD spectrum of **1** which is markedly varied due to the titration of amines. The complexation process is discussed.

Since host–guest chemistry can be a useful model for substrate-receptor biochemistry, a number of systems capable of reversible binding interactions have been developed. Macrocyclic compounds such as crown ethers, cyclodextrins, and cyclophanes have dominated this area, presumably because their interactions with smaller molecules are easily conceptualized. Another type of host is a cleft-like synthetic module having two carboxyl groups in conjunction with a spacer element, whose unusual binding properties have been revealed by Rebek and his co-workers.[1] For evaluation of the binding constants, NMR titration studies performed at about 1×10^{-3} mol dm^{-3} have usually been employed. At this concentration, the molecules of the carboxylic acid interact intermolecularly to be in equilibrium with the corresponding dimer. Indeed, a recent paper[2] reported that a cleft-like dicarboxylic acid shows NMR chemical shifts which are concentration-dependent. Since the changes in shift ceased upon reaching about 1×10^{-5} mol dm^{-3}, it was suggested that the species at the low concentration were monomeric. However, the NMR titrations at such low concentrations proved to be impractical because long acquisition times are needed for obtaining reliable chemical shift data. Instead, UV/vis spectra analysis emerged as an appropriate method. Here, we describe a binding study with the CD spectrum[3] which is performed at about 6×10^{-5} mol dm^{-3}.

Results and Discussion

Recently, we reported that a new class of chelating module, a tweezers-type dicarboxylic acid (**1**) which has two carboxyl groups bridged by an optically active linkage (Scheme 1), shows the first Cotton effect in a CD spectrum ($CHCl_3$) [λ_{ext} 337 nm ($\Delta\varepsilon$ −16.5)] (Fig. 1). This Cotton effect originates from the optically active central 2,5-diphenylthiophene π-system.[4]

The central π-system is considered to become optically active by the assistance of two remote carboxyl groups which interact with the π-system via hydrogen bonding. If one protects its carboxyl groups as the corresponding esters, the Cotton effect disappears. When the two carboxyl groups of **1** were linked by $-NH(CH_2)_4NH-$ bridge to lead to compound **2**, the sign of the first Cotton effect was inversed [λ_{ext} 338 nm ($\Delta\varepsilon$ +72.3)]. Therefore, it is reasonable to expect that, if **1** binds to various amines, a dramatic change would take place in the CD spectrum of **1**: Interaction of **1** with monoamines

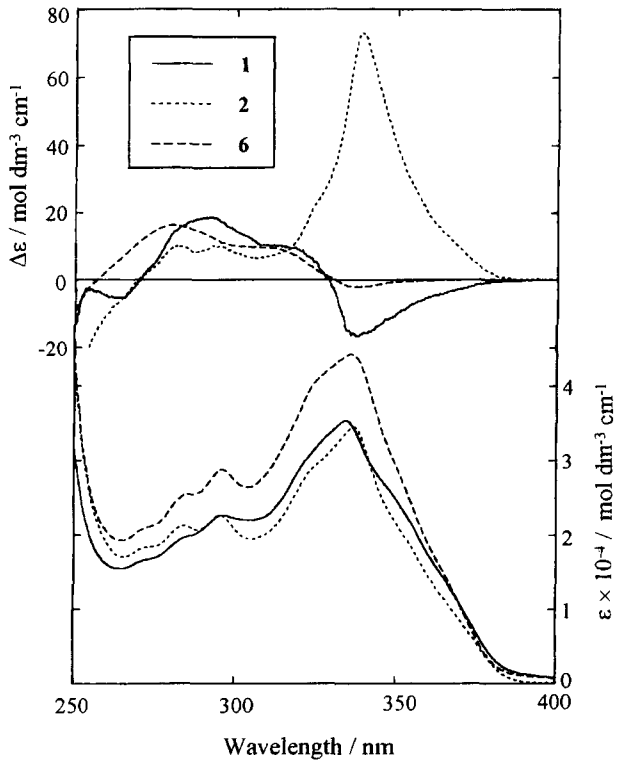
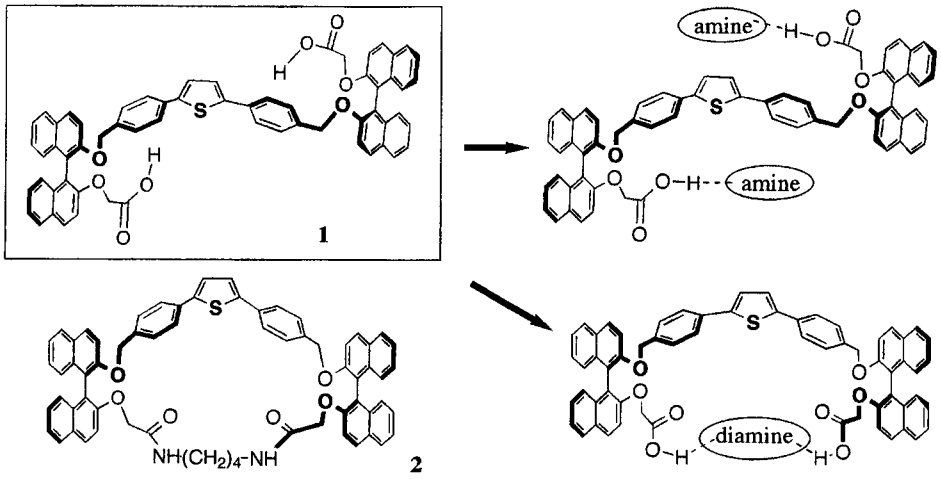


Fig. 1. CD and UV spectra of **1**, **2**, and **6** in $CHCl_3$: [**1**] 3.0×10^{-5} mol dm^{-3}; [**2**] 4.2×10^{-5} mol dm^{-3}; [**6**] 3.2×10^{-5} mol dm^{-3}.



Scheme 1.

would interrupt the optically active form of the central π-system, while diamines are presumed to form a cyclic salt with **1** under high dilute conditions and, as a result, the system would exhibit a large positive $\Delta\varepsilon$ around 338 nm.

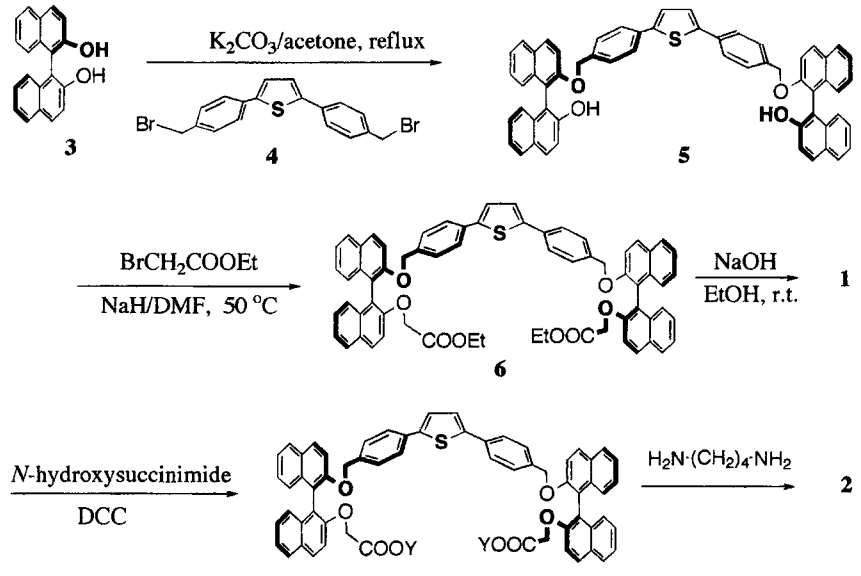
Synthesis of the Compounds (1 and 2): The compound (**1**) could be easily prepared according to Scheme 2: The reaction of 2,5-bis[*p*-(bromomethyl)phenyl]thiophene (**4**) with 2 molar amounts of 1,1′-bi-2-naphthol (**3**) (K_2CO_3 in refluxing acetone) gave a 1 : 2 substitution product (**5**), which was allowed to react with ethyl bromoacetate (NaH in DMF, 50 °C) to afford a diester derivative (**6**). The final alkaline hydrolysis (4 mol dm^{-3} aqueous NaOH in EtOH, room temperature) afforded **1**. Condensation of **1** with *N*-hydroxysuccinimide in the presence of *N*,*N*′-dicyclohexylcarbodiimide gave a bis(succiniminoxy) ester (**7**), which was subjected to the reaction with 1,4-diaminobutane to yield **2**. The details are given in the Experimental Section.

Complexation of Tertiary Amines: First we selected triethylamine (TEA) as a typical tertiary monoamine. The CD spectrum of **1** in $CHCl_3$ (5.93×10^{-5} mol dm^{-3}) was measured under portionwise addition of TEA: The first negative Cotton effect decreased gradually to finally reach $\Delta\varepsilon$ −1.6 at λ_{ext} 338 nm, as summarized in Fig. 2. This final CD spectrum resembles that of the diester (**6**) of **1**. This observation is in accord with our expectation that complexation with two molecules of TEA would eliminate the carboxylic hydrogens which interact with the central π-system. The present complexation can be expressed by the following equations:

$$\mathbf{1} + \mathrm{TEA} \overset{K_1}{\rightleftharpoons} \mathbf{1}\cdot\mathrm{TEA} \quad (1)$$

$$\mathbf{1}\cdot\mathrm{TEA} + \mathrm{TEA} \overset{K_2}{\rightleftharpoons} \mathbf{1}\cdot 2\mathrm{TEA} \quad (2)$$

In Fig. 2B, the plots of the observed $\Delta\varepsilon$ at 332.4 nm against the TEA concentration are shown. Because this complexation is associated with the study of multiple equilibria,[5] we assume that the binding constants K_1 and K_2 are identi-



Scheme 2.

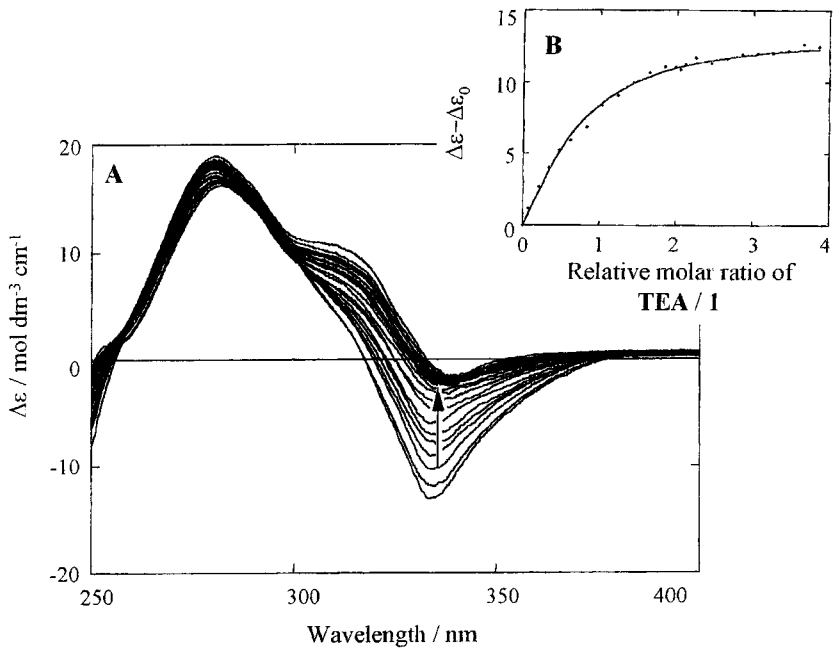


Fig. 2. A: CD Spectra of **1** in a titration with triethylamine (TEA); [**1**] = 5.9×10^{-5} mol dm^{-3} in $CHCl_3$.; [TEA] = 1.2×10^{-2} mol dm^{-3}. B: Plots of $\Delta\varepsilon-\Delta\varepsilon_0$ at 332 nm against the relative molar ratio of TEA ($\Delta\varepsilon_0$ = the initial $\Delta\varepsilon$) and that theoretical curve (line) calculated for $\Delta\varepsilon$ using $K_1 = K_2 = 1.6\times10^4$ (see text).

cal and that the concentration of free TEA can be approximated by the concentration of the added TEA.[6] According to Deranleau's treatment[5b] and the least-squares criterion,[7] the equilibrium constants (K_1 and K_2) were calculated to be 1.6×10^4 dm^3 mol^{-1}.

Next, the above solution (5.95×10^{-5} mol dm^{-3}) of **1** was titrated with 1,4-diazabicyclo[2.2.2]octane (DABCO): The first Cotton effect due to **1** was diminished, while a new Cotton effect appeared around 338 nm, as shown in Fig. 3. Its intensity reached to a maximum ($\Delta\varepsilon$ +9.2). These results are summarized in a titration curve (Fig. 3B) which shows the dependence of the $\Delta\varepsilon$ at 337 nm on the concentration of DABCO.

From this phenomenon, we can reasonably conclude that **1** and DABCO gave a cyclic 1 : 1 complex at a highly dilute concentration. The appearance of the first Cotton effect with

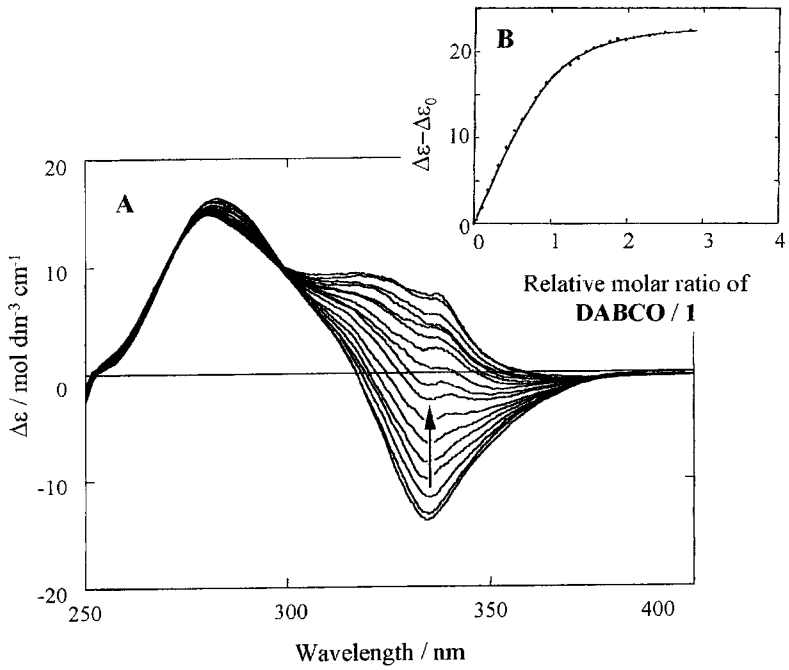


Fig. 3. A: CD Spectra of **1** in a titration with DABCO; [**1**] = 6.0×10^{-5} mol dm^{-3} in $CHCl_3$; [DABCO] = 6.2×10^{-3} mol dm^{-3}. B: Plots of $\Delta\varepsilon-\Delta\varepsilon_0$ at 337 nm against the relative molar ratio of DABCO ($\Delta\varepsilon_0$ = the initial $\Delta\varepsilon$) and that theoretical curve (line) calculated for $\Delta\varepsilon$ using $K = 1.4\times10^5$ (see text).

a positive sign also supports this explanation, because the cyclic compound (**2**) shows a positive $\Delta\varepsilon$ value (+72.3, λ_{ext} 338 nm). With MNDO/PM3 method,[9] we calculated an energy-minimized structure for the 1 : 1 complex of **1** and DABCO, this is shown in Fig. 4.

On the assumption that the 1 : 1 complex is formed directly from **1** and DABCO [Eq. 2], the titration curve was analyzed according to the Rose–Drago method[8] and the least-squares criterion to give 1.4×10^5 dm^3 mol^{-1} for its binding constant (K). Since the calculation curve fits adequately with the observed data, Eq. 3 was valid for the complexation of **1** with DABCO.

$$\mathbf{1}+\text{DABCO} \overset{K}{\rightleftharpoons} \mathbf{1}\cdot\text{DABCO} \qquad (3)$$

Complexation with Secondary Amines: Titration with piperidine caused marked changes in the CD spectrum of **1** in $CHCl_3$ (6.01×10^{-5} mol dm^{-3}). With the increasing concentration of piperidine, the first Cotton effect with a negative sign decreased and a new positive Cotton effect appeared at 339 nm, as shown in Fig. 5. In addition, the original positive second Cotton effect diminished gradually and a new negative second Cotton effect appeared at 319 nm, and two isosbestic points at 330 and 283 nm were observed. The titration curve of $\Delta\varepsilon$ against the concentration of piperidine in Fig. 5B indicated that finally a 1 : 2 complex of **1** and piperidine was obtained. Interestingly, the resulting 1 : 2 complex exhibited a large positive value for the first Cotton effect (λ_{ext} 339 nm). This is in sharp contrast with the 1 : 2 complex of **1** and TEA. These facts suggest the formation of a cyclic 1 : 2 complex (**10**) in the 1 : 2 complexation of **1** with piperidine (Scheme 3). In this case, it is likely that the cyclic 1 : 2 complex is in equilibrium with the corresponding acyclic form (**9**) and, judging from the large positive $\Delta\varepsilon$, the equilibrium has deviated to the site of **10**. Since 8- and 12-membered structures (**i** or **ii**) for a 2 : 2 complex of a carboxylic acid and a secondary amine in a crystalline state have been reported (Chart 1.),[10] we calculated both structures for the 2 : 2 complex of acetic acid and piperidine using the PM3 molecular orbital method. Results showed that the 12-membered structure is more stable by 9.6 kJ mol^{-1}. Therefore, we can propose the structure (**10**) for the cyclic 1 : 2 complex of **1** and piperidine.

We also investigated the titration of **1** with 4,4′-bipiperidine which possesses two NH groups at two remote ends. The change in the CD spectrum (Fig. 6) was analogous to that of DABCO, but the maximum value of $\Delta\varepsilon$ was relatively large (+45). The titration curve of the $\Delta\varepsilon$ at 337 nm against the

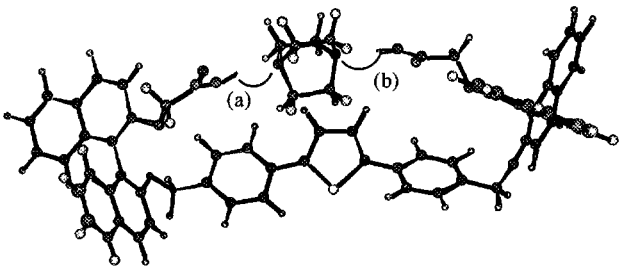
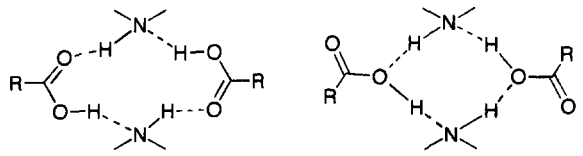


Fig. 4. An energy-minimized structure for the 1 : 1 complex of **1** and DABCO. Distance between N···HO: (a) 1.803 Å; (b) 1.798 Å.



I **II**

Chart 1.

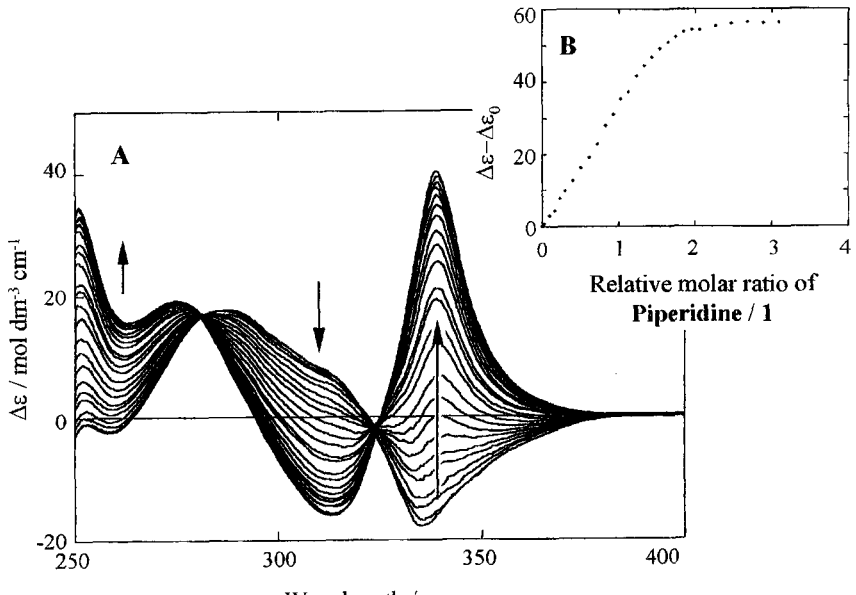
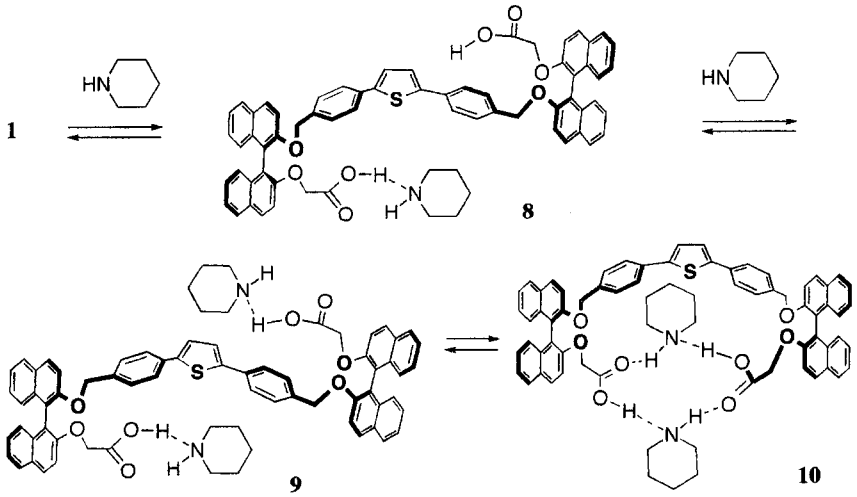


Fig. 5. A: CD Spectra of **1** in a titration with piperidine; [**1**] = 6.0×10^{-5} mol dm^{-3} in $CHCl_3$; [piperidine] = 6.2×10^{-3} mol dm^{-3}. B: Plots of $\Delta\varepsilon-\Delta\varepsilon_0$ at 339 nm against the relative molar ratio of piperidine ($\Delta\varepsilon_0$ = the initial $\Delta\varepsilon$).



Scheme 3.

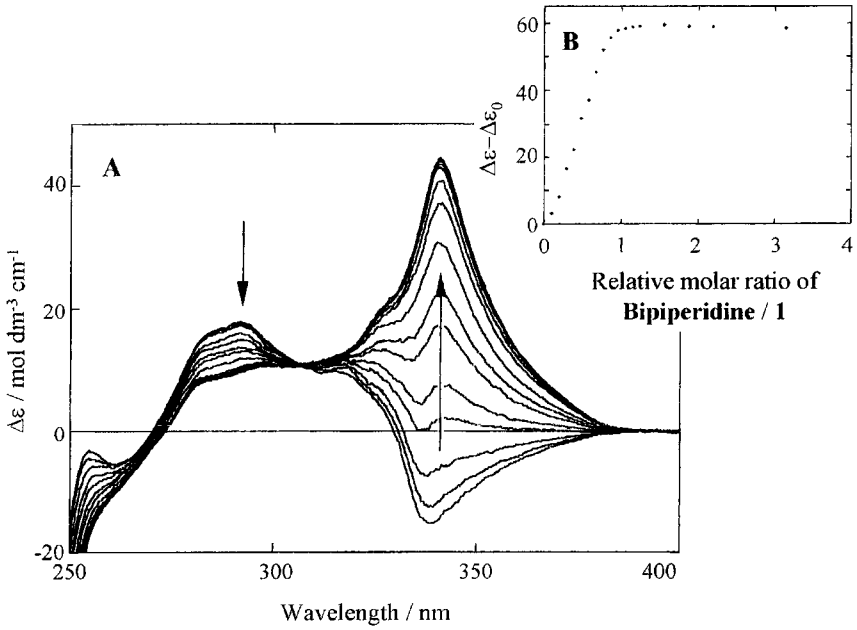


Fig. 6. A: CD Spectra of **1** in a titration with 4,4′-bipiperidine; [**1**] = 5.0×10^{-5} mol dm^{-3} in $CHCl_3$; [4,4′−bipiperidine] = 4.9×10^{-3} mol dm^{-3}. B: Plots of $\Delta\varepsilon-\Delta\varepsilon_0$ at 340 nm against the relative molar ratio of 4,4′-bipiperidine ($\Delta\varepsilon_0$ = the initial $\Delta\varepsilon$).

concentration of 4,4′-bipiperidine exhibited clearly a curving point around an equimolar amount of the bipiperidine, indicating that a tight 1 : 1 complex was formed. In the titration curve, a sigmoid line was observed between 0 and 1.0 molar equivalent of the bipiperidine. Generally, a sigmoid binding curve is related to the concept of cooperative behavior: this type of sigmoid curve can also be observed in the binding process of S ⇆ SL_2 (S = substrate; L = ligand), when two binding processes (S ⇆ SL and SL ⇆ SL_2) are cooperative.[11] Therefore, the present complexation is thought to involve a 2 : 1 complex of **1** and 4,4′-bipiperidine. As to the reason why the 1 : 1 complex of **1** and bipiperidine is stable, two possibilities could be considered: One is the size of 4,4′-bipiperidine which is fitted to the space between two carboxyl groups of **1**; the other one is a strong interaction of the carboxyl group with the NH group.

In conclusion, we have revealed that a tweezers-type dicarboxylic acid (**1**) having an optically active π-system at its center could form various complexes with tertiary amines (triethylamine and DABCO) and secondary amines (piperidine and bipiperidine)[12] under dilute conditions (about 6×10^{-5} mol dm^{-3}) in $CHCl_3$. Noteworthily, the complex formation could be followed by a marked change in the CD spectrum of **1** by the titration with the amines to enable precise analysis of the complexation process.

Experimental

General Procedures. IR spectra were obtained as KBr disks on a JASCO FT/IR-500 spectrophotometer. Optical rotations were determined with a JASCO DIP-370 polarimeter. ^{1}H NMR spectra were recorded on a Varian Gemini-2000 (300 MHz). All NMR data are reported in ppm (delta) downfield from tetramethylsilane. UV and CD spectra were recorded on JASCO V-570 and JASCO J-500, respectively. $CHCl_3$ was dried over $CaCl_2$ and distilled from P_2O_5

under N_2 atmosphere. THF was distilled from benzophenone and wired Na. These two solvents were used for the CD measurements within one week of distillation. TEA was dried from NaOH and distilled from NaH. DABCO was obtained from Kanto Chemical (Japan) without further purification. Piperidine was purified by alumina chromatography and kept over NaOH. 4,4′-Bipiperidine was obtained from 4,4′-bipiperidine dihydrochloride (Aldrich) on treatment with an aqueous solution of NaOH, followed by extraction with chloroform and evaporation.

2,5-Bis{4-[(2′-hydroxy-1,1′-bi-2-naphthyloxy)methyl]phenyl}thiophene (5). A solution of (*R*)-(+)-1,1′-bi-2-naphthol (3.05 g, 10.6 mmol) and 2,5-bis[4-(bromomethyl)phenyl]thiophene (2.13 g, 5.05 mmol) in dry acetone (400 ml) and K_2CO_3 (1.89 g, 13.7 mmol) was refluxed for 24 h. After insoluble solid was removed by filtration, the filtrate was evaporated and the oily residue was reprecipitated from methanol (350 ml). The deposited solid was gathered by filtration and subjected to column chromatography on silica gel (eluent: a 9 : 1 mixture of toluene and $CHCl_3$) to give a pale yellow powder. Further purification was performed by recrystallization from $CHCl_3$–cyclohexane: a pale yellow powder (2.51 g, 63%); mp 138—139 °C (decomp); $[\alpha]_D^{24}$ 34 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 7.99 (d, 2H, *J* = 9.1 Hz), 7.94 (d, 2H, *J* = 8.8 Hz), 7.89 (d, 4H, *J* = 8.1 Hz), 7.47 (d, 2H, *J* = 9.1 Hz), 7.41—7.19 (m, 16H), 7.17 (s, 2H), 7.07 (d, 2H, *J* = 8.1 Hz), 7.02 (d, 4H, *J* = 8.0 Hz), 5.12 (d, 2H, *J* = 12.6 Hz), 5.08 (d, 2H, *J* = 12.7 Hz), 4.94 (s, 2H); IR (KBr) 3511, 1618, 1590, 1506, 1207, 808, 748 cm^{-1}; MS (FAB$^+$) *m/z* 832. Anal. Calcd for $C_{58}H_{40}O_4S\cdot0.5H_2O$: C, 82.73; H, 4.91%. Found: C, 82.57; H, 4.84%.

2,5-Bis[4-({2′-[(ethoxycarbonyl)methoxy]-(*R*)-1,1′-bi-2-naphthyl-2-yloxy}methyl)phenyl]thiophene (6). To a solution of **5** (2.35 g, 2.8 mmol) in dry DMF (45 ml), was added NaH (0.773 g, 19.3 mmol) and the resulting mixture was stirred at room temperature till the mixture became reddish brown. Ethyl bromoacetate (3.10 ml, 27.8 mmol) was added and the reaction mixture was stirred at 50 °C for 24 h. The reaction was quenched by the addition of water and extracted with $CHCl_3$ (50 ml×3). The combined organic layers were dried over $MgSO_4$ and then evaporated. The oily residue was purified by column chromatography (silica gel; a 9 : 1 mixture of toluene and $CHCl_3$) to give **6** (2.55 g, 89%) as a pale yellow powder. Final purification was performed by reprecipitation from cyclohexane–ethyl acetate: a pale yellow solid; mp 69—70 °C; $[\alpha]_D^{24}$ 61 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 7.82—8.00 (m, 8H), 7.43 (d, 2H, *J* = 8.9 Hz), 7.15—7.40 (m, 20H), 6.97 (d, 4H, *J* = 8.1 Hz), 5.08 (d, 2H, *J* = 12.8 Hz), 5.07 (d, 2H, *J* = 12.8 Hz), 4.51 (d, 2H, *J* = 16.5 Hz), 4.48 (d, 2H, *J* = 16.5 Hz), 4.07 (q, 4H, *J* = 7.1 Hz), 1.12 (t, 6H, *J* = 7.1 Hz); IR (KBr) 3511, 1618, 1590, 1506, 1207, 808, 748 cm^{-1}; MS (FAB) *m/z* 1003 (M$^+$−1). Anal. Calcd for $C_{66}H_{52}O_8S\cdot0.4CH_3COOC_2H_5\cdot0.4C_6H_{12}$: C, 78.28; H, 5.63%. Found: C, 78.32; H, 5.60%.

2,5-Bis{4-[(2′-carboxymethoxy-(*R*)-1,1′-binaphthyl-2-yloxy)-methyl]phenyl}thiophene (1). To a solution of **6** (1.22 g, 1.22 mmol) in THF (3 ml), was added a 4 mol dm^{-3} solution of NaOH in a 1 : 1 mixture of water and EtOH (3 ml). After this mixture was stirred at room temperature for 7 h, the resulting material was extracted with diethyl ether (30 ml), acidified with hydrochloric acid, and extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, evaporated, and reprecipitated from ethyl acetate-cyclophexante to give a pale yellow powder (984 mg, 85%): Mp 109—110 °C; $[\alpha]_D^{24}$ −100 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.05—7.80 (m, 8H), 7.52 (d, 2H, *J* = 8.93 Hz), 7.41—7.12 (m, 16H), 6.97 (d, 2H, *J* = 8.38 Hz), 6.80 (d, 2H, *J* = 7.83 Hz), 5.06 (s, 4H), 4.70 (d, 2H, *J* = 16.5 Hz), 4.55 (d, 2H, *J* = 16.5 Hz); IR (KBr) 3422, 1732, 1620, 1590, 1262, 1104, 806 cm^{-1}; MS (FAB$^+$) *m/z* 948. Anal. Calcd for $C_{62}H_{44}O_8S\cdot CH_3COOC_2H_5\cdot0.5C_6H_{12}$: C, 76.79; H, 5.42%. Found: C, 76.82; H, 5.52%.

Synthesis of the Compound (2): To a solution of **1** (0.503 g, 0.531 mmol) and *N*-hydroxysuccinimide (0.140 g, 1.22 mmol) in a mixture of dry $CHCl_3$ (100 ml) and dry THF (10 ml), was added a solution of dicyclohexylcarbodiimide (0.441 g, 2.14 mmol) under ice-cooling. The resulting mixture was stirred at the same temperature for 1 h and then was warmed to room temperature. The resulting solution was evaporated and dried in vacuo. The residue was dissolved in dry toluene and insoluble matter was filtered off. After the filtrate was evaporated and dissolved in dry ethyl acetate (5 ml), cyclohexane (30 ml) was added. The deposited solid (the bis(succiniminoxy) ester derivative of **1**) was gathered by filtration to give a yellow powder (0.555 g, 92%).

A solution of this powder (200 mg, 0.195 mmol) in $CHCl_3$ (50 ml) and a solution of 1,4-diaminobutane (17 μl, 0.18 mmol) in $CHCl_3$ (50 ml) were simultaneously added dropwise to $CHCl_3$ (150 ml) over 16 h. The resulting solution was evaporated. The residual gum was dissolved in $CHCl_3$ and the insoluble solid was filtered off. The filtrate was evaporated and chromatographed on alumina (eluent: a 1 : 1 mixture of toluene and $CHCl_3$). Final purification was performed by reprecipitation from a 1 : 10 mixture of toluene and cyclohexane to gave **2** as a colorless powder (39 mg, 22%): Mp 172—173 °C; $[\alpha]_D^{24}$ 688 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 8.03 (d, 2H, *J* = 9.0 Hz), 7.93 (d, 2H, *J* = 8.0 Hz), 7.81 (d, 2H, *J* = 9.2 Hz), 7.74 (d, 2H, *J* = 8.3 Hz), 7.4—7.0 (m, 26H), 5.22 (d, 2H, *J* = 13.7 Hz), 5.18 (t, 2H, *J* = 5.8 Hz), 5.06 (d, 2H, *J* = 13.7 Hz), 4.49 (d, 2H, *J* = 14.4 Hz), 4.29 (d, 2H, *J* = 14.2 Hz), 2.3—2.1 (m, 4H), 0.61 (diffused t, 4H); IR (KBr) 3408, 2928, 1680, 1505, 1216, 803 cm^{-1}; MS (FAB) *m/z* 1000 (M$^+$). Anal. Calcd for $C_{66}H_{52}N_2O_6S\cdot H_2O$: C, 77.78; H, 5.34; N, 2.75%. Found: C, 77.87; H, 5.17; N, 2.75%.

Titration. Typically, a solution (5—6×10^{-5} mol dm^{-3}) of **1** in dry $CHCl_3$ was prepared, an aliquot (3.0 ml) of the resulting solution was transferred to a 1.0 cm path-length quartz cell, and a CD spectrum was recorded. Aliquots (3.0—5.0 μl) of a 10^{-3} mol dm^{-3} solution ($CHCl_3$) of an amine were added, and a spectrum was recorded after each addition.

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