was added. The aqueous layer was extracted with CH_2Cl_3 (3 × 5 mL), and combined CH_2Cl_2 layers were washed with 5% aqueous $NaHCO_3$ (1 × 10 mL) and H_2O (1 × 10 mL), then dried, filtered, and concentrated. Chromatography (9.9:0.1 $CHCl_3$/MeOH) afforded **24** (0.019 g, 68%): mp 169-171 °C (EtOAc/ether); IR ($CHCl_3$) 2940, 1858, 1775, 1604, 1455, 1383, 1300, 1146, 1096, 1085, 958, 914 cm^{-1}; ^1H NMR (60 MHz, CD_3COCD_3) δ 3.97 (s, 2 H), 2.95 (s, 3 H), 1.61 (s, 6 H), 1.56 (s, 6 H), 1.37 (s, 3 H); MS calcd for $C_{14}H_{17}O_3$ ($M^+ - SO_2Me$) 233.1178, found 233.1155.

Procedure for the Conversion of Mercapto Adducts 15 and 20 into Methylthio Adducts 16 and 21, Respectively. Diazabicyclo[5.4.0]undecene (DBU) (19 μL, 0.123 mmol) and CH_3I (0.1 mL, 1.6 mmol) were added to a solution of the mercapto adduct (0.021 g, 0.0616 mmol) in anhydrous benzene (10 mL). The reaction mixture was stirred for 2 days, then washed with 1 N HCl (3 × 10 mL) and H_2O (1 × 10 mL), dried, filtered, and concentrated to give the corresponding thiomethyl adduct (0.022 g, quantitative yield).

Conversion of Amino Adduct 29 into *syn*-*N*-Acetylamino Adduct 30. Acetic anhydride (0.5 mL) and pyridine (0.5 mL) were added to a solution of **29** (0.023 g, 0.071 mmol) in CH_2Cl_2 (7 mL). The solution was stirred for 23 h, then toluene was added, and the solution was concentrated to give **30** (0.026 g, quantitative yield).

Preparation of *O*-Acetyl Adduct 28. (Dimethylamino)pyridine (DMAP) (0.025 g, 0.202 mmol) and acetic anhydride (0.2 mL, 2.0 mmol) were added to a solution of the hydroxy adduct **27** (0.046 g, 0.184 mmol) in anhydrous benzene (8 mL). The solution was refluxed for 3.5 days. Additional 4-(dimethylamino)pyridine (0.045 g) and acetic anhydride (0.2 mL) were added, and refluxing was continued for 2 more days. TLC showed that the reaction was still incomplete; however, the solution wsa allowed to cool, diluted to 5 mL with EtOAc, washed with 5% (v/v) HCl (1 × 10 mL) and brine (1 × 10 mL), dried, filtered, and concentrated. Chromatography (8:2 petroleum ether/EtOAc) yielded **28** (0.030 g, 52%): mp 136-138 °C (ether); IR ($CHCl_3$) 2940, 1858, 1775, 1455, 1372, 1317, 1140, 1113, 1080, 1013, 947, 914 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 3.31 (s, 2 H), 2.00 (s, 3 H), 1.56 (s, 6 H), 1.36 (s, 6 H), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.4, 169.3, 135.8, 101.6, 60.9, 51.8, 22.0, 12.2, 11.6, 11.2; MS calcd for $C_{16}H_{20}O_5$ 292.1313, found 292.1285.

Conversion of Methoxy Adduct 26 into Chloro Adduct 25 and Hydroxy Adduct 27. Anhydrous sodium iodide (0.031 g, 0.205 mmol) and trimethylchlorosilane (27 μL, 0.205 mmol) were added to a solution of **26** (0.054 g, 0.205 mmol) in anhydrous CH_3CN (2 mL).[48] The stirred reaction mixture was monitored by TLC. After 18 h fresh trimethylchlorosilane (27 μL) was added, and 26 h later additional sodium iodide (0.031 g) and trimethylchlorosilane (27 μL) were added. After a total of 3.5 days, further sodium iodide (0.093 g) and trimethylchlorosilane (0.1 mL) were added. Twenty-four hours later the reaction mixture was quenched with H_2O (10 mL). The solution was extracted with ether (3 × 10 mL), and the combined ether extracts were washed with 5% aqueous (w/v) sodium thiosulfate (1 × 10 mL) and brine (1 × 10 mL), then dried, filtered, and concentrated. Chromatography (1:1 petroleum ether/benzene) (sample dissolved in benzene) yielded the chloro adduct **25** (0.027 g, 49%) and hydroxy adduct **27** (0.011 g, 22%) (9:1 benzene/acetone).

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Supplementary Material Available: General experimental conditions and details of the X-ray studies and tables of atomic coordinates, interatomic distances, and thermal parameters (6 pages). Ordering information is given on any current masthead page.

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Synthesis and Selective Molecular Recognition of a Macrotricyclic Receptor Having Crown Ether and Cyclophane Subunits as Binding Sites[1]

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Abstract: The synthesis and selective molecular recognition of a new type of cylindrical, macrotricyclic receptor (**1**) having crown ether and cyclophane subunits as binding sites and a large hydrophobic cavity are described. Receptor **1** was synthesized by the stepwise construction of three individually prepared subunits: bis(*p*-toluenesulfonamido)dibenzo-18-crown-6 (**6**); diaminocyclophane (**7**); ethyl 4′-(bromomethyl)biphenyl-4-carboxylate (**8**). The interaction of **1** and various (ω-phenylalkyl)ammonium picrates **2**, for which the number of methylene units varies from 3 to 9, was examined, and they were found to form 1/1 complexes. The selectivity of **1** for **2** was evaluated by comparing the stability constants (K_s') of these complexes. The K_s' values were calculated on the basis of the chemical shift changes of the protons in **2** on varying the **1**/**2** ratio. The K_s' values of the complexes with (5-phenylpentyl)ammonium (**2c**) and (6-phenylhexyl)ammonium picrates (**2d**) were more than 3 times as large as those of the other complexes; i.e., **1** showed selective molecular recognition for **2**. The selectivity could result from a cooperative phenomenon involving the electrostatic and hydrophobic interactions between the crown ether subunit and the ammonium group and between the cyclophane subunit and the phenyl group, respectively.

An understanding of the underlying factors in the selective molecular recognition of organic molecules for organic substrates is very important and has a wide-ranging ramifications, especially in the areas of chemistry and biochemistry. Naturally occurring receptors have a three-dimensional cavity, whose shape plays an important role in determining their binding ability for different substrates, supplementing the effects of the various kinds of nonbonding interactions and leading to stereo- and/or regioselective responses.[2] In the past two decades many types of artificial

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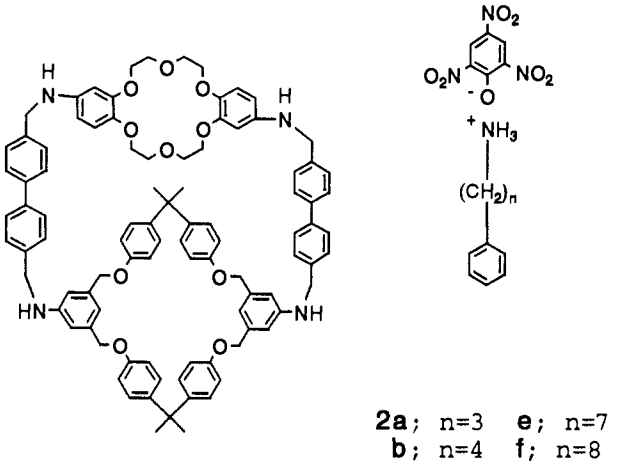
Chart I



1

2a; n=3 **e**; n=7
b; n=4 **f**; n=8
c; n=5 **g**; n=9
d; n=6

receptors capable of complexing with ionic or neutral substrates in solution have been synthesized.[2,3] These receptors can be classified into two types: acyclic receptors, most of whose conformations have to be frozen out during the process of complexation with substrates, and preorganized, cyclic receptors. It is known that the highly selective molecular recognition of cyclic receptors for substrates by host–guest interaction and/or complexation is achieved through the complementarity of their binding sites and the preorganization of the receptors.[2,4] Polycyclic receptors such as cryptands show high complementarity to substrates since they have a three-dimensional cavity.

Macrotricyclic receptors (cryptands) having two electrostatic interaction sites have been widely used as mimics of biological receptor systems and can show selective complexation with dicationic organic substrates.[5] They are typical examples of the effects that can be achieved by using the complementarity of binding sites and the preorganization of receptors. But, to realize selective complexation for more complex substrates, as is observed for enzymes, the cavity of the receptors should be highly preorganized and have various different types of binding sites.

Hydrophobic interactions also play an important role in complexation by natural receptors. Consequently, artificial, cyclic receptors having cyclophane and crown ether subunits, which can offer hydrophobic and electrostatic binding sites, respectively, are considered to be even more fascinating as biomimics. By providing binding sites at the appropriate distances and orientations, the receptors might accommodate more complex organic substrates and form highly recognized inclusion complexes. Canceill et al. reported the synthesis of a cyclotriveratrylene capped with a crown ether (speleand) and its complexation with methylammonium picrate.[6] Hamilton and his co-worker also reported the synthesis of a paracyclophane capped with a crown ether.[7] But, both groups have not showed selective binding of substrates to their respective complexes.

In this paper, we describe the synthesis and selective complexation of a novel, cylindrical, macrotricyclic receptor (**1**) having both an electrostatically interactive crown ether subunit and a hydrophobically interactive cyclophane subunit, which are separated by a faced distance (Chart I).

Crown ethers are selective receptors for cations, and cyclophanes supply a hydrophobic cavity to form complexes with aromatic compounds. Hence, (ω-phenylalkyl)ammonium picrates **2** should be substrates complementary to **1**. To determine the selectivity of **1** for **2** in molecular recognition, ammonium salts having different lengths of methylene chain were prepared, and their complexation with **1** was examined.

Results and Discussion

Synthesis of Macrotricyclic Receptor. We used *trans*-diaminodibenzo-18-crown-6 (**3**)[8] as the mother skeleton for the crown ether subunit because of its ready availability and C_2 symmetry. Dinitrocyclophane (**4**), which can form complexes with aromatic compounds with high selectivity,[9] was chosen as the mother skeleton for the cyclophane subunit. In order to position these subunits at an adequate distance and to form a preorganized cavity, ethyl 4′-methylbiphenyl-4-carboxylate (**5**) was used as the precursor for the rigid-bridge subunit.

Diamino-crown ether **3** was prepared according to the method in the literature.[8] To introduce a functionality that can be connected to the bridge subunits by alkylation, the amino groups in **3** were tosylated with tosyl chloride in pyridine to give the crown ether subunit bis(*p*-toluenesulfonamido)dibenzo-18-crown-6 (**6**) (86%). The benzene complex of dinitrocyclophane **4**, synthesized according to the procedure already reported,[9] was converted into the cyclophane subunit **7** by reduction with hydrazine hydrate in the presence of Pd/C (90%). As the bridge subunit, ethyl 4′-(bromomethyl)biphenyl-4-carboxylate (**8**) was designed to be able to react with the crown ether and cyclophane subunits by different types of reactions, namely, alkylation and acylation, respectively. The bridge subunit **8** was obtained by bromination of biphenyl derivative **5** (84%), prepared from 4-methylbiphenyl by the procedure in the literature,[10] with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide (BPO) under the light of a tungsten lamp.

The condensation of **6** and **8** in *N*,*N*-dimethylformamide (DMF) in the presence of K_2CO_3 gave the U-type diester precursor **9** (87%), which was converted into diacid chloride **10** by successive hydrolysis and treatment with thionyl chloride (82%) (see Scheme I). Diacid chloride **10** was condensed with **7** in a CH_2Cl_2/pyridine mixed solvent under high-dilution conditions to afford cyclic diamide **11** (64%). Since **11** was rather unstable, it was immediately purified by alumina column chromatography and treated with lithium aluminum hydride to both reduce the amide carbonyls and remove the tosyl groups in one step. The macrotricyclic receptor **1** obtained was purified by alumina column chromatography or alumina TLC under a nitrogen atmosphere (44%).

Synthesis of Ammonium Salts. Half-esters **12** of pentanedioic acid, heptanedioic acid, and nonanedioic acid were converted to the corresponding acid chlorides (56–93%) (Scheme II). Keto acids **13** were obtained by the Friedel–Crafts acylation of benzene with the acid chlorides, followed by hydrolysis (74–79%). The Wolff–Kishner reduction of **13** gave ω-phenylalkanoic acids (96–98%), which were converted to the corresponding amides **14** via the acid chlorides (34–58%). Reduction of **14** with borane–

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Table I. Stability Constants ($K_s' \times 10^{-2}/M^{-1}$) Calculated on the Basis of Chemical Shift Changes of the Ammonium α-Methylene Protons and of the Benzyl Protons (Parentheses) in the Substrates **2a–g**[a]

substrate	n	20 °C	40 °C	60 °C
2a	3	3.3 (3.4)	2.7 (2.9)	2.2 (2.3)
2b	4	4.4 (4.7)	3.7 (4.0)	2.8 (2.6)
2c	5	17.3 (18.2)	8.8 (8.7)	4.6 (4.5)
2d	6	17.0 (18.6)	8.2 (7.8)	4.2 (4.3)
2e	7	6.2 (7.7)	4.7 (5.3)	3.0 (2.9)
2f	8	5.0 (4.2)[b]	4.1 (4.3)	3.0 (2.7)
2g	9	2.6 (2.4)	2.1 (1.8)	1.6 (1.0)

[a] NMR (400 MHz) spectra were measured in $CDCl_3/CD_3OD$ (4/1, v/v) solutions. The K_s' values were calculated by the least-squares method by using SALS. Standard deviations were maintained below 20%. [b] Standard deviation was 29%.

THF complex or lithium aluminum hydride gave ω-phenylalkylamines **15c,e,g** with an odd methylene number (72–89%). The Hofmann rearrangement of **14** in methanol, followed by hydrolysis, gave ω-phenylalkylamines **15d,f** with an even methylene number (47–62%). Treatment of **15c–g** and commercially available 3-phenylpropylamine or 4-phenylbutylamine with picric acid in cold ether gave **2a–g** (47–87%).

Complexation. The stability constant (K_s', M^{-1}) of the complex of **1** with **2** and the thermodynamic parameters, $\Delta G'$ ($kJ \cdot mol^{-1}$), $\Delta H'$ ($kJ \cdot mol^{-1}$), and $\Delta S'$ ($J \cdot K^{-1} \cdot mol^{-1}$), for the complexation were evaluated on the basis of ^1H NMR spectral changes.[11] The ^1H NMR measurements for the complexation were carried out at 20, 40, and 60 °C in a $CDCl_3/CD_3OD$ mixed solvent (4/1, v/v). Since dynamic NMR experiments showed that the coalescence point is below 0 °C (see below), the complexation and decomplexation of **1** with **2** are considered to be fast enough at the temperatures examined. Thus, $\Delta\delta$ (the difference in chemical shift between the protons of **2** alone and those of **2** in the presence of **1**) was observed at the time-average position as a function of $\Delta\delta_{max}$ (the ultimate value for the change of the chemical shift), [R] (total concentration of **1**), [S] (total concentration of **2**), and K_s'. The K_s' value of the complex is expressed by eq 1 for a 1/1 receptor to substrate stoichiometry.[11]

$$\Delta\delta/\Delta\delta_{max} = [[R] + [S] + 1/K_s' - [([R] + [S] + 1/K_s')^2 - 4[R][S]]^{1/2}]/2[R] \quad (1)$$

^1H NMR spectra were measured for a set of solutions of **1** and **2**, for which [S] was maintained constant while [R] was changed gradually from 0 to ≈2.5 × [S]. Each $\Delta\delta$ of the ammonium α-methylene and benzyl protons in **2** was plotted against [R].[11] K_s' and $\Delta\delta_{max}$ values and related thermodynamic parameters were calculated by curve fitting of the plots to eq 1 with the statistical analysis for least-squares method (SALS).[12] Although the observational error, which occurred mainly on the preparation of the solutions, was estimated to be below 5%, the standard deviations of the values (K_s' and $\Delta\delta_{max}$), calculated from the residual sum of squares in the course of the curve fitting, were found to be usually above 20%, because the changes in the chemical shifts were only small. This problem could be solved by SALS, since SALS can be applied for the curve fitting of experimental data having several abscissas ([R] and [S], in this case) at once. Thus, ^1H NMR measurements were carried out for other sets of solutions of different [S], until the standard deviation of K_s' dropped below 20%.[12] The standard deviation of $\Delta\delta_{max}$ was generally smaller than that of K_s'. No systematic error was observed for the calculation using eq 1, indicating that the contribution of complexes of other than 1/1 stoichiometry is below the error level under our experimental conditions. The K_s' and $\Delta\delta_{max}$ of each complex are listed in Tables I and II, respectively. Furthermore, from the $1/T$ vs log K_s' plots, $\Delta H'$ and $\Delta S'$ were estimated. These values are listed in Table III with $\Delta G'$ values.

The most stable complexes were formed with **2c** and **2d** at the temperature examined. Higher temperatures resulted in lower selectivity and at 60 °C the selectivity almost disappeared (Figure 1).

The $\Delta\delta_{max}$ values of the α-, β-, γ-, and δ-methylene protons originating from **2b** for the complex of **1** with **2b** were larger than those for the corresponding complex of dibenzo-18-crown-6 (**16**) with **2b** under the same conditions (Table IV). The enlargement

Table II. $\Delta\delta_{max}$/ppm Values Calculated on the Basis of Chemical Shift Changes of the Ammonium α-Methylene Protons and of the Benzyl Protons (Parentheses) in Substrates **2a–2g**[a]

substrate	n	20 °C	40 °C	60 °C
2a	3	0.71 (0.61)	0.65 (0.57)	0.55 (0.49)
2b	4	0.69 (0.57)	0.63 (0.52)	0.53 (0.46)
2c	5	0.51 (0.34)	0.49 (0.33)	0.45 (0.31)
2d	6	0.49 (0.22)	0.48 (0.22)	0.43 (0.20)
2e	7	0.59 (0.17)	0.53 (0.16)	0.48 (0.15)
2f	8	0.61 (0.15)	0.55 (0.12)	0.46 (0.11)
2g	9	0.69 (0.13)	0.63 (0.12)	0.54 (0.12)

[a] NMR (400 MHz) spectra were measured in $CDCl_3/CD_3OD$ (4/1, v/v) solutions. The $\Delta\delta_{max}$ values were calculated by the least-squares method by using SALS. Standard deviations were maintained below 10%.

Table III. Thermodynamic Parameters for Complexes **1·2a–g**

substrate	n	$\Delta G'$[a]/kJ·mol^{-1} 20 °C	40 °C	60 °C	$\Delta H'$/ kJ·mol^{-1}	$\Delta S'$[b]/ J·K^{-1}·mol^{-1}
2a	3	14.2	14.7	15.1	−8	+22
2b	4	14.9	15.5	15.5	−11	+15
2c	5	18.2	17.6	16.9	−28	−32
2d	6	18.2	17.4	16.8	−29	−37
2e	7	15.9	16.2	15.7	−18	−5
2f	8	14.9	15.7	15.7	−10	+19
2g	9	13.5	13.7	14.1	−9	+16

[a] Standard deviations were maintained below 0.3 kJ·mol^{-1}. [b] Calculated from $1/T$ vs log K_s' plots by using the least-squares method.

Table IV. $\Delta\delta_{max}$/ppm Values for the Complexes of **2b**[a]

receptor	α	β	γ	δ
1	0.63	0.70	0.50	0.52
16	0.36	0.46	0.31	0.30

[a] NMR (400 MHz) spectra were measured in $CDCl_3/CD_3OD$ (4/1, v/v) solutions at 40 °C. Standard deviations were maintained below 5%.

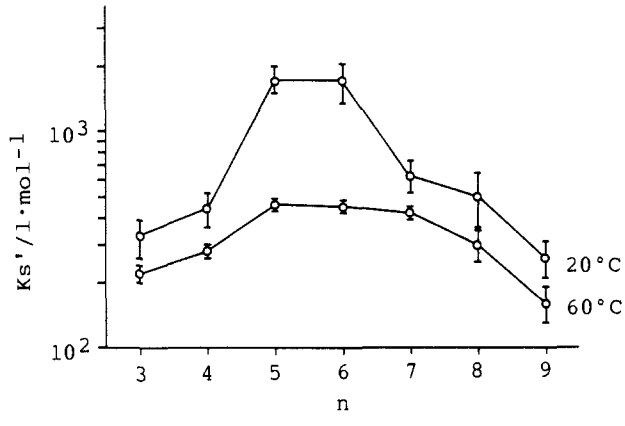

Figure 1. K_s' vs the length of the methylene chain of **2** at 20 and 60 °C in $CDCl_3/CD_3OD$ (4/1, v/v).

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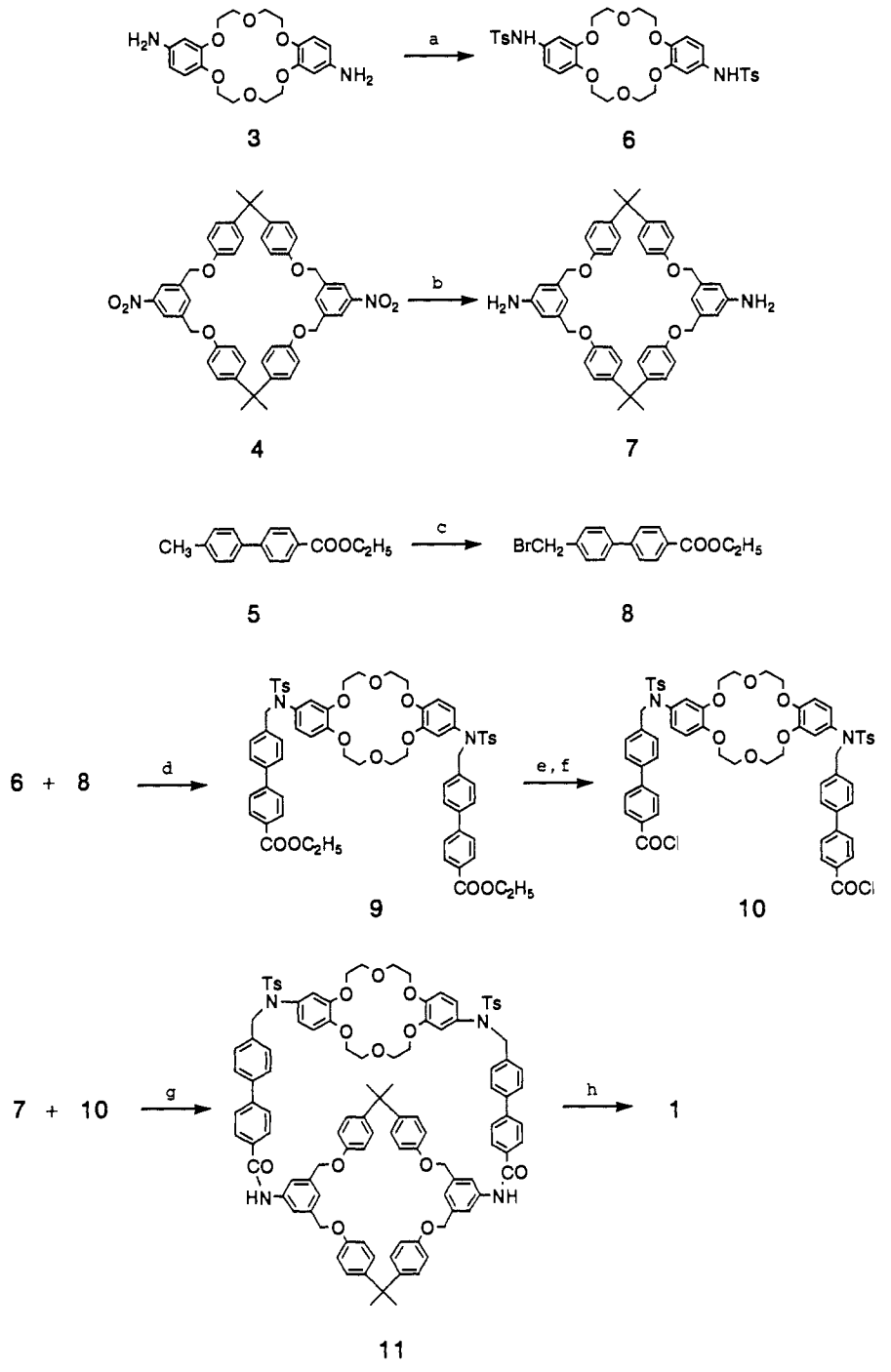
Scheme I.[a] Synthesis of Receptor **1**



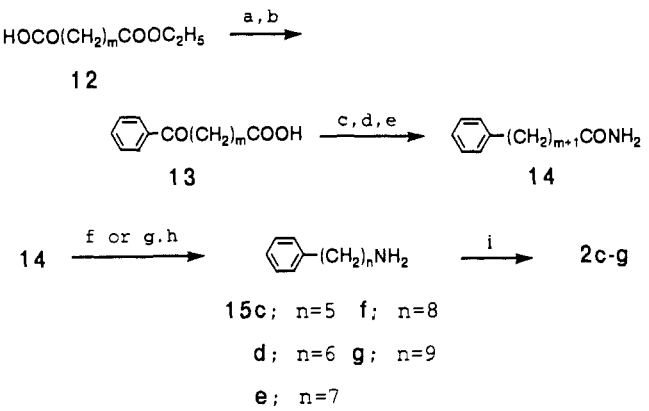
[a] Key: (a) TsCl, pyridine; (b) $H_2NNH_2 \cdot H_2O$, 5% Pd/C; (c) NBS, catalytic BPO, *hν*, CH_2Cl_2; (d) K_2CO_3, DMF; (e) NaOH, H_2O–ethanol; (f) $SOCl_2$, benzene; (g) high dilution, CH_2Cl_2–pyridine; (h) $LiAlH_4$, THF.

of $\Delta\delta_{max}$ for **1·2b** may be attributed to the shielding effect of the biphenyl groups in the bridge subunits. This result indicates that the inclusion complex of **2** was formed in the central cavity of **1** as observed for diammonium cryptates.[5]

The superstructure of **1·2** can be deduced from the values of $\Delta\delta_{max}$. The $\Delta\delta_{max}$ value of the ammonium α-methylene protons for the complexes of **1** with **2** is almost constant. This means that the environment around the ammonium α-methylene protons is almost independent of the length of the methylene chains. By contrast, the $\Delta\delta_{max}$ value of the benzyl protons depends greatly on the length of the methylene chain of **2**. These phenomena indicate that **2** is bound in a 1/1 stoichiometry within the central cavity of **1** by anchoring of the primary ammonium group to the crown ether subunit, independent of the length of its methylene chain.

In our previous report,[9] we described that dinitrocyclophane **4** formed a benzene complex in the crystalline state and that the benzene molecule was located in the hydrophobic channel between the columns formed by **4**. The conformation of **4** in the crystalline state is centrosymmetric, and the benzene molecule interacts with **4** by edge contact, since the benzene molecule may be *pulled up* by the hydrophobic interaction with the nitrobenzene moiety in the neighboring molecule of **4** in the crystalline state.[9] By contrast, the conformation of the cyclophane subunit in **1** should have C_2 or mirror symmetry to build the structure of **1**. In this situation, there exists only the hydrophobic interaction of the phenyl group in **2** with one unit of the cyclophane subunit, resulting in the location of the phenyl group in **2** slightly inside of the cavity of the cyclophane subunit. Moreover, the conformation of the crown ether subunit may be as reported in the literature.[13]

Scheme II.[a] Synthesis of Substrate **2**



[a] Key: (a) $SOCl_2$, benzene; (b) benzene, $AlCl_3$, then NaOH, H_2O; (c) $H_2NNH_2 \cdot H_2O$, KOH; (d) $SOCl_2$; (e) NH_3; (f) BH_3·THF or $LiAlH_4$, THF; (g) Br_2, NaOH, methanol; (h) H^+, H_2O; (i) picric acid, ether.

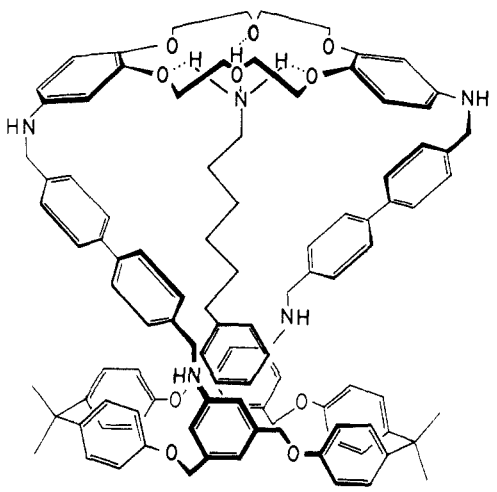


Figure 2. Schematic representation of a possible structure of the complex of macrotricyclic receptor **1** with **2d**.

On the basis of these considerations, a possible structure of **1**, in which the cyclophane subunit exists with C_2 symmetry, was examined by CPK molecular models. **2c** and **2d** can sit in the cavity of **1** by anchoring their ammonium group to the crown ether subunit while the phenyl group contacts the cyclophane subunit as shown in Figure 2. By contrast, in the cases of **2a** and **2b**, the methylene chains are too short for contact between the phenyl group and the cyclophane subunit in **1**. Moreover, the methylene chains in **2e–g** are too long for a stable complex to be formed with **1**. Therefore, the methylene chains have to take an unfavorable conformation in order for the contact between the phenyl group and the cycylophane subunit to take place and/or an unfavorable conformation change of the receptor **1** must occur. Therefore, the selectivity of **1** for **2** comes from the complementary interaction between the phenyl group and the cyclophane subunit. These correlations were also observed between **1**, in which the cyclophane subunit has *mirror symmetry*, and **2**.

The K_s' values of the complexes of dibenzo-18-crown-6 (**16**) with **2b** and with **2d** were 7.6×10^2 and 6.9×10^2, respectively, in $CDCl_3/CD_3OD$ (4/1, v/v) at 40 °C. On the other hand, the K_s' values of **1·2b** and **1·2d** were 3.7×10^2 and 8.2×10^2, respectively, under the same conditions (Table I). The K_s' value of **1·2b** is smaller than that of **16·2b**, showing that the conformation change of the crown ether subunit in **1** necessary for "induced fitting" is depressed by bridging with the cyclophane subunit, while **16** can easily change its conformation to form a stable complex

(13) Grootenhuis, P. D. J.; Kollman, P. A. *J. Am. Chem. Soc.* **1989**, *111*, 2152.

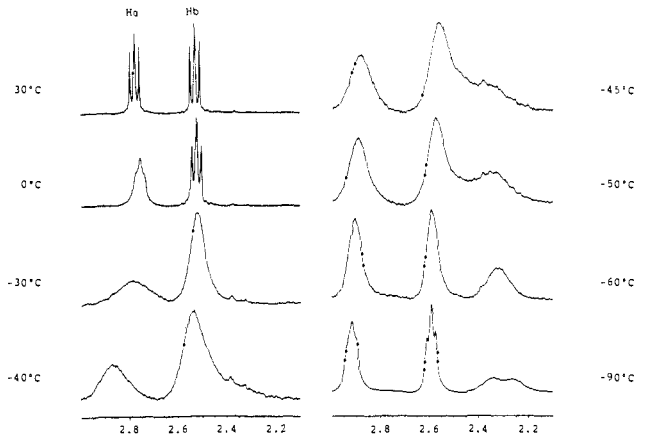


Figure 3. Variable-temperature ^1H NMR spectra of complex **1·2d** at 400 MHz in CD_2Cl_2/CD_3OD (5/2, v/v). The signals denoted as Hα and Hb are of the ammonium α-methylene and benzyl protons, respectively. [R] = 5.4×10^{-3} M, [S] = 17.6×10^{-3} M.

by induced fitting. Although there is no significant difference between the K_s' values of **16·2b** and **16·2d**, the K_s' value of **1·2d** is obviously larger than that of **1·2b**. This fact indicates that the enhancement of the K_s' value of **1·2d** in comparison with that of **1·2b** comes from the cooperative interaction between the phenyl group in **2** and the cyclophane subunit in **1**, which is absent in **16**, rather than from the primary interaction between the ammonium group and the crown ether subunit.

The assumption is strongly supported by thermodynamic parameters. In addition to the great increase in K_s' on going from the complex with **2b** to that with **2c**, marked changes, i.e., the decreases of $\Delta H'$ (−17 kJ·mol^{-1}) and $\Delta S'$ (−47 J·K^{-1}·mol^{-1}), were observed in the thermodynamic parameters (Table III). The decrease of $\Delta H'$ indicates the development of a new interaction between **1** and **2c** in **1·2c**. By contrast, the decrease of $\Delta S'$ shows the depression of the mobility of **2c** in the receptor cavity. These phenomena can be consistently explained as arising from the development of the interaction between the phenyl group in **2c** and the cyclophane subunit in **1**. The enthalpy lost by the interaction between the phenyl group and the cyclophane subunit overcomes the entropy decrease resulting from the restriction of mobility occurring during formation of the most stable complex. In the cases of (ω-phenylalkyl)ammonium salts **2e–g** having a longer methylene chain (n = 7–9), the $\Delta H'$ and $\Delta S'$ increase gradually with increasing methylene chain length, indicating that the interaction between the phenyl group of **2** and the cyclophane subunit gradually weakens again. The methylene chains in these substrates have to twist to maintain the interaction between the phenyl group and the cyclophane subunit, and their conformations may be disadvantageous. To avoid this, these substrates may form complexes with **1**, in which the phenyl group of the substrate is out of the cavity of **1**, resulting in the observed increase of $\Delta H'$ and $\Delta S'$. The K_s' values of **1·2a** and **1·2g**, which have no interaction between the phenyl group and the cyclophane subunit, become almost identical. Even in these cases, the methylene chains may still be enclosed in the central cavity of receptor **1**.

Further information on the complexation was obtained from dynamic NMR experiments of **1·2d** at temperatures from +30 to −90 °C in CD_2Cl_2/CD_3OD (5/2, v/v). When the temperature was lowered, a clear change in chemical shift of protons in the aliphatic region was observed (Figure 3). At 30 °C both ammonium α-methylene protons (Hα) and benzyl protons (Hb) were observed as two sharp triplets at time-average positions. When the temperature was lowered, at first the signal due to Hα and then that due to Hb became broad. This phenomenon indicates that the mobility of Hα is more highly restricted than that of Hb, as would be expected for the superstructure deduced on the basis of the $\Delta\delta_{max}$ value. Above the coalescence point, the chemical shifts of Hα and Hb shifted upfield when the temperature was lowered because the contribution of the complexed species of **2d** increases at lower temperature. Although a clear coalescence point

could not be observed, the broadest signal for Hα was observed at a temperature higher than that for Hb. This phenomenon is in agreement with the fact that the $\Delta\delta_{max}$ of Hα is larger than that of Hb. Below the coalescence point, both Hα and Hb split into two broad signals, one for the uncomplexed (downfield) and the other for the complexed (upfield) species. When the temperature was lowered, the signals sharpened and shifted to their own chemical shifts. Finally at −90 °C, two well-resolved signals were observed. For the uncomplexed species fine structures appeared, while the signal originating from the highly restricted complex species was broad. Although assignment of the two signals originating from the complex could not be accomplished, the $\Delta\delta_{max}$ values of 0.58 or 0.65 ppm for Hα and of 0.25 or 0.32 ppm for Hb seem to be reasonable when compared with those listed in Table II, taking into account temperature and solvent effects.

Conclusion

The results described here show that the highly preorganized host **1** having both electrostatically and hydrophobically interactive binding subunits forms inclusion complexes with complex substrates such as **2** having two different functional groups, i.e., phenyl and primary ammonium groups. Receptor **1** recognizes the distance between the two functional groups with high selectivity. Under our experimental conditions, the primary ammonium group, first of all, interacts with the crown ether subunit in **1**, and the degree of interaction between the phenyl group in the ammonium salt and the cyclophane subunit in **1** influences strongly the stability of the complex.

This is the first example of molecular recognition of the size of substrates by an artificial macropolycyclic receptor resulting from the cooperation between electrostatically and hydrophobically interacting sites. Such a system should be significant in the construction of enzymelike selective systems.

Experimental Section

Reagents and Solvents. All reagents were of reagent-grade quality and were used without further purification. CH_2Cl_2 was refluxed with and distilled from CaH_2 stored over molecular sieves (4A). 2-Methoxyethanol was distilled from K_2CO_3 and stored over molecular sieves (4A). Pyridine was refluxed with, distilled from, and stored over NaOH. CCl_4 and $SOCl_2$ were frationally distilled before use. Benzene was refluxed with, distilled from, and stored over Na wire. THF was refluxed with and distilled from $LiAlH_4$ before use. **3**[8] and **5**[10] were synthesized according to the methods in the literature starting from dibenzo-18-crown-6 (**16**) and 4-methylbiphenyl, respectively. Dinitrocyclophane **4** was synthesized according to the procedure in our previous report.[9] Wako silica gel C-200 (for normal chromatography), C-300 (for flash chromatography), and Merck basic alumina (activity II–III) were used for column chromatography. Preparative TLC was performed with Merck precoated alumina plates.

Physical and Spectroscopic Methods. Melting points were measured on a Mel-Temp laboratory device and are uncorrected. ^1H NMR spectra were recorded on a Hitachi R-40 (90-MHz) or a JEOL GX-400 (400-MHz) spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a Jasco IR-800 spectrophotometer. Calculations were performed on HITAC M-680/M-682H computers.

***trans*-Bis(*p*-toluenesulfonamido)dibenzo-18-crown-6 (6).** A solution with 2 mol equiv of tosyl chloride (5.96 g) in pyridine (150 mL) was added to a solution of *trans*-diaminodibenzo-18-crown-6 (**3**; 6.10 g, 16 mmol) in pyridine (200 mL) over a period of 1 h at 0 °C. The mixture was stirred for an additional 30 min at 0 °C and then heated under reflux for 2 h. Pyridine was removed under reduced pressure, and CH_2Cl_2 (200 mL) was added to dissolve the residue. The solution was washed thoroughly with 1 M HCl and then with water and dried over Na_2SO_4. After removal of the solvent, the red crude product was recrystallized from 2-methoxyethanol to give pure **6**: 10.2 g, 94%; mp 226–229 °C; IR (KBr) 3450, 1600, 1520, 1340, 1160 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 9.72 (s, 2 H), 7.55 (d, 4 H, J = 8.0 Hz), 7.26 (d, 4 H, J = 8.0 Hz), 6.64 (m, 6 H), 3.85 (m, 16 H), 2.30 (s, 6 H). Anal. Calcd for $C_{34}H_{38}N_2O_{10}S_2$: C, 58.44; H, 5.48; N, 4.01; S, 9.18. Found: C, 58.23; H, 5.42; N, 4.01; S, 9.18.

Diaminocyclophane (7). To a solution of the benzene complex of dinitrocyclophane **4** (802 mg, 0.92 mmol) in 2-methoxyethanol (75 mL) were added hydrazine hydrate (8 mL) and 5% Pd/C (64 mg), and the suspension was heated under reflux for 1 h. The warm solution was filtered through Celite, and the filtrate was concentrated under reduced pressure to give almost pure **7**, which was used for the synthesis of **11** without further purification: 620 mg, 97%; mp 262–263 °C; IR (KBr) 3450, 1610, 1510 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 7.16–6.50 (m, 22 H), 4.86 (s, 8 H),3.32 (br s, 4 H), 1.53 (s, 12 H).

Ethyl 4′-(Bromomethyl)biphenyl-4-carboxylate (8). A solution of ethyl 4′-methylbiphenyl-4-carboxylate (**5**; 4.67 g, 19.4 mmol), *N*-bromosuccinimide (3.80 g, 20 mmol), and benzoyl peroxide (10 mg) in CCl_4 (10 mL) was irradiated with a 200-W tungsten lamp while being heated under reflux for 3 h with vigorous stirring. After removal of the solvent under reduced pressure, the residue was dissolved in hot hexane (50 mL) and insoluble materials were filtered off. Cooling the filtrate gave **8** as a white precipitate: 5.00 g, 81%; mp 97–98 °C; IR (KBr) 1690, 1600, 1280, 1110 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.95 (d, 2 H, J = 8.5 Hz), 7.67–7.30 (m, 6 H), 4.47 (s, 2 H), 4.37 (q, 2 H, J = 7.2 Hz), 2.38 (t, 3 H, J = 7.2 Hz). Anal. Calcd for $C_{16}H_{15}BrO_2$: C, 60.21; H, 4.74; Br, 25.03. Found: C, 60.17; H, 4.80; Br, 24.80.

Diethyl Ester 9. To a solution of ethyl 4′-(bromomethyl)biphenyl-4-carboxylate (**8**; 6.40 g, 20 mmol) in DMF (84 mL) was added K_2CO_3 (24.2 g, 175 mmol), and the solution was warmed at 65 °C with vigorous stirring. A solution of *trans*-bis(*p*-toluenesulfonamido)dibenzo-18-crown-6 (**6**; 3.50 g, 5.0 mmol) in DMF (50 mL) was added to this mixture over a period of 40 min, and the mixture was stirred for an additional 23 h at 80 °C. The reaction mixture was poured into water (1000 mL) and stirred for 3 h, and the resulting precipitate was collected by filtration. The crude product was purified by silica gel column chromatography (eluent CH_2Cl_2) to give diethyl ester **9**: 5.19 g, 87%; mp 218–219 °C; IR (KBr) 1710, 1610, 1510, 1280, 1160 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.50 (d, 4 H, J = 8.4 Hz), 7.50–7.26 (m, 20 H), 6.50 (m, 6 H), 4.68 (s, 4 H), 4.35 (q, 4 H, J = 7.0 Hz), 3.90 (br s, 16 H), 2.41 (s, 6 H), 1.38 (t, 6 H, J = 7.0 Hz). Anal. Calcd for $C_{66}H_{66}N_2O_{14}S_2$: C, 67.44; H, 5.66; N, 2.38; S, 5.46. Found: C, 67.20; H, 5.67; N, 2.35; S, 5.61.

Diacid Dichloride 10. A suspension of **9** (5.19 g, 4.4 mmol) in a mixture of 4 M NaOH (5 mL) and ethanol (220 mL) was heated under reflux until the suspension turned into a clear solution. After being heated under reflux for an additional 1 h, the mixture was poured into water (160 mL) and acidified with concentrated HCl. The precipitate was collected by filtration and washed thoroughly with water to give the diacid: 4.78 g, 97%; mp 280 °C dec; IR (KBr) 1710, 1610, 1510, 1350, 1280, 1160 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 7.90 (d, 4 H, J = 8.0 Hz), 7.80–7.00 (m, 20 H), 6.90–6.40 (m, 6 H), 4.80 (s, 4 H), 4.00–3.50 (br s, 16 H), 2.41 (s, 6 H).

To a mixture of $SOCl_2$ (15 mL) and benzene (40 mL) was added the diacid (2.02 g, 1.8 mmol), and the suspension was heated under gentle reflux for 3 h, giving a clear solution. After removal of the excess $SOCl_2$ and solvent under reduced pressure, the crude product was recrystallized from a mixture of benzene (30 mL) and $SOCl_2$ (10 mL) to give **10**·2HCl as pale yellow needles: 1.61 g, 77%; mp 217–218 °C dec; IR (KBr) 1780, 1740, 1600, 1520, 1160 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.10–7.30 (m, 24 H), 6.60 (m, 6 H), 4.72 (s, 4 H), 3.88 (m, 16 H), 2.42 (s, 6 H). Anal. Calcd for $C_{62}H_{56}N_2O_{12}S_2Cl_2 \cdot 2HCl$: C, 60.59; H, 4.76; N, 2.28; Cl, 11.54. Found: C, 60.42; H, 4.56; N, 2.29; Cl, 11.72.

To remove the contained hydrogen chloride, the sample was heated 60 °C under reduced pressure (ca. 0.5 mmHg) overnight and used for the synthesis of macrotricyclic diamide **11**.

6,7,9,10,17,18,20,21-Octahydro-37,69-dioxo-53,53,59,59-tetramethyl-43,66-(methanoxy[1,4]benzenomethano[1,4]benzeneoxymethano)-2,13-(iminomethano[1,4]benzeno[1,4]benzenomethanimino-[1,3]benzenomethanoxy[1,4]benzenomethano[1,4]benzenoxymethano[1,3]-benzeniminomethano[1,4]benzeno[1,4]benzenoxymethanimino)dibenzo-[*b*,*k*][1,4,7,10,13,16]hexaoxacyclooctadecin (Macrotricyclic Diamide 11). A solution of diacid chloride **10** (577.6 mg, 0.50 mmol) in dichloromethane (100 mL) and a solution of diaminocyclophane **7** (345.4 mg, 0.50 mmol) in pyridine (100 mL) were added at equal rate and at the same time to an ice-cold mixture of pyridine (200 mL) and dichloromethane (200 mL) over a period of 4 h with vigorous stirring. After the mixture was heated under reflux for 2.5 h, the solvent was evaporated and dichloromethane (100 mL) was added to the residue. The solution was quickly washed with water (3 × 80 mL) and dried over $MgSO_4$. After removal of $MgSO_4$ and concentration of the solution, the crude product was purified by alumina column chromatography (eluent CH_2Cl_2 dried over molecular sieves (4A)) to give **11**: 567 mg 64%; mp 263–265 °C dec; IR (KBr) 3450, 1610, 1510, 1220, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 2 H), 7.82 (d, 4 H, J = 7.9 Hz), 7.62–7.50 (m, 12 H), 7.43 (d, 4 H, J = 7.9 Hz), 7.31–7.19 (m, 8 H), 7.11 (s, 2 H), 7.02 (d, 8 H, J = 9.3 Hz), 6.72 (d, 8 H, J = 9.3 Hz), 6.59 (d, 2 H, J = 8.8 Hz), 6.46–6.37 (m, 4 H), 5.06 (s, 8 H), 4.69 (s, 4 H), 4.01 (s, 2 H), 3.87 (m, 16 H), 2.44 (s, 6 H), 1.61 (s, 12 H).

As diamide **11** was very unstable in air, it was used without further purification.

6,7,9,10,17,18,20,21-Octahydro-53,53,59,59-tetramethyl-43,66-(methanoxy[1,4]benzenomethano[1,4]benzenoxymethano)-2,13-(iminomethano-[1,4]benzeno[1,4]benzenomethanimino[1,3]benzenomethanoxy[1,4]-benzenomethano[1,4]benzenoxymethano[1,3]benzeneiminomethano[1,4]-benzeno[1,4]benzenoxymethanimino)dibenzo[*b*,*k*][1,4,7,10,13,16]hexaoxacyclooctadecin (Cylindrical Macrotricyclic Receptor 1). A solution of diamide **11** (567 mg, 0.32 mmol) in THF (40 mL) was added to a suspension of $LiAlH_4$ (606 mg, 16 mmol) in THF (30 mL) under an argon atmosphere. The reaction mixture was heated under reflux for 12 h and then cooled to 0 °C, and a saturated $MgSO_4$ solution (200 mL) was added drop by drop to the solution. The THF layer was separated by decantation, and the residue was washed with ether (4 × 100 mL). After removal of the solvents, the residue was dissolved in CH_2Cl_2 (25 mL). The solution was washed with water, dried over $MgSO_4$, and concentrated. The crude product was purified by alumina column chromatography (eluent CH_2Cl_2) to give pure **1**: 202 mg, 44%; mp 263-264 °C; IR (KBr) 3450, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 8 H, J = 8.0 Hz), 7.37 (d, 4 H, J = 8.0 Hz), 7.36 (d, 4 H, J = 8.0 Hz), 7.01 (d, 8 H, J = 8.8 Hz), 6.73 (d, 8 H, J = 8.8 Hz), 6.68 (d, 2 H, J = 8.2 Hz), 6.66 (s, 2 H), 6.58 (s, 4 H), 6.24 (d, 2 H, J = 2.4 Hz), 6.13 (dd, 2 H, J = 2.4 Hz, 8.2 Hz), 4.95 (s, 8 H), 4.34 (s, 8 H), 4.08-4.02 (m, 8 H), 3.96-3.88 (m, 8 H), 1.56 (s, 12 H); HRMS (FAB) m/e for $C_{94}H_{92}N_4O_{10}$ calcd 1436.6813, found 1436.6980. Anal. Calcd for $C_{94}H_{92}N_4O_{10}\cdot 4H_2O$: C, 74.78; H, 6.68; N, 3.71. Found: C, 75.02; H, 6.55; N, 3.48.

Typical Procedure for the Measurement of K_s'. Freshly purified (alumina TLC; developing solvent, CH_2Cl_2 containing 2% methanol) macrotricyclic receptor **1** (84.5 mg) was dissolved in a $CDCl_3/CD_3OD$ (4/1, v/v) mixed solvent and diluted to 2.00 mL (29.4 mM solution). (3-Phenylpropyl)ammonium picrate (**2a**; 39.4 mg) was also dissolved in a $CDCl_3/CD_3OD$ (4/1, v/v) mixed solvent and diluted to 1.00 mL (108.1 mM solution). A 25.0-μL portion of the standard solution of the substrate was added to each of ten NMR sample tubes and then one each of 0.00-, 30.0-, 50.0-, 70.0-, 90.0-, 110.0-, 130.0-, 150.0-, 170.0-, and 190.0-μL portions of the standard solution of the receptor were added, one to each tube. Every mixture was diluted to 600 μL by the addition of a $CDCl_3/CD_3OD$ (4/1, v/v) mixed solvent, and the ^1H NMR was measured on a JEOL GX-400 instrument. The difference between the chemical shifts in the presence and in the absence of the receptor was plotted for both the ammonium α-methylene and the benzyl protons of **2a**. This curve was fitted to eq 1 with the SALS program[12] on HITAC M-680/M-682H computers.

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Registry No. 1, 106509-04-0; **1/2a** 1:1 complex, 124400-87-9; **1/2b** 1:1 complex, 124400-89-1; **1/2c** 1:1 complex, 106527-63-3; **1/2d** 1:1 complex, 124400-91-5; **1/2e** 1:1 complex, 124400-93-7; **1/2f** 1:1 complex, 124400-95-9; **1/2g** 1:1 complex, 124400-97-1; **2a**, 124400-86-8; **2b**, 124400-88-0; **2c**, 106527-62-2; **2d**, 124400-90-4; **2e**, 124400-92-6; **2f**, 124400-94-8; **2g**, 124400-96-0; **3**, 31406-52-7; **4**, 97350-55-5; **5**, 106508-97-8; **6**, 106508-99-0; **7**, 106509-03-9; **8**, 106508-98-9; **9**, 106509-00-6; 9 diacid, 106509-01-7; **10**, 106509-02-8; **11**, 106527-61-1; **12** (m = 3), 1070-62-8; **12** (m = 4), 626-86-8; **12** (m = 5), 33018-91-6; **12** (m = 6), 14113-01-0; **12** (m = 7), 1593-55-1; **13** (m = 3), 1501-05-9; **13** (m = 4), 4144-62-1; **13** (m = 5), 7472-43-7; **13** (m = 6), 24314-23-6; **13** (m = 7), 53702-23-1; **14** (m = 3), 36603-28-8; **14** (m = 4), 31274-14-3; **14** (m = 5), 107416-06-8; **14** (m = 6), 124400-98-2; **14** (m = 7), 124400-99-3; **15a**, 582-22-9; **15b**, 13214-66-9; **15c**, 17734-21-3; **15d**, 17734-20-2; **15e**, 17734-22-4; **15f**, 17734-23-5; **15g**, 117534-09-5; picric acid, 88-89-1.

Syntheses and Reactions of Silyl Carbamates. 2. A New Mode of Cyclic Carbamate Formation from *tert*-Butyldimethylsilyl Carbamate

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Abstract: Stereoselective construction of 1,2 and 1,3 amino hydroxyl systems was achieved by the intramolecular trapping of the *N-tert*-butyldimethylsilyloxycarbonyl species (silyl carbamate) activated by fluoride ion. The reaction of the silyl carbamate with 1,2-syn mesylate **3** gave the 1,2-anti cyclic carbamate **7**, exclusively, with complete inversion of the original stereochemistry of the leaving group. On the other hand, AgF- or AgF/Pd(II)-assisted cyclic carbamate formation from the (chloromethyl)homoallylamines **13b-17b** and (chloromethyl)allylamines **24b-27b** provided desired cyclic carbamates **19a-23a**, and **7**, **8**, and **29a-31a**, respectively, in an $S_{cN'}$ manner. During the formation of **19a-23a**, moderate 1,3-syn stereoselectivity was observed. High 1,2-syn stereoselectivity was accomplished by using AgF/Pd(II) system in the five-membered cyclic carbamate formation. These results were applied to the syntheses of statine **32** and its related amino acid **33**, efficiently.

Recently, 1,2 and 1,3 amino hydroxyl systems have received much attention from synthetic chemists due to their presence in a variety of natural products. Since unusual amino acids possessing the above mentioned moieties are widely distributed in biologically important peptides, development of efficient synthetic methods and application of these methods to the syntheses of such amino acids are currently of importance.[1,2] Recently, we reported the synthesis of the *N-tert*-butyldimethylsilyloxycarbonyl group (silyl carbamate)[3] from the most common urethane-type amino-protecting groups such as *N-tert*-butoxycarbonyl (*N-t*-Boc) and *N*-benzyloxycarbonyl (*N*-Z).[4] Owing to its high reactivity the silyl carbamate can be viewed as an *N-carboxylate ion equivalent*, which can be converted into several urethane-type groups by intermolecular reaction with an electrophile in the presence of fluoride ion.[3] Thus, it was considered that *intramolecular* trapping of this reactive species would provide a stereoselective method for

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