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Cyclic-tri(*N*-methyl-*meta*-benzamide)s: substituent effects on the bowl-shaped conformation in the crystal and solution states

Hiroki Kakuta [a], Isao Azumaya [b,*], Hyuma Masu [b], Mio Matsumura [c], Kentaro Yamaguchi [b], Hiroyuki Kagechika [d], Aya Tanatani [c,*]

[a] Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 1-1-1 Tsushima-Naka, Kita-ku, Okayama 700-8530, Japan
[b] Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, 1314-1 Shido, Sanuki, Kagawa 769-2193, Japan
[c] Department of Chemistry, Faculty of Science, Ochanomizu University, 2-1-1 Otsuka, Bunkyo-ku, Tokyo 112-8610, Japan
[d] Graduate School of Biomedical Science, Tokyo Medical and Dental University, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

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ABSTRACT

Cyclic trimers of 3-(*N*-alkylamino)benzoic acid (calix[3]amides) with various substituents at the *meta* position of the phenyl rings were synthesized and the effects of the substituents on the crystal structures and energy profiles in solution were examined. The calixamides existed in a *syn* conformation in the crystal state, and this was also the major conformation in solution, especially in polar solvents. The energy barrier between *syn* and *anti* conformers in the solution was not significantly affected by substituents (12.7–14.0 kcal/mol). The effect of the substituent on the temperature dependence of the *syn*/*anti* ratio are discussed.

1. Introduction

Bowl-shaped macrocyclic molecules represented by calixarenes[1] are used to the framework of the host compound, which trap complementary guests within a cavity. The molecular recognition event by the host compound can be applied to the chemical tools in the fields of analytical chemistry and biological sciences.[2] We have previously reported that cyclic-tri(*N*-methyl-*meta*-benzamide) (calix[3]amide, **1**, Fig. 1) can be easily formed by the condensation reaction of 3-(*N*-methylamino)benzoic acid in moderate yield.[3] In this reaction, the cis[4] conformational preference of the *N*-methylbenzanilide moiety[5] and the preorganization due to aromatic–aromatic interactions[6] in the intermediate species appears to be important for cyclization.

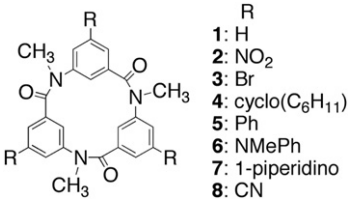

Figure 1. Cyclic triamides **1**–**8**.

The cyclic triamide **1** shows a bowl-shaped structure (*syn* conformation, Fig. 2) in the crystal,[7] where the three *N*-phenyl groups are directed to the same side. The *syn* conformation of **1** has a small cavity and molecular chirality based on the direction of the amide bond. Although the size of the cavity is rather small, compared with those of cyclodextrins and calixarenes, it plays a significant role in formation of dimers of the cyclic triamides **2** bearing 5-nitro groups in the crystalline state.[8] In the dimeric structure, the nitro group of one molecule resides in the cavity of the other molecule. Thus, the cyclic triamides, such as **1**, represent macrocyclic molecules with

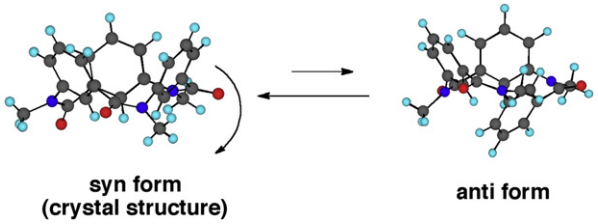

Figure 2. Conformational equilibrium of **1** in solution.

* Corresponding authors. Tel./fax: +81 3 5978 2716 (A.T); tel.: +81 87 894 5111; fax: +81 87 894 0181 (I.A.); e-mail addresses: azumayai@kph.bunri-u.ac.jp (I. Azumaya), tanatani.aya@ocha.ac.jp (A. Tanatani).

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unique functions based on conformational preference. In solution, cyclic triamide **1** exists in rapid equilibrium between the *syn* and *anti* conformations, in which one phenyl group flips to an alternate direction (Fig. 2). Therefore, understanding of the conformational properties of cyclic triamides is important in the development of functional molecules based on the bowl-shaped structure. In this study, the substituent effects on the crystal structures and the conformational equilibrium of cyclic triamide **1** are studied.

2. Result and discussion

2.1. Synthesis

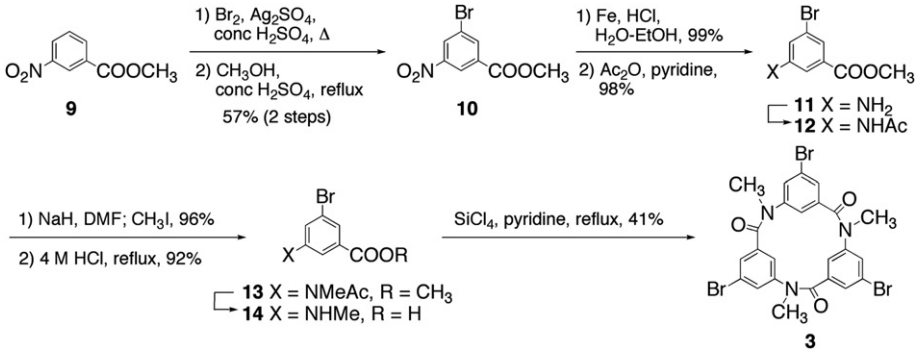
To clarify the substituent effects on the structures of cyclic triamides, compounds **3**–**8** with 5-substituents on the phenyl rings were synthesized. Several types of the substituents, such as hydrophobic aliphatic, aromatic, electron-donating amino and electron-withdrawing cyano groups were introduced by the replacement of the bromo group of cyclic amide **3**. The synthesis of the key compound **3** is shown in Scheme 1. Bromination of methyl 3-nitrobenzoate (**9**) in the presence of silver sulfate and sulfuric acid, followed by the esterification of the partially formed benzoic acid moiety, afforded methyl 3-bromo-5-nitrobenzoate (**10**) in 57% yield. After conversion of the nitro groups of **10** into methylamino groups in four steps, the condensation reaction of the compound **14** using silane tetrachloride and pyridine afforded the cyclic trimer **3** (41%) with the cyclic tetramer (7%) as a by-product.

The conversion reactions of the bromo groups of **3** into other substituents are shown in Scheme 2. The Heck reaction of **3** with cyclohexene in the conditions using tetrabutylammonium chloride as a phase transfer catalyst,[9] followed by the catalytic hydrogenation, gave tricyclohexyl compound **4** in 27% (two steps), and also the di- (30%) and monocyclohexyl (20%) compounds, and **1** (13%). Phenylation of **3** with phenylboronic acid in the presence of triphenylphosphine and palladium on carbon afforded compound **5** in 35% yield.[10] Introduction of the nitrogen atom was performed by the Buchwald's amination reactions of **3**. Aromatic methylaniline and aliphatic piperadine were reacted with **3** to give compounds **6** (70%) and **7** (39%), respectively.[11] Finally, treatment of **3** with copper(I) cyanide at 170 °C afforded compound **8** in 45% yield.[12]

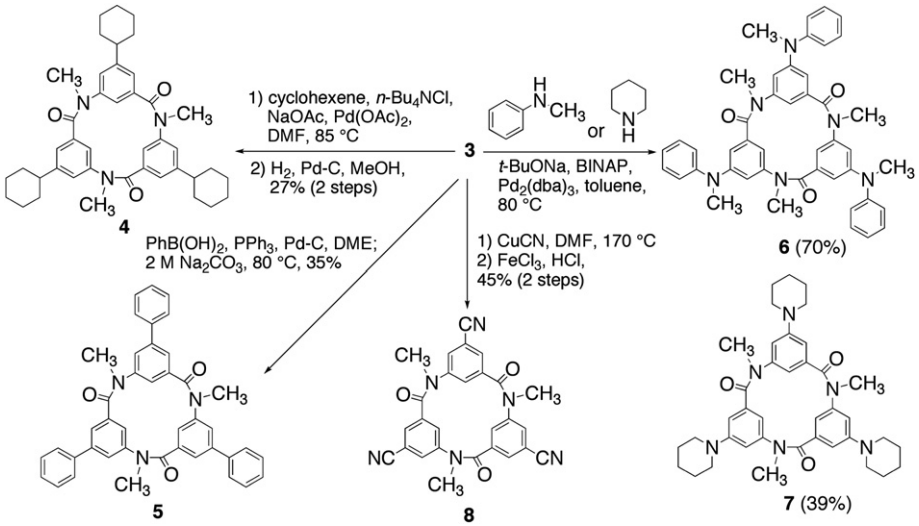
2.2. Crystal structures

X-ray crystal analyses of **3**–**5** and **8** were successfully achieved. The crystallographic data are shown in Table 1. All compounds examined have the *syn* structure similar to compound **1** (Fig. 3).

The structural parameters of the cyclic triamides including those of compound **1** and **2** are shown in Table 2. Small torsion angles of the amide bonds (Me–N–C–O, φ in Table 2) show that the amide bonds of all compounds are held in plane. In the *syn* structure of **1**, the three phenyl rings are tilted back, forming a truncated cone-shaped conformation with larger distances between the three C(5) carbons (d_1 in Table 2) and smaller distances between the three C (2) carbons (d_2 in Table 2). Other compounds **2**–**4** and **8** have



Scheme 1. Synthesis of cyclic triamide **3**.



Scheme 2. Conversion reactions of the bromo groups of **3** into other substituents.

Table 1
Crystallographic data of cyclic triamides **3**–**5** and **8**

	3	**4**	**5**	**8**
Formula	$C_{24}H_{18}N_3O_3Br_3$	$C_{42}H_{51}N_3O_3\cdot(O)$[a]	$C_{42}H_{33}N_3O_3\cdot C_6H_6$	$C_{27}H_{18}N_6O_3$
Recryst solvent	CH_2Cl_2/EtOH	CH_3CN	Benzene/*n*-C_6H_{14}	CH_2Cl_2/MeOH
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic
Space group	*P*-1	*P*-1	$P2_1/n$	$P2_1/c$
a (Å)	9.337(3)	9.406(1)	15.61(2)	14.646(2)
b (Å)	10.848(3)	11.259(1)	12.923(5)	11.369(2)
c (Å)	13.433(2)	19.233(2)	19.90(2)	15.880(3)
α (deg)	105.32(2)	94.96(1)	90	90
β (deg)	92.53(2)	93.63(1)	105.52(7)	111.750(2)
γ (deg)	113.27(2)	110.48(1)	90	90
V (Å^3)	1188.5(6)	1891.3(4)	3868(6)	2455.9(7)
Z	2	2	4	4
D_{calcd} (Mg m^{-3})	1.778	1.162	1.212	1.283
T (K)	296	296	288	299
GOF	1.004	1.047	1.175	0.864
R_1 [$I>2\sigma(I)$]	0.0587	0.0936	0.0903	0.0568
wR_2 (all data)	0.1921	0.2252	0.2382	0.1622
CCDC	779185	779186	779187	779188

[a] The positions of hydrogen atoms included in water molecules were not calculated.

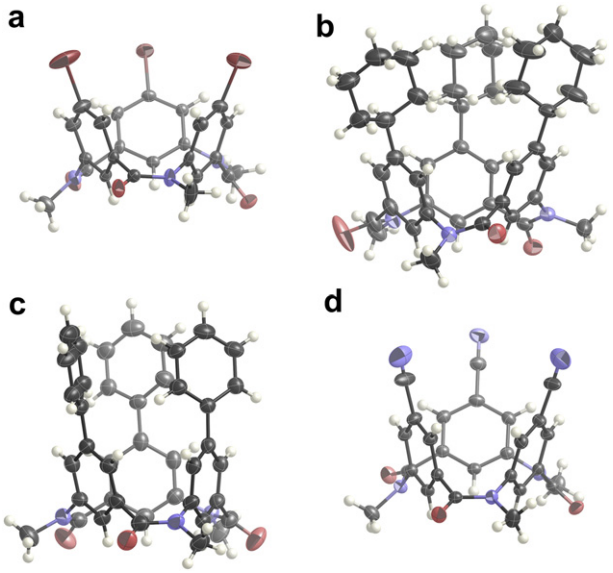
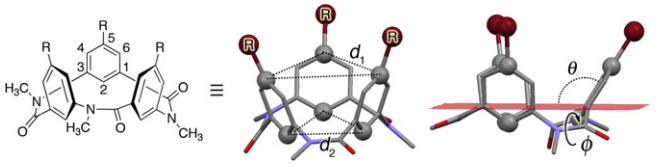


Figure 3. Thermal ellipsoid models of crystal structures of cyclic triamides **3** (a), **4** (b), **5** (c), and **8** (d). Ellipsoids are drawn at the 30% probability level while isotropic hydrogen atoms are represented by spheres of arbitrary size. Solvent molecules are omitted.

similar structural parameters. However, the cyclic structure of **5** is rather different from the structure of the other triamides. The difference of d_1 and d_2, and the dihedral angles of the phenyl rings with a plane formed by the six carbon atoms connecting to amide linkers (θ in Table 2) of **5** are significantly smaller than those of **1** or the other cyclic triamides. This indicates that the three phenyl rings of **5** are nearly perpendicular to the macrocyclic chain. These conformational characteristics of the cyclic triamides are explained by the weak intramolecular interactions and the crystal packing effect. Compound **3** formed the dimeric crystal structure similar to compound **2** (Fig. 4a). Compound **8** also formed a dimeric structure through the interdigitation of the cyano groups (Fig. 4d). These structures give the molecules a truncated cone-shaped conformation and a cavity. Compound **4** does not form the dimeric structure, but has a large d_1 value due to steric hindrance of the bulky cyclohexyl substituents (Fig. 4b). Conversely, the structure of **5** with a smaller cavity in the macrocycles arises from the aromatic–aromatic interactions between the three phenyl substituents (Fig. 4c). The dihedral angles of the three phenyl substituents are

Table 2
Structural parameters of the cyclic triamides



Comp.	d_1 Å	d_{1ave}[a]	d_2 Å	d_{2ave}[a]	θ deg	θ_{ave}[a]	φ deg	φ_{ave}[a]
1[b]	5.35	5.45	3.43	3.59	98.8	113.3	4.3	7.9
	5.89		3.65		121.4		7.8	
	5.11		3.68		119.6		11.5	
2[c]	5.32	5.23	3.59	3.62	120.2	110.5	0.3	5.5
	4.95		3.44		103.1		8.9	
	5.42		3.83		108.4		7.3	
3	5.52	5.37	3.61	3.58	122.1	112.6	7.8	7.1
	5.15		3.41		108.2		6.1	
	5.45		3.73		107.6		7.5	
4	5.29	5.05	3.72	3.65	116.5	107.2	2.1	4.0
	4.80		3.46		106.1		8.2	
	5.05		3.78		98.9		1.7	
5	4.59	4.62	3.78	3.79	93.5	100.0	3.6	1.5
	4.83		3.82		105.4		1.0	
	4.43		3.78		101.1		0.1	
8	5.29	5.15	3.75	3.64	99.0	109.0	8.5	4.9
	5.49		3.72		122.8		5.6	
	4.67		3.44		105.4		0.5	

[a] An average of three values for each compound.
[b] Ref. 7.
[c] Ref. 8.

52.6, 54.5, and 73.4°, and the distances between their centers are 4.75, 5.63, and 5.04 Å, which is similar to the values in the calculated stable benzene dimers with a T-shaped conformation (5.0 Å).[13] Such interactions between the substituents may affect the conformation of the *syn* structures of the cyclic triamides.

2.3. Conformational equilibrium in solution

The cyclic triamide **1** exists in rapid equilibrium between *syn* and *anti* conformers in solution (Fig. 2). At room temperature the ^{1}H NMR signals are broad and become two sets of sharp signals at 213 K. To clarify the substituent effects on the conformational

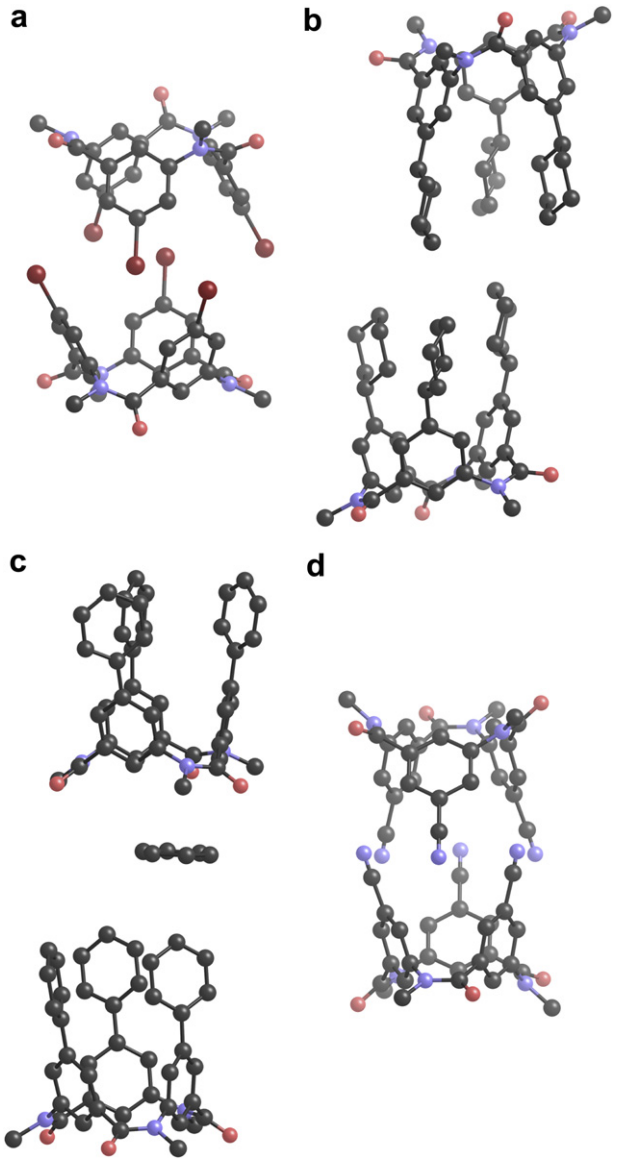


Figure 4. Packing of the crystal structures of the cyclic triamides **3** (a), **4** (b), **5** (c), and **8** (d). The hydrogen atoms for each molecule and the water molecules in the crystal of **4** are omitted.

equilibrium, temperature-dependent ^{1}H NMR spectra of compounds **3**–**8** were acquired. All compounds examined showed similar ^{1}H NMR spectral features, in which broad signals were observed at room temperature and two sets of peaks were observed at 213 K. The assignment of the conformers was essentially based on the *syn* and *anti* conformers of **1**. For the *anti* conformer, the aromatic proton signal was at higher field (6.0–6.5 ppm), corresponding to the H-2 position. The ratio of the two conformers and the coalescence points were determined using the signals arising from the *N*-methyl groups. Thermodynamic parameters of *syn*/*anti* equilibria are listed in Table 3.

In all compounds examined, the *syn* conformer is the major species in CD_2Cl_2 ($\Delta G^0<0$), and the ratio of *syn*/*anti* increased in CD_3OD. The preference for the *syn* conformation in a polar solvent arises from the large dipole moment of the *syn* conformer with three amide bonds in the same orientation. The energy barrier between the two conformers was not affected by either the substituent or solvent properties. Thus, the $\Delta G^{\neq}$ value (13.8 kcal/mol) of **5** is similar to those of other compounds (12.7–14.0 kcal/mol), and therefore the total stabilizing energies derived from aromatic–aromatic interactions are not noticeably in the *syn* and *anti* conformations, and the transition state.

The ratio of *syn* and *anti* conformers of each compound was dependent on the temperature. The plot of the equilibrium constant (ln *K*) against the temperature (1/*T*) afforded the enthalpy (ΔH^0) and entropy (ΔS^0) differences (Fig. 5, Table 3). In most cases, the ratio of the *syn* conformer increases as the temperature decreased, except compound **5** in CD_2Cl_2. The *syn* conformer is enthalpically favored, especially in the polar methanol solution. Interestingly, the entropy difference (ΔS^0) is positive and rather large in compound **5**. This means that the *syn* conformation with three sets of aromatic–aromatic contacts is more disordered than the *anti* conformation with only one aromatic–aromatic contact. This also indicates that stabilization by one aromatic–aromatic interaction in the *anti* conformation would be larger than the sum of the three aromatic–aromatic interactions in the *syn* conformation. This phenomenon is seemingly contradictory in the case of our previous report on the conformational behaviors of benzenetricarboxanilide analog **15** (Fig. 6).[14] In the case of **15**, the *syn* conformation with aromatic–aromatic interactions between three phenyl groups is enthalpically favored. The different conformational behavior of **5** arises from the geometry of the cyclic amides compared with the acyclic compound **15**, and is due to the third neighboring phenyl group inhibiting the relatively tight aromatic–aromatic interactions between two phenyl groups in the *anti*

Table 3
Thermodynamic parameters of *syn*/*anti* equilibria of the cyclic triamides

Comp.	Solvent	*Tc*	$\Delta G^{\neq}$ [d]	*K* (213 K)	ΔG^0	ΔH^0 [e]	ΔS^0 [e]
			kcal/mol	([*syn*]/[*anti*])	kcal/mol	kcal/mol	cal/mol K
1	CD_2Cl_2	268±5	13.7±0.3	5.6	−0.7	−0.8	−0.7
	CD_3OD	268±5	13.7±0.3	35	−1.5	−1.8	−1.6
3 [a]	CD_2Cl_2	268±5	13.1±0.3	1.5	−0.2	0.2	1.7
4	CD_2Cl_2	268±5	13.8±0.3	13	−1.1	−1.1	−0.3
	CD_3OD	—[c]	—[c]	71	−1.8	−1.9	−0.5
5	CD_2Cl_2	268±5	13.8±0.3	2.5	−0.4	0.7	4.9
	CD_3OD	—[c]	—[c]	51	−1.7	−0.9	3.5
6[b]	CD_2Cl_2	278±5	14.0±0.3	8.5	−0.9	−0.8	0.3
	CD_3OD	—[c]	—[c]	57	−1.7	−1.5	1.1
7	CD_2Cl_2	268±5	13.6±0.3	5.2	−0.7	−0.6	0.5
	CD_3OD	—[c]	—[c]	43	−1.6	−1.5	0.5
8[a]	CD_2Cl_2	258±5	12.7±0.3	4.0	−0.6	−1.4	−3.9

[a] Poor solubility in CD_3OD.
[b] ^{1}H NMR studies were performed for the compound bearing *N*-methyl-d_3-*N*-phenylamino groups as the substituents.
[c] Minor signals are too small to determine the coalescence point.
[d] $\Delta G^{\neq}$ was calculated by the following equation: $\Delta G^{\neq}=19.14Tc\{9.97+\log(Tc/\Delta\nu)\}$ in which *Tc* is the coalescence point, and $\Delta\nu$ is the chemical shift difference of the *N*-methyl groups.
[e] ΔH^0 and ΔS^0 were calculated by the following equation: $\ln K=-\Delta H^0/RT+\Delta S^0/R$.

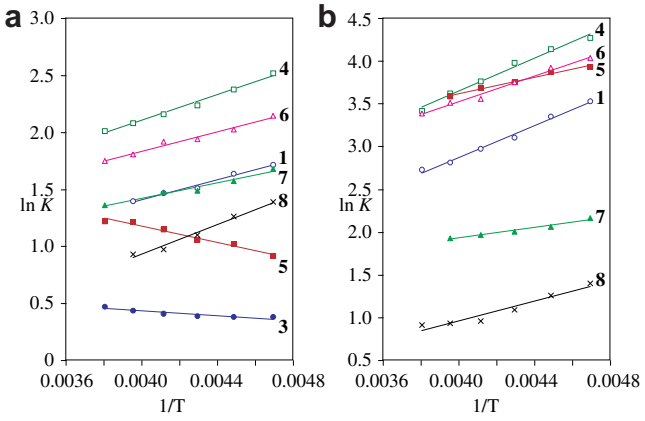


Figure 5. Temperature-dependent *syn*/*anti* equilibria in (a) CD_2Cl_2 and (b) CD_3OD.

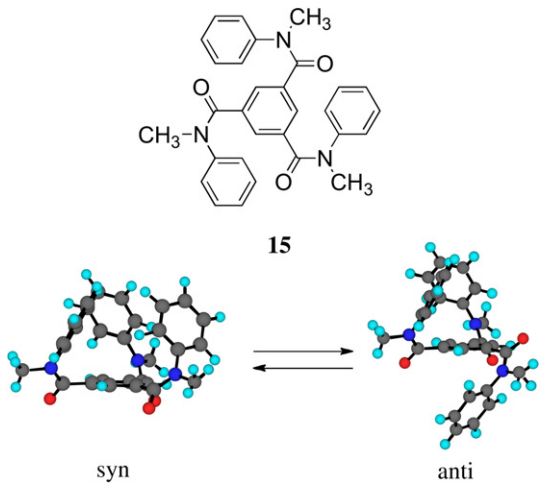


Figure 6. The *syn*/*anti* equilibrium of 1,3,5-tris(*N*-methyl-*N*-phenylamino)benzene **15**.

conformation of **5**. This results in destabilizing the aromatic–aromatic interactions between the three sets of contacts of the phenyl groups, and therefore the disordered appearance of these rings in the *syn* conformation. This consideration is not inconsistent with the feature seen in the energy profile of **5**, which is different from the other analogs.

3. Conclusion

The effects of substituents on the phenyl rings of cyclic triamide **1** were examined. The cyclic triamides with various substituents on the phenyl rings were easily synthesized from the key compound **3**. The *syn* conformations were observed in the crystal structures of all compounds examined, and were the major species in solution, especially in a polar solvent. Considering the synthetic convenience and the preferential *syn* structure with a small chiral cavity that arrange three substituents in the same orientation, the cyclic triamides should be useful constructing macrocycles with unique molecular recognition capabilities, for example, switching a recognition mode by altering the environment, such as solvent or temperature.

4. Experimental

4.1. General

Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, The University of Tokyo, and were within ±0.3% of the theoretical values. The crystals for X-ray crystallography were obtained by normal recrystallization by using the mixed solvent with proper ratio. ^{1}H NMR spectra were recorded on a JEOL JNM-GX400, and chemical shifts are expressed in ppm relative to tetramethylsilane. Temperature dependent NMR was performed by using 2–3 mg of compound in 0.5 mL of solvent at the intervals of 10° from 273 to 213 K. The thermodynamic parameters shown in Table 3 were calculated from the correlation line shown in Fig. 5 by using the equation of $\ln K = -\Delta H^0/RT + \Delta S^0/R$. Mass spectra were measured on JEOL JMS-SZ 102A (EI) or on Brucker Daltonics microTOF-2focus in the positive ion detection modes (ESI^+).

4.2. Synthesis

*4.2.1. Synthesis of methyl 3-bromo-5-nitrobenzoate (**10**).* A mixture of methyl 3-nitrobenzoate (**9**, 50.0 g, 0.28 mol), silver sulfate (48.1 g, 15 mmol), and 300 mL of sulfuric acid was stirred at 90 °C. Bromine (20 mL) was added dropwise to the mixture over 30 min and the reaction mixture was stirred at 90 °C for 1 h. After cooling, the precipitated silver bromide was filtered off and the filtrate was poured into iced water, and extracted with ethyl acetate. The organic layer was washed successively with water, satd sodium hydrosulfite, water and brine, and dried over sodium sulfate. After evaporation, the residue was dissolved in methanol (500 mL) and sulfuric acid (10 mL), and the mixture was refluxed overnight. After evaporation, the residue was poured into iced water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was recrystallized from methanol to give **10** (39.9 g, 57%). **10**: colorless needles (methanol); mp 70–71.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (t, 1H, J=1.8 Hz), 8.56 (t, 1H, J=1.8 Hz), 8.49 (t, 1H, J=1.8 Hz), and 4.00 (s, 3H); IR (KBr) 1540 cm^{-1}. Anal. Calcd for $C_8H_6BrNO_4$: C, 36.92; H, 2.31; N, 5.38. Found: C, 36.77; H, 2.01 N, 5.16.

*4.2.2. Synthesis of methyl 3-amino-5-bromobenzoate (**11**).* A mixture of iron powder (56 g, 1.0 mol), water (200 mL), and hydrochloric acid (10 mL) was heated at reflux for 20 min. A solution of **10** (105 g, 0.408 mol) in ethanol (1.6 L) was added dropwise to the refluxing mixture over 2 h, and the mixture was refluxed for 3 h. After cooling, the mixture was filtered with Celite, and the filtrate was basified with sodium carbonate. After filtration with Celite, the filtrate was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. After evaporation, the crude product (92.1 g, 99%) was recrystallized from ethyl acetate/*n*-hexane to give **11**. Compound **11**: pale yellow needles (ethyl acetate/hexane); mp 93–94.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (t, 1H, J=1.8 Hz), 7.25 (t, 1H, J=1.8 Hz), 6.99 (t, 1H, J=1.8 Hz), 3.89 (s, 3H), and 3.84 (s, 2H); IR (KBr) 3400 cm^{-1}. Anal. Calcd for $C_8H_8BrNO_2$: C, 41.74; H, 3.48; N, 6.09. Found: C, 41.96; H, 3.37; N, 6.09.

*4.2.3. Synthesis of methyl 3-acetamino-5-bromobenzoate (**12**).* Acetic anhydride (500 mL) and pyridine (5 mL) was added to compound **11** (92.1 g, 0.40 mol) at 0 °C and the mixture was stirred at room temperature for 1 h. The mixture was poured into iced water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated to give **12** (106.4 g, 98%). Compound **12**: colorless powder; mp 132–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.89 (m, 2H), 7.25 (t, 1H, J=1.8 Hz), 3.91 (s, 3H), and 2.21 (s, 3H); IR (KBr) 3400–3200, 1720, 1670 cm^{-1}. Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.10; H, 3.68; N, 5.15. Found: C, 43.98; H, 3.46; N, 5.18.

*4.2.4. Synthesis of methyl 3-bromo-5-(N-methylacetamino)benzoate (**13**).* Sodium hydride (9.6 g, 60% purity, 0.24 mol) was washed with

n-hexane, and suspended in DMF (100 mL). A solution of **12** (54.4 g, 0.20 mol) in DMF (180 mL) was dropwise added to the suspension over 1 h. Methyl iodide (15 mL, 0.24 mol) was then added to the mixture over 20 min. After 1 h, the solvent was removed under vacuum, and the residue was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated to give **13** (54.7 g, 96%). Compound **13**: colorless powder; mp 70–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.82 (t, 1H, J=1.8 Hz), 7.56 (s, 1H), 3.95 (s, 3H), 3.28 (s, 3H), and 1.92 (s, 3H); IR (KBr) 1720, 1650, 1600 cm^{-1}. Anal. Calcd for $C_{11}H_{12}BrNO_3$: C, 46.20; H, 4.20; N, 4.90. Found: C, 45.93; H, 4.12; N, 4.69.

*4.2.5. Synthesis of 3-bromo-5-(N-Methylamino)benzoic acid (**14**).* A solution of **13** (54.7 g, 0.19 mol) in hydrochloric acid (200 mL) and water (300 mL) was refluxed overnight. After cooling, the mixture was extracted with ethyl acetate. Sodium hydroxide (4 M) was added to the aqueous layer until pH=4 and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over sodium sulfate. After evaporation, the crude product (40.8 g, 92%) was recrystallized from ethyl acetate/hexane to give **14**. Compound **14**: brown prisms (ethyl acetate/hexane); mp 165–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.15 (s, 1H), 7.09 (s, 1H), 6.87 (s, 1H), 6.23 (d, 1H, J=5.1 Hz) and 3.29 (s, 3H); IR (KBr) 1700 cm^{-1}. Anal. Calcd for $C_8H_8BrNO_2$: C, 41.74; H, 3.48; N, 6.09. Found: C, 41.84; H, 3.46; N, 5.80.

*4.2.6. Synthesis of cyclic triamide **3**.* Tetrachlorosilane (0.17 ml, 1.5 mmol) was added to a solution of **14** (0.33 mmol) in dry pyridine (10 mL) at 0 °C and the mixture was heated at 130 °C for 2 days. After removal of the solvent under vacuum, the residue was extracted with methylene chloride. The organic layer was washed successively with 2 M hydrochloric acid, water, 2 M sodium hydroxide, water and brine, and dried over sodium sulfate. After evaporation, the crude product was purified by silica gel column chromatography (ethyl acetate: methylene chloride 1: 2) to give **3** (88 mg, 41%) with cyclic tetraamide (16 mg, 7%) as a by-product. **3**: colorless prisms (methylene chloride/ethanol); mp>300 °C; ^{1}H NMR (400 MHz, CD_2Cl_2, 213 K) δ 7.72 (t, minor 3H, J=1.8 Hz), 7.51 (t, minor 3H, J=1.8 Hz), 7.23 (t, major 3H, J=1.8 Hz), 7.18 (t, major 3H, J=1.8 Hz), 6.96 (t, major 3H, J=1.8 Hz), 6.36 (t, minor 3H, J=1.8 Hz), 3.38 (s, minor 9H) and 3.34 (s, major 9H); IR (KBr) 1650, 1600 cm^{-1}. Anal. Calcd for $C_{24}H_{18}Br_3N_3O_3$: C, 45.28; H, 2.83; N, 6.60. Found: C, 45.08; H, 2.72; N, 6.84.

*4.2.7. Synthesis of cyclic triamide **4**.* Palladium acetate (33.6 mg, 0.15 mmol) was added to the mixture of sodium acetate (308 mg, 3.75 mmol), tetra(*n*-butyl)ammonium chloride (417 mg, 1.5 mmol), cyclohexene, and DMF (5 mL) under Ar atmosphere in a sealed tube. After the solution turned orange, compound **3** (318 mg, 0.5 mmol) was added to the mixture. The tube was heated at 85 °C in a sealed bottle with cyclohexane for 1 week. After cooling, the mixture was diluted with methylene chloride and filtered over Celite. The filtrate was washed successively with 2 M hydrochloric acid, water and brine, and dried over sodium sulfate. After evaporation, the crude mixture was dissolved in methanol (6 mL), and was hydrogenated with 10% Pd/C (60 mg) under hydrogen atmosphere for 2 h. After filtration and evaporation, the residue was purified by silica gel column chromatography and preparative TLC to give **4** (86 mg, 27%) with **1** (27 mg, 13%), monocyclohexyl (48 mg, 20%), dicyclohexyl compounds (83 mg, 30%) as by-products. Compound **4**: colorless prisms (ethanol/hexane); mp 278–279 °C; ^{1}H NMR (400 MHz, CD_2Cl_2, 213 K) δ 7.32 (s, minor 3H), 7.09 (s, minor 3H), 6.87 (br s, major 3H), 6.76 (t, major 3H, J=1.5 Hz), 6.75 (t, major 3H, J=1.5 Hz), 6.21 (s, minor 3H), 3.36 (s, minor 9H), 3.22 (s, major 9H), 2.42 (t, minor 3H, J=12.0 Hz), 2.26 (t, major 3H, J=12.0 Hz), and 1.8–1.1 (m, 30H); IR (KBr) 1640, 1590 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{42}H_{52}N_3O_3$ (M+H$^+$): 646.4003. Found: 646.4024. Anal. Calcd for $C_{42}H_{51}N_3O_3\cdot H_2O$: C, 75.98; H, 8.05; N, 6.33. Found: C, 75.75; H, 8.17; N, 6.17.

*4.2.8. Synthesis of cyclic triamide **5**.* A mixture of **3** (127 mg, 0.2 mmol), phenylboronic acid (88 mg, 0.72 mmol), 10% Pd/C (28 mg), and triphenylphosphine (29 mg, 1.1 mmol) in dry DME (1 mL) was stirred for 15 min. Sodium carbonate (2 M) was added to the mixture and the reaction mixture was heated at 80 °C overnight. After cooling, the mixture was diluted with methylene chloride, and filtered over Celite. The filtrate was washed with water and brine, and dried over sodium sulfate. After evaporation, the residue was purified by flash silica gel column chromatography (ethyl acetate/methylene chloride 8:1) to give **5** (47 mg, 35%). Compound **5**: colorless prisms (ethyl acetate/methanol); mp 168–169 °C; ^{1}H NMR (400 MHz, CD_2Cl_2, 213 K) δ 7.72 (s, minor 3H), 7.58 (s, minor 3H), 7.5–7.3 (m, minor 15H), 7.25 (t, major 3H, J=8.1 Hz), 7.22 (s, major 3H, J=1 Hz), 7.13 (s, major 3H), 7.11 (d, major 6H, J=8.1 Hz), 6.95 (s, major 3H), 6.93 (d, major 6H, J=8.1 Hz), 6.48 (s, minor 3H), 3.37 (s, minor 9H), and 3.34 (s, major 9H); IR (KBr) 1650, 1590 cm^{-1}; HRMS (EI) calcd for $C_{42}H_{33}N_3O_3$: 627.2522. Found: 627.2524. Anal. Calcd for $C_{42}H_{33}N_3O_3\cdot 1/3H_2O$: C, 79.60; H, 5.35; N, 6.63. Found: C, 79.61; H, 5.37; N, 6.50.

*4.2.9. Synthesis of cyclic triamide **6**.* A solution of *N*-methylaniline (0.04 ml, 0.36 mmol) in dry toluene (1 mL) was added to a mixture of **3** (64 mg, 0.1 mmol), $Pd_2(dba)_3$ (5.5 mg, 0.006 mmol), BINAP (9 mg, 0.015 mmol), and sodium *tert*-butoxide (40 mg, 0.42 mmol) under Ar atmosphere, and the mixture was heated at 80 °C for 6 h. After cooling, the mixture was diluted with ethyl acetate and filtered over Celite. The filtrate was washed with water and brine, and dried over sodium sulfate. After evaporation, the residue was purified by flash silica gel column chromatography (ethyl acetate/hexane 4:1) to give **6** (50 mg, 70%). **6**: pale brown prisms (methanol); mp 124 °C; ^{1}H NMR (400 MHz, CD_2Cl_2, 213 K) δ 7.28 (t, minor 6H, J=8.1 Hz), 7.19 (t, major 6H, J=8.1 Hz), 7.05 (t, minor 3H, J=8.1 Hz), 7.01 (t, major 3H, J=8.1 Hz), 6.97 (t, minor 6H, J=8.1 Hz), 6.72 (t, major 6H, J=8.1 Hz), 6.70 (s, minor 3H), 6.53 (s, major 3H), 6.46 (s, major 3H), 6.45 (s, minor 3H), 6.43 (s, major 3H), 6.02 (s, minor 3H), 3.25 (s, minor 9H), 3.24 (s, minor 9H), 3.18 (s, major 9H), and 3.09 (s, major 9H); IR (KBr) 1640, 1590 cm^{-1}. Anal. Calcd for $C_{45}H_{42}N_6O_3$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.29; H, 6.04; N, 11.66.

*4.2.10. Synthesis of cyclic triamide **7**.* A solution of piperidine (0.07 ml, 0.72 mmol) in dry toluene (2 mL) was added to a mixture of **3** (127 mg, 0.2 mmol), $Pd_2(dba)_3$ (11.0 mg, 0.01 mmol), BINAP (19 mg, 0.03 mmol), and sodium *tert*-butoxide (81 mg, 0.84 mmol) under Ar atmosphere, and the mixture was heated at 80 °C for 8 h. After cooling, the mixture was diluted with methylene chloride and filtered over Celite. The filtrate was washed with water and brine, and dried over sodium sulfate. After evaporation, the residue was purified by flash silica gel column chromatography (ethyl acetate/*n*-hexane 4:1) to give **7** (50 mg, 39%). **7**: yellow prisms (methanol); mp>300 °C; ^{1}H NMR (400 MHz, CD_2Cl_2, 213 K) δ 6.96 (s, minor 3H), 6.72 (s, minor 3H), 6.50 (s, major 3H), 6.48 (s, major 3H), 6.31 (s, major 3H), 5.87 (s, minor 3H), 3.24 (s, minor 9H), 3.20 (s, major 9H), 3.00 (s, minor 3H), 2.89 (s, major 3H), and 1.8–1.45 (br, minor and major 9H); IR (KBr) 1640, 1590 cm^{-1}. Anal. Calcd for $C_{39}H_{48}N_6O_3$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.90; H, 7.58; N, 12.80.

*4.2.11. Synthesis of cyclic triamide **8**.* A mixture of **3** (127 mg, 0.2 mmol), copper(I) cyanide (65 mg, 0.72 mmol), and DMF (5 mL) was heated at 170 °C under Ar atmosphere for 7 h. A solution of iron (III) chloride (0.8 g) in hydrochloric acid (0.2 mL) and water (2 mL)

was added to the mixture at room temperature. The mixture was poured into water and extracted with methylene chloride. The organic layer was washed with water and brine, and dried over sodium sulfate. After evaporation, the residue was purified by flash silica gel column chromatography (ethyl acetate/hexane 4:1) to give **8** (37 mg, 45%). Compound **8**: colorless prisms (methylene chloride/methanol); mp>300 °C; ^{1}H NMR (400 MHz, CD_2Cl_2, 213 K) δ 7.83 (s, minor 3H), 7.64 (s, minor 3H), 7.43 (s, major 3H), 7.42 (s, major 3H), 7.18 (s, major 3H), 6.54 (s, minor 3H), 3.35 (s, minor 9H), and 3.27 (s, major 9H); IR (KBr) 1650, 1580 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{27}H_{18}N_6NaO_3$ (M+Na$^+$): 497.1333. Found: 497.1352. Anal. Calcd for $C_{27}H_{18}N_6O_3\cdot 1/3H_2O$: C, 67.49; H, 3.92; N, 17.49. Found: C, 67.76; H, 4.07; N, 17.42.

4.3. X-ray crystallography

Single crystal X-ray diffraction data of the crystals were collected on a four-circle diffractometer (for **3** and **4**) with graphite monochromated Cu Kα (λ=1.5418 Å) radiation or an imaging plate diffractometer (for **5**) or CCD diffractometer (for **8**) with graphite monochromated Mo Kα (λ=0.7107 Å). The crystal structure was solved by direct methods SIR2004[15] or SHELXS-97[16] and refined by full-matrix least-squares. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were included at their calculated positions. Details of each crystal data are described in Table 1 and supplementary CIF files.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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