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N-Methylated Diphenylguanidines: Conformations, Propeller-Type Molecular Chirality, and Construction of Water-Soluble Oligomers with Multilayered Aromatic Structures

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Abstract: The crystal structures of *N*,*N*′-diphenylguanidine (**1**) and its *N*-methylated derivatives were investigated, and the conformational properties of these molecules were utilized to construct water-soluble oligomers with multilayered aromatic structures. *N*,*N*′-Diphenylguanidine (**1**) afforded two types of crystals, chiral ($P2_12_12_1$) and racemic ($P2_1/c$), upon recrystallization from EtOH. In both crystals, **1** exists in the (*E*,*Z*) conformation, in which one C−N bond (length: 1.28−1.30 Å) attached to a phenyl ring shows double-bond character. In contrast, *N*,*N*′-dimethyl-*N*,*N*′-diphenylguanidine (**4a**) exists in the (*Z*,*Z*) conformation with the two aromatic rings facing each other. As judged from the crystal structures of several *N*-methylated compounds, the conformational preferences of diphenylguanidines appear to be related to those of aromatic anilides. *N*,*N*,*N*′,*N*′′-Tetramethyl-*N*′,*N*′′-diphenylguanidinium iodide (**6**) afforded chiral crystals, like **1** and *N*-methyl-*N*,*N*′-diphenylguanidine (**2**). The absolute structure of each enantiomeric propeller conformation of **6** was determined by X-ray analysis using the Bijvoet difference method. The *Z*-conformational preference of **4** allowed us to synthesize oligomeric di- or tetraguanidines (**9**−**12**) which have multilayered aromatic structures both as a crystal and in organic and aqueous solvents.

Introduction

Guanidine is one of the strongest organic bases, owing to stabilization of the guanidinium ion by the well-known Y-delocalization effect.[1,2] The hydrogen-bonding acceptor and donor abilities of the guanidino group play important roles in supramolecule formation[3] and in bioactive substances, for example, in L-arginine as a substance for NO synthesis[4] or in the active sites of various proteins,[5] as well as in drug design in the field of medicinal chemistry.[6−8]

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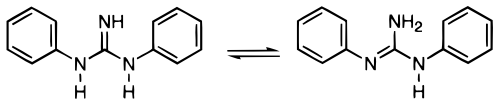
Table 1. Crystal Data of Diphenylguanidines (**1**−**6**)

	1 (chiral)	**1** (racemic)	**2**	**3**	**4a**	**4b**	**5**	**6**
formula	$C_{13}H_{13}N_3$	$C_{13}H_{13}N_3$	$C_{14}H_{15}N_3$	$C_{14}H_{15}N_3$	$C_{15}H_{17}N_3 \cdot 1/2H_2O \cdot 1/4C_6H_{14}$	$C_{15}H_{18}N_3Br$	$C_{16}H_{19}N_3$	$C_{17}H_{22}N_3I \cdot H_2O$
recrystn solvent	EtOH	EtOH	CH_2Cl_2	AcOEt/*n*-C_6H_{14}	*n*-C_6H_{14}	$CHCl_3$	*n*-C_6H_{14}	$CHCl_3$/AcOEt
crystal system	orthorhombic	monoclinic	orthorhombic	monoclinic	triclinic	triclinic	monoclinic	orthorhombic
space group	$P2_12_12_1$	$P2_1/c$	$P2_12_12_1$	Cc	$P\bar{1}$	$P\bar{1}$	$C2/c$	$P2_12_12_1$
a, Å	12.653(5)	8.906(2)	5.666(1)	11.212(2)	11.590(5)	13.034(3)	18.532(2)	12.055(3)
b, Å	20.54(2)	12.342(1)	10.126(3)	12.757(2)	16.44(2)	13.216(4)	7.736(2)	14.776(3)
c, Å	8.944(5)	21.335(2)	21.17(2)	9.281(1)	8.320(4)	9.711(2)	20.462(2)	10.466(4)
α, deg					97.21(7)	91.85(2)		
β, deg		96.66(1)		112.21(1)	90.73(3)	94.99(2)	104.273(9)	
γ, deg					77.50(7)	65.14(1)		
V, Å^3	2324(2)	2329.1(6)	1214(3)	1229.1(4)	1535(2)	1512.1(6)	2842(1)	1864.3(7)
d_{calc}, g cm^{-3}	1.207	1.205	1.232	1.217	1.167	1.407	1.184	1.472
Z	8[a]	8[a]	4	4	4[a]	4[a]	8	4
radiation	Mo Kα	Cu Kα	Mo Kα	Cu Kα	Mo Kα	Cu Kα	Cu Kα	Cu Kα
temp, K	296	296	173	296	173	296	296	296
no. unique reflctns	3231	3650	819	1135	4425	4493	2304	1938
R	0.085	0.048	0.075	0.062	0.097	0.079	0.069	0.065

[a] Two independent molecules exist in the asymmetric unit.



imino form amino form

Figure 1. Tautomerization of *N*,*N*′-diphenylguanidine (**1**, *E*,*E*-form).

The structures of various guanidines or guanidinium ions have been investigated in order to clarify their bonding and electronic properties. A highly symmetrical, planar structure of the unsubstituted guanidinium ion, $C^+(NH_2)_3$, which allows substantial electron delocalization, was elucidated empirically by X-ray analyses[9] and IR and Raman spectroscopies and also was treated by theoretical calculations.[2,10] Mono- or disubstituted neutral guanidines can exist in two tautomeric forms, conventionally named the imino form and the amino form, as illustrated for the case of *N*,*N*′-diphenylguanidine (**1**) in Figure 1. Spectroscopic studies show that the imino form is favored in monoalkylguanidines such as L-arginine in solution,[11] while monoarylguanidines[12] or guanidines substituted with an electron-withdrawing group (nitro, cyano, and so on)[1] favor the amino form. However, there are only a few examples of the determination of the tautomeric preference of neutral substituted guanidines by X-ray crystallographic analysis, owing to the strong basic properties of these molecules. Most neutral guanidines so far examined form dimeric or oligomeric structures through hydrogen-bond networks in the crystals.[13]

The C−N partial double-bond character often has interesting effects on molecular structure and physicochemical properties. As a continuation of our previous studies on the conformations of aromatic amides with unique intramolecular spatial arrangements and aromatic interactions,[14] we were interested in the stereochemical behaviors of aromatic guanidines. In this connection, diarylguanidines have recently attracted much attention in the fields of materials chemistry and medicinal chemistry.[8] Here, we describe the systematic structural analyses of *N*,*N*′-diphenylguanidine and its *N*-methylated derivatives, focusing on (i) the properties of aromatic-substituted guanidino bonds, (ii) the molecular conformational preference as compared with that of the aromatic anilides, (iii) the existence of chiral propeller-type conformations due to twisting of the guanidino bonds, and (iv) the application of the *Z*-conformational preference of *N*,*N*′-dimethylated guanidine to construct unique, water-soluble oligomers with multilayered aromatic structures.

Results and Discussion

Five diphenylguanidines and two guanidinium salts (**1**−**6**, Figure 2) were synthesized by standard procedures as described in the Supporting Information, and their crystal structures were elucidated by X-ray analyses. The crystal data are summarized in Table 1. To simplify the discussion, we adopted the following system for the structures and numbering of guanidino groups. Tautomers of diphenylguanidines are named as the imino form or amino form regardless of methyl substituents (Figure 1). In both tautomers, the phenyl-bearing nitrogen atom with the shorter C−N bond length is numbered N(1), the nitrogen with the longer C−N bond length is numbered N(2), and the nitrogen without a phenyl substituent is numbered N(3), as shown in Figure 2. Thus, the C(1)−N(1) bond always possesses much more double-bond character than the C(1)−

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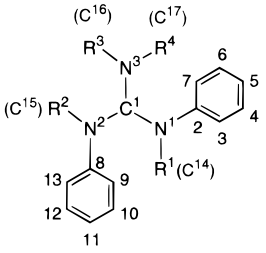

1 ($R^2 = R^3 = R^4 = H$)
2 ($R^2 = CH_3$, $R^3 = R^4 = H$)
3 ($R^2 = R^4 = H$, $R^3 = CH_3$)
4a ($R^1 = R^2 = CH_3$, $R^3 = H$)
4b (HBr salt of **4a**)
5 ($R^2 = R^3 = R^4 = CH_3$)
6 ($R^1 = R^2 = R^3 = R^4 = CH_3$)

Figure 2.

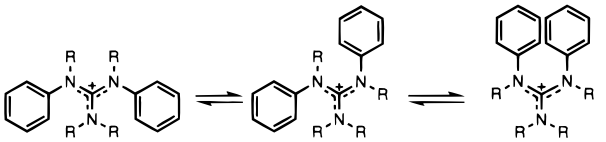

Figure 3. Possible conformations of the *N*,*N*′-diphenylguanidinium ion.

N(2) bond. *E*/*Z* conformations are defined according to the positional relationships between *N*-phenyl groups, as shown in Figure 3 for the case of the *N*,*N*′-diphenylguanidinium ion. In this definition of the geometry, the positions of the double bond or alkyl substituents are not considered.

Crystal Structure of *N*,*N*′-Diphenylguanidine (1). A crystal structure of unsubstituted *N*,*N*′-diphenylguanidine (**1**) was elucidated by Zakharov et al.[15] However, we obtained significantly different X-ray crystal data for **1**. After several attempts at recrystallization of **1** from various solvents, we obtained two types of crystals from ethanol. Although the precise recrystallization conditions leading to one form or the other remained obscure, we could get the desired type by seeding, that is, only one type of crystals formed in one flask. The two types are distinguished by their shape and crystal system (Table 1); one is chiral colorless plates (orthorhombic, space group, $P2_12_12_1$), and the other is racemic colorless prisms (monoclinic, space group, $P2_1/c$). The latter form seems to be identical to that observed by Zakharov et al. in terms of the crystal parameters. As shown in Table 1, the lattice parameters are similar to each other, but the two forms were confirmed to be distinct by powder X-ray analysis and distinguished in the IR spectra.[16]

The chiral and racemic crystals each have eight molecules of **1** in the unit cell, and the asymmetric unit contains two molecules in conformations similar to each other (Figure 4). No significant intramolecular hydrogen-bonded interaction was observed. Each molecule exists in the amino form in which the phenyl-bearing C(1)−N(1) bond has a length of 1.28−1.30 Å, close to that of a typical C═N double bond (ca. 1.28 Å), and is shorter than the other two C−N bonds of the guanidino group (Table 2). The bond length (1.37−1.39 Å) of the C(1)−N(2) bond attached to the other phenyl ring is slightly longer than that of the C(1)−N(3) bond (1.33−1.36 Å), though both have partial double-bond character. The guanidino group is planar in each case, as deduced from the bond angles and torsion angles. The order of the three bond angles correlates well to that of their opposing bond lengths, that is, the N(2)−C(1)−N(3) bond angle (111−113°) is always smaller than the other two (see the Supporting Information).

Table 2. Bond Lengths and Conformations of Guanidine Bonds

	N(1)−C(1)		N(2)−C(1)		N(3)−C(1)
compd	length (Å)	confrmtn[a]	length (Å)	confrmtn[a]	length (Å)
1 (chiral)[b]	1.286(5)	*E*	1.367(6)	*Z*	1.344(6)
	1.297(5)	*E*	1.371(6)	*Z*	1.332(6)
1 (racemic)[b]	1.287(3)	*E*	1.385(3)	*Z*	1.357(3)
	1.278(3)	*E*	1.374(4)	*Z*	1.358(3)
2	1.284(6)	*E*	1.394(6)	*Z*	1.345(7)
3	1.270(9)	*Z*	1.380(9)	*Z*	1.379(10)
4a[b]	1.40(1)	*Z*	1.40(1)	*Z*	1.27(1)
	1.39(1)	*Z*	1.40(1)	*Z*	1.26(1)
4b[b,c]	1.35(2)	*Z*	1.38(2)	*Z*	1.33(2)
	1.34(2)	*Z*	1.35(1)	*Z*	1.33(1)
5	1.298(5)	*Z*	1.409(5)	*E*	1.345(5)
6[c,d]	1.32(2)	*E*	1.36(1)	*Z*	1.32(1)

[a] *E*/*Z* conformations at C−N bonds are defined in Figure 3. [b] Two independent molecules exist in the asymmetric unit. [c] See ref 19. [d] The average values of (+)- and (−)-crystals are shown.

Compound **1** exists in the (*E*,*Z*) conformation in both the chiral and racemic crystals, where the shorter C(1)−N(1) bond is *E* and the longer C(1)−N(2) bond is *Z*. Both aromatic rings are twisted from the guanidino plane. In particular, the phenyl ring on N(1) is located nearly perpendicular to the guanidino group (65−87°), and the other phenyl group on N(2) shows a rather small dihedral angle (23−34°). The former can be ascribed mostly to the twisting around the N(1)−C(Ar) bond (torsion angles, 66−89°), and the latter to twisting around the C(1)−N(2) or/and N(2)−C(Ar) bonds, depending on the molecule. Consequently, the dihedral angle between the two phenyl rings is also large (75−87°) in all the molecules of **1**.

***N*-Methylated Diphenylguanidines.** Among seven possible neutral *N*,*N*′-diphenylguanidines substituted with *N*-methyl group(s), four (**2**−**5**, Figure 2) were subjected to X-ray crystallographic analyses (Table 1). Since crystals of *N*,*N*′-dimethyl-*N*,*N*′-diphenylguanidine (**4a**) obtained from *n*-hexane in a refrigerator (−20 °C) melted above 5 °C and were unstable under X-ray irradiation, we used a laser-stimulated fluorescence image plate as a two-dimensional area detector for quick X-ray analysis at −100 °C.[17] Interestingly, the unit cell of the crystal of **4a** ($Z = 4$) contains two molecules of water and one molecule of *n*-hexane.[18] Thus, the precise structural parameters of **4a** could not be obtained owing to the significant crystal disorder, as shown in Table 2.[19]

N-Methyl-*N*,*N*′-diphenylguanidine (**2**) exists in the amino form with the (*E*,*Z*) conformation similar to that of **1**, although, exceptionally in this series, **2** showed intramolecular hydrogen-bonded networks in the chiral crystal, with the distance (N−H···N) being 3.03 Å. In compound **2**, the phenyl group on the N(2) atom showed a large dihedral angle (63°) to the guanidino

(15) Zakharov, L. N.; Adrianof, V. G.; Struchkov, Y. T. *Kristallografiya* **1980**, *25*, 65−71.

(16) The IR absorbances at 1535 and 1360 cm^{-1} of the chiral crystals were split (1540 and 1520 cm^{-1} and 1365 and 1350 cm^{-1}, respectively) in the racemic crystals of **1** (see the Supporting Information). The relationship was confirmed by means of experiments using crystals cut in two, of which one-half was used for IR spectral measurement and the other for X-ray analysis.

(17) Tanatani, A.; Kagechika, H.; Azumaya, I.; Yamaguchi, K.; Shudo, K. *Chem. Pharm. Bull.* **1996**, *44*, 1135−1137.

(18) The crystal parameters of **4a** described in ref 17 were revised.

(19) We could not improve the analytical precision in all cases. The rather large experimental errors (for example, $^3/_{1000}$ to $^{10}/_{1000}$ in bond lengths as shown in Table 2) seems to result from some crystal disorder of guanidines, since there have been no such cases in the related aromatic amides and ureas in our experiments. We also could not obtain the precise structural parameters of the guanidinium ions **4a** and **6** (and the oligomeric compounds **9**−**12**), probably due to the existence of heavier halogen anions.

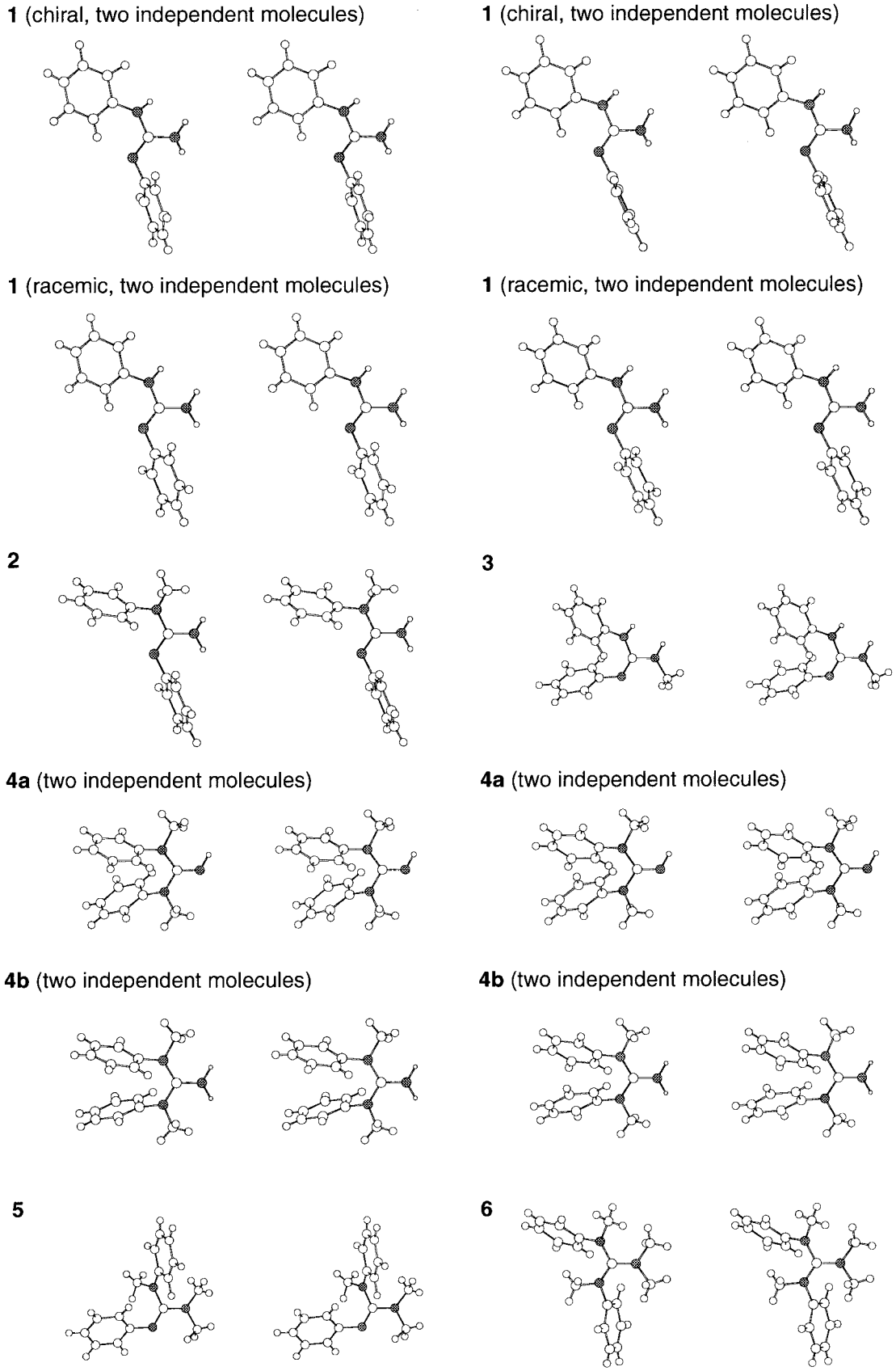

Figure 4. Stereoview crystal structures of diphenylguanidines (**1**−**6**). The counteranions and solvent molecules are omitted.

group, as did the *N*(1)-phenyl group (76°), due to the steric hindrance of the *N*-methyl group. Interestingly, the N(2) atom of **2** is slightly deviated from planarity with the three attached carbon atoms. The sum of the bond angles around the N(2) atom is 355.6°, and the distance between the N(2) atom and the plane of the three attached carbon atoms is 0.17 Å. This deviation of the nitrogen atom from planarity is exceptional in the aromatic guanidines examined, even among hindered compounds such as **5** and **6**. The methyl group on the N(2) atom of **2** exists above the *N*(1)-phenyl group of the other

molecule in the crystal, the distance (C_{Me}−Ph) being 3.29 Å.[20] This intermolecular interaction may have a significant influence on the molecular structure of **2**.

Another monomethylated compound, **3**, also exists in the amino form with a C(1)−N(1) bond length of 1.270 Å. However, the conformation of **3** is (*Z*,*Z*), different from those of **1** and **2**. This structure is regarded as the inversion of the *N*(1)-Ph group due to the steric repulsion between the phenyl and methyl groups.

A more significant conformational characteristic was observed in the crystal structure of *N*,*N*′-dimethyl-*N*,*N*′-diphenylguanidine (**4a**). The conformation of **4a** is classified as (*Z*,*Z*), like **3**, but their structures are remarkably disparate. The guanidino group of **4a** is in the imino form with C(1)−N(3) bond length of 1.26−1.27 Å. Both C(1)−N(1) and C(1)−N(2) bonds bearing the phenyl group are longer (1.39−1.40 Å). Furthermore, the conformation of **4a** is distinguished from that of **3** by the spatial relationship between the two phenyl rings in addition to the tautomerization of the guanidino bond. In compound **3**, the two phenyl rings are tilted with a large dihedral angle (59°) and a large distance between the two ring centers (4.28 Å). On the other hand, the phenyl rings of **4a** are more parallel and face each other. The dihedral angle between the two phenyl rings of **4a** (37−38°) reflects a splayed-out structure, probably due to the repulsive interactions of π-electrons. The phenyl−phenyl distances of **4a** are 2.89 and 3.85 Å for C_{ipso}−C_{ipso} and between the ring centers, respectively.

This aromatic face-to-face conformation of **4a** is retained in the crystal structure of its hydrobromide salt (**4b**), in which the dihedral angle between the two phenyl rings (31°) and the distance (3.77−3.84 Å) between the ring centers are somewhat smaller than those of **4a**.[19] We considered that these folded structures provided a basis for the construction of oligomeric multilayered aromatic molecules.

The conformation of the fully methylated neutral guanidine, *N*,*N*,*N*′-trimethyl-*N*′,*N*″-diphenylguanidine (**5**), is (*Z*,*E*), in which the shorter C(1)−N(1) bond is *Z* and the longer C(1)−N(2) is *E*, opposite to the conformation of unsubstituted **1** or **2**. The steric hindrance in **5** reasonably generates a large torsion angle (52−55°) around the C(1)−N(2) bond, which has less double-bond character (1.409 Å), and large dihedral angles of the guanidino group to both phenyl rings (49 and 67°) but does not affect the planarity of the guanidino carbon and all the nitrogen atoms. The twisting of *N*-substituents from the guanidino plane[21] is even more remarkable in the fully methyl-substituted guanidinium ion (**6**), which has an (*E*,*Z*) conformation. Both phenyl-bearing C−N bonds of **6** are distorted with torsion angles of 34−42°, and the C(1)−N(3) bond is twisted (26−31°) from the guanidino plane. These structural features of hindered guanidinium ions afford unique chiral conformations, as discussed below.

Comparison of Conformational Preference in *N*,*N*′-Diphenylguanidines and Aromatic Amides and Ureas. We previously reported the conformational properties of aromatic anilides. The amide bond of benzanilide is exclusively trans both in the crystal and in solution, while *N*-methylbenzanilide exists in the cis conformation in the crystal and takes predominantly the cis form in various solvents (for example, cis:trans = 98.6:1.4 in CD_2Cl_2 at 183 K).[14] The conformational alteration of amide bonds by *N*-methylation is illustrated in Figure 5. In this scheme, we use trans/cis nomenclature in order to distinguish the *E*/*Z* stereochemistry of guanidines, as shown in Figure 3. Thus, cis conformation means that the phenyl group is cis to the R group and the methyl group (or hydrogen atom) is cis to the C═X double bond in the general formula.

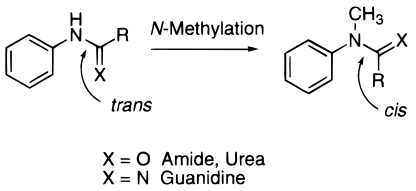

Figure 5. Conformational alteration by *N*-methylation.

The cis conformational preference is general for carbonyl compounds (X = O) such as amides (R = alkyl or aryl) and ureas (R = NR′R″).[14] Although the conformational alteration of aromatic guanidines (with an amino group as X) caused by *N*-methylation could not be simplifed due to the existence of the tautomeric amino/imino forms, the similar conformational preference was also observed in neutral guanidines. Thus, the compounds having a secondary anilino moiety (PhNH−), such as **1** and **3**, corresponding to structures with a phenylimino group as X in Figure 5, prefer the trans conformation in relation to the C(1)−N(2) bond. On the contrary, an *N*-methylated anilino moiety favors the cis conformation as shown in **4a** (X = NH) and **5** (X = NPh). Accordingly, the *N*,*N*′-dimethylated compound **4a** exists in the folded (cis,cis) conformation which is very similar to the crystal structure of *N*,*N*′-dimethyl-*N*,*N*′-diphenylurea.

Among the compounds examined, only **2** does not obey the cis preference rule; instead, the *N*-methyl group is located trans to the C(1)═N(1) double bond, at least partially due to the hydrogen-bonding (and/or CH-π) network in the crystal. On the other hand, the *N*(1)-phenyl group on the C═N double bond in the amino form is nearly perpendicular to the guanidino plane, with loss of conjugation to each other, and the geometry seems to be determined by the steric character of the substituents on the other nitrogen atoms, N(2) and N(3). Considering the structure of **3**, it appears that the steric hindrance of the *N*-methyl group is larger than that of the anisotropic bulky *N*-phenyl group.[22]

Interestingly, the conformational preference of **4a** is retained in the guanidinium salt **4b**, although the three C−N bonds in **4b** all have roughly the same partial double-bond character. The result of ab initio calculation indicated that the cis preference of *N*-methylated amides could be ascribed to destabilization of the trans form due to the steric hindrance of the *N*-methyl group and to electronic repulsion between the carbonyl lone pair electrons and the phenyl π-electrons.[22] Energetically, the former steric factor seems to be more significant than the latter electronic effect. This is in accordance with the observation of a similar cis preference in *N*,*N*′-dimethylated guanidinium ion **4b** with Y-delocalization.

In the case of guanidinium ions, the X group in Figure 5 is a substituted nitrogen atom instead of an oxygen atom. When X is a dimethylamino group (i.e., compound **6**), the molecule does not adopt a folded (cis,cis) structure like that of **4b** (X = NH_2). Steric bulkiness of the X group appears to disturb the cis preference of *N*-methylated guanidines. Thus, cis preference is applicable to neutral guanidines and even Y-delocalized guanidinium ions without a sterically bulky X group.

Conformations of Aromatic Guanidines in Solution. Cis preference of *N*-methylated amides in solution was demonstrated

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(21) Santoro, A. V.; Mickevicious, G. *J. Org. Chem.* **1979**, *44*, 117−120.

(22) Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715−4720.

Table 3. Comparison of ^{1}H NMR Chemical Shifts (δ) of Aromatic Protons in Secondary and Tertiary Anilino Groups in $CDCl_3$ at 303 K

	ortho	meta	para
N,*N*′-diphenylguanidine			
unsubstituted (**1**)	7.12	7.31	7.06
N,*N*′-dimethyl (**4a**)	6.93	7.17	6.96
N,*N*′-diphenylguanidinium salt			
unsubstituted	7.31	7.46	7.37
N,*N*′-dimethyl (**4b**)	6.80	7.16	7.12
benzanilide			
unsubstituted	7.64	7.38	7.16
N-methyl	7.04	7.22	7.12
N,*N*′-diphenylurea			
unsubstituted	7.35	7.35	7.13
N,*N*′-dimethyl	6.79	7.04	6.93

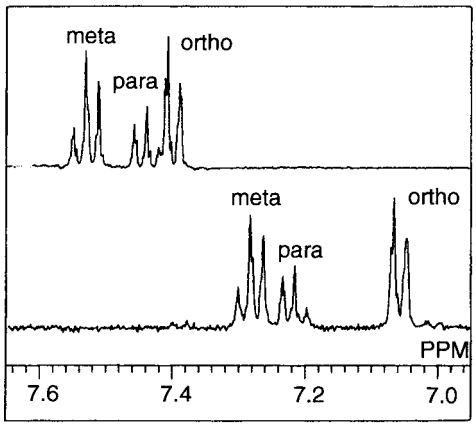

Figure 6. Comparison of ^{1}H NMR chemical shifts between *N*,*N*′-diphenylguanidinium bromide (upper) and *N*,*N*′-dimethyl-*N*,*N*′-diphenylguanidinium bromide (**4b**, lower) in D_2O at 303 K.

by measurement of temperature-dependent NMR spectra.[14] However, the isomerization barrier of C═N double bonds of less hindered guanidines is low, and furthermore, the inversion mechanism is significant in many cases.[1,23] Thus, the diphenylguanidines **1**, **3**, and **4** afforded simple ^{1}H NMR spectra in which the two phenyl rings could not be distinguished even at 183 K and no minor signals were observed. Therefore, these compounds exist in symmetrical conformations or in rapid equilibrium between several conformers. The signal of the aromatic protons of **4a** appeared at higher fields than those of **1** by 0.1−0.2 ppm (Table 3). More remarkable higher-field shifts of the aromatic proton signals were observed in the guanidinium salt **4b**, and the differences between the salts of **1** and **4b** are 0.51, 0.30, and 0.25 ppm (in $CDCl_3$) at the ortho, meta, and para positions, respectively, the values correlating well to the difference between *N*,*N*′-diphenylurea (trans form) and *N*,*N*′-dimethyl-*N*,*N*′-diphenylurea (cis form). Similar chemical shift differences were observed in their ^{1}H NMR spectra in D_2O (Figure 6). Compounds **4a** and **4b** exist predominantly in the aromatic face-to-face (*Z*,*Z*) form in various solvents, including water.

6 was expected to have a substantial barrier to isomerization, due to the steric hindrance and the impossibility of inversion.[23] Temperature-dependent NMR spectra of **6** show the presence of three conformers in equilibrium in the solution (Figure 7). The *N*-methyl groups in **6** show two singlet signals at 293 K, while seven singlet peaks are seen at 183 K. The signals of the *N*(3)-methyl groups were assigned by preparing a derivative of **6** having an *N*(1),*N*(2)-bis(trideuteriomethyl) group. On the basis of the integration of the proton signals and the anisotropic effects of intramolecular phenyl rings, all the *N*-methyl signals could be assigned to three conformers as shown in Figure 7. Thus, **6** exists in equilibrium between the (*E*,*E*), (*E*,*Z*), and (*Z*,*Z*) conformations in a ratio of 2:5:3, respectively, in CD_2Cl_2 at 183 K. The most stable conformer was (*E*,*Z*), as in the crystal, but the folded (*Z*,*Z*) conformer, which corresponds to the cis-preferential structure of **4**, exists in a significant amount in solution, despite the large steric hindrance among the four methyl groups.

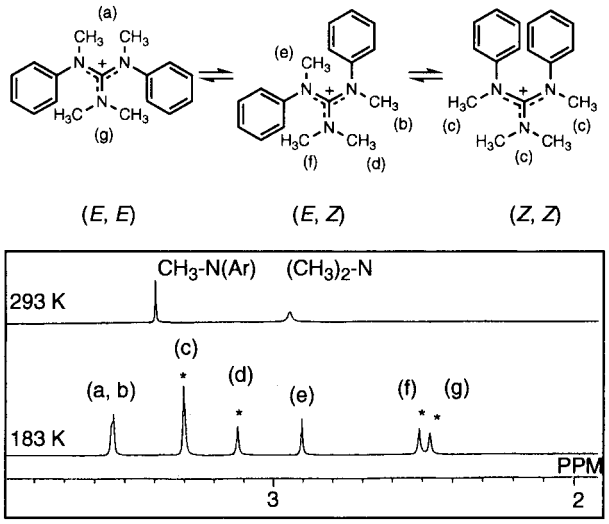

Figure 7. Conformational equibrilium and ^{1}H NMR spectra of **6** (BF_4^- salt) in CD_2Cl_2. The peaks marked by an asterisk (peaks d, f, g, and half of peak c) were assigned to dimethylamino groups. The integration ratio is (a + b):c:d:e:f:g = 1.8:2.4:1:1:1:0.8.

Novel Propeller-Type Molecular Chirality in Guanidines. Three compounds (**1**, **2**, and **6**) among the seven diphenylguanidines investigated were obtained as chiral crystals. Such chirality may result from the molecules themselves or from the crystal packing. There have recently been a number of reports on organic molecules which afford chiral crystals despite the absence of fixed asymmetric structures; this was shown to be a consequence of twisting conformations.[14c,24] In some cases, such chirality remained in solution.

As shown in Figure 8, the fully substituted guanidinium ion **6** has a conformation with all the C(1)−N bonds twisting with respect to the planar guanidino group. The twistings around the C(1)−N bonds are all in the same direction, that is, about 40° counterclockwise from the viewpoint of the nitrogen atoms in **6A**, and consequently **6** takes a chiral propeller structure. Two chiral crystals could be distinguished by their CD spectra in KBr. The crystals are optically active and enantiomeric and were designated as (+) and (−) on the basis of the sign of the ellipticity at 320 nm. We determined the absolute structures of the chiral crystals of **6** by Bijvoet difference analyses of the X-ray data;[25] the (+) and (−) crystals correspond to the enantiomers **6A** and **6B**, respectively.

As described in the previous section, the isomerization of **6** is rather fast at room temperature, and equilibration of the

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(25) (a) Bijvoet, J. M.; Peerdeman, A. F.; van Bommel, A. J. *Nature* **1951**, 271−272. (b) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876−881. The result is described in the Supporting Information.

Table 4. Crystal Data of Aromatic Di- and Tetraguanidinium Salts (**9**−**12**)

	9	**10**	**11**	**12**
formula	$C_{24}H_{30}N_6I_2$	$C_{24}H_{30}N_6I_2$	$C_{42}H_{58}N_{12}Cl_4O_2$	$C_{42}H_{62}N_{12}Cl_4O_4$
recrystn solv	MeOH/ether	MeOH/AcOEt	MeOH/AcOEt	MeOH
crystal system	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/a$	$P2_1/c$	$P2_1/c$	$P2_1/n$
a, Å	11.312(2)	10.929(2)	11.647(2)	10.854(2)
b, Å	15.420(2)	11.173(2)	25.027(3)	20.205(2)
c, Å	16.236(3)	11.895(2)	15.866(2)	13.388(2)
β, deg	101.33(1)	113.56(1)	93.52(1)	113.59(1)
V, Å^3	2776.9(8)	1331.3(5)	4616.1(9)	2690.7(6)
d_{calc}, g cm^{-3}	1.570	1.637	1.302	1.161
Z	4	2	4	2
radiation	Cu Kα	Cu Kα	Mo Kα	Cu Kα
temp, K	296	296	173	296
no. unique reflctns	4325	2105	5313	4992
R	0.057	0.041	0.066	0.069

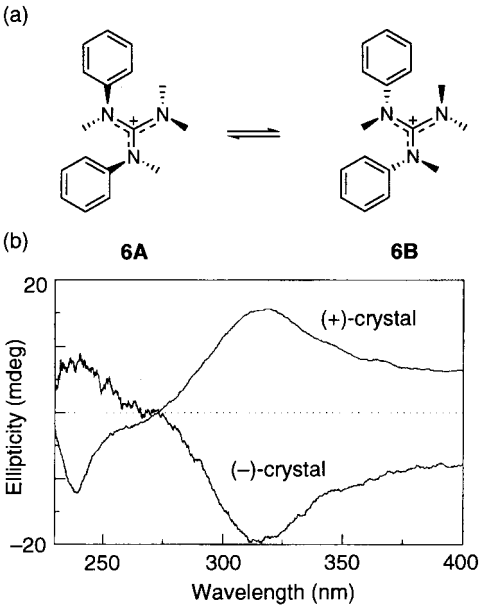

Figure 8. (a) Enantiomeric twisted conformation of **6** (*E*,*Z*-form). (b) CD spectra of two enantiomeric crystals of **6** in KBr. A mixture of 100 μg of **6** and 100 mg of KBr was well-ground and formed into a disk with a radius of 5 mm.

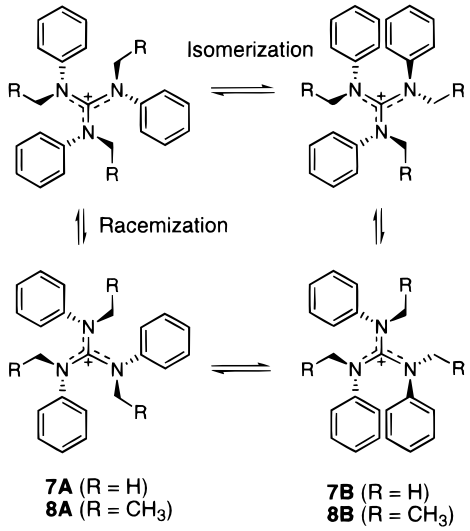

Figure 9.

isomeric conformers occurs rapidly in solution. Racemization requires the rotation of the three C(1)−N bonds but occurs rapidly in solution even when **6** is dissolved at low temperature, though the chiral conformations could be distinguished by ^{1}H NMR in the presence of chiral 1,1′-bi-2-naphthol at below 213 K (data not shown).

Thus, steric hindrance around the guanidino bond resulted in propeller-type chirality, similar to that of the triphenylmethyl cation, triphenylamine, and related compounds.[26] To obtain a more symmetrical propeller structure, we synthesized *N*,*N*′,*N*″-trimethyl-*N*,*N*′,*N*″-triphenylguanidinium iodide (**7**), which has only two possible twisting structures (**7A** and **7B**, Figure 9). The conformer **7A** is more symmetrical, with three phenyl rings located on the same side of the guanidino plane, and one (or two) bond rotation around the C(1)−N bond(s) gives the conformer **7B**, which has face-to-face aromatic moieties. In CD_2Cl_2, the NMR spectrum of **7** showed one singlet peak due to the *N*-methyl protons at room temperature, but at 183 K this was split into three singlets (2.96, 3.44, and 3.85 ppm) with equal integrations and one singlet at 3.10 ppm. Therefore, **7** exists in equilibrium between two conformers, and the ratio **7A**/**7B** is 1:3.8 in CD_2Cl_2 at 183 K. Chiral propeller conformations were also apparent in the ^{1}H NMR spectrum of the *N*-ethyl derivative **8**. In both conformations (**8A** and **8B**, in a ratio of 1:4 in CD_2Cl_2 at 183 K), the signals of the two protons of each methylene group become nonequivalent (i.e., eight different methylene proton signals) at 183 K in CD_2Cl_2 due to the rather slow interconversion between the enantiomers (see the Supporting Information), although the racemization is as fast as the conformational isomeric equilibrium rate, as in **6**. Unfortunately, X-ray crystallographic analysis of **7** or **8** was unsuccessful, although the crystals of **7** were optically active as determined from the CD spectra. Further investigation of these propeller structures is needed.

Construction of Water-Soluble Multilayered Aromatic Structures. In compounds **4a** and **4b**, cis preference resulted in face-to-face localization of the aromatic moieties. If this preference is general for the *N*,*N*′-dimethylguanidino group, it should be possible to construct water-soluble compounds with intramolecular multilayered aromatic structures.[27] Therefore, we designed and synthesized the diguanidines **9** and **10** and the tetraguanidines **11** and **12** (Figure 10). The synthetic methods for **11** and **12** are illustrated in Figure 11. *N*,*N*′-Dimethyl-*m*-phenylenediamine dihydrochloride (**18**) was condensed with 2 equiv of *N*-acetyl-*N*′-cyano-*N*,*N*′-dimethyl-*m*-phenylenediamine (**17**), prepared from *m*-nitroaniline (**13**) in

(26) Rappoport, Z.; Biali, S. E. *Acc. Chem. Res.* **1997**, *30*, 307−314 and references therein.

(27) Tanatani, A.; Kagechika, H.; Azumaya, I.; Fukutomi, R.; Ito, Y.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1997**, *38*, 4425−4428.

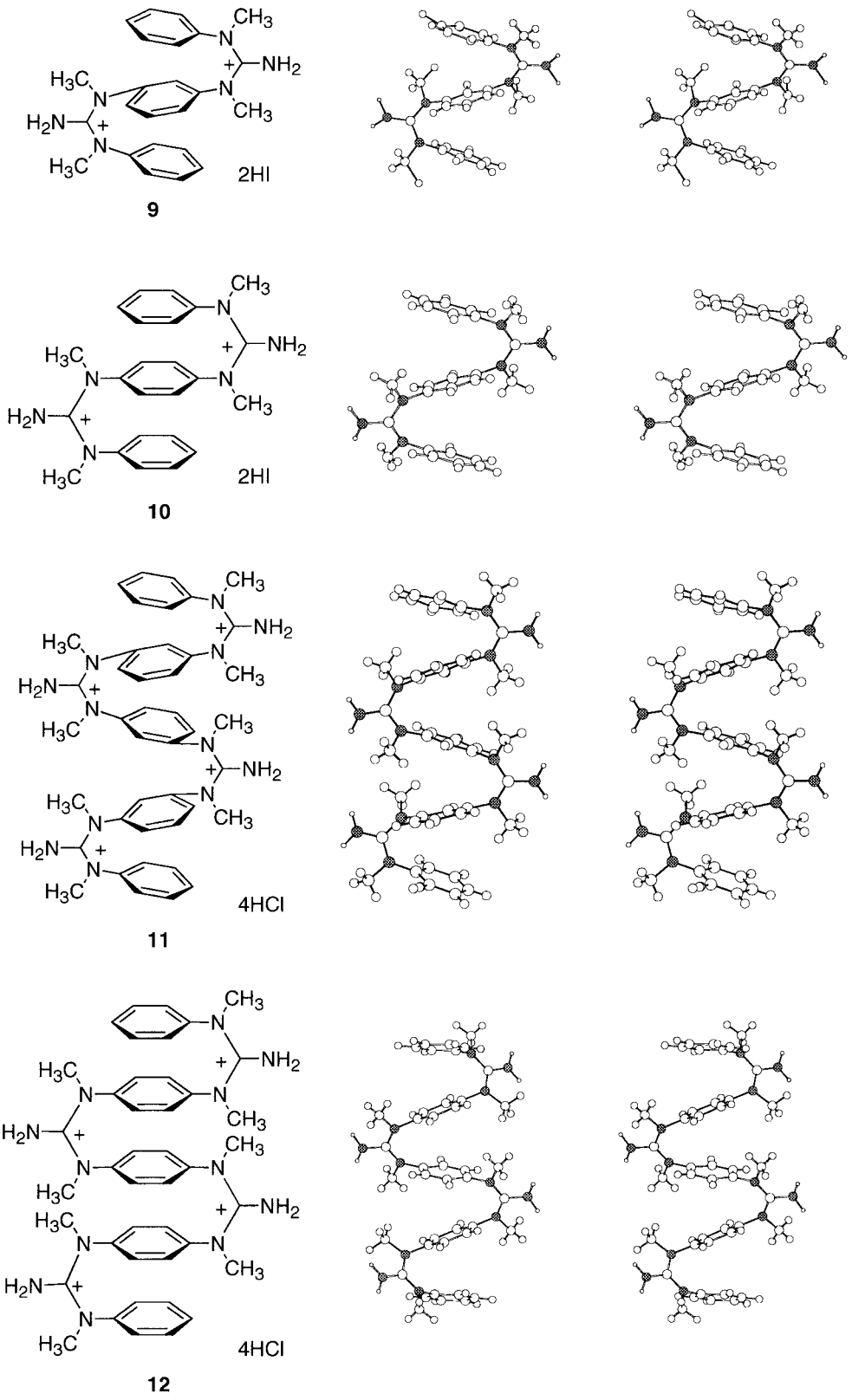

Figure 10. Stereoview crystal structures of aromatic layered guanidines (**9**−**12**). The counteranions and water molecules are omitted.

four steps, at 160 °C in chlorobenzene, to give the meta-substituted diguanidine (**19**) in 23% yield. After the deacetylation of both terminal amino groups, the hydrochloride salt of the diamine (**20**) was reacted with *N*-methyl-*N*-phenylcyanamide in the presence of $AlCl_3$ to give **11** in 46% yield. Since a similar [1 + 3 + 1] strategy for the synthesis of **12** failed at the final coupling step, probably due to the low solubility and reactivity of the para derivative of **19**, we prepared **12** by a [2 + 1 + 2] strategy with 37% yield at the final condensation.

The crystal data and structures of four oligomeric guanidinium salts (**9**−**12**) are shown in Table 4 and Figure 10. As expected from the case of **4b**, all the oligomeric compounds exhibited intramolecular multilayered aromatic structure. The partial structures of the oligomers, that is, *N*,*N*′-dimethyl-*N*,*N*′-diphen-

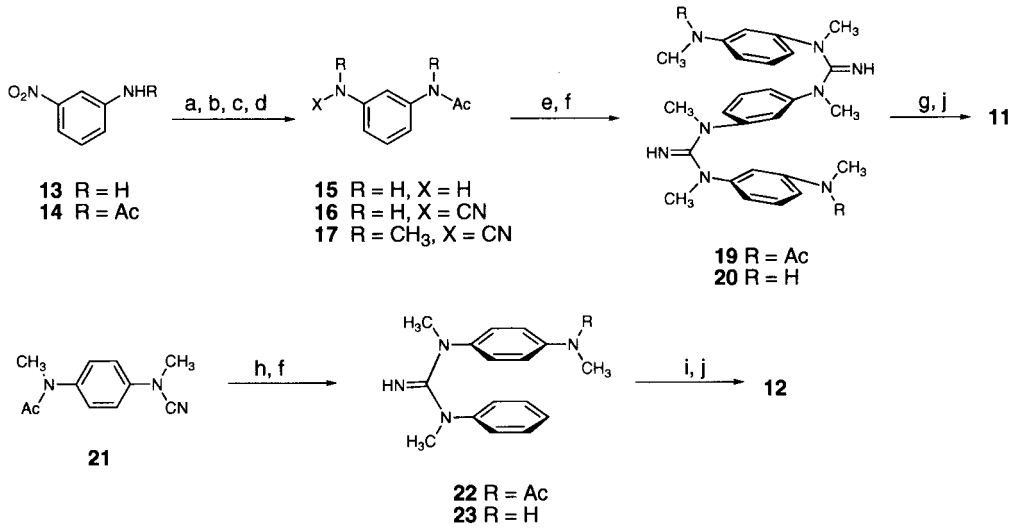

Figure 11. Synthesis of aromatic tetraguanidines **11** and **12**. Conditions: (a) Ac_2O; (b) H_2/10% Pd−C/EtOH; (c) BrCN; (d) NaH/DMF; CH_3I; (e) *N*,*N*′-dimethyl-*m*-phenylenediamine dihydrochloride (**18**)/PhCl/Δ; (f) HCl/CH_3OH; (g) HCl; *N*-methyl-*N*-phenylcyanamide/$AlCl_3$/PhCl/Δ; (h) *N*-methylaniline hydrochloride/PhCl/Δ; (i) HCl; *N*,*N*′-dicyano-*N*,*N*′-dimethyl-*p*-phenylenediamine (**24**)/$AlCl_3$/PhCl/Δ; (j) HCl/ether.

Table 5. ^{1}H NMR Chemical Shifts of Aromatic Layered Guanidines (**4b**, **9**−**12**) in D_2O at 303 K

	chemical shifts (ppm) of aromatic protons[a]		
compd	Ph-1	Ph-2	Ph-3
4b	7.06 (o), 7.28 (m), 7.22 (p)		
9	6.90 (o), 7.22 (m), 7.16 (p)	6.32 (o,o), 6.88 (o,m), 7.15 (m,m)	
10	6.97 (o), 7.23 (m), 7.18 (p)	6.81	
11	6.83 (o), 7.17 (m), 7.15 (p)	6.21 (o,o), 6.73 and 6.87 (o,m), 7.09 (m,m)	6.19 (o,o), 6.77 (o,m), 7.09 (m,m)
12	6.91 (o), 7.20 (m), 7.15 (p)	6.71 and 6.76	6.71

[a] Aromatic rings are numbered as Ph-1, Ph-2, or Ph-3 from the terminal. The positions of protons relative to guanidino group(s) are shown in parentheses. Thus, (o,o) means protons ortho to two guanidino groups.

ylguanidino moieties, resemble the structure of monomeric compound **4b**. Each guanidino moiety has a planar (*Z*,*Z*) conformation with large torsion angles (63−79°) to both of the attached phenyl rings. The dihedral angles between the face-to-face phenyl rings are ca. 30°, and those of the para-substituted oligomers (**10** and **12**) were slightly smaller than those of the meta oligomers (**9** and **11**). These deviations from aromatic parallel structure may arise from the $\pi-\pi$ repulsive interaction, since the parallel sandwich structure of the simple benzene dimer has been calculated to be less favored than tilted-parallel or T-shaped conformations.[28] Therefore, the fact that the flexible oligomeric *N*,*N*′-dimethylated guanidines formed multilayers despite this unfavorable factor is remarkable. Previously reported compounds with intramolecular aromatic layers have all had rigid backbones.[29] The alternate benzene rings of our compounds (5° for **9** and 12−17° for **11**) are more parallel, except for those of **12** (25°). Interestingly, the alternate guanidino bonds (4−9° for **11**) are nearly parallel in the tetraguanidines. Thus, the two sets of guanidino groups exist on the same sides with similar orientation in both para and meta compounds.

In the case of the meta-substituted compound **9**, the conformation is chiral along the two axes of the N−C(Ar) bonds of the central benzene ring. The structure of **9** shown in Figure 10 has (*S*,*S*) conformation. Similarly, compound **11** also exists in chiral conformation with all-*S* (or all-*R*) conformations, resulting in a well-ordered helical structure in a single molecule. Although the aromatic rings are linked at the meta position, the helical structure of **11** has the 2_1 axis, not 3_1 or 3_2, due to the tilted aromatic arrangements as shown in the view from the top of the aromatic planes of **11**. The crystals of **9** and **11** have both enantiomers in a 1:1 ratio in the unit cells and are racemic, but such intramolecular helical structures could be applicable to various aromatic compounds linked by cis-preferential *N*,*N*′-dimethylguanidino bonds.

The structures of the oligomers **9**−**12** in solution were investigated by ^{1}H NMR. Comparison of the chemical shifts of the aromatic protons, which were shifted to higher fields as in **4b** or cis-amides, suggested that these compounds exist predominantly in the layered structures in both organic solvents and D_2O (Table 5). The signals of the aromatic protons inside the layers are observed at a higher field than those of the terminal phenyl rings. Furthermore, the chemical shifts of aromatic protons in multilayered compounds, such as **11** and **12**, were always shifted to a higher field than those of the corresponding protons of less layered compounds. The preferential existence of the layered structures of these *N*,*N*′-dimethylated guanidines in various solvents was also supported by the observation of NOE enhancements (data not shown). However, the temperature-dependent NMR did not reveal distinct species; the signals showed only some broadening even at 183 K in CD_2Cl_2. Significantly, the chiral conformations of

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12 could not be distinguished by adding various chiral reagents in the NMR experiments, even though the racemization requires several bond rotations around N−C(Ar) bonds. There appears to be a rapid equilibrium between the major layered structure and the minor conformers in each oligomeric guanidinium salt.

Conclusion

The bonding and conformational properties of aromatic substituted guanidines were investigated. Neutral guanidino groups generally exist in the amino form with one short C−N bond attached to a phenyl ring, except for *N*,*N*′-dimethyl-*N*,*N*′-diphenylguanidine (**4a**), and the guanidino groups are always nearly planar; steric hindrance simply causes twisting of the C−N bonds. Consequently, fully substituted guanidinium ions exhibited chiral propeller structures. The cis preference of **4** provided the basis for the construction of oligomers with intramolecular aromatic multilayers. In some cases, the aromatic layers formed a chiral helix. Although the enantiomers of the helical compounds could not be separated, the discovery of these propeller and helical compounds opens up a new field of aromatic architecture with unique molecular chirality. Such intramolecular arrangements of aromatic layers with hydrophilicity may find applications in the fields of materials science (e.g., electronic or magnetic properties) and medicinal chemistry, as exemplified by our recent results regarding the potency of **11** and **12** as DNA minor groove binders.

Experimental Section

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, University of Tokyo and were within ±0.3% of the theoretical values. NMR spectra were recorded on a JEOL JNM-A500 (500 MHz) or a JEOL JNM-GX400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane in $CDCl_3$ and DMSO-d_6 or sodium 2,2-dimethyl-2-silapentane-5-sulfonate in D_2O. IR spectra were obtained with a Shimadzu IR-408 IR spectrometer, and values are expressed in cm^{-1}. *N*,*N*′-Diphenylguanidine (**1**) was purchased from WAKO Co. and recrystallized from EtOH. Detailed synthetic methods and physicochemical data for compounds **2**−**12** are described in the Supporting Information.

X-ray Crystallography. The X-ray crystal structure analyses were performed on crystals of compounds **1**−**12**. Diffraction data were obtained on a Rigaku AFC7S four-circle diffractometer and a Rigaku RAXISIIC imaging plate diffractometer with graphite-monochromated Cu Kα radiation (λ = 1.540 50 Å) and Mo Kα (λ = 0.710 70 Å) radiation, respectively. Generally, indexing was performed from three oscillations which were exposed for 4.0 min, and a total of 15 oscillation images within the 2θ value of 50.0° were collected in the analyses using the imaging plate area detector. The crystal data are given in Tables 1 and 5. The crystal structures were solved by the direct method, and the hydrogen atoms were located on a difference electron-density map.

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Supporting Information Available: Detailed synthetic methods, spectral data, and X-ray crystallographic data for the compounds **1**−**12** (66 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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