(*Cis*)-PREFERENCE OF *N,N'*-DIMETHYL-*N,N'*-DIPHENYLGUANIDINE AND THE GUANIDINIUM SALT. CONSTRUCTION OF WATER-SOLUBLE AROMATIC LAYERED STRUCTURE

Aya TANATANI,[a] Hiroyuki KAGECHIKA,[a] Isao AZUMAYA,[a] Kentaro YAMAGUCHI[b] and Koichi SHUDO*,[a]

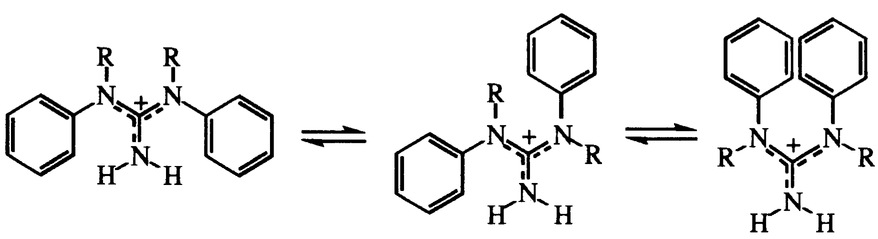
Faculty of Pharmaceutical Sciences, University of Tokyo,[a] 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan, and Chemical Analysis Center, Chiba University,[b] 1-33 Yayoi-cho, Inage-ku, Chiba 263, Japan

N,N'-Dimethyl-*N,N'*-diphenylguanidine (**2a**) and the corresponding guanidinium salt (**2b**) have crystal structures in which two phenyl groups are located face-to-face. Similar (*cis, cis*) conformations were also observed in various solvents. These structures may be useful as key building blocks to construct water-soluble aromatic layered molecules.

KEY WORDS aromatic guanidine; guanidinium salt; *N,N'*-dimethyl-*N,N'*-diphenylguanidine; face-to-face conformation; aromatic architecture

Guanidine is a strong organic base, the salt (guanidinium ion) being stabilized by Y-delocalization,[1] and is an efficient functional group as a hydrogen bond donor/acceptor in the field of supramolecular chemistry.[2] Guanidino groups also play key roles in a number of drugs and biologically active substances.[3] Recently, diarylguanidines, such as *N,N'*-di-*o*-tolylguanidine (DTG), have received considerable attention as ligands of σ-receptors[4] or *N*-methyl-D-aspartate (NMDA) receptors.[5] The activities of aromatic guanidines depend significantly upon the substituents on the guanidino group. Previously, we reported that steric change of the amide bond by *N*-methylation altered the biological activities of aromatic amides.[6] Compared to the extensive investigations on amide stereochemistry,[7] little work has been done on the guanidine group. In this paper, we describe (*cis, cis*)-conformational preference of *N,N'*-dimethylated guanidines, affording molecules with water-soluble aromatic layered structure.

Comparison of the ^{1}H-NMR spectra of *N,N'*-diphenylguanidine (**1a**) and *N,N'*-dimethyl-*N,N'*-diphenylguanidine (**2a**) showed large chemical shift differences in the signals of their aromatic protons (Table 1). A similar tendency was observed in the corresponding guanidinium salts **1b** (**1a**·HCl, R = H in Fig. 1) and **2b** (**2a**·HBr, R = CH_3 in Fig. 1). The signals of the aromatic protons of the *N,N'*-dimethylated compounds are shifted to higher field, which indicates that there is a large conformational difference between **1** and **2**. The two phenyl groups of **1** are equivalent in $CDCl_3$ even at -50 °C, so the conformation of **1** is (*trans, trans*) or in rapid equilibrium between (*trans,*



(*trans, trans*) (*trans, cis*) (*cis, cis*)

Fig. 1. Three Possible Conformations of Guanidinium Salt

Table 1. ^{1}H-NMR Chemical Shifts of Guanidines (Aromatic Protons)

	Chemical shifts (δ) [a]		
	ortho	*meta*	*para*
1a	7.12	7.31	7.06
1b	7.31	7.46	7.37
2a	6.93	7.17	6.96
2b	6.80	7.16	7.12

a) ppm in $CDCl_3$ at 30°C.

* To whom correspondence should be addressed.

trans)/(*trans*, *cis*)/(*cis*, *trans*), rather than (*cis*, *cis*). On the other hand, the appearance of the aromatic protons of **2** at higher field suggested that **2** exists mainly in (*cis*, *cis*) conformation. In contrast to the lower-field shifts in the guanidinium salt **1b** compared to **1a**, there are no significant differences in chemical shifts between **2a** and **2b**. This also supports (*cis*, *cis*) conformation, since the two phenyl group would be sterically twisted from the guanidinium plane. It is noteworthy that (*cis*, *cis*) conformation was also predominant in D_2O and other polar protic/aprotic solvents.

In order to clarify the (*cis*, *cis*) preference of *N,N'*-dimethylated guanidines, we examined their crystal structures. Free *N,N'*-dimethyl-*N,N'*-diphenylguanidine (**2a**), prepared from *N*-methylaniline and *N*-methyl-*N*-phenylcyanamide, was a colorless oil at room temperature, and was recrystallized from *n*-hexane at below -20 °C in a refrigerator. Therefore, X-ray structure analysis of **2a** was carried out at -100 °C by using a laser-stimulated fluorescence image plate as a two-dimensional area detector.[8] This made possible rapid analysis of the unstable crystal of **2a**, which contains two molecules of water and one molecule of *n*-hexane besides two molecules of **2a** in one unit cell.[9] X-Ray structural analysis of **2b** (mp 248 °C),[9] was done by the usual method at room temperature.[10]

As shown in Fig. 2, **2a** and **2b** have folded (*cis*, *cis*) structures in which the two phenyl groups are located face-to-face. Their structures are clearly different from those of **1** and related diaryl guanidines.[11] The bond angles around nitrogens (N_1 and N_2) and the central carbon (C*) indicated these atoms in both compounds to have sp^2 character (Table 2). The three C–N bonds in **2b** have almost the same length (1.33 – 1.38 Å, partial double bond character), being longer than the C–N_1 or C-N_2 bond and shorter than the C–N_3 bond in free guanidine **2a**. Torsion angles relevant to the C–N bonds of **2a** and **2b** are 30 – 40°. From these results, stabilization by Y-delocalization may exist in the (*cis*, *cis*) conformation of **2b**. The conformations are characterized by the large torsion angles between the phenyl and guanidino groups (Table 2). The dihedral angles are 62° (for **2a**) and 68 – 73° (for **2b**) between the phenyl and guanidino least-squares planes. Thus, the two phenyl

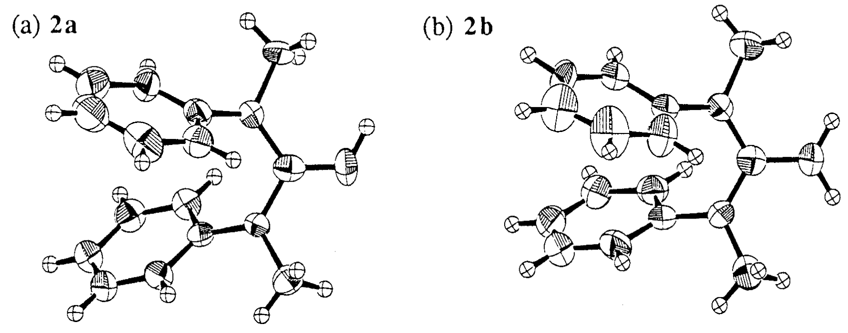
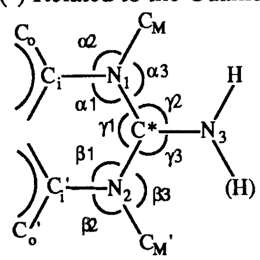


Fig. 2. Crystal Structures of (a) **2a** and (b) **2b**
Solvent molecules (for **2a**) and a counter anion (for **2b**) have been removed in order to clarify the conformations of the guanidines.

Table 2. Bond Lengths (Å), Bond Angles (°) and Torsion Angles (°) Related to the Guanidino Groups

	2a [a]	2b [a]
Bond lengths (Å)		
C*—N_1	1.40(1), 1.39(1)	1.38(2), 1.35(1)
C*—N_2	1.40(1), 1.40(1)	1.35(2), 1.34(2)
C*—N_3	1.27(1), 1.26(1)	1.33(2), 1.33(1)
Bond angles (°)		
α1	123.0(10), 123.0(10)	122(1), 120(1)
α2	119(1), 117(1)	121(1), 117(1)
α3	117(1), 116(1)	115(1), 120(1)
β1	123.2(9), 121.9(9)	122(1), 122(1)
β2	119(1), 118.7(9)	118(1), 116(1)
β3	115(1), 118(1)	119(1), 120(1)
γ1	112(1). 113(1)	116(1), 118(1)
γ2	123(1), 125(1)	121(1), 120(1)
γ3	124(1). 121(1)	122(1), 121(1)



	2a	2b
Torsion angles (°)		
C_o–C_i–N_1–C*	147(1), -136(1)	-50(1), -132(1)
$C_{o'}$–$C_{i'}$–N_2–C*	-40(1), -147(1)	-48(1), 49(1)
C_i–N_1–C*–N_2	-39(1), 31(1)	-30(1), 32(1)
N_1–C*-N_2–C_i'	-32(1), 39(1)	-32(1), 34(1)

[a] Two molecules exist in an asymmetric unit.

groups are located face-to-face with dihedral angles of 37 – 38° for **2a**, and 31° for **2b**. The deviation from the parallel aromatic structure may result from the repulsive π–π interaction of the phenyl groups. A similar splayed-apart structure was also observed in sterically rigid 1,8-diphenylnaphthalene.[12)]

The preference of (*cis*, *cis*) conformation of **2** should be closely related to the structural change of aromatic amides and ureas caused by *N*-methylation.[6,10,13)] In *N*-methylbenzanilide and *N,N'*-dimethyl-*N,N'*-diphenylurea, the *N*-methyl groups are located *cis* to the carbonyl oxygen atom. The crystal structures of **2a** and **2b** are very similar to that of *N,N'*-dimethyl-*N,N'*-diphenylurea, in which the dihedral angle between the two face-to-face phenyl groups is 35°. This implies that the electronic properties of the carbonyl group (or oxygen atom), such as the attractive interaction with the *N*-methyl group, are not important for the *cis*-preference of *N*-methylated amides and ureas. Since the electronic structure of the Y-delocalized guanidinium group is very different from those of carbonyl groups in amide or urea bonds, this finding should be helpful to understand the origin of their *cis*-preference.

In conclusion, *N,N'*-dimethylated guanidine and guanidinium salt exhibited preference for (*cis*, *cis*) conformation. This conformational property may be important in the interaction of aromatic guanidines with σ- or NMDA receptors, and in other guanidine-related biological functions. The aromatic layered conformations of *N,N'*-dimethylated guanidines **2** observed in the crystal state are retained in various solvents including water. Aromatic multidecked structures are of much interest because of their possible electrical or magnetic properties. Thus, (*cis*, *cis*)-guanidinium structures should be useful as key building blocks to construct water-soluble aromatic layered architecture.

REFERENCES AND NOTES

1) Gund P., *J. Chem. Educ.*, **49**, 100-103 (1972); Mills N. S., Shapiro J., Hollingsworth M., *J. Am. Chem. Soc.*, **103**, 1263-1264 (1981); Ohwada T., Itai A., Ohta T., Shudo K., *J. Am. Chem. Soc.*, **109**, 7036-7041 (1987).
2) Selected papers: Galán A., de Mendoza J., Toiron C., Bruix M., Deslongchamps G., Rebek J. Jr., *J. Am. Chem. Soc.*, **113**, 9424-9425 (1991); Jubian V., Dixon R. P., Hamilton A. D., *J. Am. Chem. Soc.*, **114**, 1120-1121 (1992); Ariga K., Anslyn E. V., *J. Org. Chem.*, **57**, 417-419 (1992); Perreault D. M., Chen X., Anslyn E. V., *Tetrahedron*, **51**, 353-362 (1995).
3) For example, the guanidino group in arginine participates in nitric oxide formation: Fukuto J. M., Stuehr D. J., Feldman P. L., Bova M. P., Wong P., *J. Med. Chem.*, **36**, 2666-2670 (1993).
4) Scherz M. W., Fialeix M., Fischer J.B., Reddy N. L., Server A. C., Sonders M. S., Tester B. C., Weber E., Wong S. T., Keana J. F. W., *J. Med. Chem.*, **33**, 2421-2429 (1990).
5) Reddy N. L., Hu L.-Y., Cotter R. E., Fischer J. B., Wong W, J., McBurney R. N., Weber E., Holmes D. L., Wong S. T., Prasad R., Keana J. F. W., *J. Med. Chem.*, **37**, 260-267 (1994).
6) Kagechika H., Himi T., Kawachi E., Hashimoto Y., Shudo K., *J. Med. Chem.*, **32**, 2292-2296 (1989).
7) Stewart W. E., Siddall III T. H., *Chem. Rev.*, 70, 517 (1970); Oki M., *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH Publishers, Inc.Florida, 1985.
8) The method will be reported elsewhere. A crystallographic study using this technique: Fujita M., Oguro D., Miyazawa M., Oka H., Yamaguchi K., Ogura K., *Nature*, **378**, 469-471 (1995).
9) Crystal data of **2a** ($C_{15}H_{17}N_3 \cdot H_2O \cdot 1/2C_6H_6$): triclinic; space group, $P\bar{1}$; Z, 4 (two independent mols); a, 11.590(5) Å; b, 16.44(2) Å; c, 8.320(4) Å; α, 97.21(7)°; β, 90.73(3)°; γ, 77.50(7)°; *V* 1535(2) $Å^3$; D_{calc}, 1.104 g/cm^3; R, 0.097; **2b** ($C_{15}H_{18}N_3Br$): triclinic; space group, $P\bar{1}$; Z, 4 (two independent mols); a, 13.034(3) Å; b, 13.216(4) Å; c, 9.711(2) Å; α, 91.85(2)°; β, 94.99(2)°; γ, 65.14(1)°; *V* 1512.1(6) $Å^3$; D_{calc}, 1.477 g/cm^3; R, 0.079.
10) Azumaya I., Kagechika H., Yamaguchi K., Shudo K., *Tetrahedron*, **51**, 5277-5290 (1995).
11) The crystal structure of **1** showed (*trans*, *cis*) guanidine conformation with interesting features; the details will be published elsewhere. Crystallographic studies on related compounds: Zakhararov L. N., Adrianof V. G., Struchkov Y. T., *Kristallografiya*, **25**, 65-71 (1980); Brown C. J., Gash D. J., *Acta Cryst.*, **C40**, 562-564 (1984); Antolini L., Marchetti A., Preti C., Tagliazucchi M., Tassi L., Tosi G., *Aust. J. Chem.*, **44**, 1761-1769 (1991).
12) Clough R. L., Kung W. J., Marsh R. E., Roberts J. D., *J. Org Chem.*, **41**, 3603-3609 (1976).
13) Yamaguchi K., Matsumura G., Kagechika H., Azumaya I., Ito Y., Itai A., Shudo K., *J. Am. Chem. Soc.*, **113**, 5474-5475 (1991); Itai A., Toriumi Y., Saito S., Kagechika H., Shudo K., *J. Am. Chem. Soc.*, **114**, 10649-10650 (1992), and references cited therein.

(Received March 5, 1996; accepted April 3, 1996)