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Asymmetric crystallization of bisguanidinobenzene derivatives

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Abstract—We show that the mono-N-methylated and -ethylated derivatives of the achiral compound bisguanidinobenzene undergo spontaneous asymmetric crystallization into a chiral form with chiral space group $P2_12_12_1$. The absolute configurations of the chiral crystals were determined by X-ray crystallography and correlated with circular dichroism (CD) spectra recorded in the solid state. The corresponding protonated and isopropylated derivatives, by contrast, afforded achiral crystals.

1. Introduction

Optical resolution is one of the most important methods for obtaining desired chiral materials. In this method, however, chiral materials can be separated only by the use of chiral sources. On the other hand, some of the compounds, such as amide A,[1] sulfonamide B,[2] and guanidine C[3] (Fig. 1) spontaneously crystallize into chiral forms, and application of spontaneous crystallization to absolute asymmetric synthesis has been reported.[4] Guanidines act not only as superbases[5] but also as key units in the formation of supramolecules.[6] Recently we have developed guanidine chemistry focusing on uncovering potential abilities of guanidinyl functions as chiral auxiliaries.[7] In the course of these studies, a new bisguanidinobenzene derivative, *o*-phenylenebis(*N*,*N*′-dimethyl-*N*,*N*′-ethylene)guanidine (**1**, Scheme 1) was designed as a potential hydrogen acceptor[8] and was found to form an isolable crystalline complex with a hydrogen donor, even a weak hydrogen donor such as benzyl alcohol. It is notable that the bisguanidinobenzene **1**

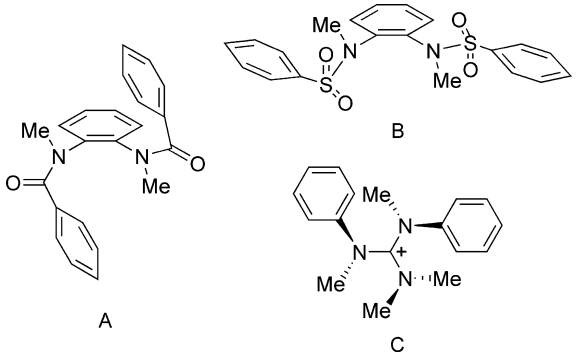
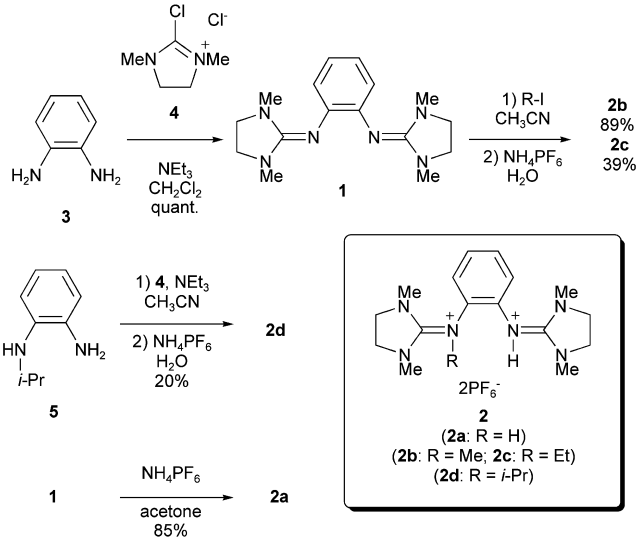


Figure 1. Structures of chiral-crystal-forming compounds.



Scheme 1. Synthesis of **2**.

Keywords: Asymmetric crystallization; Guanidine; CD; X-ray diffraction.
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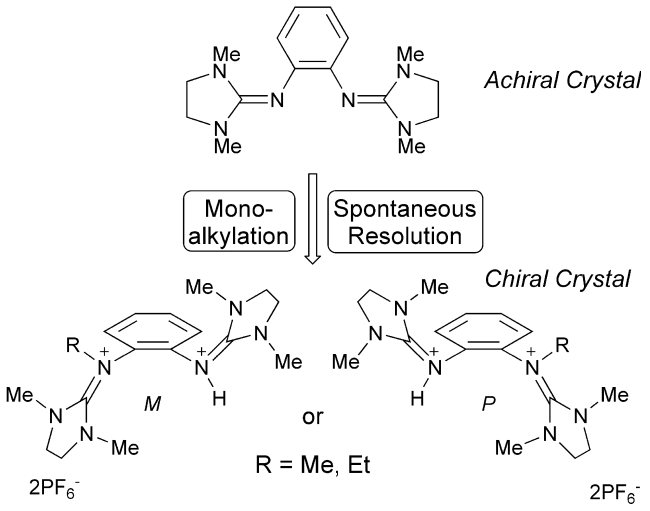


Figure 2. Asymmetric crystallization of bisguanidinobenzene derivatives.

co-crystallized in chiral form with benzoic acid in the absence of a chiral source when water was incorporated.[9] In this communication, we report on the ability of mono-N-methylated (or -ethylated) bisguanidinobenzene to asymmetrically crystallize to give enantiomeric crystals (Fig. 2).

Bisguanidinobenzene **1** was prepared from *o*-diaminobenzene (**3**) by treatment with 2-chloro-1,3-dimethylimidazolium chloride[10] (=DMC, **4**) (Scheme 1). Mono-N-methylated and -ethylated compounds (**2b** and **2c**, respectively) were obtained by reaction of **1** with the alkyl iodide, followed by salt formation using NH_4PF_6. Note that only mono-alkylation proceeded even in the presence of excess alkyl halide, and isopropylation did not occur. The mono-N-isopropylated bisguanidinobenzene **2d** was obtained by treatment of *N*-isopropyldiaminobenzene (**5**)[11] with DMC and then NH_4PF_6. Recrystallization of **2b**, **2c**, and **2d** from acetone/ethyl acetate (ca. 1:1–2:1) afforded colorless prisms analyzable by X-ray crystallography. Ortep drawings of each (Fig. 3) show that the compounds have a trans configuration; the structural and crystal features of each compound are listed in Table 1.[12] The *N*-methyl and *N*-ethyl compounds (**2b** and **2c**, respectively) were found to crystallize in chiral space group $P2_12_12_1$, in which each crystal consists of a single *P* (right-handed helicity) or *M* (left-handed helicity) enantiomer, and the absolute configurations were determined by the Flack parameter.[13] Identical crystals of **2c** were also obtained when the compound was recrystallized from methanol rather than acetone/ethyl acetate. On the other hand, the *N*-isopropyl compound **2d** crystallized in achiral space group $P2_1/c$, in which each crystal consists of a racemic mixture.

Solid-state circular dichroism (CD) spectra of *N*-methyl (**2b**) and *N*-ethyl (**2c**) compounds (Fig. 4), measured in KBr tablets, were very similar, with characteristic peaks at 235 and 267 nm for **2b** and 227 and 269 nm for **2c**. The absolute structure determined by X-ray crystallography was associated with the form of the CD spectra:

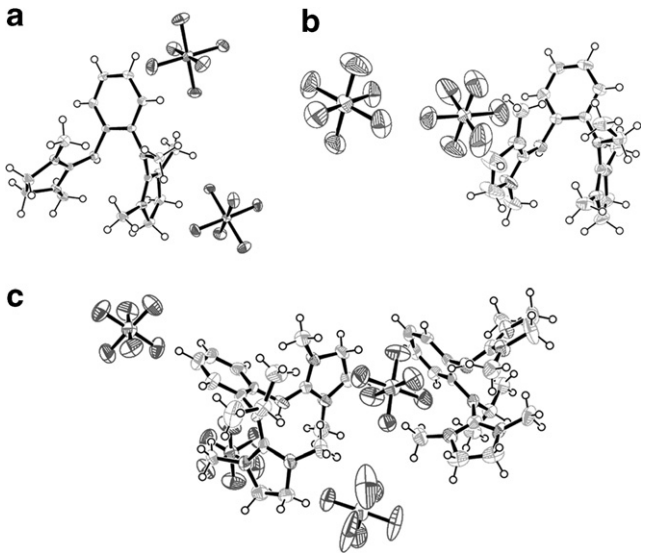
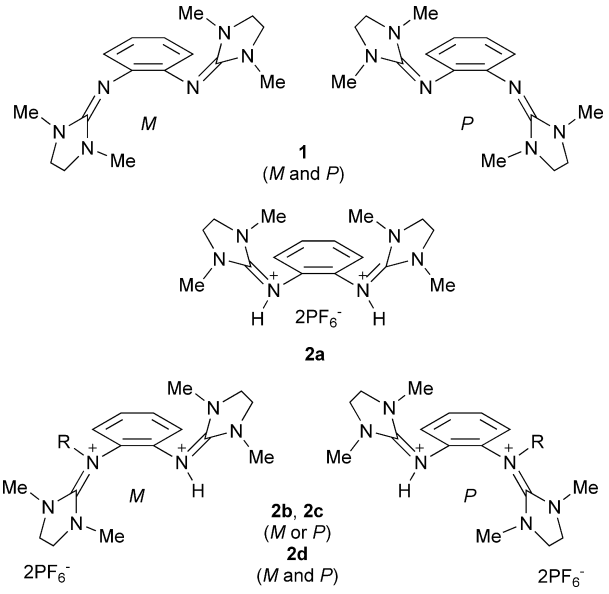


Figure 3. Ortep drawings of (a) *P*-**2b**, (b) *P*-**2c**, and (c) **2d** (two molecules).

Table 1. Structural and crystal properties of **1** and **2**



	R	Configuration	Crystal system	Space group	Chirality
1	—	trans	Monoclinic	$P2_1/c$	Achiral
2a	—	cis	Monoclinic	$P2_1/n$	Achiral
2b	Me	trans	Orthorhombic	$P2_12_12_1$	Chiral
2c	Et	trans	Orthorhombic	$P2_12_12_1$	Chiral
2d	*i*-Pr	trans	Monoclinic	$P2_1/c$	Achiral

the *P* and *M* enantiomers correspond to (−) and (+) signs in the CD spectra. The chirality of the crystal could be controlled using a seed with the desired chirality: *P*-**2b** and *M*-**2b** crystals were obtained from *P*-**2b** and *M*-**2b** seeds, respectively. The Cotton effect observed in the solid-state spectra of **2b** and **2c** was not observed in the solution spectra. As expected, **2d** was CD-inactive.

To investigate the structural features required for asymmetric crystallization, crystals of the diprotonated

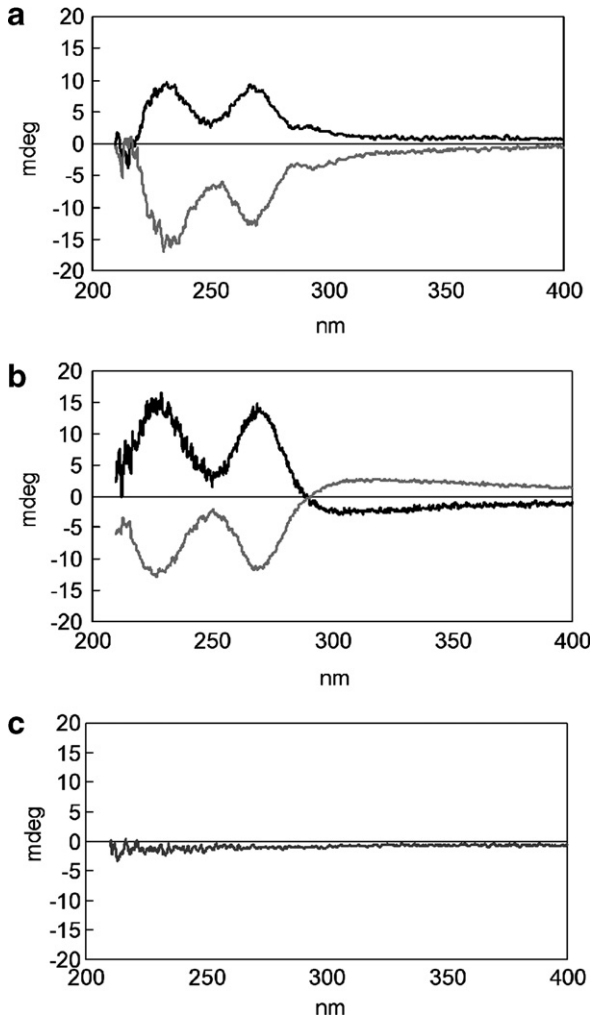


Figure 4. Solid-state CD spectra of (a) **2b**, (b) **2c** and (c) **2d** (100 μg of each sample/100 mg of KBr).

compound **2a** were prepared by recrystallization from acetone/ethyl acetate. X-ray diffraction analysis showed that **2a** has a cis structure with achiral space group $P2_1/n$ (Table 1). The crystal of **2a** was CD-inactive, as expected. We also attempted to crystallize bisguanidinobenzene **1**, which is obtained as a viscous oil, from acetone/ethyl acetate, methanol, or other solvents at room temperature (rt), but the compound remained in oil form. Single crystals of **1** were obtained, however, by freezing the oil at −18 °C. From X-ray crystallographic data, **1** was found to crystallize in achiral space group $P2_1/c$ with a trans configuration (Table 1).

Thus, bisguanidinobenzene itself and the protonated salt do not crystallize asymmetrically, whereas mono-N-methylated and -N-ethylated bisguanidinobenzenes do undergo asymmetric crystallization.[14] Interestingly, the ability to asymmetrically crystallize was again lost on going to mono-N-isopropylated bisguanidinobenzene, which contains the bulkier isopropyl moiety.

The structural features of our *N*-methyl (**2b**) and *N*-ethyl (**2c**) bisguanidinobenzenes show some similarities with those of the reported chiral amide A[1] and sulfonamide B[2]: amide A and sulfonamide B have C_2 symmetry, and **2b** and **2c** have pseudo-C_2 symmetry. In these four crystals, the chirality originates from the restriction of two Ar–N bonds in the solid phase. Unlike the structures of **2b**, **2c**, A, and B, the previously reported chiral guanidine C[3] has a propeller-like structure in which the chirality arises from steric repulsions of the substituent on the acyclic guanidine nitrogen. In contrast, our cyclic bisguanidinobenzenes **2b** and **2c** are rather planar, and not propeller-like. Thus, the bisguanidinobenzenes **2b** and **2c** represent a new class of chiral-crystal-forming compounds.

As mentioned above, the Cotton effect observed in the CD spectra of **2b** and **2c** in the solid state disappeared when the compounds were dissolved in a solvent, suggested rapid racemization in the solution phase. We therefore performed dynamic ^{1}H NMR analysis on the *N*-ethyl and *N*-isopropyl derivatives (**2c** and **2d**, respectively), and considered the results along with those we obtained previously[15] for the N-protonated and *N*-methyl derivatives (**2a** and **2b**, respectively). Similar to our previous results for **2a** and **2b**, which showed no separation or significant broadening of *N*-methyl peaks due to the restriction of Ar–N and/or C=N bond rotation (even at 179 K),[16] we observed only two *N*-methyl peaks in the ^{1}H NMR spectra of the *N*-ethyl derivative **2c** (δ 2.84 and 2.91) and *N*-isopropyl derivative **2d** (δ 2.93 and 3.08) at rt. In contrast to the spectra of **2a** and **2b**, however, peak broadening of the *N*-methyl peaks was observed in the spectra of both **2c** and **2d** at 179 K, indicating that the presence of a bulky substituent on the guanidine nitrogen atom partially restricted bond rotation; however, this effect was not sufficient to completely restrict Ar–N and/or C=N bond rotations. Thus, racemization in *N*-methyl (**2b**) and *N*-ethyl (**2c**) bisguanidinobenzenes may be caused by cis-trans isomerization through rotation of the Ar–N bond.

In conclusion, we found that mono-N-methylated and -ethylated bisguanidinobenzenes undergo spontaneous chiral crystallization, and that the crystallization of these compounds could be rigidly controlled by use of a seed crystal with the desired chirality. We are currently investigating ways to retain the chirality of these crystals on dissolution in a solvent, as this is important in molecular recognition and asymmetric synthesis applications.

2. Experimentals

Bisguanidinobenzenes **1**, **2a**, and **2b** were synthesized by the method previously described by us.[8,15]

2.1. *N*,*N*′-Bis(1,3-dimethyl-2-imidazolidinylidene)-*N*-ethyl-*o*-benzenediammonium bis(hexafluorophosphate) (2c)

To a solution of **1** (1.00 g, 3.34 mmol) in acetonitrile (5.0 mL) was added ethyl iodide (0.26 mL, 3.2 mmol) and the reaction mixture was stirred at 70 °C for 3.5 h, and evaporated. To complete the reaction, after further addition of ethyl iodide (0.13 mL, 1.6 mmol) and aceto-

nitrile (1.5 mL) the reaction mixture was stirred at 70 °C for 5 h and evaporated to give slightly yellowish crystals (1.45 g). To a part of the crystals (1.26 g) were added H_2O (2.2 mL) and NH_4PF_6 (1.26 g, 7.73 mmol) and the whole was stirred for 2 min. Filtration of the precipitates formed afforded colorless solids (2.02 g), which were recrystallized from acetone/ethyl acetate to give **2c** as colorless prisms (695 mg, 39% from **1**): Mp 231–237 °C; IR (ATR) 3357, 1595; ^{1}H NMR (400 MHz, acetone-d_6): δ 1.34 (t, $J = 7.2$ Hz, 3H), 2.84 (s, 6H), 2.91 (s, 6H), 3.84 (d, $J = 0.9$ Hz, 4H), 3.98 (s, 4H), 4.03 (q, $J = 7.2$ Hz, 2H), 7.43 (ddd, $J = 8.1$, 7.3, 1.4 Hz, 1H), 7.54 (dd, $J = 8.2$, 1.4 Hz, 1H), 7.60 (ddd, $J = 8.2$, 7.3, 1.3 Hz, 1H), 7.75 (dd, $J = 8.1$, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 13.7, 34.3, 35.2, 47.2, 49.7, 49.8, 125.4, 128.5, 130.5, 130.8, 131.1, 138.1, 156.6, 161.6; MS (FAB) m/z: 329 $[M-H-2PF_6]^+$, 475 $[M-PF_6]^+$. Anal. Calcd for $C_{18}H_{30}N_6F_{12}P_2$: C, 34.85; H, 4.87; N, 13.55. Found: C, 34.86; H, 4.89; N, 13.61.

2.2. *N*,*N*′-Bis(1,3-dimethyl-2-imidazolidinylidene)-*N*-isopropyl-*o*-benzenediammonium bis(hexafluorophosphate) (2d)

To a solution of *N*-isopropyl-1,2-diaminobenzene (**5**) (100 mg, 0.666 mmol) in CH_3CN (2.0 mL) was added triethylamine (0.40 mL, 2.8 mmol). A solution of DMC (**4**), (277 mg, 1.44 mmol) in CH_3CN (0.5 mL) was added to the above solution under ice cooling, and the mixture was stirred at rt for 3 h and at 70 °C for 13 h. After further addition of triethylamine (0.45 mL, 3.2 mmol) and a solution of **4** (315 mg, 1.64 mmol) in CH_3CN (0.5 mL), the whole was stirred at rt for 2 h and at 70 °C for 6 h, and evaporated. The resulting brown solids (1.32 g) were purified by column chromatography (NH-coated SiO_2 with hexane/ethyl acetate to ethyl acetate/ethanol) to afford an orange oil (169 mg, 67%) [IR (ATR) 1594; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (d, $J = 6.7$ Hz, 6H), 2.65 (s, 6H), 2.93 (s, 6H), 3.40 (s, 4H), 3.99 (s, 4H), 4.12 (sep, $J = 6.7$ Hz, 1H), 6.81–6.84 (m, 2H), 7.11 (ddd, $J = 8.1$, 7.3, 1.2 Hz, 1H), 7.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 34.8, 36.5, 48.1, 49.6, 53.9, 77.2, 119.3, 122.8, 127.4, 128.7, 146.5, 157.0, 163.2; HRMS (FAB) m/z: 343.2578 (calcd for $C_{19}H_{31}N_6$ $[M-I]^+$: 343.2610)]. To a solution of the oil (169 mg, 0.405 mmol) in H_2O (0.2 mL), was added NH_4PF_6 (148 mg, 0.909 mmol) and stirred at rt for 2 min. The supernatant was removed and the residue was dried in vacuo to afford slightly brown solids (162 mg), which were recrystallized from acetone/ethyl acetate to give **2d** as colorless prisms (76.8 mg, 30%). Mp 234–239 °C; IR (ATR) 3338, 1612; ^{1}H NMR (400 MHz, acetone-d_6): δ 1.55 (d, $J = 6.8$ Hz, 6H), 2.93 (s, 6H), 3.08 (s, 6H), 3.91 (s, 4H), 4.10 (s, 4H), 4.49 (sep, $J = 6.8$ Hz, 1H), 7.50 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.67 (m, 2H), 7.96 (d, $J = 8.2$ Hz, 1H), 8.81 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 21.9, 34.4, 35.6, 49.6, 50.0, 56.0, 128.0, 128.6, 131.1, 131.2, 131.9, 137.6, 156.9, 162.4; MS (FAB) m/z: 343 $[M-H-2PF_6]^+$, 489 $[M-PF_6]^+$. Anal. Calcd for $C_{19}H_{32}N_6F_{12}P_2$: C, 35.97; H, 5.08; N, 13.25. Found: C, 35.63; H, 4.82; N, 13.29.

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Supplementary data

^{1}H NMR and ^{13}C NMR copies and the crystal data of **1**, **2a**, **2b**, **2c**, and **2d**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.144.

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9. The chiral crystals were obtained by complexation of bisguanidinobenzene **1** and (2*S*,3*S*)-(+)-*O*,*O*′-dibenzoyltartaric acid. In these crystals, only one enantiomer of the trans form of **1** exists. Surprisingly, the chiral crystal was also obtained from the complex of **1** and achiral benzoic acid and water. In these crystals, the complex formed a helical supermolecule carrying only the trans enantiomer of **1**. The chirality disappeared when the crystal was dissolved in a solvent. These results will be reported elsewhere in the near future.

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