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# 3-(Dimethylboryl)pyridine: Synthesis, Structure, and Remarkable Steric Effects in Scrambling Reactions

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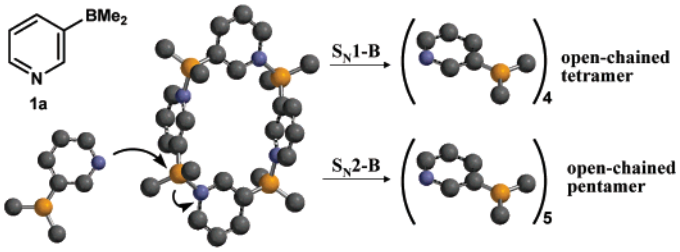


A facile method for the synthesis of 3-(dimethylboryl)pyridine (**1a**) is described. Compound **1a** assembles into a rigid cyclic tetramer stabilized via intermolecular boron−nitrogen coordination bonds both in the crystalline state and in solution. The outstanding structural feature of **1a**, as compared with previously reported 3-(diethylboryl)pyridine (**2a**) (which adopts a cone conformation), is that the tetramer of **1a** adopts a 1,2-alternate conformation. To investigate the effect of substituents at the boron atom on the stabilities of the oligomers, scrambling experiments of the component molecules using **1**, **2**, and 3-(di-*n*-butylboryl)pyridines **3** were carried out. Although heating at 80−90 °C for 20 h was required to attain the equilibrium of the scrambling reactions when the component molecules of the tetramers were **2** or **3**, the scrambling in **1** proceeded under relatively mild conditions (60 °C, 3 h). This difference in reaction conditions required for **1**, as compared to conditions required for **2** or **3**, could not be explained solely by the stabilities based on bond lengths or THC.[1g] It appears that whereas only an $S_N1$-type pathway may be involved in the scrambling of **2** or **3**, both $S_N1$- and $S_N2$-type mechanisms operate simultaneously during scrambling reactions of **1** or an intermediate mechanism between $S_N1$ and $S_N2$ operates, which was supported by kinetic studies and calculations using model compounds.

## Introduction

The effect of substituents at a tetrahedral boron atom on the stability of amine−borane complexes and nucleophilic substitution at the boron atom have been extensively studied.[1] The steric bulk of the groups attached to the boron atom contributes to the stability of the boron−nitrogen bond, and lowers the acidity toward the amine ligand as the bulkiness of the substituents increases.[1e−g] When steric crowding around the boron atom is reduced, the mechanism for exchange with a ligand switches from a dissociation mechanism to a bimolecular displacement.[1a−d,h,i] Previously, Sugihara et al. reported that 3-(diethylboryl)pyridine (**2a**) assembles into a rigid cyclic tetramer stabilized via intermolecular boron−nitrogen coordination bonds

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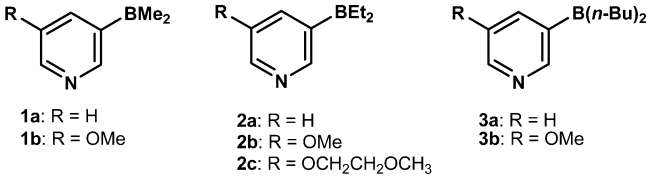
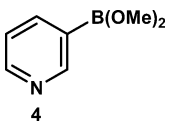
and undergoes scrambling with 3-(diethylboryl)-5-(2-methoxyethoxy)pyridine (**2c**).[2] It is important to investigate how the substituent at a boron atom influences the self-assembling feature of 3-borylpyridine from the viewpoint of the molecular design of more sophisticated systems. Furthermore, since little is known about the kinetics of these self-assembling systems,[3] the mechanism of the scrambling reaction is worthy of investigation.

To address these issues, we prepared two compounds: 3-(dimethylboryl)pyridine (**1a**) and 3-(di-*n*-butylboryl)pyridine (**3a**), where the *B*-ethyl groups of **2a** are replaced by methyl or *n*-butyl groups, respectively. The synthesis of **3a** has been reported by Terashima et al.[4a] Here we report the synthesis of **1a** and its structural features. In addition, the effects of substituents at the boron on the stabilities of the oligomers were examined by scrambling reactions using **1**, **2**, and **3**. Studies on the concentration dependence of the reactants and DFT calculations using simplified models are also presented in an attempt to provide simple rationalizations for the observed effects.




## Results and Discussion

**Synthesis.** A common method for introducing a dialkylboryl group onto a pyridine ring involves the lithiation of bromopyridine followed by trapping with trialkylborane or dialkylmethoxyborane.[4] However, this method is not suitable for the synthesis of **1** since trimethylborane required for **1** is very expensive and difficult to handle.[5] We instead chose a nucleophilic substitution approach using alkyl pyridylboronate with methyllithium. The reaction of 3-bromopyridine with *n*-butyllithium, followed by triisopropylborate at −78 °C, provided isopropyl 3-pyridylboronate, which was treated with hydrochloric acid at ambient temperature.[4a,6] The resulting boronic acid was subsequently heated at 80 °C in methanol to give methyl 3-pyridylboronate (**4**)[7] (45% yield) together with free



**4**

boronic acid (19%). Crude **4** was treated with 4 equiv of methyllithium at −78 °C to furnish **1a** in 81% yield as colorless crystals (mp 169−171 °C). Similarly, methoxy derivative **1b** was synthesized from 3-bromo-5-methoxpyridine[8] in 21% overall yield as colorless crystals (mp 158−160 °C).[7] Importantly, in the above approach methyllithium predominantly attacked the boron atom of the boronate and not the carbon atom of the methoxy group. Compounds **2b** and **3b** were prepared in a conventional manner.[4] The expected structures of all these borylpyridines were fully supported by spectral data and elemental analysis, and the compounds were stable and showed no sign of degradation after storage for 1 year at −30 °C.

**Vapor Pressure Osmometry, Mass Spectrometry, and NMR Spectroscopy.** Vapor pressure osmometry (VPO) was performed on a Knauer digital vapor pressure osmometer (using benzil as a standard) to estimate the average aggregate size of the compounds. Various concentrations of **1a** in chloroform (from 0.014 to 0.101 mol $dm^{-3}$) at 40 °C, and in tetrahydrofuran (from 0.012 to 0.082 mol $dm^{-3}$) at 45 °C, provided values of 3.7 and 3.8, respectively, suggesting that **1a** forms a tetramer on average in these solvents. In each experiment, the VPO plots between the concentration and the reading were linear ($r$ = 0.9990 in chloroform, $r$ = 0.9995 in THF) within experimental error. Since the measured values are independent of the solvent (even in tetrahydrofuran, which has a high affinity for trivalent boron atoms), it appears that the boron atom in **1a** is protected from coordination with an oxygen atom of the solvent by head-to-tail intermolecular interactions. Furthermore, **3a** in chloroform at 40 °C gives a VPO value of 3.7, consistent with the formation of a tetramer.

In the EIMS (20 eV) spectrum of **1a**, in addition to the $M^+ - Me$ peak (*m*/*z* 104, relative intensity 100%) and the parent peak as a monomer ($M^+$, 119, 50%), extremely weak peaks of $2M^+ - Me$ (223, 6%), $3M^+ - Me$ (342, 4%), and $4M^+ - Me$ (461, 1%) were observed. This result indicates that the energy required for ionization was so high that the aggregated molecule dissociated. In contrast, the negative charge accelerating ESI-MS measurement of **1a** in THF in the presence of LiCl provided charged peaks of moderate intensity at *m*/*z* 511.5 (intensity, 100%), 392.5 (28%), and 273.4 (6%), corresponding to the $[4M + Cl]^-$, $[3M + Cl]^-$, and $[2M + Cl]^-$ charge states, respectively (Figure S5 in the Supporting Information). The observed and theoretical isotopic distributions of each fragment were in close agreement, consistent with the formation of tetramers. ESI-TOF-MS spectrum of **1b** in THF−$CH_3CN$ (ca. 1:1) in the presence of LiCl showed charged peaks at *m*/*z* 631.4 (43%), 482.3 (100%), and 333.2 (66%), which are assignable to $[4M + Cl]^-$, $[3M + Cl]^-$, and $[2M + Cl]^-$, respectively. Similarly, ESI-TOF-MS spectra of **3a** and **3b** in THF in the presence of LiCl displayed charged peaks at *m*/*z* 847.8 (29%), 644.6 (28%), and 441.4 (32%) (**3a**), and 967.8 (100%), 734.6 (21%), and 501.4 (35%) (**3b**), which are assignable to $[4M + Cl]^-$, $[3M + Cl]^-$, and $[2M + Cl]^-$, respectively.

The $^{11}B$ NMR spectra of **1a**, **1b**, **3a**, and **3b** in $CDCl_3$ displayed a strong signal at −2.05, −1.61, −1.38, and −1.11 ppm, respectively, showing that monomer−oligomer equilibrium

(2) (a) Sugihara, Y.; Miyatake, R.; Takakura, K.; Yano, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1925. (b) Sugihara, Y.; Takakura, K.; Murafuji, T.; Miyatake, R.; Nakasuji, K.; Kato, M.; Yano, S. *J. Org. Chem.* **1996**, *61*, 6829.

(3) (a) Gazzaz, H. A.; Robinson, B. H. *Langmuir* **2000**, *16*, 8685. (b) Stahl, I.; Kiedrowski, G. *J. Am. Chem. Soc.* **2006**, *128*, 14014. (c) Menger, F. M.; Shi, L. *J. Am. Chem. Soc.* **2006**, *128*, 9338.

(4) (a) Terashima, M.; Kakimi, H.; Ishikura, M.; Kamata, K. *Chem. Pharm. Bull.* **1983**, *31*, 4573. (b) Ishikura, M.; Mano, T.; Oda, I.; Terashima, M. *Heterocycles* **1984**, *22*, 2471.

(5) The price and boiling point of trimethylborane is U.S. $1080.00/10 g and −20 °C, respectively. In addition, this reagent is not commercially available in Japan because it is a high-pressure gas.

(6) (a) Fischer, F. C.; Havinga, E. *Recueil* **1965**, *84*, 439. (b) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394.

(7) Takeuchi, M.; Kijima, H.; Hamachi, I.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 699. In this paper and in private communications, Takeuchi et al. described the synthesis of **4**, involving the hydrolysis of **2a** (ref 4a) followed by esterification in 19% yield. On the basis of the procedure reported by Ogawa et al. (*J. Am. Chem. Soc.* **1996**, *118*, 5783) and Wong et al. (*J. Org. Chem.* **2002**, *67*, 1041), which does not involve the production of boronic acid, we attempted the synthesis by reacting the lithiate of 3-pyridyl with trimethylborate, followed by removal of solvent and treatment with methanol. Unfortunately, polymeric materials were obtained.

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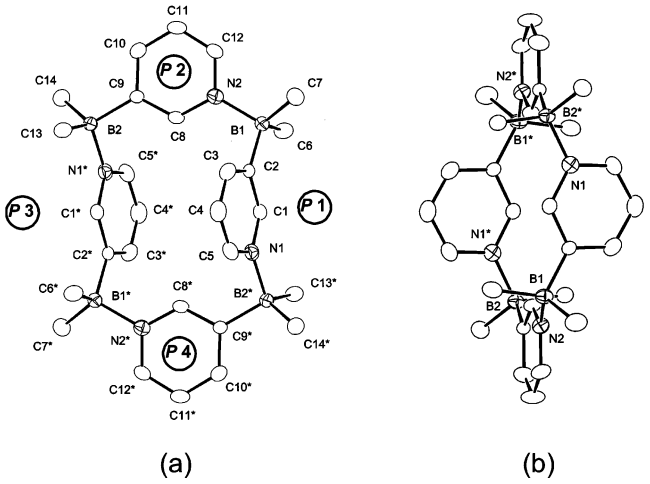



**FIGURE 1.** An ORTEP drawing of compound **1a**: (a) top view and (b) side view.

**TABLE 1. Selected Geometric Properties of the Tetramer of 1a**[a]

| | | | |
|---|---|---|---|
| Bond Lengths (Å) | | | |
| B(1)−N(2) | 1.640(3) | B(2)−N(1) | 1.633(3) |
| B(1)−C(2) | 1.632(3) | B(2)−C(9) | 1.637(3) |
| B(1)−C(6) | 1.611(4) | B(2)−C(13) | 1.608(3) |
| B(1)−C(7) | 1.623(3) | B(2)−C(14) | 1.620(3) |
| Bond Angles (deg) | | | |
| N(2)−B(1)−C(2) | 106.8(2) | N(1)−B(2)−C(9) | 106.2(2) |
| N(2)−B(1)−C(6) | 106.1(2) | N(1)−B(2)−C(13) | 111.3(2) |
| N(2)−B(1)−C(7) | 110.8(2) | N(1)−B(2)−C(14) | 107.3(2) |
| C(2)−B(1)−C(6) | 112.8(2) | C(9)−B(2)−C(13) | 108.9(2) |
| C(2)−B(1)−C(7) | 107.6(2) | C(9)−B(2)−C(14) | 110.5(2) |
| C(6)−B(1)−C(7) | 112.6(2) | C(13)−B(2)−C(14) | 112.4(2) |
| B(1)−N(2)−C(8) | 121.8(2) | B(2)−N(1)−C(1) | 123.5(2) |
| B(1)−N(2)−C(12) | 120.9(2) | B(2)−N(1)−C(5) | 119.6(2) |
| C(8)−N(2)−C(12) | 116.9(2) | C(1)−N(1)−C(5) | 116.9(2) |
| Dihedral Angles (deg) | | | |
| C(9)−C(8)−N(2)−B(1) | | −172.1(2) | |
| C(11)−C(12)−N(2)−B(1) | | 172.4(2) | |
| C(2)−C(1)−N(1)−B(2) | | −178.2(2) | |
| C(4)−C(5)−N(1)−B(2) | | 178.5(2) | |

[a] Numbers in parentheses are estimated standard deviations.

is exclusively to the side of the oligomer. The VPO, ESI-MS, and $^{11}$B NMR studies of **1** and **3** clearly indicate that these borylpyridines mainly form cyclic tetramers in solution.

**Structure in the Crystalline State.** Compound **1a** could be recrystallized from chloroform or benzene. Single-crystal X-ray crystallographic studies revealed the cyclic tetrameric structure of **1a,** as shown in Figure 1 and outlined in Tables 1 and S1 in the Supporting Information. The outstanding structural feature of **1a** is a 1,2-alternate conformation, which is in contrast with the cone conformation of the tetramer of **2a**.[2] Two of the four pyridine rings (*P*1 and *P*3) face each other in the upward and downward directions and are perpendicular to the plane of the tetramer, whereas the other set of pyridine rings (*P*2 and *P*4) lie on this plane.

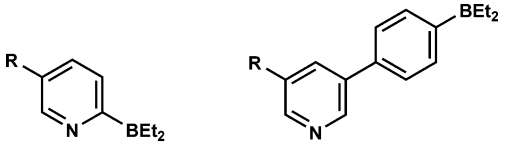
The distance between the boron atom and the nitrogen atom is 1.633 and 1.640 Å, which is almost the same as that (1.636, 1.639 Å) of the tetramer of **2a**. The bond angles constituted by the boron atom and the three substituents enable us to calculate the tetrahedral character (THC) of the boron atom as proposed by Toyota and Ōki,[1g] allowing correlation to the strength of the coordination bonds rather than to the length of the coordination bond. The THC values for **1a** are estimated to be 85.7% (B1) and 89.5% (B2), which are slightly higher than those (79.7%, 84.2%) of **2a**. Hence, the coordination bonds of the tetramer of **1a** seem to be slightly stronger than those of **2a**.

**TABLE 2. Scrambling Reactions**[a]

| entry | reactants | conditions[b] |
|---|---|---|
| 1 | **1a** and **1b** | 60 °C, 3 h |
| 2 | **2a** and **2b** | 80 °C, 20 h |
| 3 | **3a** and **3b** | 90 °C, 19 h |
| 4 | **1a** and **1b** | 60 °C, 3 h[c] |
| 5 | **1a** and **2a** | 60 °C, 6 h |
| 6 | **1a** and **3a** | 60 °C, 10 h |

[a] Reactions were carried out in toluene-$d_8$ in an NMR tube at the stated temperature, unless otherwise noted. [b] The reactions were monitored until no further changes in the $^1$H NMR spectra were observed. [c] Reaction was carried out in 1,2-dichloroethane-$d_4$.

**Scrambling and Mixing Behavior.** Scrambling experiments of the component molecules provided further information concerning the stability of the tetramers. It has been reported that the dimer composed of 2-(diethylboryl)pyridines (**5a**, **5b**) remained stable even at 130 °C for 24 h,[9] although complete scrambling of the component molecules of 3-(diethylboryl)-pyridine (**2a**, **2c**) tetramers occurred upon heating at 100 °C for 24 h.[2b] Furthermore, 3-[4′-(diethylboryl)phenyl]pyridine (**6a**) is scrambled with the corresponding methoxy derivative **6b** at ambient temperature.[10] On the basis of these experiments and calculations, it has been pointed out that the relative stabilities of the tetramers are correlated with both the magnitude of the THC at the boron atom (**2a**, average 82%; **5a**, 97%; **6a**, 68%) and the length of the intermolecular boron−nitrogen coordination bond (**2a**, average 1.638 Å; **5a**, 1.611 Å; **6a**, average 1.673 Å).[10]




To gain insight into the steric effect of *B*-alkyl groups on the stability of the tetramers, we performed scrambling reactions using **1**, **2**, and **3**. When an equimolar mixture of **1a** and **1b** in toluene-$d_8$ was heated at 60 °C, $^1$H NMR spectroscopy showed that **1a** and **1b** were readily scrambled into tetramers (see Figure S6 in the Supporting Information). Although the products were not isolated, the scrambled products would give rise to new $^1$H NMR signals. The ESI-TOF-MS spectrum of the scrambled products in THF−$CH_3CN$ (ca.1:1) in the presence of LiCl showed charged peaks at *m*/*z* 601.8, 571.8, and 541.7, corresponding to $[(\mathbf{1a})(\mathbf{1b})_3 + Cl]^-$, $[(\mathbf{1a})_2(\mathbf{1b})_2 + Cl]^-$, and $[(\mathbf{1a})_3(\mathbf{1b}) + Cl]^-$, respectively, which support the formation of scrambled products (see Figure S7 in the Supporting Information). As summarized in Table 2, heating at 80−90 °C for 20 h was required to attain equilibrium of the component molecules in the scrambled tetramers of **2a** and **2b**, or **3a** and **3b**. Surprisingly, the rate of scrambling decreased in the order **1** > **2** ≥ **3**; this was unexpected since the stability of **1**, judging from the bond length or THC, is almost the same or slightly

(9) Murafuji, T.; Mouri, R.; Sugihara, Y.; Takakura, K.; Mikata, Y.; Yano, S. *Tetrahedron* **1996**, *52*, 13933.

(10) Wakabayashi, S.; Sugihara, Y.; Takakura, K.; Murata, S.; Tomioka, H.; Ohnishi, S.; Tatsumi, K. *J. Org. Chem.* **1999**, *64*, 6999.

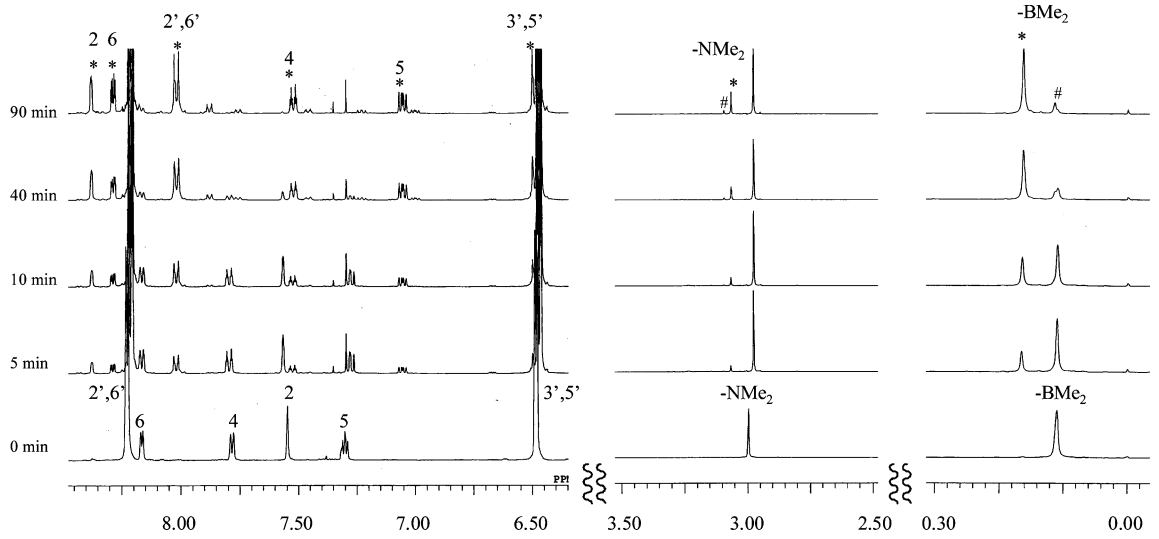


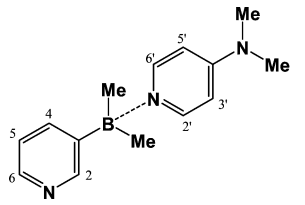

**FIGURE 2.** $^1$H NMR spectra of a mixture of **1a** and **7** in $CDCl_3$ at ambient temperature. The spectrum at 0 min was measured at −20 °C, after mixing **1a** and **7** at −15 °C. Signals assigned to **8a** were indicated by asterisks.

higher than that of **2** and **3**.[11] This led us to investigate the kinetics of the scrambling (vide infra).

Further information was derived from the following two experiments. First, even when 1,2-dichloroethane-$d_4$ was used instead of toluene-$d_8$ as the solvent, the conditions required for scrambling remained unchanged, indicating little assistance of the solvent in the cleavage of the B−N coordination bonds (entry 4 in Table 2). Second, **2a** or **3a** could surprisingly be scrambled with **1a** at 60 °C after 6−10 h (entries 5 and 6 in Table 2). It is apparent that these observations cannot be explained solely by stability as judged from bond length or THC, or by the unimolecular dissociative process of B−N bonds.[12]

Hawthorne et al. reported that nucleophilic substitutions with tri-*n*-butylphosphine in the trimethylamine−borane complex involve a second-order displacement process ($S_N2$-B) as well as a dissociative process ($S_N1$-B).[1b−d] To determine whether an $S_N2$-B mechanism is involved in the above scrambling reactions, we studied the reaction kinetics using model compounds.[13] In a preliminary experiment, when a mixture of **1a** (tetramer) and 4 equiv of 4-(dimethylamino)pyridine (**7**) in $CDCl_3$ was allowed to stand at ambient temperature, a set of new $^1$H NMR signals started to grow within 5 min (Figure 2). After 90 min the signals of the tetramer of **1a** disappeared almost completely, and the obtained spectrum suggested the formation of a new 1:1 complex of **1a** and **7**. The NOE, observed between the protons of the methyl groups at $\delta$ 0.16 and the H-2′, -6′, suggests that this is a dimethyborane−pyridine type complex **8a**. A byproduct (ca. 15%), observed at 90 min and showing $NMe_2$ and $BMe_2$ signals ($\delta$ 3.09 and 0.12, respectively) in a 1:1 ratio, may be due to isomeric 1:1 complex **8b**.

The kinetics of the reaction of the **1a**, **1b**, and **2b** tetramers with **7** were studied at 0 °C in $CDCl_3$. In each run, the initial reaction rate was measured by monitoring the disappearance




**8a** **8b**

of the tetramer in the $^1$H NMR spectrum as a function of time. Within 3−10% disappearance of the tetramer, the tetramer decreased almost linearly. The results are summarized in Table 3. The discrepancies in rates obtained from the methyl proton probe and the methoxy proton probe in **1b** seem to be within experimental error.

It was found that the data indicate that the rate of the reaction of **1a** or **1b** with **7** is faster than that of **2b** and is dependent on the concentration of **7**, although the second-order rate equation is not completely obeyed. In contrast, the rate of the reaction of **2b** with **7** was not affected by the concentration of **7**. The results of these concentration-dependence studies indicate that the former reaction proceeds by an $S_N2$-type mechanism as well as an $S_N1$-type one, or by an intermediate mechanism between $S_N1$ and $S_N2$ pathways, as demonstrated by Jencks and Richard.[14] In contrast, the reaction of **2b** with **7** seems to proceed predominantly by an $S_N1$-type mechanism. We believe this is due to steric effects as **7** approaches the tetrahedral boron atom of the tetramer.

**Calculations.** DFT calculations at the B3LYP/6-31G* level of theory for simplified models support the above conclusions.[15] We estimated the activation energies for the exchange of pyridine (**9**) with the pyridine−dialkylborylbenzene complex

(11) Since single crystals of **3** could not be obtained, the molecular structure was calculated by AM1. The THC value of the boron atom and the length of the B−N bond in **3a** are estimated to average 80.8% and 1.634 Å, respectively.

(12) Using AM1 calculations, we also estimated the enthalpic contribution to the free energy change associated with self-assembly: **1a**, 11.2 kcal/mol; **2a**, 10.9 kcal/mol; **3a**, 9.2 kcal/mol. This order is not consistent with the scrambling conditions, nor does it support sole unimolecular dissociation of the B−N bond during scrambling.

(13) As model compounds for monomer, we also used pyridine, 4-methylpyridine, or 4-methoxypyridine. However, standing at ambient temperature for several days remained unchanged.

(14) (a) Jencks, W. P. *Chem. Soc. Rev.* **1982**, *10*, 345. (b) Amyes, T. L.; Toteva, M. M.; Richard, J. P. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jones, M., Jr., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2004; p 41.

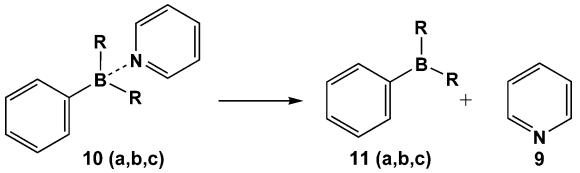
(15) For the calculations of the complex of borane with aldehyde, THF, and ammonia, etc., see: DiMare, M. *J. Org. Chem.* **1996**, *61*, 8378. Also see ref 1h.

**TABLE 3. Kinetics of the Reaction of Borylpyridines 1a, 1b, and 2b with 7**[a]

| substrate | [substrate], mol dm$^{-3}$ | [**7**], mol dm$^{-3}$ | $-\Delta\{[\text{substrate}]/([\text{substrate}] + [\text{substrate}\cdot\mathbf{7}])\}/\Delta t$, min$^{-1}$ | rate $\times 10^5$,[b] mol dm$^{-3}$ min$^{-1}$ |
|---|---|---|---|---|
| **1a** | 0.113 | 0.120 | $6.98 \times 10^{-4}$ [c] | 7.9 [c] |
| | 0.116 | 0.230 | $1.05 \times 10^{-3}$ | 12.2 |
| | 0.114 | 0.464 | $1.52 \times 10^{-3}$ | 17.3 |
| **1b** | 0.060 | 0.120 | $8.58 \times 10^{-4}$ [c] ($6.23 \times 10^{-4}$)[d] | 5.1[c] (3.7)[d] |
| | 0.113 | 0.109 | $1.06 \times 10^{-3}$ ($8.41 \times 10^{-4}$) | 12.0 (9.5) |
| | 0.114 | 0.216 | $1.24 \times 10^{-3}$ ($1.15 \times 10^{-3}$) | 14.1 (13.1) |
| | 0.113 | 0.429 | $1.43 \times 10^{-3}$ ($1.49 \times 10^{-3}$) | 16.2 (16.8) |
| | 0.229 | 0.205 | $1.01 \times 10^{-3}$ ($9.73 \times 10^{-4}$) | 23.1 (22.3) |
| **2b** | 0.105 | 0.105 | $1.72 \times 10^{-4}$ [d] | 1.8[d] |
| | 0.109 | 0.211 | $1.71 \times 10^{-4}$ | 1.9 |
| | 0.112 | 0.451 | $1.79 \times 10^{-4}$ | 2.0 |

[a] Reactions were carried out in an NMR tube at 0 °C. [b] Rates were calculated by multiplying the decreasing rate with the initial concentration of the substrate. [c] Obtained from the methyl proton probe. [d] Obtained from the methoxy proton probe.

**TABLE 4. Calculated Energies (au) of 9−11 and the Dissociation Energies of 10**[a]




| R | **10**[b] | **11**[b,c] | **9** | $\Delta E$, kcal/mol |
|---|---|---|---|---|
| $CH_3$ | −584.649436 | −336.348099 | −248.284981 | 10.3 |
| $C_2H_5$ | −663.272125 | −414.968063 | −248.284981 | 12.0 |
| *n*-$C_4H_9$ | −820.527985 | −572.224191 | −248.284981 | 11.8 |

[a] Calculated at the B3LYP/6-31G* level. [b] For **10** and **11**, compounds bearing a methyl, ethyl, or *n*-butyl group as R are represented as **a**, **b**, or **c**, respectively. [c] **11** denotes the trigonal structure at the boron atom.

(**10**), where the alkyl group is either methyl, ethyl, or *n*-butyl. The results for $S_N1$- and $S_N2$-type processes are summarized in Tables 4 and 5, respectively.

In the $S_N1$-type process, steric crowding around the boron atom had a little influence on the dissociation energy ($\Delta E$) of the B−N coordination bond (Table 4). Steric effects on the activation energies were remarkably pronounced in reactions dominated by an $S_N2$-type mechanism, with bimolecular substitution occurring extremely easily in methyl complex **10a**. In the process, the pentacoordinate structure **12a** would be in the transition state, with an energy 5.60 kcal/mol higher than that of the initial state, **10a** and **9** (Table 5). This energy gap is smaller than the dissociation energy (10.3 kcal/mol) of **10a** and

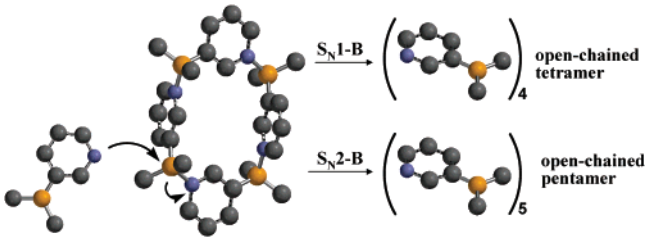


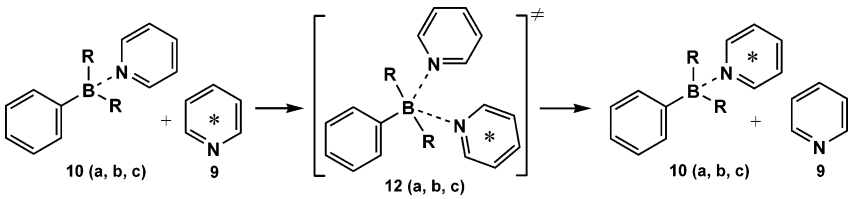

**FIGURE 3.** Initial two pathways for the scrambling reaction of **1a**.

highlights the importance of the $S_N2$-type mechanism in substitution reactions at the tetrahedral boron atom, as mentioned by Hawthorne et al.[1b−d] and Ōki et al.[1h]

The above experimental and theoretical data suggest that both $S_N1$- and $S_N2$-type reaction pathways may be involved in scrambling reactions of **1**, as shown in Figure 3. An intermediate mechanism between $S_N1$ and $S_N2$ might operate.[14] The nucleophile in the $S_N2$-type displacement would be a small quantity of monomer or open-chained oligomer present in equilibrium with tetramer. Furthermore, once such species were regenerated from cleavage of a cyclic tetramer by nucleophilic attack, they might act as new catalytic nucleophiles and accelerate the scrambling reaction. In contrast, the scrambling of **2** or **3** seems to occur predominantly via an $S_N1$-type mechanism. The complex mixture of oligomers would, finally, converge on the thermally equilibrated cyclic tetramers.

In summary, a simple route for the synthesis of 3-(dimethylboryl)pyridines **1** has been developed. Compound **1a** forms a rigid cyclic tetramer both in the crystalline state and in solution,

**TABLE 5. Calculated Energies (au) of 9, 10, 12 and the Activation Energies for the Exchange Reaction**[a]




| R | **10**[b] | **9** | **12**[b,c] | $\Delta E^{\ddagger}$, kcal/mol |
|---|---|---|---|---|
| $CH_3$ | −584.649436 | −248.284981 | −832.925534 | 5.60 |
| $C_2H_5$ | −663.272125 | −248.284981 | −911.451555 | 66.2 |
| *n*-$C_4H_9$ | −820.527985 | −248.284981 | −1068.70265 | 69.2 |

[a] Calculated at the B3LYP/6-31G* level. [b] For **10** and **12**, compounds bearing a methyl, ethyl, or *n*-butyl group as R are represented as **a**, **b**, or **c**, respectively. [c] **12** denotes an $S_N2$-like transition state, where the boron atom is in a hypervalent state.

stabilized via intermolecular boron−nitrogen coordination bonds. The occurrence of both $S_N1$- and $S_N2$-type reaction mechanisms or an intermediate one between $S_N1$ and $S_N2$[14] may account for the scrambling behavior of **1**. Therefore, the present study provides insights useful for understanding substituent effects on the kinetic stability of self-assembling molecular systems.

## Experimental Section

**Methyl 3-Pyridylboronate (4).** To a solution of 3-bromopyridine (1.6 mL, 15.6 mmol) in ether (70 mL) was added a hexane solution of *n*-butyllithium (1.5 M, 10.9 mL, 16.4 mmol) at −78 °C for 5 min. After 1 h of stirring, triisopropyl borate (4.3 mL, 18.6 mmol) was added. The resulting yellow solution was stirred for 12 h. After evaporation of the solvent in vacuo, to the pale yellow solid was added water (15 mL) and concentrated hydrochloric acid (1.7 mL) until pH 5−6 at 0 °C to produce the white precipitates. After filtration, the solid (1.585 g) was suspended in anhyd methanol (70 mL) and heated at 80 °C for 30 min to yield a mixture of the boronate **4** and the free boronic acid as a colorless solid (1.417 g, mp >200 °C). Since the contents of **4** is ca. 70% judging from the $^1$H NMR spectrum, the yield of **4** is estimated to be 45%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.52 (s), 6.86 (t, $J$ = 5.6 Hz), 7.00 (t, $J$ = 5.6 Hz), 7.26−7.39 (m), 7.77 (d, $J$ = 7.1 Hz), 8.05 (d, $J$ = 7.3 Hz), 8.14 (d, $J$ = 4.6 Hz), 8.40−8.85 (m), 9.32 (s), 9.41 (s), 9.62 (s), 10.14 (s), 10.45 (s), 10.51 (s), 10.56 (s). IR (KBr) 3700−2800 (br), 1609, 1589, 1417 (strong), 1363 (s), 1311 (s), 1204, 1155, 1074, 713 cm$^{-1}$.

**3-(Dimethylboryl)pyridine (1a).** To **4** (497 mg, 70% contents, 2.30 mmol) in THF (12 mL) was added dropwise an etheral solution of methyllithium (0.55 M, 18 mL, 9.9 mmol) at −78 °C for 12 min. The mixture was gradually warmed to ambient temperature over 12 h. To this was added water (10 mL) and the solution was extracted twice with ether (10 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$, and concentrated. The crude product was subjected to silica gel (7 g) column chromatography with a mixture of benzene and hexane (1:1) as an eluent to afford **1a** (222 mg, 1.87 mmol, yield 81%) as colorless crystals. Mp 169−171 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.11 (s, 6H), 7.30 (dd, 1H, $J$ = 5.9, 7.6 Hz), 7.56 (s, 1H), 7.81 (dt, 1H, $J$ = 1.7, 7.3 Hz), 8.18 (d, 1H, $J$ = 5.6 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 11.0, 123.8, 128.3, 140.6, 143.6, 147.2. $^{11}$B NMR (192 MHz, $CDCl_3$) $\delta$ −2.05. EIMS (20 eV) *m*/*z* 461 ($4M^+$ − Me, 1%), 342 ($3M^+$ − Me, 4%), 223 ($2M^+$ − Me, 6%), 119 ($M^+$, 50%), 104 ($M^+$ − Me, 100%). ESI-MS (LiCl in THF, negative mode)*m*/*z* 511.5 (4M + $Cl^-$, 100%), 392.5 (3M + $Cl^-$, 28%), 273.4 (2M + $Cl^-$, 6%). IR (KBr) 2924 (s), 2831, 1601, 1480, 1445, 1408 (s), 1333, 1298, 1291 (s), 1250, 1200, 1042 (s), 1028, 1017, 967 (s), 797, 702 (s) cm$^{-1}$. Anal. Calcd for $C_7H_{10}BN$: C, 70.67; H, 8.47; N, 11.77. Found: C, 70.29; H, 8.58; N, 11.65.

**3-(Dimethylboryl)-5-methoxypyridine (1b).** The preparation was carried out from 3-bromo-5-methoxypyridine[8] in a manner similar to that described for **1a**. Colorless crystals. Mp 158−160 °C. Yield, 21% from 3-bromo-5-methoxypyridine. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.10 (s, 6H), 3.83 (s, 3H), 7.24 (s, 1H), 7.31 (d, 1H, $J$ = 2.7 Hz), 7.80 (d, 1H, $J$ = 2.7 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 11.2, 55.6, 127.3, 128.3, 128.9, 140.5, 156.0. $^{11}$B NMR (128 MHz, $CDCl_3$) $\delta$ −1.61. IR (KBr) 2919, 1595, 1572 (s), 1455, 1406 (s), 1294 (s), 1283 (s), 1250, 1177, 1038 (s), 970 (s), 878 (s), 704 cm$^{-1}$. EIMS (70 eV) *m*/*z* 432 ($3M^+$ − Me, 2%), 283 ($2M^+$ − Me, 5%), 149 ($M^+$, 57%), 134 ($M^+$ − Me, 100%). HRMS (EI) *m*/*z* calcd for $C_8H_{12}BNO$ 149.1012, found 149.1052. ESI-TOF-MS (THF−$CH_3CN$, LiCl) *m*/*z* 631.4 (43%, 4M + $Cl^-$), 482.3 (100%, 3M + $Cl^-$), 333.2 (66%, 2M + $Cl^-$).

**3-(Diethylboryl)-5-methoxypyridine (2b).** To a solution of 3-bromo-5-methoxypyridine (500 mg, 2.7 mmol) in ether (10 mL) was added dropwise a hexane solution of *n*-butyllithium (1.5 M, 1.9 mL, 5.94 mmol) at −78 °C for 4 min. After 1 h of stirring, diethylmethoxyborane (0.78 mL, 3.0 mmol) was added and the solution was stirred at −78 °C for 1 h and 0 °C for 0.5 h. The mixture was poured into a mixture of ether (30 mL) and water (10 mL) and extracted. The aqueous layer was extracted with ether (2 × 15 mL). The combined extracts were washed with brine (2 × 10 mL) and dried over $MgSO_4$. The dried solution was concentrated and subjected to silica gel (10 g) column chromatography with benzene−hexane (1:1) as an eluent to afford **2b** (0.322 g, 1.8 mmol, yield 67%) as colorless crystals. Mp 169−170 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.48 (t, 6H, $J$ = 7.5 Hz), 0.65 (q, 4H, $J$ = 7.5 Hz), 3.79 (s, 3H), 7.24 (s, 1H), 7.36 (s, 1H), 7.65 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 9.2, 14.6, 55.5, 127.6, 128.3, 128.9, 142.2, 155.8. $^{11}$B NMR (128 MHz, $CDCl_3$) $\delta$ 0.68. EIMS (70 eV) *m*/*z* 177 ($M^+$, 45%), 148 ($M^+$ − Et, 100%). ESI-TOF-MS (LiCl, THF−$CH_3CN$) *m*/*z* 743.5 (4M + $Cl^-$, 26%), 566.4 (3M + $Cl^-$, 44%), 389.2 (2M + $Cl^-$, 100%). IR (KBr) 2905 (s), 1597, 1572 (s), 1456, 1406 (s), 1287 (s), 1252, 1177, 1049, 1036 (s), 858 cm$^{-1}$. Anal. Calcd for $(C_{10}H_{16}BNO)_4C_6H_6 = C_{46}H_{70}B_4N_4O_4$: C, 70.26; H, 8.97; N, 7.13. Found: C, 70.46; H, 8.89; N, 7.24.

**3-(Di-*n*-butylboryl)-5-methoxypyridine (3b).** To a solution of 3-bromo-5-methoxypyridine (805 mg, 4.28 mmol) in ether (12 mL) was added dropwise a hexane solution of *n*-butyllithium (1.6 M, 2.8 mL, 4.48 mmol) at −78 °C for 2 min. After 1 h of stirring, a THF solution of triethylborane (1.0 M, 4.5 mL, 4.5 mmol) was added and stirring was continued for 12 h. A solution of iodine (1.2 g, 4.7 mmol) in THF (3 mL) was added slowly at ambient temperature. After 1 h of stirring, the mixture was diluted with ethyl acetate, and washed with 10% $Na_2S_2O_3$ aq solution and brine. The dried solution was concentrated and subjected to silica gel (15 g) column chromatography with benzene as an eluent to afford **3b** (542 mg, 2.33 mmol, yield 54%) as a colorless solid. Mp 175−177 °C. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 0.65−1.30 (18H), 3.82 (s, 3H), 7.22 (s, 1H), 7.26 (s, 1H), 7.67 (s, 1H). $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 14.2, 23.8, 26.7, 28.2, 55.5, 127.2, 128.3, 128.6, 142.3, 155.7. $^{11}$B NMR (192 MHz, $CDCl_3$) $\delta$ −1.11. IR (KBr) 2909 (s), 1570 (s), 1456, 1406, 1254 cm$^{-1}$. EIMS (70 eV) 233 ($M^+$, 18%), 174 (62%), 134 (100%). HRMS (EI) *m*/*z* calcd for $C_{14}H_{24}BNO$ 233.1951, found 233.1969. ESI-TOF-MS (THF, LiCl) *m*/*z* 967.8 (4M + $Cl^-$, 100%), 734.6 (3M + $Cl^-$, 21%), 501.4 (2M + $Cl^-$, 35%). Anal. Calcd for $C_{14}H_{24}BNO$: C, 72.12; H, 10.38; N, 6.01. Found: C, 72.27; H, 10.15; N, 5.65.

**Vapor Pressure Osmometry Results. 1a:** 3.7 in chloroform at 40 °C [benzil (10.9, 35.7, 71.7, 124.7 for 0.006, 0.021, 0.044, 0.080 mol dm$^{-3}$, respectively), **1a** (6.5, 17.4, 27.7, 44.3 for 0.014, 0.036, 0.060, 0.101 mol dm$^{-3}$, respectively)]; 3.8 in THF at 45 °C [benzil (20.3, 41.4, 77.5, 122.0 for 0.0072, 0.0207, 0.042, 0.070 mol dm$^{-3}$, respectively), **1a** (8.9, 14.7, 23.7, 39.9 for 0.012, 0.030, 0.049, 0.082 mol dm$^{-3}$, respectively)]. **2b:** 3.9 in chloroform at 40 °C [benzil (12.3, 34.9, 71.4, 123.6 for 0.0061, 0.0199, 0.0427, 0.0820 mol dm$^{-3}$, respectively), **2b** (5.3, 13.0, 20.9, 33.7 for 0.0118, 0.0295, 0.0492, 0.0820 mol dm$^{-3}$, respectively)], 4.1 in THF at 45 °C [benzil (11.4, 38.8, 69.3, 129.7 for 0.0053, 0.0212, 0.0394, 0.0788 mol dm$^{-3}$, respectively), **2b** (3.8, 12.7, 19.7, 31.7 for 0.0118, 0.0295, 0.0491, 0.0724 mol dm$^{-3}$, respectively)]; 3.8 in *N*,*N*-dimethylformamide at 90 °C [benzil (4.4, 17.7, 33.5, 64.2 for 0.0055, 0.0213, 0.0405, 0.0765 mol dm$^{-3}$, respectively), **2b** (4.4, 17.7, 33.5, 64.2 for 0.0055, 0.0213, 0.0405, 0.0765 mol dm$^{-3}$, respectively)]. **3a:** 3.7 in chloroform at 40 °C [benzil (13.0, 36.1, 74.1, 135.9 for 0.0061, 0.0205, 0.0442, 0.085 mol dm$^{-3}$, respectively), **3a** (8.7, 18.7, 28.3, 46.5 for 0.015, 0.038, 0.063, 0.105 mol dm$^{-3}$, respectively)].

**Kinetic Method.** To $CDCl_3$ solution of **1a**, **1b**, or **2b** in an NMR tube was added a pre-cooled $CDCl_3$ solution of **7** at ca. −15 °C and the mixture was quickly transferred to NMR apparatus. $^1$H NMR spectra were measured at intervals of 5 min at 0 °C for 1−1.5 h.

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**Supporting Information Available:** General methods, $^1$H NMR spectra of **1a**, **1b**, **2b**, and **3b**, and ESI-MS spectrum of **1a**, $^1$H NMR and ESI-TOF-MS spectra of the scrambled product of **1a** and **1b**, X-ray crystallographic details for **1a**, and computational details for **9**, **10a**−**c**, **11a**−**c**, and **12a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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