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A conformational study of [3.3](3,5)pyridinophane

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ABSTRACT

A variable temperature ^{1}H NMR study of the [3.3](3,5)pyridinophane indicated that the *syn*(chair/chair) is more stable than *syn*(chair/boat) by 0.2 kcal/mol in solution, whereas the trimethylene bridges show disorder even at −150 °C in the solid state. A transition state search by ab initio MO calculations suggested two competitive conformational changes for *syn*(chair/chair)–*syn*(chair/boat) conversion via a bridge wobble or a ring inversion in the [3.3](3,5)pyridinophane.

The conformational isomerism of the [3.3]metacyclophanes (MCPs), which is partially amenable to study by the variable temperature (VT) NMR method, is one of the most interesting phenomena in [3.3]MCP chemistry. The stable isomers and their relative thermodynamic stability as well as the energy barrier for an isomerism can be estimated by this method. The data based on the conformational analysis of the [3.3]MCPs have been accumulated.[1] Since the first synthesis of the parent [3.3]MCP **1** (Fig. 1),[2] we have synthesized various types of [3.3]MCPs[3] and examined their conformational processes in solution by the VT ^{1}H NMR method and MO calculations.[3a–c] Semmelhack et al. observed the *syn*(chair/chair) conformer in the low temperature ^{1}H NMR spectrum of the [3.3]MCP, and suggested that the thermodynamic stability order of *syn*(chair/chair) (**Scc**) > *syn*(chair/boat) (**Scb**) > *syn*(boat/boat) (**Sbb**) is based on the molecular mechanic calculations.[4] They postulated that the conformational process with energy barrier of ca. 11 kcal/mol was ascribed to a bridge wobble (BW). We then proposed that the benzene ring inversion (RI) should exist in solution based on the racemization experiment of the chiral [3.3]MCP-Cr(CO)$_3$ complexes.[3b] Mitchell reported the detailed conformational changes in the 2,11-dithia[3.3]MCP by the VT NMR method and MO calculations, and suggested the pathway from **Scc** to **Scb** through anti conformers for the **Scc**–**Scb** conversion.[5]

Furthermore, the conformational study of the [3.3](2,6)pyridinophane **2** ([3.3](2,6)PyP) has been examined[6] to propose the presence of a weak attractive interaction via intramolecular hydrogen bonds between the pyridyl nitrogen lone pair electrons and the axial hydrogen atoms (H$_{ax}$) on the central carbon atoms of the bridge in the **Sbb** form.[3f] Then, we reported the conformational analysis of the 2,11-diaza[3.3](3,5)PyP **4a** (N$_2$[3.3](3,5)PyP)[6] and formation of the doubledecker type 2:2 complexes of **4b** with Cu^{2+} or Pd^{2+}.[7] Tsuge et al. also reported the formation of the 2:2 macrocycles between the S$_2$[3.3](3,5)PyP **5** and the *cis*-Pd complex.[8] Quite lately, Zhou Ming et al. prepared the Ag(I) complexes of **5** showing quite interesting structural properties.[9] We now report the conformational analysis of the [3.3](3,5)PyP **3**, which is the parent compound of the 2,11-dihetero-substituted [3.3](3,5)PyPs, by the ^{1}H VT NMR spectra, X-ray structural analysis, and ab initio MO calculations.

In a previous paper, we reported the synthesis of the two- to four-layered [3.3](3,5)PyPs.[10] The [3.3](3,5)PyP **3** was synthesized by the *p*-(tolylsulfonyl)methyl isocyanide (TosMIC) method in the

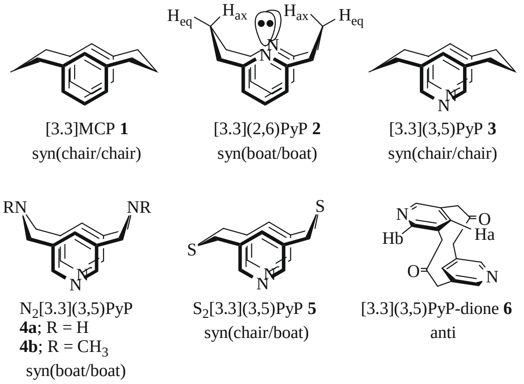

Figure 1. [3.3]Metacyclophane **1**, [3.3](2,6)pyridinophane **2**, and [3.3](3,5)pyridinophanes **3–6**.

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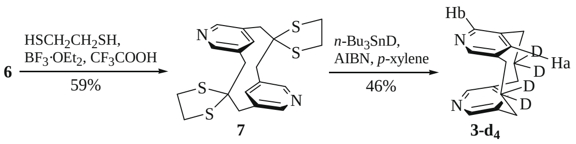
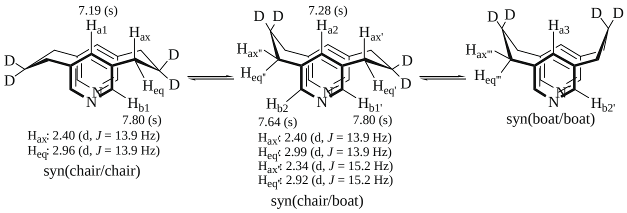


Scheme 1. Synthetic route to **3-d$_4$**.

coupling reaction between 3,5-bis(chloromethyl)pyridine and its TosMIC adduct, followed by the Wolff–Kishner reduction of the resultant [3.3](3,5)PyP-2,11-dione **4**.

The [3.3](3,5)PyP **3** shows a significant temperature-dependent ^{1}H NMR spectrum as observed for the [3.3]MCP **1**,[3a–c] [3.3](2,6)PyP **2**,[3f] and N$_2$[3.3](3,5)PyP **4a**.[6] In order to simplify the signals of the trimethylene bridge protons of **3**, four deuteriums were introduced into the 2,11-positions (Scheme 1). The dione **6** was converted into the dithioacetal **7** (59%),[11] and subsequent hydrogenolysis with n-Bu$_3$SnD in the presence of AIBN produced **3-d$_4$** (46%).[12]

Figures 2A and B show the aromatic and benzylic proton signals of the ^{1}H NMR spectra (600 MHz, CD$_2$Cl$_2$) of **3-d$_4$** at various temperatures. The preferred syn geometry of **3** is supported by the deshielded aromatic proton signal (H$_a$: δ 7.13, CDCl$_3$) compared to the corresponding proton of the dione **6** (H$_a$: δ 6.07, CDCl$_3$) with the *anti* geometry.[10] The sharp singlets of the aromatic proton (Ha: δ 7.22; Hb: δ 7.84) and benzylic proton (δ 2.75) signals at 20 °C suggest a rapid conformational isomerism on the NMR time scale, that is, wobbling of the bridge and ring inversion of the pyridine ring. As the temperature is lowered, both the aromatic and benzylic proton signals broaden, and each aromatic proton signal was resolved into two signals (Ha: δ 7.19 and 7.28; Hb: δ 7.64 and 7.80). Similarly, the benzylic proton signal is resolved into three pairs of double doublets at −95 °C (Fig. 2C), indicating the presence of two syn conformers at this temperature. Our conformational study of the [3.3]MCPs[3a,b] showed the following results: (1) the aromatic proton H$_a$ is slightly deshielded in the boat form due to the steric compression effect and (2) the magnitude of the geminal coupling constant J_{gem} of the benzylic protons depends on the conformation of the trimethylene bridges (chair or boat), and the J_{gem} values are 14.6 and 13.8 Hz for the boat and chair conformations, respectively. As described above, the J_{gem} value of the chair conformation is smaller than that of the boat conformation in the benzylic proton signals of [3.3]MCPs. Thus, the J_{gem} values of 13.9 and 15.2 Hz can be assigned to the chair and boat conformations, respectively. Presence of only two kinds of aromatic proton signals (H$_{a1}$: δ 7.19; H$_{b1}$: δ 7.80) and a pair of double doublets with the J_{gem} values of 13.9 Hz for the benzylic proton signals suggests the major conformer of **3-d$_4$** to be **Scc** (Scheme 2).The minor conformer is ascribed to **Scb** based on the presence of three kinds of the aromatic protons [H$_{a2}$: δ 7.28; H$_{b1'}$: δ 7.80 (overlapped with H$_{b1}$); H$_{b2}$: δ 7.64] and two pairs of benzylic proton signals with the geminal coupling constants of 13.9 Hz and 15.2 Hz [H$_{ax'}$: overlapped with H$_{ax}$; H$_{eq'}$: δ 2.99 (d, J = 13.9 Hz); H$_{ax''}$: δ 2.34 (d, J = 15.2 Hz); H$_{eq''}$: δ 2.92 (d, J = 15.2 Hz)]. The population of **Scc** and **Scb** at −95 °C in CD$_2$Cl$_2$ was estimated to be 1.8:1.0 on the basis of the integral of the aromatic proton signals H$_a$ (H$_{a1}$:H$_{a2}$), which suggested that **Scc** is more stable than **Scb** by 0.2 kcal/mol.[13]



Scheme 2. Possible *syn* conformers of **3-d$_4$** in CD$_2$Cl$_2$.

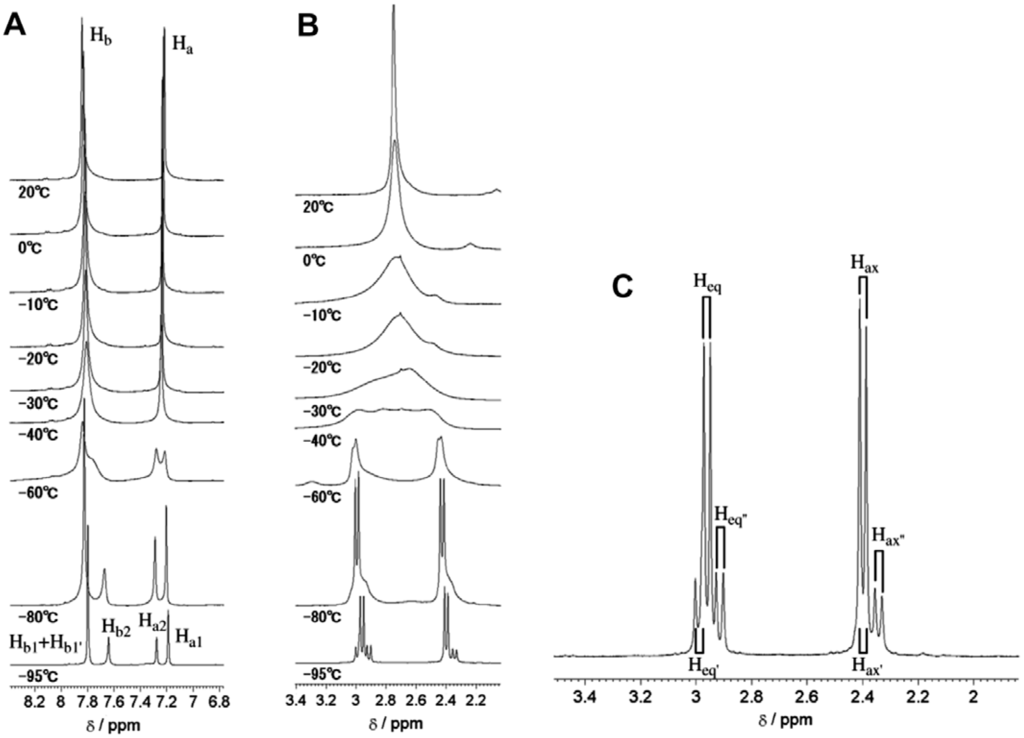
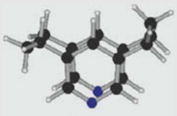
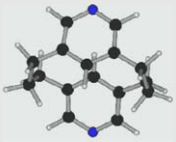
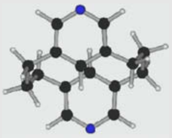
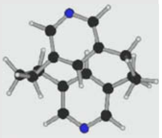


Figure 2. VT ^{1}H NMR spectra of the aromatic protons (A), benzylic protons (B), and expanded ^{1}H NMR spectrum of the benzylic protons at −95 °C (C) of **3-d$_4$** in CD$_2$Cl$_2$ (600 MHz).

Table 1
Relative thermodynamic stability of **3** (kcal/mol, 25 °C)

	 **Scc**	 **Scb**	 **Sbb**
RHF/6-31G(d)	0	1.43	2.83
B3LYP/6-31G(d)	0	0.97	2.18
B3LYP/6-311G(d)	0	1.02	2.28
MP2/6-31G(d)	0	0.56	1.00
	 **Acc**	 **Acb**	 **Actwb**
RHF/6-31G(d)	3.82	4.63	2.58
B3LYP/6-31G(d)	3.55	4.18	2.51
B3LYP/6-311G(d)	3.35	3.90	2.25
MP2/6-31G(d)	3.48	5.57	1.88

The observed energy barrier in **3-d$_4$** between **Scc** and **Scb** is estimated to be 10.9 kcal/mol ($T_c = -30$ °C),[14] which is comparable to that of [3.3]MCP **1** (11.6 kcal/mol[3b]). In order to estimate the relative thermodynamic stability of **3**, we examined the ab initio MO calculations for the *syn* and *anti* conformers. Table 1 shows the relative thermodynamic stability of the possible conformers based on the RHF, DFT, and MP2 calculations (GAUSSIAN 03[15]). All the calculations predicted the following stability order: **Scc** > **Scb** > **Sbb**, and the relative stability between **Scc** and **Scb** (0.2 kcal/mol) was well regenerated by the MP2 method.

In contrast to the most stable conformer **Scc** in solution, the trimethylene bridges of **3** show disorder even at −150 °C in the solid state (Fig. 3).[16] The two pyridine rings tilt 20.7° and the twist angle is 1.9°. The tilt and twist angles of N_2[3.3](3,5)PyP **4a**[6] and S_2[3.3](3,5)PyP **5**[8] are reported to be 23.5° and 16.8° as well as 0° and 4.3°, respectively. The transannular distance of **3** between C9 and C18 (2.980 Å) is longer than that of the diaza analogue **4a** (2.925 Å), but shorter than that of the dithia analogue **5** (3.096 Å), while the distance between N1 and N2 of **3** is in the opposite order (3.906 Å for **3**, 4.001 Å for **4a**, and 3.868 Å for **5**).

In the crystal-packing of the N_2[3.3](3,5)PyP **4a**, two kinds of intermolecular hydrogen bonds are formed between the bridging amine nitrogen atom and the amine hydrogen atoms, in which the one bridging amine is participated in three hydrogen bonds, while the other one only interacts with an amine hydrogen atom. This hydrogen bonding may stabilize **Scc** and **Scb** in the solid state of **4a**.[6] Similarly, in the S_2[3.3](3,5)PyP **5**, only one bridging sulfur atom participates in intermolecular hydrogen bond, and **5** assumes **Scb** in the solid state.[8] In the crystal-packing diagrams of **3** (Fig. 4), weak intermolecular CH/π-type interactions are expected between C9-H13B and H13C as well as C18-H4B and H4C on the *bc*-plane because of the short mean value of 2.8 Å (Fig. 4A), and this is in contrast to those of **4a** and **5**, in which the major crystal-packing force is consisted by intermolecular hydrogen bonding network. Hydrogen bonds between N1–H9 and N2–H18 (both 2.578 Å) along the *c*-axis are also observed (Fig. 4B), which is much shorter than the sum of van der Waals radii[17] of hydrogen and nitrogen atoms (2.70 Å).

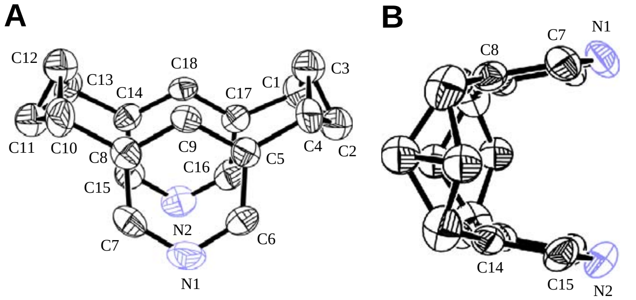


Figure 3. Molecular structures of **3** (−150 °C); top (A) and side (B) views. Hydrogen atoms are omitted for clarity.

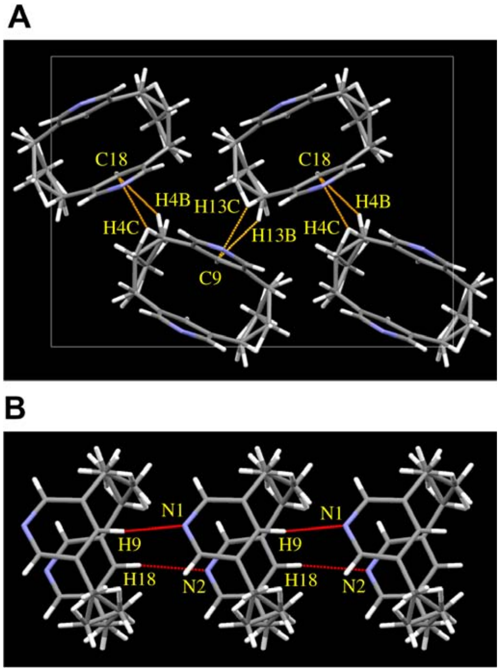


Figure 4. Short contacts of **3**; CH/π-type interactions on the *bc*-plane (A) and hydrogen bonds between N1—H9 and N2—H18 along the *c*-axis (B).

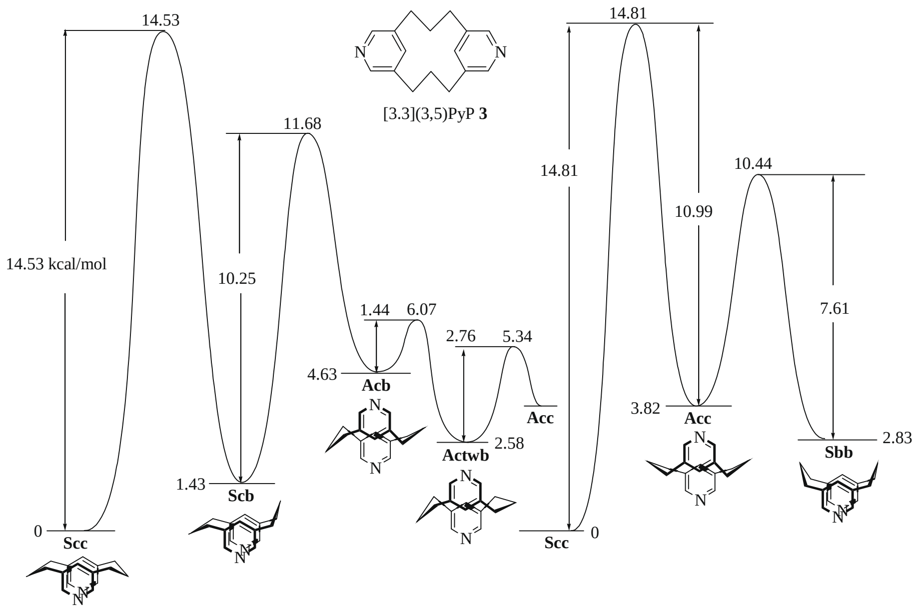


Figure 5. Potential energy diagram for the conformational isomerism of the [3.3](3,5)PyP **3**. Relative energies (zero-point energy corrected, in kcal/mol) calculated using GAUSSIAN 03 (RHF/6-31G(d), keyword for TS search: Opt = (TS, CalcAll, NoEigentest, Tight)).

We performed a transition state (TS) search for the conformational isomerism of **3** and obtained a detailed potential energy diagram based on the RHF/6-31G(d) calculations (Fig. 5). We also carried out a similar search for the 2,11-dithia[3.3]MCP as a reference (Supplementary data). All the transition states except for the TS (**Scc** to **Scb**) were obtained in such a way, starting from the local minimum structure and walking uphill to the potential energy surface to the saddle point. For TS (**Scc** to **Scb**), an estimate of the geometry of the TS was used as the initial structure. From the potential energy diagram, we can describe the entire process of the conformational isomerism, especially the conversion between the **Scc** and **Scb**. For the 2,11-dithia[3.3]MCP, the conversion seems to occur through the *anti*(chair/chair) **Acc** conformer, as pointed out by Mitchell.[5] However, the situation is slightly different for **3**. Two competitive routes can be observed for the forward process (**Scc** to **Scb**); that is, a BW (**Scc** to **Scb**) and a RI (**Scc** to **Acc** to **Actwb** to **Acb** to **Scb**) with comparable activation energies, 14.5 kcal/mol (**Scc** to **Scb**) and 14.8 (**Scc** to **Acc**), respectively. The lower energy process could be altered depending on the basis set and model chemistry. For example, with RHF/6-311++G(d,p), the activation energy of the TS (**Scc** to **Acc**; 14.37 kcal/mol) becomes slightly lower than those of TS (**Scc** to **Scb**; 14.39 kcal/mol). On the other hand, the backward process (**Scb** to **Scc**) would exclusively proceed through **Acc**, since the interconversion energies between the anti conformers and the activation energy of TS (**Acc** to **Scc**) are substantially lower than that of TS (**Scb** to **Scc**). This energetic view is also applicable to the backward process of 2,11-dithia[3.3]MCP (**Scb** to **Scc**).

In conclusion, this study indicates that the stable conformer is different in solution and in the solid state because of the severe intermolecular interactions in the latter. The VT ^{1}H NMR study shows that the **Scc** is more stable than **Scb** by 0.2 kcal/mol, and the MP2 method well regenerates the results. A theoretical simulation of the conformational change of the [3.3](3,5)PyP **3** suggests two competitive routes for the forward process (**Scc** to **Scb**); that is, a BW (**Scc** to **Scb**) and a RI (**Scc** to **Acc** to **Actwb** to **Acb** to **Scb**). The preferable backward process (**Scb** to **Scc**) is expected to occur through **Acc**. By a similar approach, the conformational analysis of the [3.3]MCP **1** has been re-examined and the result will be reported elsewhere.

Acknowledgments

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Supplementary data

The supplementary data include the synthetic procedure for **3-d$_4$**, a summary of the crystallographic data and refinement details of **3** and **6**, the ^{1}H NMR spectra of **3-d$_4$** and **7**, and the computational results. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.051.

References and notes

1. Ernst, L. *Progr. Nucl. Magn. Resonan. Spectrosc.* **2000**, *37*, 47–190.
2. Shinmyozu, T.; Inazu, T.; Yoshino, T. *Chem. Lett.* **1976**, 1405–1406.
3. (a) Sako, K.; Hirakawa, T.; Fujimoto, N.; Shinmyozu, T.; Inazu, T.; Horimoto, H. *Tetrahedron Lett.* **1988**, *29*, 6275–6278; (b) Sako, K.; Shinmyozu, T.; Takemura, H.; Suenaga, M.; Inazu, T. *J. Org. Chem.* **1992**, *57*, 6536–6541; (c) Takemura, H.; Kariyazono, H.; Yasutake, M.; Kon, N.; Tani, K.; Sako, K.; Shinmyozu, T.; Inazu, T. *J. Org. Chem.* **1999**, *64*, 9077–9079; (d) Shinmyozu, T.; Hirakawa, T.; Wen, G.; Osada, S.; Takemura, H.; Sako, K.; Rudzinski, J. M. *Liebigs Ann.* **1996**, 205–210; (e) Shinmyozu, T.; Hirai, Y.; Inazu, T. *J. Org. Chem.* **1986**, *51*, 1551–1555; (f) Sako, K.; Tatemitsu, H.; Onaka, S.; Takemura, H.; Osada, S.; Wen, G.; Rudzinski, J. M.; Shinmyozu, T. *Liebigs Ann.* **1996**, 1645–1649.
4. Semmelhack, M. F.; Harrison, J. J.; Gutierrez, D. C.; Rafii, S.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 7508–7514.
5. Mitchell, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 2352–2357.
6. Satou, T.; Shinmyozu, T. *J. Chem. Soc., Perkin Trans. 2* **2002**, 393–397.
7. Satou, T.; Sabae, M.; Iizuka, S.; Akita, M.; Shinmyozu, T. unpublished results.
8. Tsuge, A.; Matsubara, A.; Moriguchi, T.; Sei, Y.; Yamaguchi, K. *Tetrahedron Lett.* **2006**, *47*, 6607–6609.
9. Zhou, M.; Hen, Z-B.; Fan, P.; Li, S.; Gui, Y-R., submitted for publication.
10. Shibahara, M.; Watanabe, M.; Aso, K.; Shinmyozu, T. *Synthesis* **2008**, 3749–3754.
11. Krois, D.; Lehner, H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 477–481.

12. Gutierrez, C. G.; Stringham, R. A.; Nitasaka, T.; Glasscock, K. G. *J. Org. Chem.* **1980**, *45*, 3393–3395.
13. $\Delta G^0 = -RT \ln K$ where $R = 1.986\ \mathrm{kcal\ deg^{-1}\ mol^{-1}}, T = 178\ \mathrm{K}, K = 1.8$.
14. (a) Mannschreck, A.; Rissmann, G.; Vögtle, F.; Wild, D. *Chem. Ber.* **1967**, *100*, 335–346; (b) Calder, I. C.; Garratt, P. J. *J. Chem. Soc. B* **1967**, 660–662. $\Delta G^{\neq} = RT_c(22.96 + \ln T_c - \ln \Delta \nu')$ where $\Delta \nu' = (\Delta \nu^2 + 6J^2)^{1/2}$. $\mathbf{1-d_4} : \Delta \nu = 340\ \mathrm{Hz}, J = 13.9\ \mathrm{Hz}, T_c = 243\ \mathrm{K}(-30\ ^\circ\mathrm{C})$
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. GAUSSIAN 03, Revision C.02, Gaussian, Wallingford, CT, 2004.
16. Crystallographic data (excluding structure factor) for structures of **1** and **4** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 693263 and CCDC 693262, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 33603; e-mail: deposit@ccdc.cam.ac.uk).
17. Pauling, L. *The Nature of the Chemical Bond*; Cornell University Press: Ithaca, NY, 1960. p 260.