One-step Synthesis of 2,11,20-*N*,*N*',*N*''-Tribenzyl-2,11,20-triaza[3.3.3](2,6)pyridinophane. Reinvestigation of the Reaction of Benzylamine with 2,6-Bis(bromomethyl)pyridine

Geunsu Lee, Yuji Miyahara,* and Takahiko Inazu
Department of Chemistry, Faculty of Science, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812

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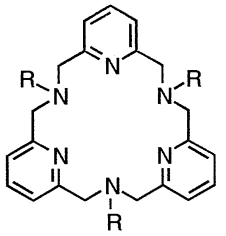
The reaction of benzylamine with 2,6-bis(bromomethyl)-pyridine has now been found to provide the trimeric title compound as the major product instead of the reported dimer. When the reaction was conducted in two steps, a new tetrameric pyridinophane was isolated as the major product.

Recently we have found that *N*,*N*',*N*''-trimethyl-2,11,20-triaza[3.3.3](2,6)pyridinophane, **1** (R=Me), is a very strong and selective host with a molecular cavity suitable for ions such as Ca^{2+} and *t*-butylammonium thiocyanate.[1] In order to modify the characteristics of **1** (R=Me) as a host molecule by changing the groups on the bridging nitrogens, we synthesized tribenzyl derivative **1** (R=$PhCH_2$) by benzoylation of **1** (R=H) with benzoyl chloride [**1** (R=PhCO): mp 175-176 °C, 54%) followed by BH_3-reduction [**1** (R=$PhCH_2$): mp 195-196 °C, 58%].[2,3]



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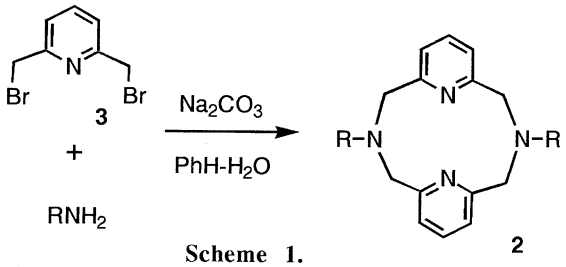
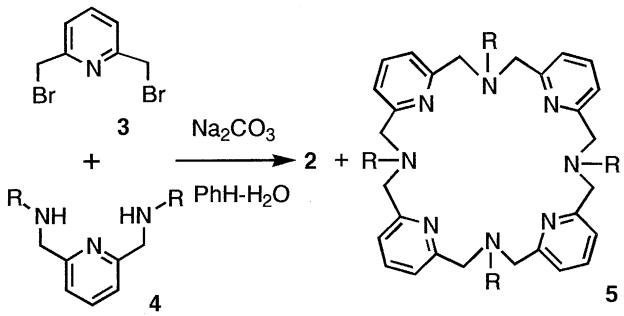
In comparing the benzyl trimer **1** (R=$PhCH_2$) with the corresponding dimer, 2,11-*N*,*N*'-dibenzyl-2,11-diaza[3.3](2,6)-pyridinophane **2** (R=$PhCH_2$), which has recently been reported by Che et al.,[4] we noticed that not only the reported mp 193-195 °C, but the ^1H NMR data of the "dimer" were surprisingly close to the data of the trimer. Since the trimeric structure of our sample was firmly established by its synthetic route and FAB mass spectrometry,[3] we decided to reinvestigate the Che's "dimer" **2**. The reported procedure is very simple and consisted of refluxing a mixture of 2,6-bis(bromomethyl)pyridine **3** and benzylamine for 12 h in the presence of sodium carbonate in a benzene-water two-phase system (Scheme 1).



Scheme 1.

The yield of the "dimer" **2** (R=$PhCH_2$) claimed is as high as 60%. We found that the product, obtained in 45% yield after purification by recrystallization, was exactly the same as the sample of the benzyl trimer **1** (R=$PhCH_2$) prepared via the benzoylation-reduction route. Apparently, after establishing the structure of the *t*-butyl dimer **2** (R=*t*-Bu) by X-ray crystallographic analysis, Che et al. assumed the dimeric structure for the rest of their cyclization products including the benzyl compound **1** (R=$PhCH_2$) without determining the molecular weights.

These remarkable findings led us to reexamine the synthesis of **2** (R=*t*-Bu). It should be noted that Che et al. did not describe the cyclization of **3** with *t*-butylamine in one-step. Instead, they used a two-step procedure, where **3** was first treated with excess of *t*-butylamine to obtain **4** (R=*t*-Bu), which was then cyclized with **3**[4] (Scheme 2). Since this two-step procedure furnished the dimer **2** (R=*t*-Bu) in high yield (72%; reported:[3] 42%), the possible tetramer **5** (R=*t*-Bu) could not be isolated. However, when the one-step procedure was employed, the yield of the dimer dropped to 41% and the tetramer was formed in 22% yield.[2,5] Interestingly, no trimer was detected in the crude product.



Scheme 2.

Since the two-step method eliminates the possibility of the trimer formation, it was expected that the dimer **2** (R=$PhCH_2$) would be produced preferentially when benzylamine was used as the starting material. Contrary to our expectation, the second step of the two-step procedure gave the dimer **2** (R=$PhCH_2$) in only 7% yield and the major product (44%) was the tetramer **5** (R=$PhCH_2$) (Scheme 2).[2,3,5] Thus, the dimer formation is clearly unfavorable when benzyl groups are attached to the bridging nitrogens.

This striking difference in the cyclization reactions between the benzyl and *t*-butyl groups may be attributed to the conformations of the corresponding reaction intermediates. The stochastic search method to find the grobal minimum structure in

the MM3(94) program[6] reveals that the lowest energy structure of the intermediate for dimer formation in the benzyl case is **A** as depicted in Figure 1, in which one of the benzyl groups is stacked with the pyridine unit and the reacting centers are so separated that they can meet only after substantial movements to provide the dimer **2** (R=$PhCH_2$). On the other hand, the lowest energy conformer of the intermediate in the *t*-butyl case is **B** and the pyridine rings are stacked as in the product and the simple rotation of the pyridine ring around the single bond as shown in Figure 1 leads to ring closure to the dimer **2** (R=*t*-Bu). It should be noted that the benzyl intermediate in a conformation closely related to **B** is 1.34 kcal/mol higher in steric energy than the conformation **A** and less favored.

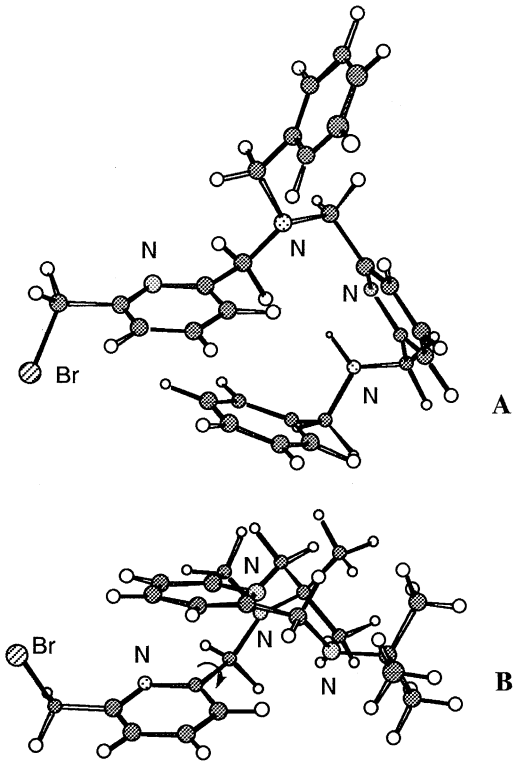


Figure 1. Lowest energy conformers of the intermediates for dimer formation predicted by MM3(94).

This simple one-step route to the benzyl trimer **1** (R=$PhCH_2$) is particularly valuable in view of the fact that the trimer has also exhibited excellent complexation abilities for Na^+, K^+, Ca^{2+}, and *t*-butylammonium ions in our preliminary studies as in the case of the methyl-substituted trimer. We are currently extending the scope of the reaction to trimeric pyridinophanes with a variety of aryl- and heteroarylmethyl groups on the bridging nitrogens and examining the effects of these substituents on complexation.

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References and Notes

1 G. Lee, H. Takemura, Y. Miyahara, N. Shimizu, and T. Inazu, Abstract 2C18, Chugoku-Shikoku-Kyushu Regional Meeting of Chemical Society of Japan, Ehime, Oct. 1995.

2 All the new compounds reported in this paper have been fully characterized by elemental analyses and instrumental methods.

3 **2** (R=$PhCH_2$): mp 163-165 °C; FAB MS *m/z* 421 ($[M+1]^+$); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.89 (s, 8H, $PhCH_2$), 3.98 (s, 4H, bridging CH_2), 6.75 (d, *J*=7.59, 4H, $PyH_{3,5}$), 7.10 (t, *J*=7.59, 2H, PyH_4), 7.30 (t, *J*=7.26, 2H, PhH_4), 7.40 (m, 4H, $PhH_{3,5}$), and 7.56 (d, *J*=6.93, 4H, $PhH_{2,6}$); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 63.78 ($PhCH_2$), 64.62 (bridging CH_2), 122.64 ($PyC_{3,5}$), 127.21 (PhC_4), 128.37 ($PhC_{3,5}$), 129.06 ($PhC_{2,6}$), 135.27 (PyC_4), 139.68 (PhC_1), 157.72 ($PyC_{2,6}$).
2 (R=*t*-Bu): mp 211.5-212.5 °C (lit.[4] mp 210-212 °C); FAB MS *m/z* 353 ($[M+1]^+$); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.32 (s, 18H, *t*-Bu), 3.97 (s, 8H, CH_2), 6.73 (d, *J*=7.59, 4H, $PyH_{3,5}$), 7.07 (t, *J*=7.59, 2H, PyH_4); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 28.20 (*t*-$BuCH_3$), 56.34 (*t*-BuC) 58.17 (CH_2), 122.37 ($PyC_{3,5}$), 135.65 (PyC_4), 159.84 ($PyC_{2,6}$).
1 (R=$PhCH_2$): mp 195-196 °C; FAB MS *m/z* 631 ($[M+1]^+$); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.72 (s, 6H, PhCH2), 3.76 (s, 12H, bridging CH_2), 6.97 (d, *J*=7.59, $PyH_{3,5}$), 7.24-7.31 (m, 9H, PhH), 7.35 (t, *J*=7.59, 3H, PyH_4), 7.47 (d, *J*=7.26, 6H, PhH); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 60.09 ($PhCH_2$), 61.13 (bridging CH_2), 120.67 ($PyC_{3,5}$), 127.06 (PhC_4), 128.32 ($PhC_{3,5}$), 128.90 ($PhC_{2,6}$), 135.92 (PyC_4), 139.66 (PhC_1), 158.56 ($PyC_{2,6}$).
5 (R=$PhCH_2$): mp 72-73 °C; FAB MS *m/z* 841 ($[M+1]^+$); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.63 (s, 8H, $PhCH_2$), 3.73 (s, 16H, bridging CH_2), 7.12-7.29 (m, 12H, PhH), 7.36 (d, *J*=6.93, 8H, PhH), 7.43 (d, *J*=7.59, 8H, $PyH_{3,5}$), 7.58 (t, *J*=7.92, 4H, PyH_4); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 58.38 ($PhCH_2$), 59.84 (bridging CH_2), 120.76 ($PyC_{3,5}$), 126.97 (PhC_4), 128.19 ($PhC_{3,5}$), 128.81 ($PhC_{2,6}$), 136.84 (PyC_4), 138.76 (PhC_1), 158.81 ($PyC_{2,6}$).

4 C.-M. Che, Z.-Y. Li, K.-Y. Wong, C.-K. Poon, T. C. W. Mak, and S.-M. Peng, *Polyhedron*, **13**, 771 (1994).

5 The tetramers which have not been reported heretofore are very promising as host molecules with larger cavities as compared to the trimers. The details of their properties and uses as hosts will be reported shortly.

6 The MM3(94) program implemented in molecular modeling software SYBYL Ver. 6.1 by Tripos Associates Inc. was used.