HETEROCYCLES, Vol. 86, No. 1, 2012, pp. 159 - 164. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 22nd June, 2012, Accepted, 2nd August, 2012, Published online, 3rd August, 2012
DOI: 10.3987/COM-12-S(N)48

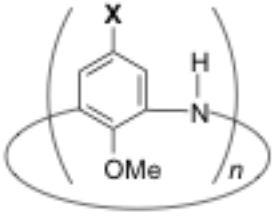
SYNTHESIS OF *p*-CHLOROAZACALIX[5]ARENE PENTAMETHYL ETHER: RING SIZE-DEPENDENT DEPROTECTION OF *N*-BENZYL GROUPS

Hirohito Tsue,* Kazuyuki Miyata, Daisuke Takahashi, Hiroki Takahashi, Kohei Sasaki, and Rui Tamura

Graduate School of Human and Environmental Studies, Kyoto University, Yoshida-nihonmatsu, Sakyo-ku, Kyoto 606-8501, Japan. e-mail: tsue.hirohito.3c@kyoto-u.ac.jp

Abstract – Syntheses of chlorinated azacalix[4]arene and azacalix[5]arene have been investigated. While the preparation of the former failed in the final *N*-debenzylation step, the latter was successfully obtained. The observed ring size-dependent deprotection was interpreted by steric effect.

Azacalixarenes have recently emerged as a new family of calixarene, and their intriguing host-guest chemistry based on the introduction of nitrogen atoms as the bridging units are reported.[1] Their complexation phenomena particularly in the solid state are of great interest because the bridging nitrogen atoms act as conjugation sites with the aromatic system to increase the electron density of the π-cloud, thereby boosting intermolecular interactions with guest species. Indeed, we thus far reported that purely organic crystals of azacalixarenes **1**–**4**[2] rapidly and selectively captured CO_2, a greenhouse gas of environmental importance. Among them, azacalix[5]arene **2** exhibits the selective sorption of CO_2 even at ambient temperature and pressure conditions.[2c,2d] Besides, the smallest homologue **1** deposits single crystals showing highly selective CO_2 uptake, and its CO_2 sorption state is successfully analyzed at an atomic level by means of X-ray crystallography, demonstrating that CH/O interactions between the *tert*-butyl groups of **1** and a molecule of CO_2 trapped in the crystal lattice play an important role in the observed highly selective CO_2 uptake.[2e]



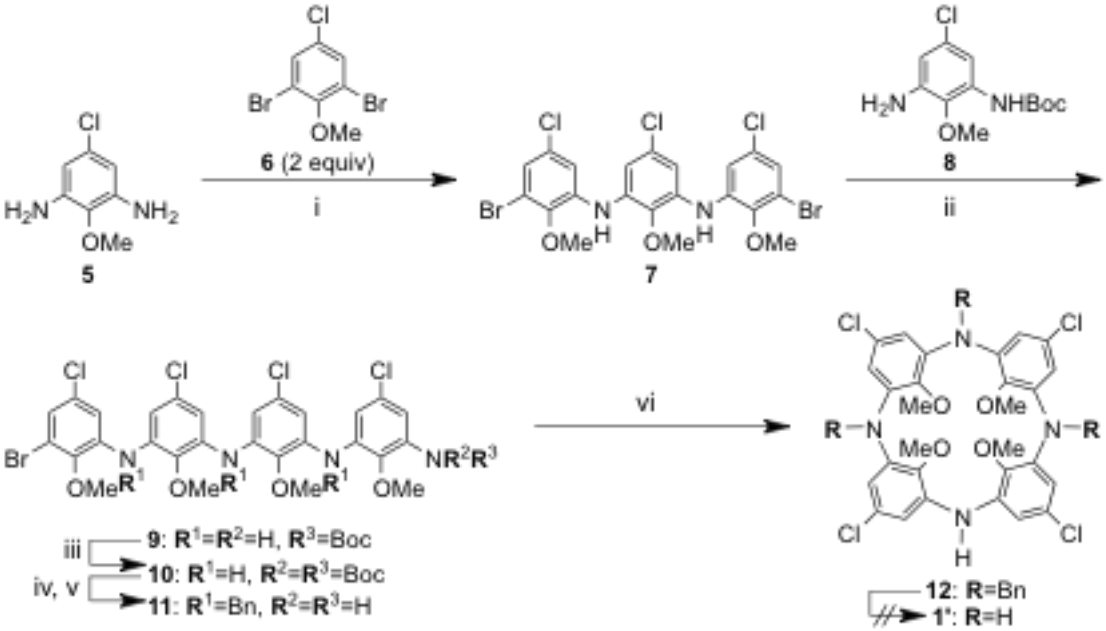
1: *n* = 4, **X** = *t*-Bu
2: *n* = 5, **X** = *t*-Bu
3: *n* = 6, **X** = *t*-Bu
4: *n* = 7, **X** = *t*-Bu

1': *n* = 4, **X** = Cl
2': *n* = 5, **X** = Cl

This paper is dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday.

In this context, we anticipate that the replacement of *tert*-butyl groups attached at para positions of **1** and **2** with halogen atoms leads to the enhancement of intermolecular interactions with CO_2 because of the formation of halogen bond.[3] In conventional *p-tert*-butylcalixarenes with methylene bridges, halogenated derivatives are easily available via a post halogenation method involving retro Friedel-Crafts de-*tert*-butylation, followed by halogenation.[4] In azacalix[4]arene **1**, however, *O*-demethylation that is essential before carrying out retro Friedel-Crafts reaction was found to be challenging because of the low stability of the demethylated products to oxidation.[5] In the present study, to establish synthetic pathway for halogenated derivatives **1'** and **2'**, we have selected chlorine as a halogen atom and employed a convergent stepwise approach which is applied by us to the syntheses of *tert*-butyl derivatives **1** and **2**.[2d] As an outcome, a larger derivative **2'** was successfully obtained, whereas the synthesis of **1'** failed because the final *N*-debenzylation step never proceeded in spite of our various attempts. Here we report the ring size-dependent *N*-debenzylation reaction observed in the syntheses of **1'** and **2'**.

We first investigated the preparation of **1'** by modifying our previously reported procedure for the synthesis of *tert*-butyl derivative **1**.[2d] As shown in Scheme 1, Buchwald-Hartwig aryl amination reaction of monomers **5** and **6** was carried out to prepare liner trimer **7**, which was subsequently reacted with Boc-monoprotected monomer **8** to yield linear tetramer **9**. The resulting product **9** was subjected to the additional Boc protection of the terminal amino group, *N*-benzylation of the bridging nitrogen atoms, and



Scheme 1. Attempted synthesis of *p*-chloroazacalix[4]arene **1'**. (i) 5 mol% $Pd(OAc)_2$, 7.5 mol% DPEphos, 2.4 equiv *t*-BuONa, PhMe, 80 °C, 16 h, 53%. (ii) 10 mol% $Pd(OAc)_2$, 15 mol% DPEphos, 1.1 equiv *t*-BuONa, PhMe, 90 °C, 15 h, 68%. (iii) 1.5 equiv Boc_2O, 0.1 equiv DMAP, THF, reflux, 8 h, 75%. (iv) 3.1 equiv BnBr, 4.0 equiv NaH, DMF, 0 °C to rt, 14 h. (v) TFA, CH_2Cl_2, rt, 22 h, 59% in two steps. (vi) 20 mol% $Pd(dba)_2$, 30 mol% (±)-BINAP, 2.0 equiv *t*-BuONa, PhMe, reflux, 18 h, 43%.

deprotection of Boc groups to give linear tetramer **11**. Tribenzylated azacalix[4]arene **12**[6] was obtained in 43% yield by intramolecular cyclization of **11** using a Pd(0)-catalyzed Buchwald–Hartwig aryl amination reaction. Despite our numerous efforts, however, the final deprotection of *N*-benzyl groups of **12** was not accomplished, and this experimental result was in a sharp contrast to the same reaction for *tert*-butyl derivative **13** of which the *N*-benzyl groups were smoothly cleaved in quantitative yield by using 20% $Pd(OH)_2/C$ as a catalyst under a hydrogen atmosphere.[2d] All attempted hydrogenolysis reactions of chlorinated derivative **12** under essentially the same conditions using PtO_2, 10% Pd/C, or 20% $Pd(OH)_2/C$ in the absence and presence of acetic acid as an additive resulted in the recovery of unreacted **12**.[7] This was also the case for the homogeneous *N*-debenzylation reaction of **12** with TMSI, though successful deprotection was achieved by this reagent in the synthesis of a larger homologue **2'** (vide infra).

13

To explore a reason for the observed unsuccessful *N*-debenzylation reaction of **12**, DFT calculations at a B3LYP/6-31G(d,p) level were carried out for chlorinated derivative **12** and *tert*-butyl derivative **13**. As shown in Figure 1, a large difference in electrostatic potentials was found for their bridging nitrogen atoms. Negative areas at the nitrogen atoms of **12** are reduced as compared to those of **13**, suggesting that

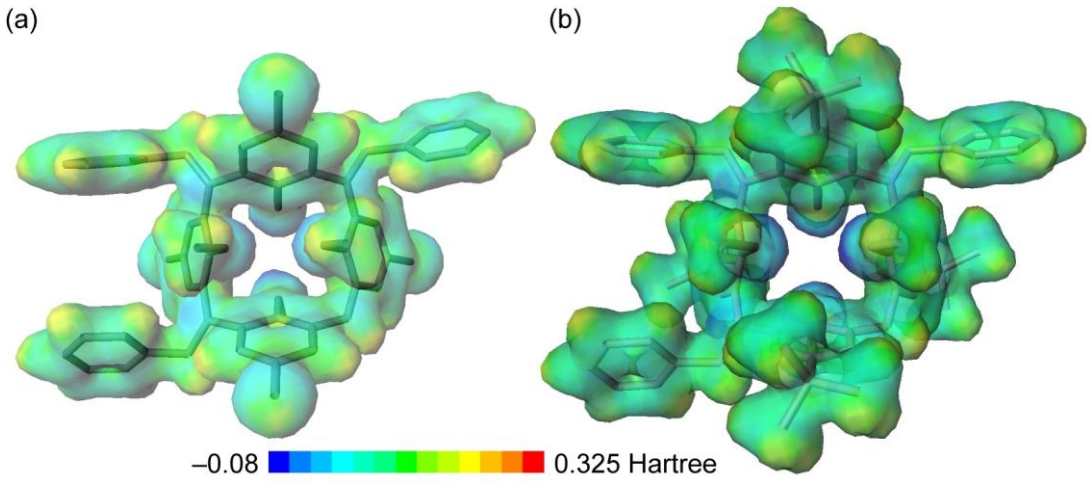


Figure 1. Electrostatic potential maps of (a) chlorinated derivative **12** and (b) *tert*-butyl derivative **13**. All hydrogen atoms are omitted for clarity.

coordination to catalyst is less effective in **12** than **13**. Besides, unlike conventional methylene-bridged calix[4]arenes, molecular framework of azacalix[4]arenes is too rigid to permit ring inversion even in solution.[8] Accordingly, it seems likely that, because of electronic and steric effects, both heterogeneous catalysts and TMSI uneasily approach the relevant reaction sites of **12** and thus lead to no debenzylation reaction.

Contrary to the unsuccessful synthesis of **1'**, we succeeded in preparing a larger homologue **2'** by modifying our synthetic procedure established for *tert*-butyl derivative **2**.[2d] As shown in Scheme 2, liner pentamer **17** was obtained by Buchwald-Hartwig aryl amination reaction of monomers **5** and **6**, followed successively by *N*-benzylation of the bridging nitrogen atoms of **14**, by Pd(0)-catalyzed aryl amination reaction of **15** with benzophenone imine, and finally by hydrolysis of the resultant ketimine **16** with HCl. Subsequent intramolecular ring-closing reaction of **17** was achieved by a Buchwald-Hartwig aryl amination reaction to give tetrabenzylated azacalix[5]arene **18** in 65% yield. As a final step, all *N*-benzyl groups of **18** were smoothly deprotected by TMSI to afford **2'**[9] in 76% yield. The successful synthesis of **2'** was unambiguously confirmed by X-ray crystallographic analysis[10] (Figure 2), implying that the final deprotection reactions of *N*-benzyl groups of **12** and **18** were dependent on their ring size. In other words, it is very likely that azacalix[4]arene **12** blocks any reagents from approaching the reaction sites because of steric hindrance arising from its rigid framework,[8,11] and more flexible azacalix[5]arene **18** allows enough space to promote *N*-debenzylation reaction to successfully produce **2'**.

In conclusion, we have investigated the syntheses of **1'** and **2'** in which *tert*-butyl groups of **1** and **2** are replaced by chlorine atoms. A larger derivative **2'** was successfully synthesized, whereas the preparation of **1'** failed because the final *N*-debenzylation reaction never happened. It has been drawn from the present study that, judging from the successful synthesis of **2'**, steric hindrance rather than electronic

Scheme 2. Synthesis of *p*-chloroazacalix[5]arene **2'**. (i) 10 mol% $Pd(OAc)_2$, 15 mol% DPEphos, 2.0 equiv *t*-BuONa, PhMe, 80 °C, 25 h, 21%. (ii) 6.2 equiv BnBr, 6.9 equiv NaH, DMF, 0 °C to rt, 7 h, 82%. (iii) 1.0 equiv $Ph_2C{=}NH$, 5 mol% $Pd(dba)_2$, 15 mol% (±)-BINAP, 2.5 equiv *t*-BuONa, PhMe, 80 °C, 4 h, 43%. (iv) 1.2 M HCl, THF, rt, 5 h, 98%. (v) 10 mol% $Pd(dba)_2$, 30 mol% (±)-BINAP, 2.5 equiv *t*-BuONa, PhMe, 80 °C, 30 h, 65%. (vi) 4.0 equiv TMSI, $CHCl_3$, 50 °C, 23 h, 76%

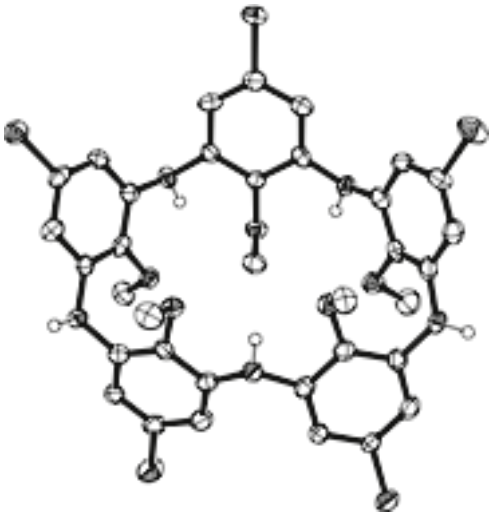


Figure 2. ORTEP drawing[12] of *p*-chloroazacalix[5]arene **2'**. The displacement ellipsoids are drawn at the 50% probability level. All hydrogen atoms but for the bridging NH atoms are omitted for clarity.

effect plays a major role in the observed ring size-dependent deprotection of *N*-benzyl groups. Investigations on the gas sorption behaviors of **2'** are in progress in our laboratory to gain a further insight into the host–guest chemistry of this new calixarene family in the solid state.

ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 23550052) from Japan Society for the Promotion of Science (JSPS).

REFERENCES AND NOTES

1. H. Tsue, K. Ishibashi, and R. Tamura, in 'Heterocyclic Supramolecules I', ed. by K. Matsumoto, Springer-Verlag, Berlin Heidelberg, 2008, pp. 73–96; (b) M.-X. Wang, *Chem. Commun.*, 2008, 4541; (c) H. Tsue, K. Ishibashi, and R. Tamura, *J. Synth. Org. Chem. Jpn.*, 2009, **67**, 898; (d) M.-X. Wang, *Acc. Chem. Res.*, 2012, **45**, 182.
2. (a) H. Tsue, K. Ishibashi, S. Tokita, H. Takahashi, K. Matsui, and R. Tamura, *Chem. Eur. J.*, 2008, **14**, 6125; (b) H. Tsue, K. Matsui, K. Ishibashi, H. Takahashi, S. Tokita, K. Ono, and R. Tamura, *J. Org. Chem.*, 2008, **73**, 7748; (c) H. Tsue, K. Ishibashi, S. Tokita, and K. Sakai, *Jpn. Unexam. Pat. Appl. Publ.*, 2010-174002; (d) H. Tsue, K. Ono, S. Tokita, K. Ishibashi, K. Matsui, H. Takahashi, K. Miyata, D. Takahashi, and R. Tamura, *Org. Lett.*, 2011, **13**, 490; (e) H. Tsue, H. Takahashi, K. Ishibashi, R. Inoue, S. Shimizu, D. Takahashi, and R. Tamura, *CrystEngComm*, 2012, **14**, 1021.
3. C. D. Gutsche, 'Calixarenes Revisited', ed. by J. F. Stoddart, Royal Society of Chemistry, Cambridge, 1998, pp. 104–107.
4. P. Metrangolo and G. Resnati, *Chem. Eur. J.*, 2001, **7**, 2511.

5. K. Ishibashi, Thesis, Kyoto University, 2008.

6. **12**: a light orange solid. mp 201–203 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28–7.18 (m, 15H, Ar-H), 6.74 (s, 4H, Ar-H), 6.58 (d, J = 2.5 Hz, 2H, Ar-H), 6.41 (d, J = 2.5 Hz, 2H, Ar-H), 5.11 (d, J = 16.5 Hz, 2H, $ArCH_2$), 5.09 (d, J = 16.5 Hz, 1H, $ArCH_2$), 4.88 (s, 1H, NH), 4.64 (d, J = 16.5 Hz, 2H, $ArCH_2$), 4.59 (d, J = 16.5 Hz, 1H, $ArCH_2$), 3.07 (s, 6H, OMe), 2.95 (s, 6H, OMe); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.7, 144.8, 143.3, 142.9, 141.9, 138.4, 137.9, 128.8, 128.7, 127.6, 127.5, 127.4, 127.2, 115.9, 115.8, 113.3, 113.1, 69.6, 60.2, 59.6, 59.2, 58.7, 53.4, 31.9, 29.8, 29.4; IR (KBr) ν 3404 cm^{-1} ($\nu_{N\text{-}H}$); HRMS (ESI) Calcd for $C_{49}H_{42}Cl_4N_4O_4Na$ $[M+Na]^+$: m/z 913.1852. Found: m/z 913.1851; Anal. Calcd for $C_{49}H_{42}Cl_4N_4O_4$: C, 65.93; H, 4.74; N, 6.28. Found: C, 65.71; H, 4.83; N, 6.28.

7. No cleavage of the C(sp^2)-Cl bonds of **12** was observed after the heterogeneous hydrogenolysis reactions. For reference, no dechlorination of **12** proceeded even by using a catalytic system of $[Cp^*RhCl_2]_2$ and 2-propanol (K. Fujita, M. Owaki, and R. Yamaguchi, *Chem. Commun.*, 2002, 2964).

8. (a) H. Tsue, K. Ishibashi, S. Tokita, K. Matsui, H. Takahashi, and R. Tamura, *Chem. Lett.*, 2007, **36**, 1374; (b) K. Ishibashi, H. Tsue, H. Takahashi, and R. Tamura, *Tetrahedron: Asymmetry*, 2009, **20**, 375.

9. **2'**: a light orange solid. mp >300 ℃; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.90 (s, 10H, Ar-H), 6.27 (br s, 5H, NH), 3.27 (s, 15H, OMe); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 141.2, 138.7, 129.1, 114.0, 59.8; HRMS (ESI) Calcd for $C_{35}H_{31}Cl_5N_5O_5$ $[M+H]^+$: m/z 776.0762. Found: m/z 776.0810; Anal. Calcd for $C_{35}H_{30}Cl_5N_5O_5 \cdot 0.75CH_2Cl_2$: C, 51.02; H, 3.77; N, 8.32. Found: C, 51.30; H, 3.88; N, 8.13.

10. Crystal data for **2'**: monoclinic, space group $C2/c$, a = 17.89(2) Å, b = 16.24(1) Å, c = 24.09(2) Å, β = 92.41(1)°, V = 6991(10) Å^3, Z = 8, D_c = 1.478 g cm^{-3}, μ = 0.466 mm^{-1}, T = 123(2) K, 7889 independent reflections, 475 refined parameters, $R1$ = 0.1199 ($I > 2\sigma(I)$), $R1$ = 0.1759 (all reflections), $wR2$ = 0.3006, S = 1.166. CCDC-886591 contains the supplementary crystallographic data for this paper. Free copy of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

11. (a) K. Ishibashi, H. Tsue, N. Sakai, S. Tokita, K. Matsui, J. Yamauchi, and R. Tamura, *Chem. Commun.*, 2008, 2812; (b) K. Ishibashi, H. Tsue, H. Takahashi, S. Tokita, K. Matsui, and R. Tamura, *Heterocycles*, 2008, **76**, 541.

12. L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.