

**De-*tert*-butylation of
p-*tert*-Butylcalix[4]arene with Nafion:
A New Route to the Synthesis of
Completely and Partially Debutylated
p-*tert*-Butylcalix[4]arenes**

Seung Gul Rha and Suk-Kyu Chang*

*Department of Chemistry, Chung-Ang University,
Seoul 156-756, Korea*

Received August 28, 1997

There have been many recent attempts in the selective functionalization of the lower rim of calixarenes to construct unique supramolecular systems.^{1,2} In contrast to this, relatively little work is done on the selective functionalization of the upper rim.³ Generally,⁴ functionalization of the upper rim of calixarenes has been performed at all of the *para* positions simultaneously without any distinct regioselectivity. *tert*-Butyl groups on *para* position of calixarenes are useful for the synthetic purposes as a positional protecting group which can be easily removed by AlCl₃-catalyzed transalkylation,⁵ and ingenious further functionalization can be performed by utilizing this handle.⁶ Besides the standard 4-fold de-*tert*-butylation of *p*-*tert*-butylcalix[4]arene by AlCl₃,⁷ Reinhoudt et al. were able to remove selectively two *tert*-butyl groups from dialkoxy-*p*-*tert*-butylcalix[4]arene by making use of the difference in reactivity between phenol and alkylated phenols.⁸ The synthetic strategies to prepare directly the partially dealkylated calixarenes are highly desirable in view of the molecular design of novel supramolecular systems with specific functions by utilizing the characteristics of *p*-*tert*-butyl group.⁹ In this paper, we report the partial as well as complete de-*tert*-

butylation of *p*-*tert*-butylcalix[4]arene by utilizing Nafion,¹⁰ a superacidic perfluororesinsulfonic acid, as a first step toward the preparation of key intermediates for the design of novel mixed-functionalized supramolecular calix[4]arenes.

p-*tert*-Butylcalix[4]arene **1** was treated with Nafion (in H form, 30 wt % of calixarene) to obtain the debutylated products in toluene under refluxing condition (N₂ atmosphere).¹¹ The progress of the reaction was followed by means of NMR spectroscopy and HPLC (silica column, hexane/THF 19:1) and found to proceed in a stepwise manner to yield from mono- to tetra-debutylated compounds **2–6** (Scheme 1). After 24 h of reaction in refluxing toluene, all the butyl groups of *p*-*tert*-butylcalix[4]arene were found to be removed to afford *p*-H-calix[4]arene **6** in 80% yield (Table 1, entry 2), that is somewhat higher than the standard AlCl₃-catalyzed reaction (yield: 66–70%).⁷ During the course of the reaction, there appeared all of the five possible compounds sequentially with varying numbers of *tert*-butyl groups at upper rim including two regioisomers of 1,2- and 1,3-di-*tert*-butylcalix[4]arene. A representative time course of the reaction, which was monitored with the aid of HPLC and NMR spectroscopy, is given in Figure 1. The two regioisomers of 1,2- and 1,3-di-*tert*-butylcalix[4]arene could not be represented as separate entities due to the difficulties in complete separation.

Varying structures of debutylated calix[4]arenes exhibited characteristic ¹H and ¹³C NMR spectra in their *tert*-butyl, bridging methylene, and aromatic resonances. They all showed a pair of broadened signals around δ 4.2 and 3.5 attributable to the bridging methylene protons. In ¹³C NMR spectra, all the compounds showed the expected number of resonances except for the mono-debutylated derivative **2**. The appearance of especially diagnostic signals above δ 140,¹² which is ascribable to the quaternary carbons bearing oxygen or *tert*-butyl groups, is quite useful for the identification of the individual calix[4]arenes and for the monitoring of the progress of the reaction. As expected from the symmetry of the compounds, di-debutylated compounds exhibit three lines at δ 149.1, 146.5, and 144.7 for **3** and at δ 148.6, 146.6, and 144.5 for **4**,^{9a} and tri-debutylated calix[4]arene **5** shows four lines at δ 149.0, 148.8, 146.6, and 144.7 in this region, respectively. However, mono-debutylated compound **2** exhibits only four lines at δ 149.1, 146.8, 146.4, and 144.6 in contrast to the five lines expected from the symmetry consideration, which might be due to the accidental overlapping of the resonances.

In view of the synthetic importance of the partially debutylated calix[4]arenes,^{3,9,13,14} the optimization for the synthesis of individual debutylated compounds was at-

(1) (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991.

(2) (a) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933. (b) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (c) Pochini, A.; Ungaro, R. In *Comprehensive Supramolecular Chemistry*; Vogtle, F., Ed.; Pergamon: Oxford, 1996; Vol. 2, Ch. 2.

(3) (a) van Loon, J.-D.; Arduini, A.; Verboom, W.; Ungaro, R.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1989**, *30*, 2681. (b) Verboom, W.; Durie, A.; Egberink, R. J. M.; Asfari, Z.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 1313. (c) de Mendoza, J.; Carramolino, M.; Cuevas, F.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N.; Verboom, W.; Ungaro, R.; Casnati, A. *Synthesis* **1994**, *47*. (d) Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032. (e) Arduini, A.; Fanni, S.; Manfredi, G.; Pochini, A.; Ungaro, R.; Sicuri, A. R.; Uguzzoli, F. *J. Org. Chem.* **1995**, *60*, 1448. (f) Shokova, E.; Khomich, A. N.; Kovalev, V. V. *Tetrahedron Lett.* **1996**, *37*, 543.

(4) (a) Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2652. (b) Gutsche, C. D.; Lin, L.-G. *Tetrahedron* **1986**, *42*, 1633.

(5) (a) Tashiro, M. *Synthesis* **1979**, 921. (b) Tashiro, M.; Yamato, T. *J. Org. Chem.* **1981**, *46*, 1543. (c) Tashiro, M.; Yamato, T. *J. Org. Chem.* **1985**, *50*, 2939.

(6) (a) Shinkai, S.; Araki, T.; Tsubaki, T.; Arimura, T.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2297. (b) Beer, P. D.; Drew, M. G. B.; Hazlewood, C.; Heseck, D.; Hodacova, J.; Stokes, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 229. (c) Xie, D.; Gutsche, C. D. *J. Org. Chem.* **1997**, *62*, 2280.

(7) Gutsche, C. D.; Levine, J. A.; Sujeeth, P. K. *J. Org. Chem.* **1985**, *50*, 5802.

(8) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639.

(9) (a) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1995**, *60*, 6070. (b) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1996**, *61*, 2511.

(10) (a) Olah, G. A.; Iyer, P. S.; Prakash, G. K. S. *Synthesis* **1986**, 513. (b) Olah, G. A.; Prakash, G. K. S.; Iyer, P. S.; Tashiro, M.; Yamato, T. *J. Org. Chem.* **1987**, *52*, 1881. (c) Yamato, T.; Hideshima, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1991**, *56*, 3955.

(11) The recovered Nafion resin could be reused for the next reaction, but the efficiency was significantly reduced compared with the fresh resin.

(12) Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, *37*, 3899.

(13) van Loon, J.-D.; Verboom, W.; Reinhoudt, D. N. *Org. Prep. Proced. Int.* **1992**, *24*, 437.

(14) Sharma, S. K.; Gutsche, C. D. *J. Org. Chem.* **1996**, *61*, 2564.

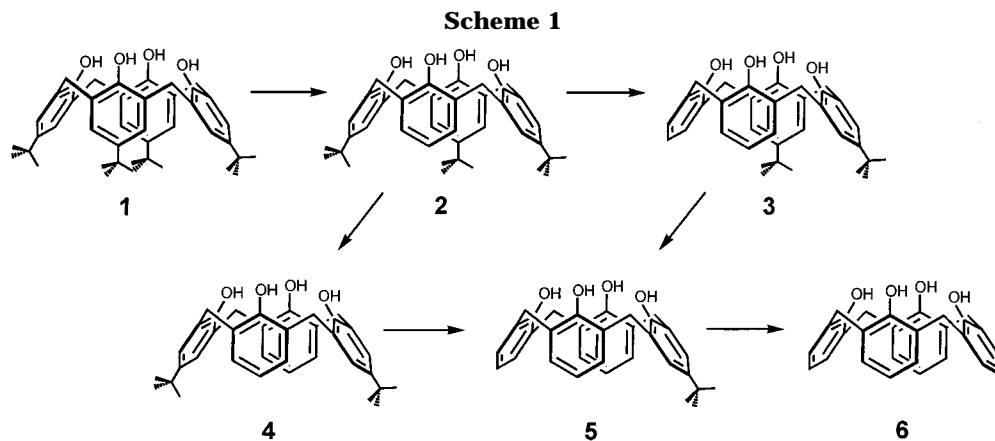


Table 1. De-tert-butylation of *p*-tert-Butylcalix[4]arene by Nafion-H

entry	solvent	temp (°C)	time (h)	yield (6) (%)
1	benzene	reflux	72	0
2	toluene	reflux	24	80
3	toluene	100	72	very slow (<5%)
4	xylene	reflux	8	68
5	xylene	120	18	74
6	xylene	100	72	very slow (<5%)

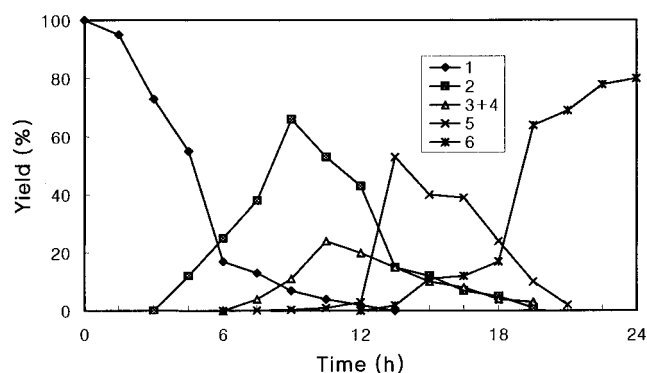


Figure 1. Time-course profile for the de-tert-butylation of *p*-tert-butylcalix[4]arene by Nafion-H in refluxing toluene.

tempted. Due to the rather nonspecific nature of the debutylation reaction by the Nafion-H in the present system, the establishment of optimum condition for the selective debutylation to yield varying products was attempted with the help of the time course profile of the reaction. The mono-debutylated product **2** with three *tert*-butyl groups was found to build up in relatively large quantity at the earlier part of the reaction, and up to 48% of **2** was obtained after ca. 8 h of the reaction. After this, the di-*tert*-butyl derivatives consisting of 1,2- and 1,3-regioisomers **3** and **4**^{9a} followed by the mono-*tert*-butyl derivative **5** appeared and found to start to build up. However, the optimization for the synthesis of the regioisomers **3** and **4** by Nafion seems to be impractical. That is because not only the compounds **3** and **4** accumulate in relatively low concentration compared with mono-debutylated and tri-debutylated analogues **2** and **5**, but also the chromatographic behavior of two regioisomers **3** and **4** are rather similar for the practical separation of the products. Interesting thing to note is the fact that, among the di-*tert*-butylated derivatives **3** and **4**, the isolated yield of proximal derivative **3** (5%) is higher than that of the distal derivative **4** (2%). Somewhat higher yield of **3** might be due to the statistical and steric effects of the reaction. That is, there are two

proximal *tert*-butyl groups compared to the one distal group relative to the debutylyated phenol ring of tri-*tert*-butyl derivative **2**. Furthermore, the access of Nafion-H to the proximal position should be easier than the distal position due to the obvious steric reason. That might lead to the higher yield of proximal **3** compared with distal analogue **4**. At the later stage of the reaction, the reaction mixture is rather complex but contains the mono-*tert*-butyl derivative **5** as a major component along with the dibutyl derivatives **3** and **4** and completely debutylyated derivative **6**. So, the optimization of the synthesis of mono-*tert*-butyl derivative **5** was attempted at around 14 h of reaction, and 35% of **5** could be isolated.

The optimization of the debutylation reaction was also attempted in other closely related solvents, such as benzene and xylene. In xylene at refluxing condition, the reaction rate was significantly improved and all the *tert*-butyl groups were removed within 8 h with somewhat reduced yield (68%, entry 4), while in benzene no noticeable reaction was proceeded at all even after 3 days of refluxing condition (entry 1). However, in xylene, despite the shortened reaction time compared with the reaction in toluene, the reaction mixture was highly colored and a clear-cut estimation for the optimization of the partially debutylyated product was not easy, possibly due to much drastic reaction condition. Another interesting result is the finding that a significant temperature effect was observed in the reaction: a 10 °C change in temperature resulted in big difference on the yields of the reaction in toluene (entries 2 and 3). We also tried to perform the synthesis of partially debutylyated products through the obvious attempt of the cautious quenching of the reaction mixture for the standard AlCl₃-catalyzed reaction of *p*-tert-butylcalix[4]arene, but failed to obtain reproducible results.

Although the debutylation reaction with Nafion requires more strenuous reaction condition¹⁵ of refluxing toluene than the widely employed AlCl₃-catalyzed reaction, one can obtain the partially debutylyated compounds, which are otherwise unavailable without the troublesome protection and deprotection procedures employing the lower rim. Furthermore, as for the complete debutylation to obtain **6**, the synthetic procedure is somewhat more

(15) Although the reaction condition for the utilization of Nafion in the debutylation is rather harsh and requires longer time than the standard AlCl₃ catalyzed reaction, recently reported development employing high surface area Nafion resin/silica nanocomposites might be helpful for the practical application of Nafion resin in the debutylation reaction. Harmer, M. A.; Farneth, W. E.; Sun, Q. *J. Am. Chem. Soc.* **1996**, *118*, 7708.

convenient than the standard AlCl_3 -catalyzed reaction with a minimum procedure for the workup; just filtering off the solid polymeric Nafion, and allow the *p*-H-calix[4]arene to crystallize from the reaction mixture.

Experimental Section

General. All chemicals, including *p*-*tert*-butylcalix[4]arene and Nafion-H, were purchased from Aldrich and used without further purification. Solvents were HPLC grade and dried prior to use. ^1H NMR and ^{13}C NMR spectra were recorded on a 300 or 500 MHz spectrometer with TMS as an internal standard. HPLC analyses were conducted with a Gilson 305 System liquid chromatograph. Mass spectra and elemental analysis data were obtained at the Basic Science Institute in Seoul, Korea. Silica gel 60 (Merck, 70–230 mesh) and silica gel (Merck, 230–400 mesh) were used for column chromatography and flash column chromatography, respectively.

Procedure for the Debutylation of *p*-*tert*-Butylcalix[4]arene. A solution of **1** (1.0 g, 1.54 mmol) in 50 mL of toluene was added Nafion-H (300 mg), and the reaction mixture was heated at reflux under N_2 atmosphere for 24 h. The progress of the reaction was monitored by TLC (hexane/THF, 9:1). After complete reaction, the reaction mixture was filtered to remove Nafion-H, and the solvent was evaporated until about one-third of its volume. The solution was allowed to crystallize at room temperature to yield 520 mg (80%) of **6**⁷ as colorless crystal.

Procedure for the Partial Debutylation of *p*-*tert*-Butylcalix[4]arene. For the optimization of the synthesis of **2**, **3**, **4**, or **5**, the reaction was quenched by cooling after suitable reaction time, and the crude reaction mixture was chromatographed on silica gel (hexane/THF, up to 9:1) or Chromatotron. Subsequent recrystallization from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ afforded crystalline **2**–**5**.

After 8 h of reaction, the chromatographic separation of the crude reaction mixture afforded **2** (48%). **2**: mp > 350 °C; R_f = 0.52 (hexane/THF, 9:1); ^1H NMR (CDCl_3) δ 10.26 (s, 4H), 7.06–7.02 (m, 8H), 6.71 (t, 1H, J = 7.6 Hz), 4.24 (br s, 4H), 3.53 (br s, 4H), 1.22 (s, 18H), 1.19 (s, 9H); ^{13}C NMR (CDCl_3) δ 149.1, 146.8, 146.4, 144.6, 129.1, 128.7, 128.0, 127.8, 127.4, 126.0, 125.8, 122.2, 34.0, 32.4, 32.2, 31.4, 31.3, 30.8; MS (FAB+) m/e 592 (M^+). Anal. Calcd for $\text{C}_{40}\text{H}_{48}\text{O}_4$: C, 81.04; H, 8.16. Found: C, 81.10; H, 8.01.

After 10 h of the reaction, the reaction mixture was complex, showing many spots in TLC, and contains some of di-debutylated products **3** and **4**, along with significant amount of **1**, **2**, and **5**. Compounds **3** (5%) and **4**^{9a} (2%) could be isolated from the reaction mixture after careful chromatographic separation using the Chromatotron. **3**: mp 348–349 °C; R_f = 0.41 (hexane/THF, 9:1); ^1H NMR (CDCl_3) δ 10.18 (s, 4H), 7.07–7.01 (m, 8H), 6.72 (t, 2H, J = 7.6 Hz), 4.24 (br s, 4H), 3.53 (br s, 4H), 1.21 (s, 18H); ^{13}C NMR (CDCl_3) δ 149.1, 146.5, 144.7, 129.2, 128.8, 128.7, 128.4, 128.0, 127.4, 126.1, 125.8, 122.2, 33.9, 32.3, 32.1, 31.8, 31.3; MS (FAB+) m/e 536 (M^+). Anal. Calcd for $\text{C}_{36}\text{H}_{40}\text{O}_4$: C, 80.56; H, 7.51. Found: C, 80.78; H, 7.62.

After 14 h of the reaction, compound **5** (35%) could be readily separated by column chromatography from the reaction mixture. **5**: mp 283–286 °C; R_f = 0.29 (hexane/THF, 9:1); ^1H NMR (CDCl_3) δ 10.21 (s, 4H), 7.05 (d, 2H, J = 7.6 Hz), 7.05 (s, 2H), 7.03 (d, 4H, J = 7.5 Hz), 6.72 (t, 2H, J = 7.5 Hz), 6.71 (t, 1H, J = 7.5 Hz), 4.24 (br s, 4H), 3.53 (br s, 4H), 1.22 (s, 9H); ^{13}C NMR (CDCl_3) δ 149.0, 148.8, 146.6, 144.7, 129.1, 128.9, 128.8, 128.5, 128.4, 128.3, 127.5, 125.9, 122.3, 122.2, 34.1, 32.2, 31.8, 31.5; MS (FAB+) m/e 480 (M^+). Anal. Calcd for $\text{C}_{32}\text{H}_{32}\text{O}_4$: C, 79.97; H, 6.71. Found: C, 79.83; H, 6.87.

Acknowledgment. This work was supported by KOSEF (96-0501-04-01-3) and Ministry of Education of Korea (BSRI 97-3450) and gratefully acknowledged.

JO971607+