ORGANIC LETTERS

2000
Vol. 2, No. 20
3071−3074

Fragmentation Reaction via an Ipso-Attack in the Multistep Synthesis of Regioselectively Functionalized Calix[8]arene

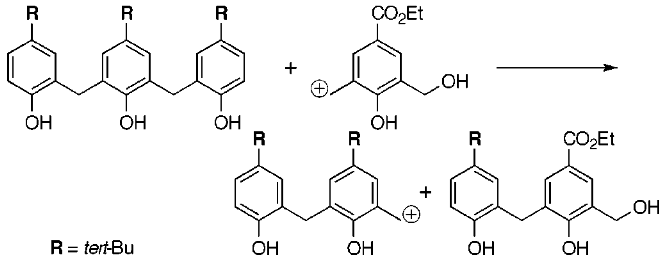
Hirohito Tsue,* Kazutaka Enyo, and Ken-ichi Hirao

Division of Material Science, Graduate School of Environmental Earth Science,
Hokkaido University, Sapporo 060-0810, Japan

tsue@ees.hokudai.ac.jp

Received June 13, 2000

ABSTRACT



The acid-catalyzed convergent synthesis of a calix[8]arene containing a regioselectively functionalized upper rim has been investigated through the isolation and identification of cyclic and acyclic byproducts. Theoretical calculations demonstrated that the synthetic process involves two types of reaction mechanisms, one of which leads to the favorably constructed framework, while the other causes undesirable fragmentation via ipso-substitution. A possible rationale is proposed to explain the overall reaction pathways which derive the calix[8]arene along with the byproducts.

“Calixarene” is a general term for a series of macrocyclic phenol condensates, which are linked via methylene bridges and which play an important role in host−guest chemistry.[1] Synthetic strategies for the construction of such frameworks are generally classified into two main groups, i.e., (1) one-step and (2) multistep syntheses.[1c] The former has been extensively utilized for preparing calixarenes with uniformly functionalized upper rims, and systematic and extensive studies by Gutsche enable the ring size to be controlled by simply adjusting the reaction conditions used.[2] On the other hand, the latter has mainly been applied to the synthesis of calixarenes which contain different substituents at the upper rim.[3] However, the latter methodology is usually associated with long and tedious reaction steps, which cause poor overall yields and also present a large barrier to its conventional use, although this method has permitted the synthesis of regioselectively substituted calixarenes with well-defined molecular structures. We have previously reported the successful application of the latter methodology to the preparation of calix[8]arene **1**,[4] in which the upper rim is regioselectively functionalized by two different types of substituents. However, contrary to prior expectations, a variety of linear and cyclic byproducts including a ring-

---

(1) (a) Gutsche, C. D. *Calixarenes Revisited*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry, No. 6; The Royal Society of Chemistry: Cambridge, 1998. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, 1991. (c) Gutsche, C. D. *Calixarenes*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry, No. 1; The Royal Society of Chemistry: Cambridge, 1989.

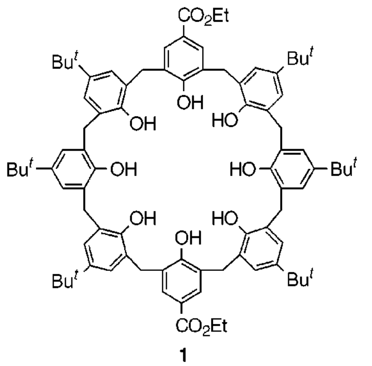
(2) (a) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234. (b) Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1990**, *68*, 238. (c) Munch, J. H.; Gutsche, C. D. *Org. Synth.* **1990**, *68*, 243.

(3) See, for example: (a) Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200. (b) Zetta, L.; Wolff, A.; Vogt, W.; Platt, K.-L.; Böhmer, V. *Tetrahedron* **1991**, *47*, 1911. (c) No, K.; Kim, J. E.; Kwon, K. M. *Tetrahedron Lett.* **1995**, *36*, 8453.

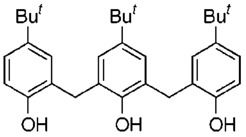
(4) Tsue, H.; Ohmori, M.; K, Hirao *J. Org. Chem.* **1998**, *63*, 4866.

10.1021/ol006195x CCC: $19.00

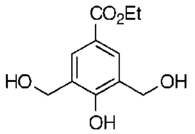
shrunken calix[6]arene were found as contaminants in the synthesis of **1**. This finding prompted us to isolate and identify these side reaction products and to investigate the reaction mechanism by which they are produced. In this Letter, we describe the molecular structures of the byproducts and the key reaction mechanism via ipso-substitution, which appears to be commonly involved in the multistep synthesis of calixarenes.



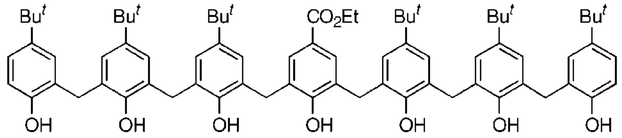
1



2



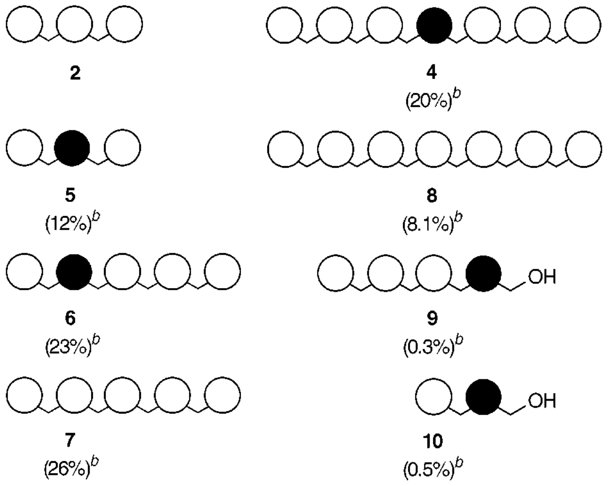
3



4

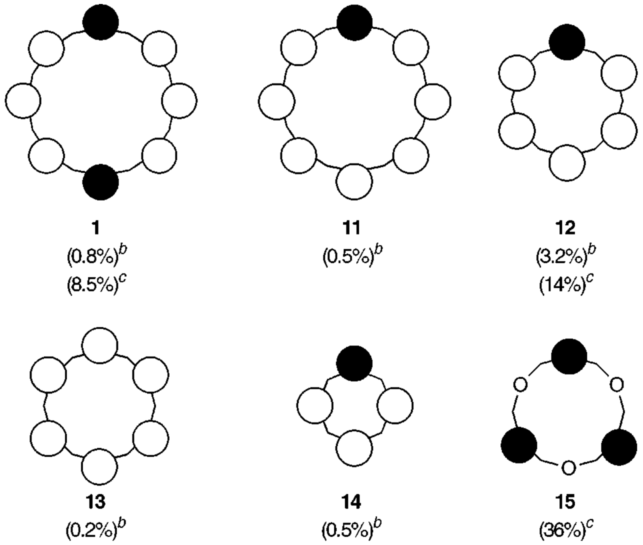
According to the previous report,[4] calix[8]arene **1** was prepared by the application of a convergent "7 + 1" fragment condensation, which was an extension of Böhmer's "3 + 1" methodology.[3] Starting from the acid-catalyzed condensation of **2**[5] and **3**,[6] the resultant "7" fragment **4** (20%) was allowed to react with the "1" fragment **3** in the presence of a catalytic amount of *p*-TsOH to afford the desired calix[8]arene **1** (8.5%). The fairly low yields in these two steps are reflected in the fact that both steps were accompanied by the formation of a variety of side reaction products, which were purified by repeatitive flash column chromatography and identified on the basis of spectral and microanalytical data (see Supporting Information). Charts 1 and 2 schematically summarize the molecular structures of the byproducts which were isolated from the two reaction steps.

Chart 1. Schematic representation of the reaction products which have acyclic molecular structures[a]



[a] Black and white dots represent 4-ethoxycarbonylphenol-2,6-diyl and 4-*tert*-bytylphenol-2,6-diyl groups, respectively. [b] Yields in the reaction **2** + **3** → **4**.

Chart 2. Schematic representation of the reaction products with cyclic molecular structures[a]



[a] Black and white dots represent 4-ethoxycarbonylphenol-2,6-diyl and 4-*tert*-bytylphenol-2,6-diyl groups, respectively. [b] Yields in the initial step **2** + **3** → **4**. [c] Yields in the second step **4** + **3** → **1**.

In the initial step **2** + **3** → **4**, a total of 82 wt % of the reaction products was recovered and identified, and all the compounds which are depicted in Charts 1 and 2 were obtained with the sole exception of homooxacalix[3]arene **15**. Acyclic products consisted of trimer **5**, two types of pentamers **6** and **7**, two types of heptamers **4** and **8**, and two types of terminally hydroxymethylated condensates **9** and **10**, along with the unreacted **2**, while the cyclic molecules were comprised of two types of calix[8]arenes **1** and **11**, two calix[6]arene derivatives **12** and **13**, and calix[4]arene **14**. On the other hand, in the second step **4** + **3** → **1**, a total of 54 wt % of the reaction mixture was identified, and only cyclic byproducts such as ring-shrunken calix[6]arene **12** and homooxacalix[3]arene **15** were obtained, along with the recovered heptamer **4** and the desired calix[8]arene **1**. Very interestingly, in these two reactions, the linear byproducts were constructed of only an odd number of aryl residues, except for benzyl alcohols **9** and **10**, whereas the cyclic molecules contained an even number of the residues, with the single exception of **15**. An important point in these two reactions is that the starting materials **2**, **3**, and **4** would not be expected to afford compounds such as **5**, **6**, **7**, **8**, **10**, **11**, **12**, and **13**, although the formations of homooxacalix[3]arene

---

(5) Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48*, 1536.
(6) Zinke, A.; Ott, R.; Leggewie, E.; Hassanein, A.; Zankl, G. *Monatsh. Chem.* **1956**, *87*, 552; *Chem. Abstr.* **1957**, *51*, 2845c.

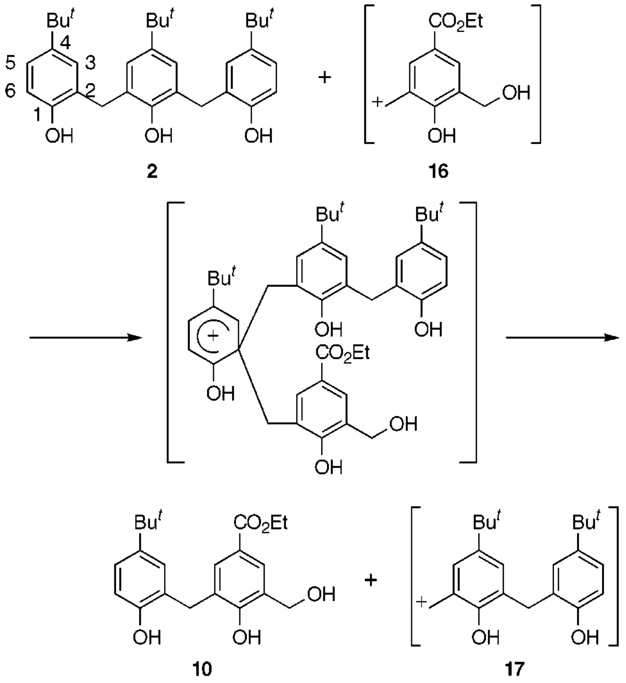
15 from **3** and of calix[4]arene **14** from **2** and **3** are easily understandable.

To further explore the mechanism for this reaction, the acid-lability of **1**, **2**, and **4** was examined by exposing each compound to acidic conditions, which were essentially identical with that used for the acid-catalyzed condensation reactions **2** + **3** → **4** and **4** + **3** → **1**. However, these compounds were recovered quantitatively and revealed no detectable changes, indicating that they are stable under these conditions. It is thus reasonable to assume that none of the byproducts are generated directly from molecules **1**, **2**, and **4**. It is particularly interesting to note that calixarenes **12**−**14** are not formed through the direct [8]-to-[6] or [8]-to-[4] shifts of **1** at least under the reaction conditions examined herein, although Mendoza[7] reported the direct transformation of a calix[6]arene into a calix[4]arene under acidic conditions, and Gutsche[8] also reported a similar interconversion from *p*-*tert*-butylcalix[8]arene to the bimolecular *p*-*tert*-butylcalix-[4]arene in the presence of NaOH. In contrast to the stability of **1**, **2**, and **4**, the similar treatment of a byproduct **9** under the same acidic condition resulted in the formation of a complicated reaction mixture. Considering the synthetic processes of the target compound **1** and the intermediate **4**, the results of this experiment clearly suggest that the benzyl alcohol moiety present in **3**, **9**, and **10** serves as a trigger for inducing side reactions, from which the byproducts shown in Charts 1 and 2 are derived.

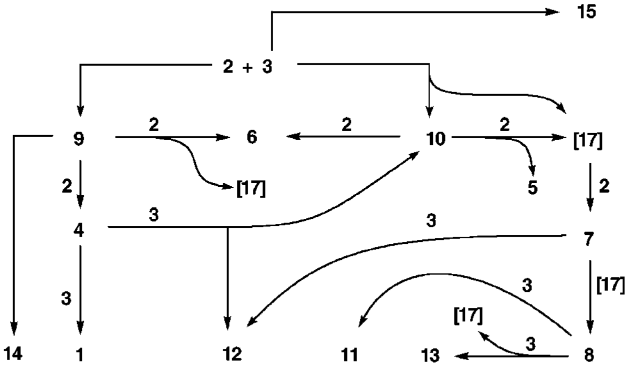
With this in mind, an aromatic electrophilic substitution reaction between phenol condensate **2** and benzyl cation **16**, which could be generated in situ from benzyl alcohol **3** and an acid catalyst of *p*-TsOH, was analyzed as a typical case of such a reaction by using a semiempirical molecular orbital calculation based on MOPAC PM3[9] according to the Klopman's general perturbation equation.[10] The theoretical calculations clearly showed that the orbital coefficients of the highest occupied molecular orbital (HOMO) in **2** appeared only in one of the terminal phenol rings, the carbon atoms of which are numbered in Scheme 1, and that the ortho- and para-positions of the ring were susceptible to attack by the electrophile **16**. The regioselectivity was estimated to increase in the order of 6- < 2- < 4-positions.[11] In other words, the point of this theoretical prediction is that a reaction at the 6-position would favorably extend the linear structure of the product, whereas that at the 2-position leads to an undesirable fragmentation reaction through a Meisenheimer complex, to give a benzyl alcohol **10** and a benzyl cation **17**, as illustrated in Scheme 1. This prediction is in reasonable agreement with the experimental fact that compound **10** was isolated as a byproduct from the reaction mixture. On the other hand, the 4-position in **2** was calculated to be the highest reactive cite and the *tert*-butyl cation would be expected to be a good leaving group. Nevertheless, the electrophilic attack at the 4-position appears not to occur, mainly due to the steric hindrance arising from the bulky *tert*-butyl group. Indeed, none of the corresponding byproducts were involved in the reaction products. Consequently, the formation of the various side reaction products can be attributed to the participation of an additional reaction pathway, which would result from the newly formed benzyl alcohol **10** and benzyl cation **17** which are capable of reacting with other molecules present in the same reaction system.

Scheme 2 shows a possible explanation for the complete reaction diagram, which shows that the synthetic pathways

Scheme 1. A Competitive Fragmentation Pathway via Ipso-Substitution



Scheme 2. A Possible Explanation of All the Reaction Pathways. The Presence of Fragmentation Reaction via Ipso-Attack Is Designated as Branched Arrows



---

[7] de Mendoza, J.; Nieto, P. M.; Prados, P.; Sánchez, C. *Tetrahedron* **1990**, *46*, 671.

[8] (a) Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* **1986**, *51*, 742. (b) Dhawan, B.; Chen, S.-I.; Gutsche, C. D. *Makromol. Chem.* **1987**, *188*, 921.

[9] Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.

[10] (a) Klopman, G. In *Chemical Reactivity and Reaction Paths*; Klopman, G., Ed.; Wiley & Sons: New York, 1974; pp 55−165. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.

[11] Perturbation energies at the 2-, 4-, and 6-positions were estimated to be 0.48, 0.84, and 0.36 eV, respectively.

leading to calix[8]arene **1** are associated with numerous competitive side reactions. The formation of **1**, **4**, **9**, **14**, and **15** can be easily understood, while it is likely that the other molecules are formed as above through undesirable fragmentation reactions via ipso-attack. Although the side reactions in Scheme 2 remain to be proved by actually examining the reactions of each byproduct, the scheme is a reasonable one, since the key intermediates **4**, **7**, and **8** in the formation of calixarenes **11**, **12**, and **13** were theoretically predicted to have reactivities similar to **2**. The orbital coefficients of the HOMOs in these molecules were found only in the one terminus, and the regioselectivities of the aromatic electrophilic substitution reactions with benzyl cation **16** were calculated to increase in the same order as that predicted for **2**.[12] In particular, from the mechanistic point of view, the results of the theoretical calculations are in good agreement with Gutsche's recent study[13] of the reaction mechanism which involves ipso-substitution in the acid-induced one-step formation of calix[*n*]arenes ($n = 4-20$) from linear oligomers of *p*-*tert*-butylphenol and formaldehyde. Accordingly, judging from the above, it seems reasonable to presume that Scheme 2 represents a plausible, though inconclusive, interpretation for explaining the complete reaction pathways leading to calix[8]arene **1** along with the observed byproducts.

In conclusion, it follows from the present study that the formation of calix[8]arene **1** is very sensitive to regioselectivity in the aromatic electrophilic substitution reactions, although consideration must also be given to steric hindrance as a factor. In light of our present result and those reported by Böhmer, who obtained a calix[4]arene as the exclusive product in the attempted synthesis of a calix[5]arene using "3 + 2" methodology,[14] it seems quite likely that a fragmentation reaction via ipso-attack is frequently involved in the multistep preparation of calixarenes especially under acidic conditions.[15] To locate a method for suppressing the undesirable pathways, the nature and generality of the reaction are being investigated in our laboratory.

Acknowledgment. We thank the GC-MS and NMR Laboratory, Faculty of Agriculture, Hokkaido University, for FDMS measurements. We are also grateful to Ms. Hiroko Matsumoto and Ms. Akiko Maeda at the Center for Instrumental Analysis, Hokkaido University, for the measurement of elemental analysis. This research was supported, in part, by Grant-in-Aid for Encouragement of Young Scientists (Nos. 09740456 and 12740334) from the Ministry of Education, Science, Sports and Culture, Japan.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H NMR spectra of all new compounds, and the results of theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006195X

---

[12] Perturbation energies at the 2- and 6-positions were estimated to be 0.51 and 0.36 eV for **4**, 0.51 and 0.36 eV for **7**, and 0.51 and 0.36 eV for **8**, respectively.

[13] Stewart, D. R.; Gutsche, C. D. *J. Am. Chem. Soc.* **1999**, *121*, 4136.

[14] Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.

[15] A similar ipso-substitution reaction under neutral condition was supposed in the heat-induced synthesis of calix[5]arenes. See: Biali, S. E.; Böhmer, V.; Columbus, I.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2261.