Pergamon

Tetrahedron Letters 42 (2001) 6855–6858

TETRAHEDRON
LETTERS

Synthesis of troponoid analogues of calix[4]arene by the reaction of dichlorocarbene with calix[4]arene

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Received 16 February 2001; revised 25 July 2001; accepted 26 July 2001

Abstract—Troponoid analogues of calixarene, having a tropone or a cyclohepta[*b*]chromen-6(11*H*)-one ring were synthesized by the reaction of dichlorocarbene with *p*-*tert*-butylcalix[4]arene. The cyclohepta[*b*]chromene derivative dimerized easily to give *meso*- and *dl*-dimers. © 2001 Published by Elsevier Science Ltd.

Calixarenes have a variety of possibilities as a host molecule which includes various ions and molecules in their cavities.[1] Numerous efforts have been made to synthesize their derivatives aiming at the selective complexation and a similar family of compounds including heterocyclic analogues. It is well known that tropolone has a strong affinity for many metal ions and the many stable metal chelates are isolated.[2] Tropone ring is highly polarized and has large dipole moment. The introduction of the troponoid ring into calixarene, therefore, is expected to give rise to peculiar complexation ability. A synthesis of a tropolone analogue of calixarene was reported recently,[3] but its structure seems to be still debatable.[4] Herein we present a synthesis of calixarene analogues having a chlorotropone and a cyclohepta[*b*]chromene moiety in the position of a phenol ring of calixarene.

It is known that dichlorocarbene reacts with alkoxynaphthalenes and phenanthrenes to give chlorotropone derivatives,[5] but does not react with phenyl ethers. With phenols,[6] it gives aldehydes (Reimer–Tiemann reaction)[7] or dichloromethylcyclohexadienones with *ortho*- and *para*-substituted phenols.[7] As the latter products can be converted to seven-membered rings,[8,9] we applied the carbene reaction to calixarene to prepare a tropone ring through norcaradienol formation.

When *p*-*tert*-butylcalix[4]arene (**1**) was heated in dimethoxyethane or tetrahydrofuran with sodium trichloroacetate added in portions, five products were isolated along with unreacted calixarene after chromatography. Phase transfer reaction catalyzed by benzyltributylammonium ion gave the same products in poor yields.

The least polar compound **2** among the products was attributed to an orthoformate from its ^{13}C and ^{1}H NMR spectra. The other four compounds exhibited each 12 sp^3 carbons and 25 sp^2 carbons, one of which was assigned to a carbonyl carbon. The main product **3** was isolated in 30% yield. Its ^{1}H NMR spectrum showed eight doublet protons in an aromatic region and broad signals of methylene protons between δ 3.2 and 4.9, but at −40°C eight separated methylene doublets were observed at δ 3.31 (d, $J=12.3$ Hz), 3.46 (d, $J=13.2$ Hz), 3.48 (d, $J=14.0$ Hz), 4.26 (d, $J=13.2$ Hz), 4.34 (d, $J=14.0$ Hz), 4.35 (d, $J=13.6$ Hz), 4.40 (d, $J=13.6$ Hz), and 4.79 (d, $J=12.3$ Hz). This was explained by the slow conformational inversion between the mirror images. In addition, a carbonyl carbon signal observed at δ 183.5 strongly suggested the formation of a tropone ring; that is, ring enlargement of one phenol ring to a tropone ring occurred in one step through a norcaradienol intermediate.

The observed long range coupling of aromatic protons of **3** suggested that the positions of the two protons of tropone ring had the *meta* relation. Thus, the structure of **3** must be a 2-chloro- or 3-chlorotropone derivative via 1,2- or 2,3-cyclopropanation of **1** (see Fig. 1). The nuclear Overhauser effect (NOE) between *tert*-butyl groups and aromatic protons supported this conclusion; that is, no cyclopropanation occurred at the C_3–C_4 position of the phenol ring of **1**, because of the

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0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)01362-4

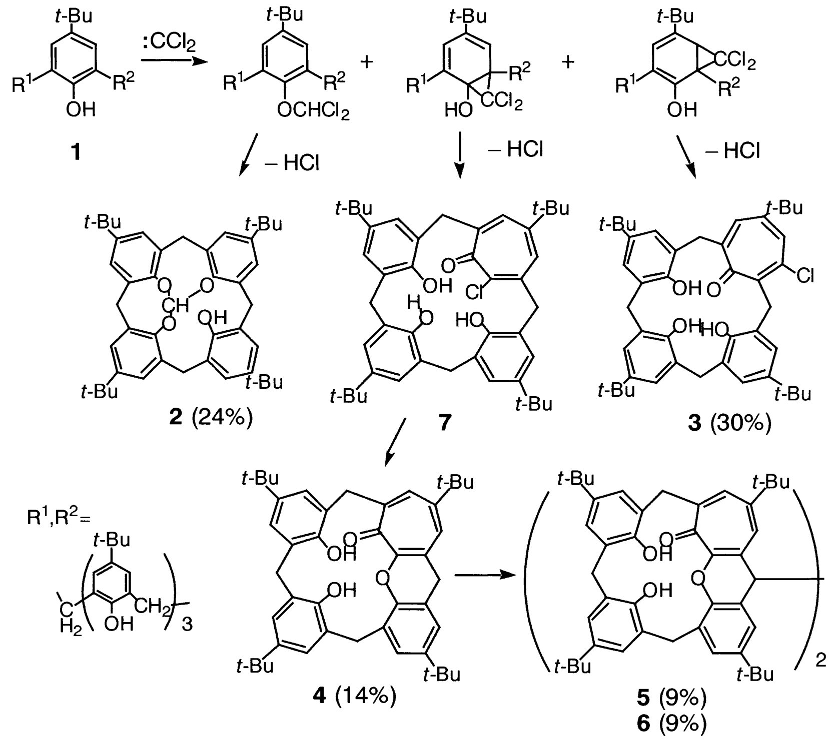


Figure 1. The reaction mechanism of the formation of troponoid calixarenes.

bulkiness of the *tert*-butyl group. The phenolic hydroxylic protons at δ 9.53, 10.33, and 11.78 showed that they are strongly hydrogen bonded as similar as calixarene, and therefore it must be a cone conformer. The proton at δ 7.91, which was assigned to the troponoid proton, revealed NOE with the benzene ring proton at

Table 1. ^{1}H NMR of troponoid calixarenes and other products

Assignment	**2**	**3**[a,b]	**4**[a,b]	**5**[a,c]	**6**[a,c]
tert-Bu	1.22	1.16	1.10	1.04	1.05
	1.27	1.19	1.13	1.07	1.08
	1.33 (×2)	1.23	1.330	1.07	1.08
		1.36	1.333	1.08	1.10
CH_2/CH	3.93 (17.6, 2H)	3.31 (12.3)	3.35 (13.7)	3.40 (13.7)	3.40 (13.8)
	4.03 (17.6, 2H)	3.46 (13.2)	3.44 (13.0)	3.42 (13.0)	3.42 (13.0)
	4.15 (17.6, 2H)	3.48 (14.0)	3.44 (13.0)	3.43 (13.0)	3.43 (13.0)
	4.45 (17.6, 2H)	4.26 (13.2)	3.74 (18.5)	3.71 (s)	3.74 (s)
	6.15 (CH, s)	4.34 (14.0)	4.16 (18.5)	–	–
		4.35 (13.6)	4.54 (13.0)	4.55 (12.0)	4.54 (13.0)
		4.40 (13.6)	4.91 (13.0)	4.95 (12.0)	4.94 (13.0)
		4.79 (12.3)	5.14 (13.7)	5.32 (13.7)	5.27 (13.8)
OH	4.56	9.53	8.82	8.72	8.68
		10.33	10.30	10.61	10.51
		11.78	–	–	–
H–C=[d]	7.03 (s; 2H)	6.89 (2.2)	6.74 (2.4, Hh)	6.69 (2.2)	6.69 (2.4)
	7.07 (s; 2H)	7.00 (2.2)	6.86 (2.2, He)	6.89 (2.2)	6.88 (2.2)
	7.14 (2.2; 2H)	7.04 (2.5)	6.90 (2.2, Hf)	6.90 (2.2)	6.89 (2.2)
	7.14 (2.2; 2H)	7.08 (2.2)	6.97 (br, Hb)	6.05 (1.8)	6.31 (1.8)
		7.18 (2.2)	6.97 (br, Hc)	6.36 (2.2)	6.20 (2.4)
		7.59 (2.5)	7.03 (2.4, Hg)	7.00 (2.2)	7.00 (2.4)
		7.35 (1.8)	7.41 (2.2, Hd)	7.43 (2.2)	7.41 (2.4)
		7.91 (1.8)	7.66 (1.8, Ha)	7.63 (1.8)	7.65 (1.8)

[a] Figures in parentheses are coupling constants of doublets in Hz.

[b] 270 MHz at −30°C.

[c] 600 MHz at 0°C.

[d] Assignments of the aromatic protons of **4** are based on COSY and NOE experiments, and those of **5** and **6** are based on comparison with **4**. For the position of the proton Ha–h, see Fig. 2.

6.89, whereas the other troponoid proton at 7.35 showed no NOE with other protons. This observation suggested that **3** was attributable to a 3-chlorotropone rather than a 2-chlorotropone derivative. Further evidence for the structure of **3** was obtained from the relationship between **3** and **4**. As **3** was stable and **4** was not obtained by heating **3** in the reaction conditions, **3** must not be the precursor of **4**. Thus, **3** was assigned to the 3-chlorotropone derivative.

The third product **4** similarly showed a carbonyl carbon at δ 179.2 and **4** was suggested to be an isomer of **3**. However, its mass spectrum suggested that further dehydrochlorination occurred, and the structure was assigned to a cyclohepta[*b*]chromen-6(11*H*)-one derivative which was formed by the intramolecular cyclization of a 2-chlorotropone derivative (**7**). This was supported by the observed NOE between the aromatic protons of **4**, Hb and Hc, Hd and He, Hf and Hg, and Hh and Ha. The cyclization of a 3-chlorotropone derivative to an isomeric cyclohepta[*b*]chromen-10(11*H*)-one derivative is unlikely because of its large strain.

The ^{1}H NMR spectra of the rest, **5** and **6**, closely resembled that of **4**, except two up-field shifted aromatic protons, one of which was assigned to a tropone proton. Further, a methine proton was newly observed instead of methylene protons (see Table 1). Their ^{13}C NMR spectra disclosed 25 carbons to indicate that they are dimers of **4**. This was supported by the mass spectrum of **6** showing the molecular ion at m/e 1315 $(M+1^{+})$. They must be formed by the coupling of a pyranyl radical, which was generated by deprotonation of a pyranyl proton of **4** and subsequent air oxidation. In fact, **5** and **6** were formed by the reaction of **4** with AgOAc or ammonia (Fig. 2).

The stereochemistries of **5** and **6** were determined by the comparison of chemical shifts of their tropone and benzene ring protons with those of **4**. Their protons neighbouring to a pyran ring, Hb and Hc, were largely shielded by the anisotropy of the counter part of rings (see the underlined parts in Table 1), whereas the other protons were unchanged. The up-field shift of a tropone ring proton (Hb) in **5** ($\Delta\delta=0.92$) is larger than that in **6** (0.66). As the aromaticity of tropone is considered to be small[10–12] and the anisotropy of tropone ring is not as large as benzene,[13] the protons above the benzene ring must be more shielded than those above the tropone ring in **5** and **6**. Therefore, Hb in **5** must lie above the benzene ring of another cyclohepta[*b*]chromene moiety and that in **6** must be above the tropone ring. Thus, **5** is assigned to the *meso*-dimer and **6** to the *dl*-dimer. Comparison of Hc led to the same conclusion by the smaller shift for **5** ($\Delta\delta=0.61$) than for **6** (0.77) (Fig. 3).

In conclusion, troponoid analogues (**3** and **4**) of calixarene and the dimer of **4** were synthesized by one-pot reaction of dichlorocarbene with **1**. The compound did not show sufficient complexation ability,[14] but the method for converting calixarene to its troponoid analogue was established and will be applied to related compounds.[15] The conditions and limitations of this unusual reaction will be further studied.

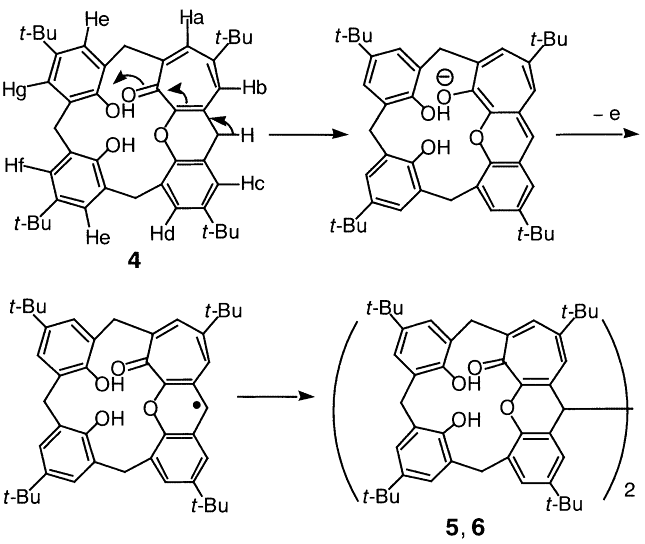
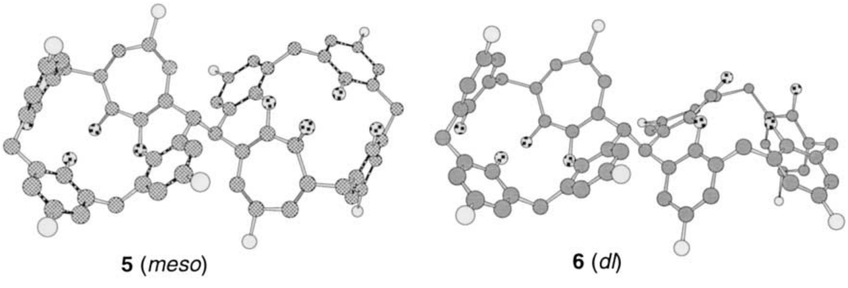


Figure 2. Dimerization of **4** to **5** and **6**.



5 (*meso*) **6** (*dl*)

Figure 3. The conformations of the *meso*- and *dl*-dimers, **5** and **6**. Hydrogen atoms have been removed for clarity and *tert*-butyl groups are shown as white balls. Dotted balls indicate oxygen atoms.

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4. Recently, the synthesis of 5-sulfonatotropolonocalix[4]arene from ammonium 5-sulfonatotropolone was reported by Poh et al.[3] They showed the ^{1}H NMR spectrum in DMSO-d_6 at 92°C to assign the signals to four conformers. But there still remain some anomalies for the assignment. For example, the partial cone has two singlets and two doublets, whose *meta* coupling constant, however, seems to be more than 10 Hz. In addition, the chemical shift values of methylene carbons, as low as δ 44–56, are so much deshielded comparing to those (δ 30–35) of other calixarenes.
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14. The complexation ability of compounds **3** and **4** with several metal ions was investigated, but no sufficient information was obtained for complexation. The UV spectra of **3** or **4** did not change by the addition of the thiocyanates of Li^+, Na^+, K^+, Cs^+, Rb^+, NH_4^+, Mg^{2+}, Zn^{2+}, Ba^{2+}, and Hg^{2+}, and the addition of $AgNO_3$, $CuCl_2$, $Co(SCN)_2$, $Ni(SCN)_2$, $FeSO_4$, and $FeCl_3$ did not affect the ^{1}H NMR spectra of **3** and **4**. An explanation was given to this unexpected result by the MM2 calculation of the conformation of **3**. The cavity of **3** was smaller than that of **1** due to the parallel orientation of the two phenol rings neighbouring the tropone ring, and that of **4** became shallow by the formation of cyclohepta[*b*]chromene ring. The loss of one hydroxy group may decrease the ability of **4** as a host. These are based on our selection of calix[4]arene as starting material, and an improvement is expected by using larger ring compounds, e.g. calix[6]arene.
15. The hydroxy proton of calix[4]arene is strongly hydrogen-bonded. For tropone formation, it looks important that the phenolic hydroxy proton is intramolecularly hydrogen bonded. Some phenols having methoxy or alkoxymethyl groups at the *ortho* position gave tropone derivatives similarly.