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*To the 85th Anniversary of birthday of late Yu.G. Gololobov*

# Synthesis and Antioxidant Activity of 3,5-Di-*tert*-butyl-4-hydroxyphenylthiomethyltetraalkylcalix[4]resorcinarenes

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**Abstract**—Deamination of dimethyl- and diethylaminomethylated tetraalkylcalix[4]resorcinarenes with 3,5-di-*tert*-butyl-4-hydroxyphenylmercaptan afforded new 3,5-di-*tert*-butyl-4-hydroxyphenylthiomethyltetraalkylcalix-[4]resorcinarenes. High antioxidant activity of the synthesized alkylcalix[4]resorcinarenes was established in the model reaction of initiated oxidation of styrene.

**Keywords:** calix[4]resorcinarenes, 3,5-di-*tert*-butyl-4-hydroxyphenylmercaptan, antioxidant activity

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Sulfides of hindered phenols are of particular interest as multifunctional antioxidants because of their possibility to show antioxidative intramolecular synergism [1, 2]. Calixarene platform can further enhance the antioxidant activity due to the effect of pre-organization of functional groups attached thereto [3], and wide possibilities for adjusting hydrophilic-lipophilic balance.

We have previously reported the synthesis of 3,5-di-*tert*-butyl-4-hydroxyphenylthiomethylated tetramethylcalix[4]resorcinarene **1** by reacting dimethyl- and diethylaminomethylated tetramethylcalix[4]resorcinarenes **2a** and **2b** with 3,5-di-*tert*-butyl-4-hydroxyphenylmercaptan **3** [4] (Scheme 1).

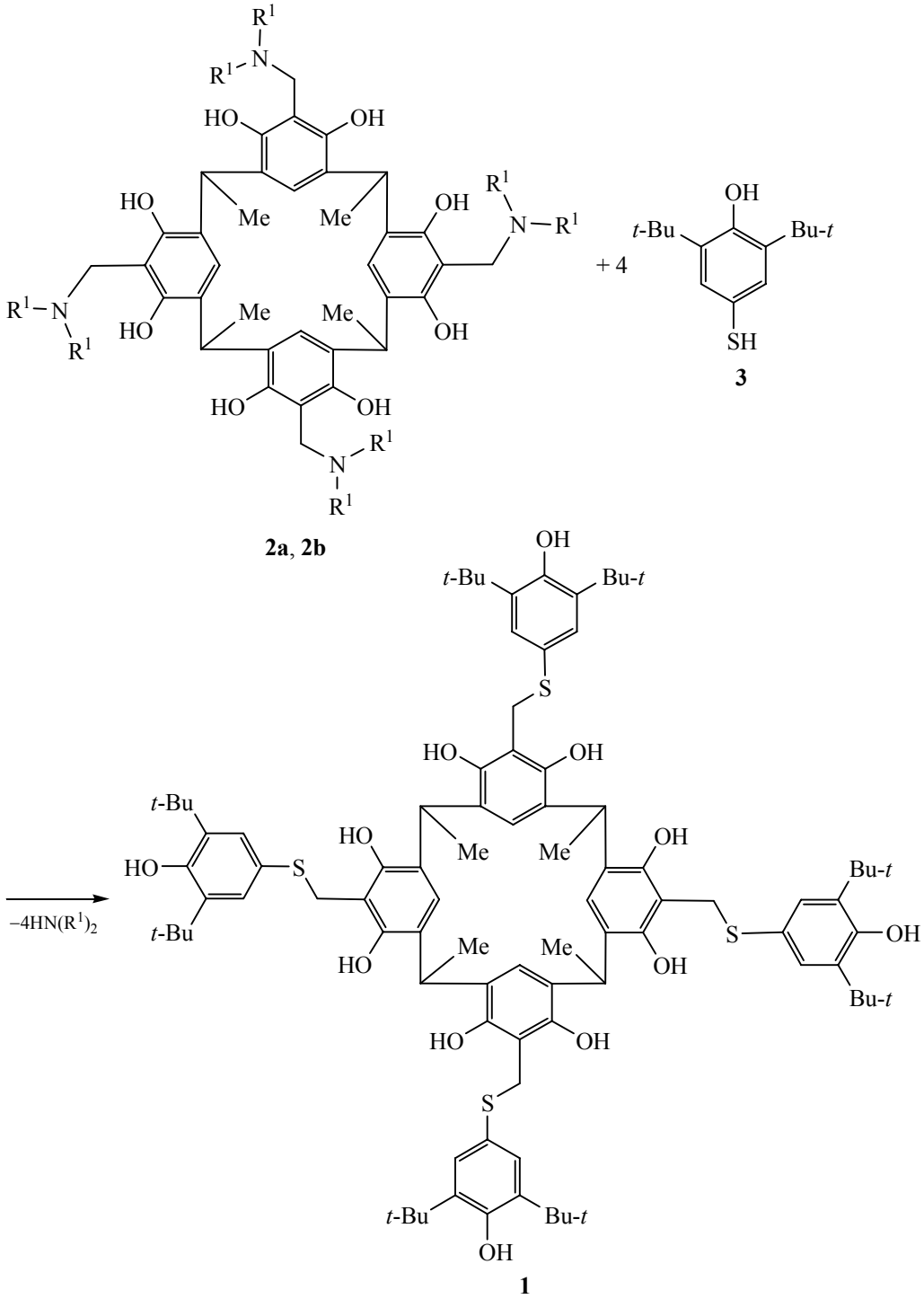
It has been found that the reaction is greatly influenced by supramolecular organization of the starting dialkylaminomethylated calix[4]resorcinarenes. The molecules of calix[4]resorcinarene **2a** form dimers in the crystal, in which dimethylaminomethyl group of adjacent molecules are included into the macrocycle cavities to each other. These steric hindrances prevent the nucleophilic attack [5]. This leads to a loss of reactivity of calix[4]resorcinarene **2a** when removing residual solvent molecules during storage accompanied by the formation of these dimers, and its restoration by washing the dried sample with dimethylsulfoxide and then with water. According to X-ray diffraction data, compound **2b** forms no dimers in the crystal [5] and its reactivity during storage is not reduced [4].

In this work we performed synthesis of 3,5-di-*tert*-butyl-4-hydroxyphenylthiomethyltetraalkylcalix[4]-resorcinarenes **4a**–**4c** differing by the length of hydrocarbon substituent at the lower rim of the calix[4]-resorcinarene platform.

In contrast to compound **1** [4], in the case of calix [4]resorcinarenes **4a**–**4c** supramolecular organization of the corresponding macrocyclic Mannich bases had no effect on the synthesis process. The reactions proceeded smoothly involving both dimethylaminomethyl and diethylaminomethyl derivatives. Note that reactions of tetraalkylcalix[4]resorcinarenes with 3,5-di-*tert*-butyl-4-hydroxybenzylacetate, when heptyl and nonyl moieties were present at the lower rim of the calix[4]resorcinarene, resulted in the formation of macrocycles containing only two 3,5-di-*tert*-butyl-4-hydroxybenzyl fragments [6]. In the present work we managed to obtain the tetrasubstituted derivatives with a satisfactory yield.

Antioxidant activity of calix[4]resorcinarenes **1**, **4b**, and **4c** was studied in a model reaction of styrene

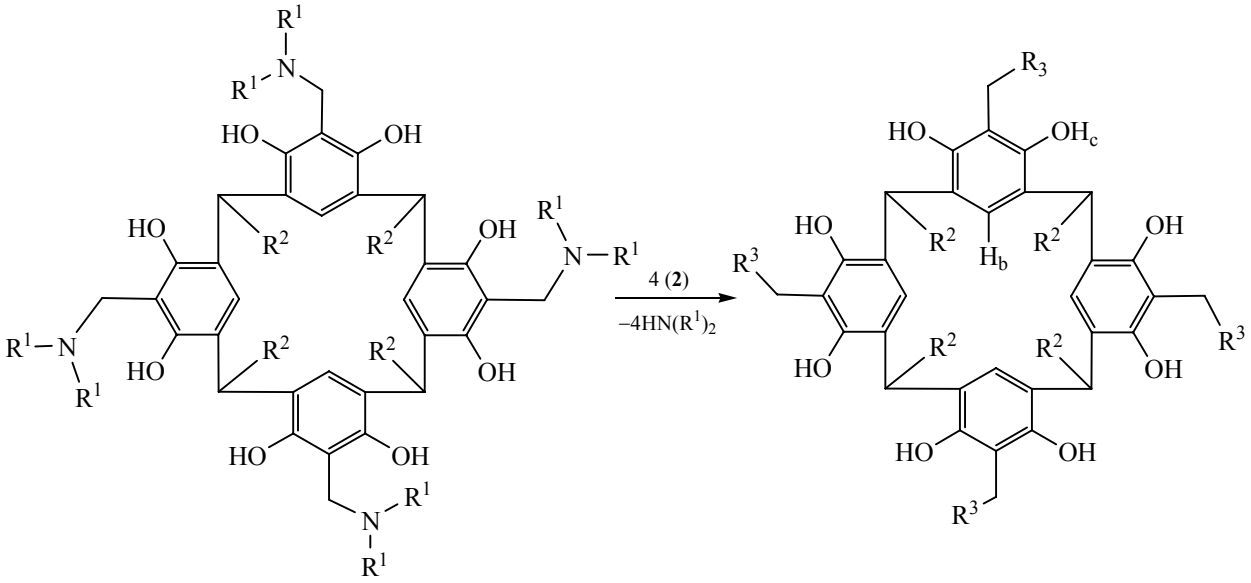
**Scheme 1.**



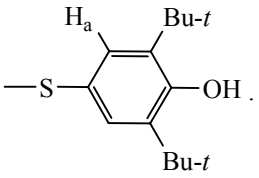

$R^1$ = Me (**a**), Et (**b**).

oxidation initiated by 2,2'-azobisisobutyronitrile (AIBN). Quantitative characteristics of antioxidant activity were the values of the oxidation rate $w_O$, the induction period of oxidation τ, and effective inhibition constant $f \times k_7$, where $f$ is an inhibitor capacity, which is equal to the number of radical intermediates destruction in one inhibitor molecule in acts of chain termination, $k_7$ is a rate constant of chain termination of oxidation (see table).

**Scheme 2.**




**5a–5d** **4a–4c**

$R^1$ = Me (**5a**, **5c, 5d**), Et (**5b**); $R^2$ = Et (**4a**), $C_7H_{15}$ (**4b**), $C_9H_{19}$ (**4c**); $R^3$ =  .

As seen from the data given in the table, the synthesized calix[4]resorcinarenes **1**, **4b**, and **4c** inhibited significantly styrene oxidation, and the antioxidant activity of calix[4]resorcinarenes decreased with increasing length of the hydrocarbon chain at the lower rim. Apparently, the reason for this may be self-assembly of the molecules similar to those detected previously among 3,5-di-*tert*-butyl-4-hydroxybenzylated calix[4]resorcinarenes [3], which can lead to spatial shielding of the antioxidant phenol moieties. It should be noted that even with such negative effect calix[4]resorcinarenes **4b** and **4c** outperformed industrial antioxidant (3,5-di-*tert*-butyl-4-hydroxybenzyl)sulfide **6**. This fact shows the availability of calix[4]resorcinarene platform for efficient synthesis of multifunctional antioxidants.

## EXPERIMENTAL

$^1$H NMR spectra were recorded on a Bruker AVANCE-600 spectrometer (600.13 MHz) using residual proton signals of the deuterated solvents as internal reference. Elemental analysis was performed on a Perkin Elmer PE 2400 series 2 CHNS/O-analyzer. IR spectra were registered on a Bruker Vector-22 FT-IR spectrometer.

The kinetics of initiated styrene oxidation in chlorobenzene medium at 60°C was studied on a gasometric apparatus [7] by registering in time the amount of absorbed oxygen. Styrene concentration was 1 mol/L, AIBN, 0.122 mol/L, inhibitors **1**, **4b** and **4c,** 0.002 mol/L. The initiating rate [$w_i$ 1.38 × $10^{-6}$ mol $L^{-1}$ $s^{-1}$)] and $f \times k_7$ value were calculated according to [8, 9]. The value of the induction period

Kinetic parameters of initiated oxidation of styrene in the presence of inhibitors

| Inhibitor | $w_O \times 10^6$, mol $L^{-1}$ $s^{-1}$ | τ, s | $f \times k_7$, L $mol^{-1}$ $s^{-1}$ |
|---|---|---|---|
| Without inhibitor | 24.31 | – | – |
| **1** | 2.52 | 1350 | 11040 |
| **4b** | 3.18 | 918 | 8764 |
| **4c** | 4.06 | 783 | 6864 |
| **6** | 5.80 | 702 | 4805 |

of oxidation was determined by extrapolating the straight section of the kinetic oxidation curve on the time axis.

Calix[4]resorcinarene **1** was synthesized by the method described in [4]. Chlorobenzene was purified as described in [10]. 2,2'-Azobisisobutyronitrile was twice recrystallized from ethanol before use, mp 132°C.

**4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,19-tetrakis(3,5-di-*tert*-butyl-4-hydroxyphenylthiomethyl)-2,8,14,20-tetraethylpentacyclo[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (4a).** *a.* A mixture of 0.50 g (0.60 mmol) of calix[4]resorcinarene **5a**, 0.63 g (2.66 mmol) of mercaptan **3**, and 18 mL of *o*-xylene was stirred at 125°C under argon for 14 h. Then the solvent was removed; the residue was washed with hexane and dried. Yield 0.66 g (68 %), mp > 180°C (decomp.). IR spectrum, ν, cm$^{-1}$: 3633, 3367 (OH), 1607 (C=C$_{Ar}$). $^1$H NMR spectrum (30°C, $CDCl_3$), δ, ppm: 0.84 t (12H, $CH_3$, $^3J_{HH}$ 7.0 Hz), 1.25 s (72H, $CMe_3$), 2.10–2.25 m (8H, $CH_2$), 4.12 s (8H, $CH_2S$), 4.15 t (4H, CH, $^3J_{HH}$ 7.3 Hz), 5.18 s (4H, OH), 7.11 s (8H, $H_a$), 7.12 s (4H, $H_b$), 7.60 s (8H, $OH_c$). Found, %: C 72.34; H 8.20; S 7.63. $C_{96}H_{128}O_{12}S_4$. Calculated, %: C 71.96; H 8.05; S 8.00.

*b.* Similarly from 0.30 g (0.34 mmol) of calix[4]-resorcinarene **5b** and 0.36 g (1.49 mmol) of mercaptan **3** were obtained 0.38 g (70%) of calix[4]resorcinarene **4a**.

**4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,19-tetrakis(3,5-di-*tert*-butyl-4-hydroxyphenylthiomethyl)-2,8,14,20-tetraheptylpentacyclo-[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (4b)** was prepared similarly from 0.3 g (0.26 mmol) of calix[4]resorcinarene **5c** and 0.27 g (1.13 mmol) of mercaptan **3**. Yield 0.32 g (65%), mp > 200°C (decomp.). IR spectrum, ν, cm$^{-1}$: 3620, 3361 (OH), 1603 (C=C$_{Ar}$). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.93 t (12H, $CH_3$, $^3J_{HH}$ 7.1 Hz), 1.25 s (72H, $CMe_3$), 1.26–1.49 m (40H, $C_5H_{10}$), 2.08–2.19 m (8H, $CH\underline{CH}_2$), 4.13 s (8H, $CH_2S$), 4.26 t (4H, CH, $^3J_{HH}$ 7.6 Hz), 5.19 s (4H, OH), 7.11 s (8H, $H_a$), 7.16 s (4H, $H_b$), 7.65 s (8H, $OH_c$). Found, %: C 73.84; H 9.12; S 6.13. $C_{116}H_{168}O_{12}S_4$. Calculated, %: C 74.00; H 8.99; S 6.81.

**4,6,10,12,16,18,22,24-Octahydroxy-5,11,17,19-tetrakis(3,5-di-*tert*-butyl-4-hydroxyphenylthiomethyl)-2,8,14,20-tetranonylpentacyclo-[19.3.1.1$^{3,7}$.1$^{9,13}$.1$^{15,19}$]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (4c)** was prepared similarly from 0.30 g (0.24 mmol) of calix[4]resorcinarene **5d** and 0.25 g (1.03 mmol) of mercaptan **3**. Yield 0.29 g (63%), mp > 300°C (decomp.). IR spectrum, ν, cm$^{-1}$: 3635, 3344 (OH), 1610 (C=C$_{Ar}$). $^1$H NMR spectrum (30°C, $CDCl_3$), δ, ppm: 0.50–1.60 m (76H, $C_9H_{19}$), 1.27 br.s (72H, $CMe_3$), 4.00–4.50 br.s (8H, $CH_2S$; 4H, CH), 5.10–5.30 br.s (4H, OH), 6.90–7.30 br.s (8H, $H_a$; 4H, $H_b$; 8H, $OH_c$). Found, %: C 75.12; H 9.35; S 6.00. $C_{124}H_{184}O_{12}S_4$. Calculated, %: C 74.65; H 9.30; S 6.43.

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## REFERENCES

1. Terakh, E.I., Prosenko, A.E., Nikulina, V.V., and Zaitseva, O.V., *Russ. J. Appl. Chem*., 2003, vol. 76, no. 2, p. 253. DOI: 10.1023/A:1024602729156.
2. Prosenko, A.E., Terakh, E.I., Gorokh, E.A., Nikulina, V.V., and Grigor'ev, I.A., *Russ. J. Appl. Chem*., 2003, vol. 76, no. 2, p. 248. DOI: 10.1023/A:1024650612317.
3. Consoli Grazia, M.L., Galante, E., Daquino, C., Granata, G., Cunsolo, F., and Geraci, C., *Tetrahedron Lett*., 2006, vol. 47, no. 37, p. 6611. DOI: 10.1016/j.tetlet.2006.07.021.
4. Nugumanova, G.N., Barsukova, T.A., Bukharov, S.V. Mukmeneva, N.A., Burilov, A.R., and Syakaev, V.V., *Russ. J. Org. Chem*., 2010, vol. 46, no. 7, p. 1097. DOI: 10.1134/S1070428010070250.
5. Gubaidullin, A.T., Nikolaeva, I.L., Kharitonov, D.I., Litvinov, I.A., Bashmakova, N.I., Burilov, A.R., Pudovik, M.A., and Konovalov, A.I., *Russ. J. Gen. Chem*., 2002, vol. 72, no. 2, p. 259. DOI: 10.1023/A:1015481804340.
6. Kasymova, E.M., Burilov, A.R., Pudovik, M.A., Chernova, A.V., Shagidullin, R.R., Konovalov, A.I., Mukmeneva N.A., Bukharov, S.V., and Nugumanova, G.N., *Russ. J. Gen. Chem*., 2007, vol. 77, no. 3, p. 458. DOI: 10.1134/S1070363207030206.
7. Tsepalov, V.F. and Shlyapintokh, V.Ya., *Doklady Akad. Nauk SSSR*, 1959, vol. 124, no. 4, p. 833.
8. Shlyapintokh, V.A., Karpukhin, O.N., Postnikov, L.M., Zakharov, I.V., Vichutinskii, A.A., and Tsepalov, V.F., *Khemilyuminestsentnye metody issledovaniya medlennykh khimicheskikh protsessov* (Chemiluminescent Methods for Studying Slow Chemical Processes), Moscow: Nauka, 1966.
9. Denisov, E.T. and Azatyan, V.V., *Ingibirovanie tsepnykh reaktsii* (Inhibition of Chain Reactions), Chernogolovka: IPKhF RAN, 1997.
10. Weissberger, A., Proskauer, E.S., Riddick, J.A., and Toops, E.E., *Organic Solvents*, New York; London, 1955.