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Trans-etherification of catechol-type benzylic ether with diols as a route to new sterically hindered bis-catechols

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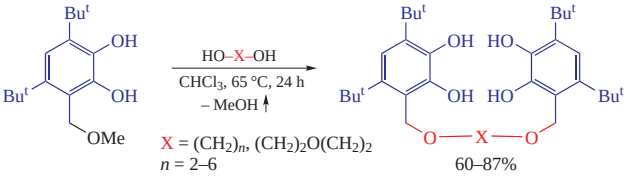
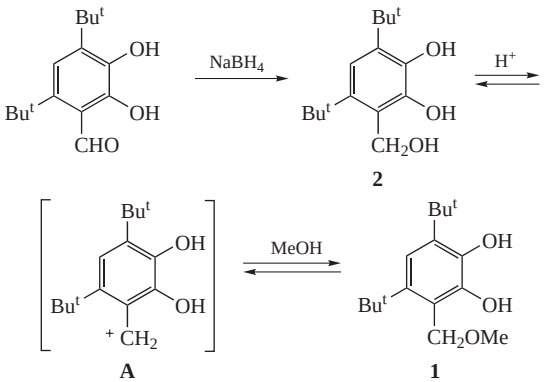
The trans-etherification of 4,6-di-*tert*-butyl-2,3-dihydroxybenzyl methyl ether with α,ω-alkanediols under mild conditions ($CHCl_3$, 65 °C) leads to new sterically hindered bis-catechols in high yields. The molecular structures of three of them was determined by single-crystal X-ray diffraction.



The interest to di- and oligomeric catechols is caused by their wide application as extractants of heavy metals,[1] as ligands in coordination[2] and supramolecular chemistry,[3] antioxidants and inhibitors of free radical processes,[4] and substrates in design of nanoporous 3D polymers.[5] A special place is occupied by sterically hindered catechols. The presence of sterical hindrance (two tertiary carbons at the aromatic ring of catechol) significantly increases the kinetic stability of oxidized forms of catechol preventing self-condensation processes. These facts make 3,5- and 3,6-di-*tert*-butylcatechols interesting for using in coordination chemistry of stable complexes with radical-anion semiquinone ligands.[6] The stable *o*-quinones find application as photoactive components of visible light-induced free radical polymerization of (meth)acrylic oligomers.[7] The ease of redox transformation of the catechol–quinone system is a challenge for obtaining new oligomeric catechols and *o*-quinones.

The main approach to oligomeric catechols is based on 'protected' catechols (*e.g.*, veratrol derivatives) with final deprotection,[8] which would increase the number of synthetic stages. Earlier the synthesis of unprotected functionalized 3,5-di-*tert*-butylcatechols by the Michael reaction[9] as well as the application of 4,6-di-*tert*-butyl-2,3-dihydroxybenzaldehyde[10] and 4,6-di-*tert*-butyl-3-(methoxymethyl)catechol[11] **1** as building blocks in reactions with diamines and 1,3,5-trimethoxybenzene, respectively, were reported.



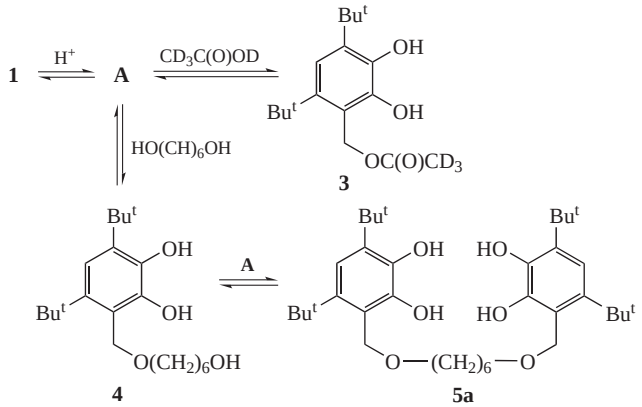
Scheme 1

Here, a simple one-step metal free catalytic method for the synthesis of new sterically hindered bis-catechols with diol spacers between catechol fragments is reported.

Previously, catechol **1** was synthesized by the reduction of 4,6-di-*tert*-butyl-2,3-dihydroxybenzaldehyde in MeOH solution followed by treatment of the reaction mixture with sulfuric acid,[12] when catechol benzylic alcohol **2** was generated *in situ* and underwent etherification with excess MeOH (Scheme 1). Apparently, the intermediate in this reactions was benzylic carbocation **2** (a protonated form of *o*-quinonemethide[13]) which can trap O-nucleophiles[14] used in excess. As for diols, linked bis-catechols could not be obtained by this procedure for statistic reasons.

Earlier we have found that ether **1** can be used for alkylation of electron-rich (het)arenes under the mild conditions (AcOH, 50 °C).[11] Likewise, we anticipitated that compound **1** can be coupled with diols leading to bis-catechols according to trans-etherification mechanism involving carbocations **A** (see Scheme 1).

This reaction is reversible and acid-catalyzed.† The dissolution of catechol **1** in a mixture $CDCl_3$–AcOH-d_4–hexane-1,6-diol leads to the generation of carbocation **A** in the system (Scheme 2).



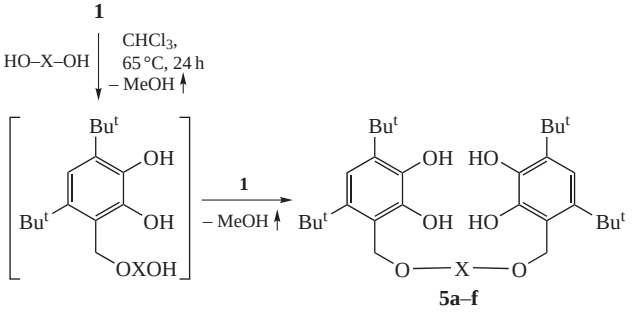
Scheme 2

† Description and calculation of the kinetic experiment are given in Online Supplementary Materials.

The carbocation **A** reacts non-selectively with all O-nucleophiles **1**, **3**, **4** and **5a**, present in the system, giving in 2 h an equilibrium mixture of starting **1**, acetate **3**, and monoether **4** with bis-catechol **5a** in a ratio of 3 : 1 : 2.6. The decrease in the AcOH-d_4 content caused deceleration of the process. However, it is worth noting that the content of the products of trans-etherification increases. In the absence of acid, the reaction proceeded slowly and stopped completely in the presence of basic triethylamine. However, it seemed unreliable to achieve high yield of the bis-product upon raising amounts of acid additive.

As the reaction could proceed in the absence of acetic acid (being either an additional nucleophile), it seemed reasonable to simplify the procedure and to accomplish successive alkylation of both hydroxy groups of diol (Scheme 3). The conversion of ether **1** was 15% after 1 h at 45 °C in $CDCl_3$ (^{1}H NMR data). Most probably, compound **1** itself catalyzed the trans-etherification. To shift the equilibrium towards the products, it was necessary to remove methanol from the system. Heating the mixture of compound **1** with α,ω-alkanediols in a molar ratio 2 : 1 at 65 °C in $CHCl_3$ with slow evaporation of MeOH cleanly afforded bis-catechols **5a–f** (see Scheme 3).‡ The presence of an acid as homogeneous catalyst (AcOH-d_4) did not allow us to reach high yields of the product, under acid-free conditions the yields of bis-catechols **5a–f** reached 60–87%.

Bis-catechols **5a–f** were isolated by recrystallization from *n*-hexane and characterized by NMR and IR spectroscopy. The crystal structures of compounds **5c**,**d**,**f** were confirmed by X-ray diffraction analysis.§



a X = $(CH_2)_6$, 81% **d** X = $(CH_2)_3$, 87%
b X = $(CH_2)_5$, 82% **e** X = $(CH_2)_2$, 80%
c X = $(CH_2)_4$, 86% **f** X = $(CH_2)_2O(CH_2)_2$, 60%

Scheme 3

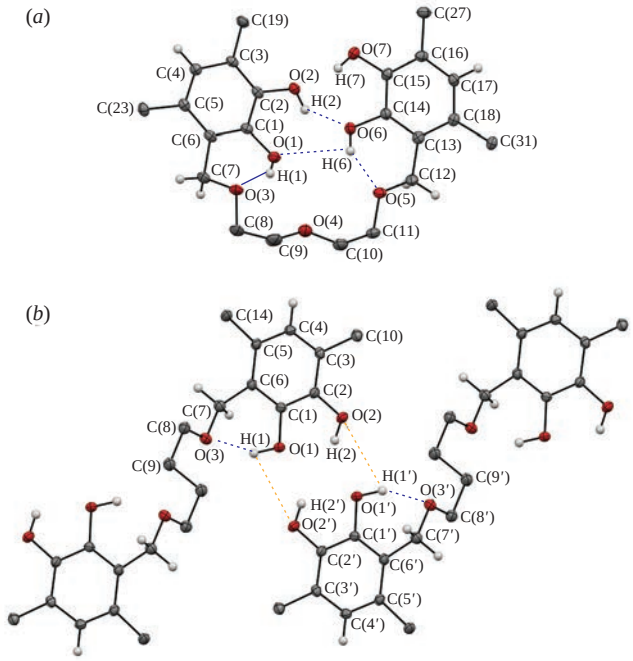


Figure 1 The molecular structures of compounds (*a*) **5f** and (*b*) **5c**. The thermal ellipsoids are given with a 30% probability. Hydrogen atoms (with the exception of OH groups) are not shown for clarity.

The molecular structures of compounds **5c** and **5f** are shown in Figure 1 and that of **5d** is given in Online Supplementary Materials. Two types of H-bonds (intra- and intermolecular) are observed in crystals. Intramolecular H-bonds fix the conformation of catechol ethers. The oxygen atom O(3) of the ether fragment is turned towards the OH groups of the catechol fragment: the dihedral angles O(3)–C(7)–C(6)–C(1) are in the range of 36.0–65.3°, and the distances O(1)···O(3) [and also O(4)···O(5) in **5d**, O(5)···O(6) in **5f**] are 2.57–2.83 Å. The obtained values are significantly less than the analogous distance in 4,6-di-*tert*-butyl-3-(methoxymethyl)-*o*-benzoquinone (the distance O(2)···O(3) is 3.07 Å, and the angle O(3)–C(7)–C(6)–C(1) is 77.8°). For quinone, these H-bonds are absent.[12]

According to ^{1}H NMR studies in DMSO-d_6, catechol moieties in all the obtained compounds are equivalent, namely the singlet signals from Bu^t groups are found at 1.28–1.29 and 1.31–1.32 ppm, from CH_2 groups at 4.63–4.70 ppm, the signal of C_{Ar}–H at 6.69–6.71 ppm. In addition, OH group signals at 7.79–7.81 and

‡ *General procedure for the preparation of bis-catechols* **5a–f**. Diol (2.5 mmol) and 4,6-di-*tert*-butyl-3-(methoxymethyl)catechol **1** (1.33 g, 5 mmol) were dissolved in $CHCl_3$ (20 ml) and this was refluxed for 24 h with gradual evaporation of the mixture to 10 ml. Then the reaction mixture was cooled and the solvent was fully removed. The residue was recrystallized from *n*-hexane to afford white crystalline powders.

For characteristics of bis-catechols **5a–f**, see Online Supplementary Materials

§ *Crystal data for* **5c**,**d**,**f**.

Crystals of **5c** ($C_{34}H_{54}O_6$, M = 558.77) are monoclinic, space group $P2_1/c$, a = 9.5182(7), b = 15.4117(9) and c = 11.1199(8) Å, β = 93.932(7)°, V = 1627.36(19) Å^3, Z = 2, d_{calc} = 1.140 g cm^{-3}, μ = 0.076 mm^{-1}, F(000) = 612, 24478 reflections collected, 3191 independent reflections (R_{int} = 0.0429). Final R indices: R_1 = 0.0401 [$I > 2\sigma(I)$], wR_2 = 0.1031 (all data), GOF = 1.033. Largest diff. peak/hole: 0.291/–0.198 e Å^{-3}.

Crystals of **5d** ($C_{33}H_{52}O_6$, M = 544.74) are triclinic, space group P-1, a = 15.2122(5), b = 15.2891(5) and c = 16.3234(5) Å, α = 66.5230(1)°, β = 66.0510(1)°, γ = 84.7040(1)°, V = 3171.51(18) Å^3, Z = 4, d_{calc} = = 1.141 g cm^{-3}, μ = 0.077 mm^{-1}, F(000) = 1192, 28797 reflections collected, 12420 independent reflections (R_{int} = 0.0247). Final R indices: R_1 = 0.0403 [$I > 2\sigma(I)$], wR_2 = 0.1033 (all data), GOF = 1.038. Largest diff. peak/hole: 0.238/–0.227 e Å^{-3}.

Crystals of **5f** ($C_{34}H_{54}O_7$, M = 574.77) are orthorhombic, space group $P2_12_12_1$, a = 10.4399(4), b = 11.7539(6) and c = 27.3482(11) Å, V = 3355.9(3) Å^3, Z = 4, d_{calc} = 1.138 g cm^{-3}, μ = 0.078 mm^{-1}, F(000) = 1256, 57720 reflections collected, 9785 independent reflections (R_{int} = 0.0360). Final R indices: R_1 = 0.0405 [$I > 2\sigma(I)$], wR_2 = 0.0967 (all data), GOF = 1.048. Largest diff. peak/hole: 0.255/–0.247 e Å^{-3}.

The X-ray data were collected on an automatic Bruker D8 QUEST (**5d**,**f**) and an Agilent Xcalibur E (**5c**) diffractometers (MoKα-radiation, ω-scan technique, λ = 0.71073 Å) at 100 K. The intensity data were integrated by SAINT[15] and CrysAlisPro[16] programs for **5d**,**f** and **5c**, respectively. SADABS[17] (**5d**,**f**) and SCALE3 ABSPACK[18] (**5c**) were used to perform area-detector scaling and absorption corrections. The structures were solved by a direct method with a dual-space algorithm using SHELXT program[19] and were refined on F^2 using SHELXTL[20] package. All non-hydrogen atoms were found from Fourier-synthesis of electron density and were refined anisotropically. The hydrogen atoms were placed in calculated positions and refined in the riding model. H atoms of the catecholato OH groups were located from difference Fourier synthesis and refined isotropically.

CCDC 1844624–1844626 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

7.92–7.96 ppm indicate the presence of the intramolecular hydrogen bonds of medium strength which are retained in solution. The ^{13}C NMR spectroscopy data also confirm the equivalence of catechol fragments in solution.

In summary, 4,6-di-*tert*-butyl-3-(methoxymethyl)catechol acts as the O-alkylating agent of alcohols in the trans-etherification reaction under mild conditions. This acid-catalyzed reaction is reversible and can be used for the synthesis of oligomeric 3,5-di-*tert*-butylcatechols and for the acid-free preperation of bis-catechols from α,ω-alkanediols. These compounds seem promising as ligands in coordination and supramolecular chemistry, inhibitors of free radical processes and starting materials for the synthesis of oligomeric photoinitiators.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.031.

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