Synthesis of Triscatechol Derivatives – Building Blocks with an Idealized C₃-Symmetry for Metallo-Supramolecular Chemistry

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Abstract: A series of triscatechols with an idealized axis of C₃-symmetry were synthesized. Hereby amide, imine or direct bonds are introduced as linkage between the catechol units and various C₃-symmetric backbones.

Key words: Pd-coupling, amide, imine, catechol, ligand

Metallo-supramolecular chemistry is a still growing field of research in which structural as well as functional aspects play an important role.¹ In order to perform systematic studies, it is essential to have simple and versatile entries to prepare appropriate ligands which can be introduced into metal-directed self-assembly processes.²

Just recently, we described the formation of a huge supramolecular tetrahedron ¹ (Figure 1) which is assembled from four rigid planar triscatecholate ligands ² and four titanium(IV) ions in the presence of potassium, sodium or lithium cations. Due to its size, the tetrahedron is able to encapsulate guests in its interior and exchange of the guest species can be investigated.³

In addition, we found that the flexible ligand ³ as well is able to form a related tetrahedron if no influences are active which favor the formation of other structures.⁴ The conformation at the imine unit plays a crucial role in the control of the assembly of different supramolecular aggregates.⁵

In metal complexes catechol imines usually prefer the conformation A with the lone pair at nitrogen directing away from the negatively charged catecholate oxygen atoms. However, this repulsion can be compensated by binding with metal ions (A’).⁶ A similar conformational situation as in A’ is observed for catecholate amides B with a hydrogen bond connecting the nitrogen and oxygen atom.⁶ Due to the preferred conformations, A adopts a more open (‘bigger’) structure as A’ or B does. The geometry of an aryl catechol C can be described as ‘somewhere in between’ (Figure 2).

In the free ligands, the situation is different. In the imine, hydrogen bonding (or partial hydrogen transfer) occurs between the internal hydroxyl group and the imine nitrogen D.⁵ Similar hydrogen bonding is observed in the catechol amides between OH and the amide carbonyl oxygen atom E.⁶ In aryl catechols there is no significant conformational difference between the coordinated ligand C and the uncoordinated one F (Figure 2).

In this paper we describe the preparation of a series of triscatechol ligands, which in their idealized form possess an axis of C₃-symmetry.⁷ Hereby catechol imines are prepared by imine formation (e.g. following a Sonogashira coupling reaction), catecholate amides are obtained by simple condensation, and aryl catechol derivatives are formed by Suzuki coupling.

Catechol Amides

A triscatechol amide ⁴ with an axis of C₃-symmetry was described by Raymond et al. and a corresponding tetranu-
clear tetrahedral metal complex was obtained by self-assembly. However, ligand 4 is rather small which leads to a metal complex with a cavity, which is too small for the encapsulation of guest species.8 Therefore, we prepared the larger derivative 5 by condensation of tris(4-aminophenyl)amine (6) with three equivalents of 2,3-dimethoxybenzoic acid (7) by activation with HBTU [O-(1-benzotriazolyl)-N,N,N',N'-tetramethyluronium hexafluorophosphate] and ethyldiisopropylamine.9 The obtained protected compound 8 is reacted with BBr3 to yield the unprotected ligand 5 in 95%10 (Scheme 1). Ligand 5 and its precursor 8 are characterized by standard methods.

**Catechol Imines**

The preparation of compound 3 from tris(2-aminooethyl)amine and 2,3-dihydroxybenzaldehyde (10) was already described by Vigato et al.11 The catechol imine 2 analogously is formed by simple condensation of tris(4-aminophenyl)amine with three equivalents of 2,3-dihydroxybenzaldehyde (10) in methanol. The product precipitates and can be isolated by filtration. Thus, the triscatechol imine 2 is obtained in 85% yield.

The triscatechol imine 11 is obtained starting from 1,3,5-tribromobenzene. In a Sonagishira coupling reaction, which was published recently, three equivalents of 4-alkylaniline are attached to the 1,3,5-benzene platform in 62% yield in the presence of bis(triphenylphosphane) palladium dichloride and copper(I) iodide.12 The thus obtained triamine 9 is reacted with the aldehyde 10 in methanol, as was described for the preparation of 2 and 3, and the ligand 11 is obtained in 86% as an orange solid (Scheme 2). Compound 11 represents a large and rigid triscatechol imine ligand, which is even bigger than ligand 2.
The hydrogen-bonding interactions, which are shown in Figure 2, D and E, are reflected in the $^1$H NMR chemical shifts of 5, 2, 3, or 11 in DMSO-$d_6$. The signal of the OH groups in 3-position is shifted to low field due to hydrogen bonding to the neighboring OH-group in 2-position. The resonances appear at $\delta = 9.90$ (5), 9.17 (2), 8.80 (3) and 9.29 (11). Additionally, very strong hydrogen bonding occurs between OH in 2-position and either the imine nitrogen or the carbonyl oxygen, resulting in shifts $\delta = 11.80$ (5), 13.30 (2), 13.71 (3) and 12.93 (11). The pronounced low field shift of the signal in case of the imines compared to the amides represents a partial proton transfer from hydroxide to the imine nitrogen,5,13 which is observed in many salicyl imine derivatives (vide infra).

We were able to obtain crystals of compound 3 which were suitable for an X-ray structure analysis (Figure 3). In the solid state 3 adopts a bowl shaped arrangement with the triethylamine moiety defining the curvature of the bowl and the three catechol imines forming the wall. One of the three catechol imine units adopts a form as represented by structure D. Here the distances within the N$\cdots$H–O system are 1.09 Å (H–O) and 1.54 Å (N$\cdots$H). The other two catechols show a structure, which can be described as the keto enamine D’. Proton transfer between OH and =N occurs, leading to short N–H distances of 0.90 and 0.92 Å, while the distances between O and H are long with 1.84 and 1.78 Å, respectively. Proton transfer in the phenol imine/keto enamine system is well known and leads to thermo- as well as photochromic behavior of such compounds.5,11,13

![Figure 3](image_url) Solid-state structure of 3 and two different forms of the catechol imine units as observed in the solid state

**Catechol Aryl Derivatives**

Catechol aryl derivatives are prepared by Suzuki coupling reaction of 2,3-dimethoxyphenylboronic acid (12)14 with the tribromoaryl derivatives 13 and 14 in the presence of Pd(PPh$_3$)$_4$ and Na$_2$CO$_3$ in toluene–ethanol.15 After recrystallization from methanol, we obtained the ligand precursors in 71% (15) or 88% (16) yield, respectively. The methyl ether groups of compounds 15 and 16 are cleaved by reaction with BBr$_3$ in dichloromethane.10 Hereby, the smaller triscatechol 17 is isolated in 97% yield, while the bigger derivative 18 is obtained in 98% (Scheme 3).

![Scheme 3](image_url) Preparation of the triscatechol aryl derivatives 17 and 18

In conclusion, we have presented the preparation of three different types of triscatechol ligands with catechol amide, imine, or aryl connectivity. The derivatives possess an axis of C$_3$-symmetry and they should be appropriate building blocks for the metal-directed self-assembly of supramolecular tetrahedra.

The different compounds possess edges of different lengths of the idealized triangular structure (which is represented by the distance between two hydrogen atoms in 4-position of two catechol moieties). Models of the ligands show that this size varies from 11 to 27 Å (Figure 4).
While we already could show that 2 and 3 form molecular tetrahedra, coordination studies with the other ligands are currently performed in our laboratories. The formation of tetrahedra of varying size should enable a fine tuning of the interaction with different guest species.

$^1$H and $^13$C NMR spectra were recorded on a Varian Inova 400 spectrometer. FT-IR spectra were recorded by diffuse reflection (KBr) or neat on a Bruker IFS spectrometer. Mass spectra (EI, 70 eV; FAB) were taken on a Finnigan MAT 95 or 212 mass spectrometer. Elemental analyses were obtained with a Heraeus CHN-O-Rapid analyzer. Melting points: Büchi B-540 (uncorrected). The compounds 6,14 9,15 and 1216 were prepared as described in the literature.

$^{N,N',N''-(Nitrilotri-4,1-phenylene)tris(2,3-dimethoxybenzamide}}$ (8)

2,3-Dimethoxybenzoic acid (7; 188 mg, 1.03 mmol), HBTU (470 mg, 1.24 mmol) and ethyldiisopropylamine (147 mg, 1.14 mmol) were dissolved in MeCN (25 mL). Tris(4-aminophenol)amine (6; 100 mg, 0.34 mmol) was added after 20 min. The mixture was stirred at r.t. for 2 d and the solvent was removed in vacuo. The residue was dissolved in EtOAc and the organic phase was dried (MgSO$_4$) and the solvent was removed in vacuum to obtain 210 mg (78%) of 8 as a green solid; mp 192 °C (dec.).

IR (KBr): 3416, 1619, 1504, 1462, 1366, 1322, 1273, 1208, 1028, 871, 836, 781, 734, 558 cm$^{-1}$. MS (EI): $m/z=212$ [M$^+$].

$^{N,N',N''-(Tri(2,3-dihydroxybenzylidene)-2,2',4',4'-triminotriphenylamine}}$ (2)

Yield: 442 mg (85%); yellow solid.

IR (KBr): 3416, 1619, 1504, 1462, 1366, 1322, 1273, 1208, 1028, 871, 836, 781, 734, 558 cm$^{-1}$. MS (EI): $m/z=650$ ([M$^+$]).

$^{N,N',N''-(Tri(2,3-dihydroxybenzylidene)-2,2',2'-triminotriphenylamine}}$ (3)

Yield: 442 mg (85%); yellow solid.

IR (KBr): 3416, 1619, 1504, 1462, 1366, 1322, 1273, 1208, 1028, 871, 836, 781, 734, 558 cm$^{-1}$. MS (EI): $m/z=506$ ([M$^+$]).

N,N,N’-Tri(2,3-dihydroxybenzylidene)-4,4’,4”-(1,3,5-benzene-triyltri-L-2-ethylenethiobenzene)(11)
Yield: 160 mg (86%); orange solid; mp 187 °C (dec.); Rf = 0.19 (CH2Cl2–MeOH, 15:1).
IR (KBr): 3437, 1620, 1574, 1503, 1460, 1365, 1272, 1207, 1070, 1029, 873, 837, 780, 732, 568 cm⁻¹.
1H NMR (DMSO-d6, 400 MHz): δ = 12.93 (br, 3 H), 9.29 (br, 3 H), 8.98 (s, 3 H), 7.81 (s, 3 H), 7.71 (d, J = 8.5 Hz, 6 H), 7.52 (d, J = 8.5 Hz, 6 H), 7.14 (dd, J = 7.9, 1.5 Hz, 3 H), 6.98 (dd, J = 7.9, 1.5 Hz, 3 H), 6.82 (d, J = 7.9 Hz, 3 H).
13C NMR (DMSO-d6, 100 MHz): δ = 164.9 (CH), 149.8 (C), 148.8 (C), 146.1 (C), 143.3 (CH), 124.2 (C), 123.4 (C), 123.1 (CH), 122.4 (C), 119.9 (CH), 119.8 (CH), 119.4 (CH), 114.1 (CH), 91.3 (C), 88.7 (C).
MS (EI): m/z = 783 ([M]+).

Protected Trisocatechol Aryl Derivatives 15,16; General Procedure
The ether-protected catechol aryls (15,16) (1 equiv, ca. 0.4 mmol) were dissolved in CH2Cl2 (20 mL). To this solution was added BBr3 (10 equiv) with cooling in an ice bath. After overnight at r.t., the mixture was quenched with MeOH, evacuated in vacuum and the residue was dissolved in EtOAc. After washing with H2O, the organic phase was dried (MgSO4) and the solvent was removed in vacuum.

5”-(2’,3’-Dimethoxy-4-biphenylyl)-2,2”’,5,5”’-tetramethoxy-1’,1”’,4’,4”’,1”’’’,4’’’,1’’’’’,5’’’’’’’,5’’’’’’’’’’-quinquephenyl (16)
Yield: 235 mg (71%); grey solid; mp 188 °C (dec.).
IR (KBr): 3438, 1590, 1519, 1469, 1386, 1359, 1328, 1300, 1266, 1235, 1209, 1157, 1120, 1069, 1015, 893, 830, 781, 731, 679, 591, 534 cm⁻¹.
1H NMR (CD3OD, 400 MHz): δ = 7.88 (s, 3 H), 7.77 (d, J = 8.4 Hz, 6 H), 7.71 (d, J = 8.4 Hz, 6 H), 6.85 (d, J = 8.0, 1.9 Hz, 3 H), 6.81 (dd, J = 8.0, 1.9 Hz, 3 H), 6.76 (t, J = 8.0 Hz, 3 H).
13C NMR (CD3OD, 100 MHz): δ = 152.9 (C), 146.5 (C), 137.5 (C), 135.8 (C), 128.9 (CH), 123.8 (CH), 122.7 (CH), 111.4 (CH), 60.6 (CH3), 55.9 (CH3).
MS (EI): m/z = 630 ([M]+).
Anal. Calcd for C24H18O6·2 H2O: C, 75.66; H, 4.79. Found: C, 75.38; H, 4.76.

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References


(19) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-232929. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, CambridgeCB2 1EZ, UK [fax: +44 (1223) 336 033, e-mail: deposit@ccdc.cam.ac.uk].