Preparation of Amino Acid-Bridged Dicatechol Ligands for Dinuclear Titanium(IV) Complexes

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Abstract: Amino acid-bridged dicatechol ligands 2a–e-H₄ were prepared by peptide coupling reactions. Under special conditions, an unusual BBr₃-promoted amide to methyl ester transformation was observed for the asparagine and glutamine side chain functions. The ligands were used in coordination studies with titanium(IV) ions in the presence of an alkali metal carbonate. Double-stranded complexes Li₂[(2a–e)-H₄(OR)₂]₂(OR)₂Ti₂ which have alcoholate coligands (R = CH₃, C₂H₅, C₃H₅) bridging the metals were selectively formed with lithium counter cations. On the other hand, with potassium or sodium cations triple-stranded complexes M₄[(2b–e)-H₄(OCMe₂)₃]₃Ti₂ (M = Na, K) were obtained in addition to the double-stranded M₂[(2b–e)-H₄(OCMe₂)₂]₂(OR)₂Ti₂. The ligands form dinuclear complexes [((1a–e)-H₄)₂Ti₂(OCH₃)₂]²⁻ with titanium(IV) ions in the presence of an alkali metal carbonate as base in methanol solution. Amino acids form a chiral pocket in which the alkoxide coligands were fixed by coordination to the two metal centers. Triple-stranded helicate-type complexes [((1a–e)-H₄)₂(OCMe₂)₃]²⁻ could not be observed with the ligands 1.⁵,⁶

Key words: peptide coupling, amino acid, ligands, metal complex, template effect

Introduction

Enzymes are nature’s molecular machines to catalyze chemical reactions which are essential for the functioning of organisms on a molecular level. Despite their high complexity they are made from a small pool of approximately 20 amino acid building blocks. Hereby binding of substrates occurs by hydrogen bonding, electrostatic, hydrophobic/hydrophilic and charge-transfer interactions with amino acid side chains which are appropriately arranged on the surface or in cavities of the enzyme.¹ In metalloenzymes, the metal centers are not only able to support a specific folding of the peptide chains, but also might introduce an additional metal-coordination binding site for substrates or even a catalytically active center.² Recently we described the preparation of the dicatechol derivatives 1-H₄, which possess the nonpolar, hydrophobic amino acids glycine (a), alanine (b), valine (c), leucine (d) or phenylalanine (e) as spacers.³ The derivatives 1 form dinuclear complexes [((1a–e)-H₄)₂(OCMe₂)₂]²⁻ with titanium(IV) ions in the presence of an alkali metal carbonate as base in methanol solution (Figure 1). They have some common structural features with the active centers of dinuclear metalloenzymes.⁴ The amino acids form a chiral pocket in which the alkoxide coligands were fixed by coordination to the two metal centers. Triple-stranded helicate-type complexes [((1a–e)-H₄)₂(OCMe₂)₃]²⁻ could not be observed with the ligands 1.⁵,⁶

Figure 1  Amino acid-bridged dicatechol ligands 1a–e-H₄ and a complex, which is formed from the phenylalanine-bridged ligand 1e. Only the thermodynamically most favored isomer of [(1e)₂Ti₂(OCH₃)₂]²⁻ out of seven possible isomers is shown.

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All our recent synthetic, metal coordination and structural studies were performed with nonpolar, hydrophobic amino acids as spacers of the ligands 1a–e-H₄. However, to enable some additional weak secondary interactions between the amino acids and functionalized alkoxide coligands, we need to substitute the alkyl-bearing amino acids by others, which possess appropriate functionalities in the side chain.

In this study we present the synthesis of seven new amino acid-bridged dicatechol ligands 2a–e-H₄, which bear polar, uncharged (amide: 2a, 2b; ester: 2a', 2b'); phenol: 2c), basic (imidazole: 2d), or conformationally constrained (proline: 2e) amino acids as spacers (Figure 2). Preliminary coordination studies which were monitored by FT-ICR MS show that the ligands form dinuclear metal complexes with titanium(IV) ions and that we are able to introduce different types of alkoxides as coligands. For the first time we observed triple-stranded complexes which are formed in addition to the double-stranded ones.

**Preparation of the Amino Acid-Bridged Dicatechols 2a–e-H₄**

The earlier preparation of the ligands 1a–e-H₄ was done by use of the unprotected amino acid. First 2,3-dimethoxybenzoic acid (7) and then 2,3-(dimethoxy)benzylamine (4) were attached. The reactions were performed in DMF/CH₂Cl₂ with DCC/NHS (dicyclohexylcarbodiimide/N-hydroxysuccinimide) or EDC/HOBt [ethyl(dimethylaminopropyl)carbodiimide/hydroxybenzotriazole] as coupling reagent. Following this protocol we obtained the compounds 1a–e-H₄ with up to 10–20% racemization at the α-position of the amino acid residue.  

An independent study with isoleucine as amino acid revealed that the partial epimerization takes place during the second coupling step. To suppress this epimerization, we tested several solvents and found out that, e.g. acetone leads to a full epimerization during the second amide coupling.

The epimerization can be suppressed by inverting the coupling procedure. Therefore, in our new approach we started with an N-Fmoc-protected amino acid 3 and attached 2,3-(dimethoxy)benzylamine (4) to the C-terminus. After removal of the Fmoc group, 2,3-dimethoxybenzoic acid (7) was connected to the C-terminus. In preliminary studies with isoleucine derivatives it was found, that the use of HBTU/Hünig’s base (i-Pr₂NEt)³ as coupling reagents in acetonitrile as solvent was most appropriate for amide bond formation without epimerization at the α-carbon.

Following this strategy, we prepared the ligands 2a–d-H₄ (Scheme 1). We used Fmoc-protected amino acids (Fmoc-Asn-OH: 3a, Fmoc-Gln-OH: 3b, Fmoc-Tyr(Me)-OH: 3c, Fmoc-His(Mtt)-OH: 3d) as starting materials. Hereby the tyrosine derivative 3c bore an additional methyl group to protect the phenolic OH, while the imidazole of 3d was protected by an Mtt (methyltrityl) group. Coupling with 2,3-(dimethoxy)benzylamine (4) proceeded smoothly by use of HBTU/Hünig’s base in acetonitrile to afford the derivatives 5a–d in 82–95% yield. The Fmoc protecting group of 5 was removed by reaction with piperidine⁴ in acetonitrile. The advantage of this solvent was that we could obtain pure amines by simple extraction of the reaction mixture with hot n-hexane. The amines 6a–d remained in the acetonitrile phase and were obtained in very high yields (91%–quant.).

A second amide coupling with HBTU/Hünig’s base was performed in acetonitrile to attach 2,3-dimethoxybenzoic acid (7) to the amines 6. The protected ligand precursors 8a–d were obtained in 63–96% yield. The methyl ethers of 8a,b were cleaved by reaction with BBr₃¹¹ in chloroform to give the asparagine- (2a-H₄, 73%) and glutamine-bridged ligands (2b-H₄, 80%). However, this procedure highly depends on the reaction conditions and the work-up of the reaction mixture. Following the general procedure for methyl ether cleavage, side products 2a'-H₄ and 2b'-H₄ (vide infra) were observed. However, 2a-H₄ and 2b-H₄ were obtained by reaction with
BBr₃ at 0 °C followed by work-up with ethanol instead of methanol.

The formation of the side products could be maximized by performing the cleavage and quenching the reaction mixture at high temperatures. Hereby an amide to methyl ester transformation occurred at the side chain of the amino acid residues (Scheme 2). In case of the asparagine bridged derivative 8a, the corresponding ester 2a'-H₄ was observed as the minor component of a 1:4 mixture with 2a-H₄. We were able to obtain the corresponding ester of the glutaric acid derivative 2b'-H₄ in 60% yield in pure form.

Scheme 2  BBr₃-promoted amide to ester transformation.

The Mtt protecting group of 8d was not affected by BBr₃. Only the methyl groups were removed and the intermediate 9 was formed in 43%. However, ligand 2d-H₄ was finally obtained in quantitative yield by cleavage of the Mtt-group of 9 with trifluoroacetic acid and triisopropylsilane in dichloromethane (Scheme 1).

Due to solubility problems, the methyl ethers of the tyrosine derivative 8c had to be removed by reaction with BBr₃ in chloroform. Compound 2c-H₄ was obtained in 98% yield by concomitant ether cleavage at the catechol as well as at the tyrosine moiety.

Scheme 1  Preparation of the asparagine, glutamine, tyrosine, and histidine-bridged dicatechol ligands 2a–e-H₄.

Scheme 3  Preparation of the proline-bridged ligand 2e-H₄.
Scheme 3 shows that the sterically constrained proline-bridged ligand 2e-H₄ was obtained as was described for the corresponding derivatives 2a–d-H₄. The attachment of the amine 4 to Fmoc-protected proline 3e proceeded in 99% yield to form 5e. After quantitative cleavage of the Fmoc-group, the benzoic acid 7 was coupled to 6e and the ligand precursor was obtained in 87% yield. Final ether cleavage afforded the ligand 2e-H₄ in 84%.

Preparation of Amino Acid-Bridged Dinuclear Titanium(IV) Complexes

We investigated the coordination behavior of the ligands 2a–e-H₄ with titanium(IV) ions in methanol and tested some selected examples in the presence of ethanol or allyl alcohol as solvent (Scheme 4). In most cases ¹H NMR spectroscopy showed complicated and broad spectra, which were due to the presence of many different species. As an exceptionally well resolved spectrum the one of Li₂[(2c)₂(OCH₃)₂Ti₂] in methanol-d₄ has to be mentioned which shows the presence of only one isomer (see Experimental section).

Because the NMR spectra were often not sufficiently informative, we performed extensive ESI MS studies, to find out if the complex formation was successful and what kind of species was formed. The results are listed in Table 1. Coordination studies of the ligands 2a–e-H₄ with titanium(IV) ions in the presence of lithium carbonate in methanol resulted in the exclusive formation of Li₂[(2a–e)₂(OCH₃)₂Ti₂]. Negative ESI MS showed the corresponding peaks for the dianions [(2a–e)₂(OCH₃)₂Ti₂]²⁻ and the monoanions Li[(2a–e)₂(OCH₃)₂Ti₂]⁻ with correct isotopic pattern.

If sodium or potassium carbonate were used as base, the corresponding dinuclear double-stranded complexes [(2b,c,e)₂(OCH₃)₂Ti₂]²⁻ were observed as well by ESI MS (Figure 3). However, the potassium derivatives of 2b showed a characteristic peak for the triple-stranded K₂[(2b)₃Ti₂]²⁻ at m/z = 686. In case of the sodium and potassium salts of the titanium complexes of 2c and 2e always the triple-stranded complex [(2c,e)₃(OCH₃)₂Ti₃]⁴⁻ was observed in addition to the double-stranded [(2b,c,e)₂(OCH₃)₂Ti₂]²⁻. For the glutaric ester only double-stranded complexes [(2b)₂(OCH₃)₂Ti₂]²⁻ are observed independent of the counter ions.

Our observations show that a specific formation of the double-stranded coordination compounds with two coligands is only guaranteed, if lithium is the counter cation. This template effect by the small Li⁺ cation is not understood yet, but has to be considered in the preparation of

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Table 1 Results of Negative ESI MS Spectrometry of the Complexation Studies of Ligands 2a–e-H₄ with Titanium(IV) Ions in the Presence of Alkali Metal Carbonate with Methanolate (CH₃O), Ethanolate (C₂H₅O), or Allyl Alcoloholate (C₃H₅O) as Coligands

<table>
<thead>
<tr>
<th>L₁/X/L₂</th>
<th>X₂[(L₁)₂(L₂)₂Ti₂] (m/z)</th>
<th>X₄[(L₁)₃Ti₂] (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>– 2X⁺</td>
<td>– X⁺ – 3X⁺ – 2X⁺ – X⁺</td>
<td></td>
</tr>
<tr>
<td>2a/Li/CH₃O</td>
<td>464 – 935 – – –</td>
<td></td>
</tr>
<tr>
<td>2b/Li/CH₃O</td>
<td>478 – 963 – – –</td>
<td></td>
</tr>
<tr>
<td>2b/Na/CH₃O</td>
<td>478 – 979 – – –</td>
<td></td>
</tr>
<tr>
<td>2b/K/CH₃O</td>
<td>478 – 995 – 686 –</td>
<td></td>
</tr>
<tr>
<td>2b/Li/CH₃O</td>
<td>493 – 993 – – –</td>
<td></td>
</tr>
<tr>
<td>2b/Na/CH₃O</td>
<td>493 – 1009 – – –</td>
<td></td>
</tr>
<tr>
<td>2b/K/CH₃O</td>
<td>493 – 1025 – – –</td>
<td></td>
</tr>
<tr>
<td>2c/Li/CH₃O</td>
<td>513 – 1033 – – –</td>
<td></td>
</tr>
<tr>
<td>2c/Na/CH₃O</td>
<td>513 – 1049 474 722 1467</td>
<td></td>
</tr>
<tr>
<td>2c/K/CH₃O</td>
<td>513 – 1065 479 738 1515</td>
<td></td>
</tr>
<tr>
<td>2d/Li/CH₃O</td>
<td>– – 978 – – –</td>
<td></td>
</tr>
<tr>
<td>2e/Li/CH₃O</td>
<td>– – 901 – – –</td>
<td></td>
</tr>
<tr>
<td>2e/Na/CH₃O</td>
<td>447 – 917 408 623 1269</td>
<td></td>
</tr>
<tr>
<td>2e/K/CH₃O</td>
<td>447 – 933 – 639 1317</td>
<td></td>
</tr>
<tr>
<td>2b/Li/CH₃O</td>
<td>492 – 991 – – –</td>
<td></td>
</tr>
<tr>
<td>2e/Li/C₃H₅O</td>
<td>539 – 1085 – – –</td>
<td></td>
</tr>
<tr>
<td>2e/Li/C₃H₅O</td>
<td>473 – 953 – – –</td>
<td></td>
</tr>
</tbody>
</table>

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double-stranded complexes with coligands of the type \([\text{[(2)}\text{OR}2\text{Ti2]}\)]2–. In addition, we performed the complex formation of ligand 2b-H4 with titanium(IV) ions in ethanol in the presence of lithium carbonate, which smoothly produced \(\text{Li}_2[\text{[(2b)}\text{OC3H5}2\text{Ti2]}\)] containing bridging ethanolate coligands.

Allyl alcohol-bridged dinuclear titanium complexes \(\text{Li}_2[\text{[(2c,e)}\text{OC3H5}2\text{Ti2]}\)] were obtained, if the reaction of the ligands 2c,e-H4 with titanium(IV) and lithium carbonate proceeded in allyl alcohol as solvent. Here the purification of the complex salts had to be performed in allyl alcohol to prevent an exchange of the coligands.

**Conclusion**

In this paper, we have presented the preparation of amino acid-bridged dicatecholate ligands, which bear functional groups in the side chain. With our new procedure, the preparation proceeds smoothly with acceptable to good yields without racemization. All ligands specifically form double-stranded dinuclear coordination compounds.

Currently, we are investigating whether more functionalized coligands can be introduced and whether we finally can perform chemical reactions in the ligand sphere of our double-stranded dinuclear coordination compounds.

1H and 13C NMR spectra were recorded on a Varian Mercury 300 or Inova 400 spectrometer. FT-IR spectra were recorded by diffuse reflectance (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. FT-ICR ESI mass spectra were measured on a Bruker Bioapex II FTMS equipped with a 7 Tesla magnet. Elemental analyses were obtained with a Heraeus CHN-O-Rapid analyzer. Melting points: Büchi B-540 (uncorrected).

**Coupling of Fmoc-Amino Acids 3 with 2,3-(Dimethoxy)benzylamine (4); General Procedure**

To a solution of the Fmoc-protected amino acid derivative 3 (1 equiv) in MeCN (50–200 mL) were added HBTU (1.2 equiv) and disopropylethylamine (1.1 equiv). The mixture was stirred for 20 min at r.t. and 2,3-(dimethoxy)benzylamine (4; 1 equiv) was added. After 18–24 h at r.t., work-up was done by isolation of the precipitated product 5 by filtration and washing with cold MeCN. Eventually the precipitate can be dissolved in EtOAc, and the EtOAc layer was washed successively with aq NH4Cl, NaHCO3, H2O, and brine, dried (MgSO4) and the solvent removed in vacuum (Method A). If the product did not precipitate from MeCN, the solvent was removed and purification of the residue was done as described for method A (Method B).

**5a**

Method A: yield: 1.49 g (95%); colorless solid; mp 200 °C.

**5b**

Method A: yield: 2.44 g (87%); colorless solid; mp 194 °C.

**Synthesis 2005, No. 7, 1125–1135 © Thieme Stuttgart · New York**
Anal. Calcd for C_{29}H_{31}N_{3}O_{6}: C, 67.30; H, 6.04; N, 8.12. Found: C, 67.72; H, 6.00; N, 8.67.

Method B; yield: 1.67 g (82%); colorless solid; mp 188 °C.

IR (KBr): 3434, 3421, 3312, 1665, 1637, 1548, 1482, 1085, 1057, 988 cm\(^{-1}\).

Yield: 860 mg (ca. 100%); colorless solid; mp 128 °C.

IR (KBr): 3443, 3421, 3312, 1665, 1637, 1548, 1482, 1085, 1057, 988 cm\(^{-1}\).

Yield: 414 mg (91%); colorless solid; mp 128 °C.

IR (KBr): 3443, 3421, 3312, 1665, 1637, 1548, 1482, 1085, 1057, 988 cm\(^{-1}\).

Yield: 3.33 g (96%); colorless solid; mp 73 °C.

IR (KBr): 3443, 3421, 3312, 1665, 1637, 1548, 1482, 1085, 1057, 988 cm\(^{-1}\).

Yield: 7.35 (m, 2 H), 7.32 (s, 1 H), 7.31 (m, 5 H), 7.11 (m, 5 H), 6.97 (m, 3 H), 6.83 (d, J = 7.9 Hz, 2 H), 6.63 (s, 1 H), 4.45 (m, 2 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.65 (m, 1 H), 3.02 (m, 2 H), 2.35 (s, 3 H).

MS (FAB, DMSO): m/z = 345 [M + H]\(^{+}\).

Anal. Calcd for C_{29}H_{31}N_{3}O_{6}: C, 67.30; H, 6.04; N, 8.12. Found: C, 68.79; H, 6.03; N, 8.26.

Removal of the Fmoc-Protecting Group from 5; General Procedure

The Fmoc-protected compounds 5 (1 equiv) were suspended in MeCN (100 mL) and piperidine (6 equiv) was added. The mixture was stirred for 24 h at r.t. The MeCN phase was extracted with hot n-hexane (5 × 30 mL) and the MeCN was removed in vacuum to obtain the amines 6.
6c Yield: 543 mg (quant.); brown oil.

IR (neat): 3315, 3218, 1725, 1644, 1519, 1429 cm\(^{-1}\).

\[ ^1\text{H NMR (300 MHz, CDCl}_3\): } \delta = 7.98 (t, J = 8.0 Hz, 1 H), 6.64 (d, J = 8.0 Hz, 2 H), 4.44 (d, J = 6.0 Hz, 2 H), 3.85 (s, 3 H), 3.85 (s, 3 H), 3.73 (m, 1 H), 2.02 (m, 2 H), 1.91 (m, 2 H), 1.68 (m, 2 H).

\[ ^1^\text{C NMR (130 MHz, CDCl}_3\): } \delta = 170.8 (C), 152.8 (C), 148.0 (C), 123.9 (CH), 120.9 (C), 120.5 (CH), 60.5 (CH), 58.9 (CH), 56.5 (CH), 49.7 (CH\(_2\)), 39.7 (CH\(_2\)), 32.1 (CH\(_3\)), 26.9 (CH\(_3\)).

MS (EI): \text{m/z} = 265 \text{ [M + H]}^+.


8a Yield: 1.28 g (63%); colorless solid; mp 192 °C.

IR (KBr): 3419, 3291, 3256, 2180, 1663, 1636, 1534, 1481.51, 1434, 1267, 1214, 1084 cm\(^{-1}\).

\[ ^1\text{H NMR (300 MHz, DMSO-d}_6\): } \delta = 8.90 (br, 1 H, NH), 8.25 (t, 1 H, J = 6.2 Hz, NH), 7.40 (m, 1 H), 7.20 (m, 1 H), 6.95 (m, 4 H), 4.79 (dd, J = 8.1, 2.3 Hz, 1 H), 4.29 (d, J = 6.2 Hz, 2 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 2.60 (dd, J = 8.1 Hz, 2 H).

\[ ^1^\text{C NMR (130 MHz, DMSO-d}_6\): } \delta = 174.3 (C), 169.6 (C), 158.3 (C), 152.3 (C), 150.0 (C), 148.2 (C), 147.1 (C), 128.2 (C), 126.3 (CH), 124.1 (CH), 121.9 (CH), 120.4 (CH), 118.3 (CH), 114.9 (CH), 61.5 (CH), 60.4 (CH\(_3\)), 56.6 (CH\(_3\)), 56.5 (CH\(_3\)), 56.1 (CH\(_3\)), 50.6 (CH\(_3\)), 39.4 (CH\(_2\)), 37.5 (CH\(_3\)).

MS (ESI, pos): \text{m/z} = 446 \text{ [M + H]}^+.


8b Yield: 1.27 g (88%) of a colorless solid; mp 167 °C (dec.).

IR (KBr): 3299, 1662, 1626, 1539, 1429, 1355, 1332, 1172, 942, 989, 868 cm\(^{-1}\).

\[ ^1\text{H NMR (400 MHz, CDCl}_3\): } \delta = 7.04 (dd, J = 8.0, 1.6 Hz, 1 H), 6.99 (t, J = 8.0 Hz, 1 H), 6.97 (m, 1 H), 6.85 (m, 1 H), 4.79 (m, 1 H), 4.52 (m, 2 H), 3.77 (s, 3 H), 3.73 (s, 3 H), 3.68 (s, 3 H), 3.67 (s, 3 H), 2.15 (m, 2 H), 1.84 (m, 2 H).

\[ ^1^\text{C NMR (100 MHz, CDCl}_3\): } \delta = 176.0 (C), 171.2 (C), 165.7 (C), 152.6 (C), 152.4 (C), 147.7 (C), 146.7 (C), 131.1 (C), 125.6 (CH), 124.1 (CH), 121.8 (CH), 120.7 (CH), 120.4 (CH), 115.7 (CH), 111.7 (CH), 61.3 (CH\(_3\)), 60.4 (CH\(_3\)), 55.8 (CH\(_3\)), 55.5 (CH\(_3\)), 49.1 (CH\(_3\)), 38.2 (CH\(_2\)), 31.3 (CH\(_3\)), 29.3 (CH\(_3\)).

MS (EI): \text{m/z} = 460 \text{ [M + H]}^+.

Anal. Calcd for C\(_{26}\)H\(_{29}\)N\(_3\)O\(_8\); C, 74.98; H, 6.47; N, 9.99. Found: C, 73.99; H, 6.23; N, 10.15.

8c Yield: 400 mg (87%); yellow oil.

IR (KBr): 3266, 2945, 2837, 1653, 1633, 1512, 1479, 1271, 1082, 1001, 750 cm\(^{-1}\).

\[ ^1\text{H NMR (400 MHz, CD}_3\text{OD\): } \delta = 7.49 (m, 2 H), 7.07 (m, 3 H), 6.94 (t, J = 8.0 Hz, 1 H), 6.85 (t, J = 8.0 Hz, 1 H), 6.73 (d, J = 8.0 Hz, 2 H), 6.68 (m, 1 H), 4.78 (t, J = 6.8 Hz, 1 H), 4.37 (m, 2 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.70 (s, 3 H), 3.05 (m, 2 H).

\[ ^1^\text{C NMR (100 MHz, CD}_3\text{OD\): } \delta = 171.3 (C), 165.5 (C), 158.5 (C), 155.5 (C), 152.4 (C), 147.9 (C), 146.7 (C), 131.2 (C), 130.2 (C), 128.3 (C), 125.6 (CH), 124.2 (CH), 124.0 (CH), 121.0 (CH), 120.9 (C), 115.9 (CH), 113.8 (CH), 111.8 (CH), 61.5 (CH), 61.1 (CH), 60.3 (CH), 55.6 (CH), 55.5 (CH), 55.4 (CH), 38.1 (CH), 37.9 (CH).\)

MS (ESI, pos): \text{m/z} = 509 \text{ [M + H]}^+.

Cleavage of the Methyl Ethers 8a,b; Optimized Procedure

The derivatives 8a,b (1 equiv) were dissolved in CHCl₃ (10 mL). At 0 °C, BBr₃ (8 eq) was added and the suspension was stirred at r.t. for 24 h. The mixture was slowly hydrolyzed with EtOH (10 mL) at 0 °C. After the solvents were removed, the residue was dissolved in EtOAc and washed with H₂O and brine. The organic phase was dried (MgSO₄) and the solvent was removed to obtain 2a,b.

**2a-H₄**

Yield: 190 mg (73%); slightly brown solid; mp 72 °C.

IR (KBr): 3380, 2983, 1699, 1641, 1594, 1459, 1482, 1457, 1335, 1268, 1169, 743 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.19 (d, J = 7.4 Hz, 1 H), 6.94 (d, J = 7.4 Hz, 1 H), 6.75 (m, 4 H), 4.74 (t, J = 3.2 Hz, 2 H), 4.68 (m, 1 H), 2.99 (m, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 177.0 (C), 169.5 (C), 158.4 (C), 152.4 (C), 149.3 (C), 148.3 (C), 145.9 (C), 142.8 (C), 131.1 (C), 124.8 (CH), 122.6 (CH), 119.4 (CH), 118.9 (CH), 114.6 (CH), 114.3 (CH), 51.9 (CH), 38.4 (CH2), 35.6 (CH2).

MS (EI): m/z = 390 [M + H]+.

Anal. Calcd for C₁₉H₂₁N₃O₇: C, 56.57; H, 5.25; N, 10.42. Found: C, 56.83; H, 5.12; N, 6.64.

**2b-H₄**

Compound 8b (100 mg, 1 equiv) was dissolved in CH₂Cl₂ (10 mL). At r.t., BBr₃ (10 eq) was added and the mixture was refluxed for 48 h. MeOH was added to the hot mixture and refluxed for an additional 5 h. The solution was allowed to cool down and the solvents were removed in vacuum. The residue was dissolved in EtOAc and washed with H₂O and brine. The organic phase was dried (MgSO₄) and the solvent was removed under reduced pressure. So far it was not possible to obtain the product in pure form.

1H NMR spectrum shows a mixture of 20% of 2a-H₄ and 80% of 2b-H₄.

1H NMR (400 MHz, CDCl₃): δ = 7.23 (dd, J = 1.5, 7.9 Hz, 1 H), 6.98 (dd, J = 1.5, 7.9 Hz, 6.70 (m, 4 H), 4.77 (d, J = 3.5 Hz, 2H), 4.73 (m, 1 H), 3.65 (s, 3 H, 20% int), 3.15 (dd, J = 7.19 (d, J = 8.1 Hz, 1 H), 6.59 (m, 4 H), 4.55 (t, J = 5.4 Hz, 1 H), 4.26 (d, J = 8.2 Hz, 2 H), 3.52 (s, 3 H), 2.34 (m, 1 H), 2.26 (m, 1 H), 2.11 (m, 1 H), 1.98 (m, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 172.6 (C), 172.5 (C), 169.5 (C), 154.7 (C) double intensity, 145.1 (C) double intensity, 143.1 (C), 124.6 (C), 119.9 (CH), 119.1 (CH), 118.4 (CH), 118.3 (CH), 118.1 (CH), 114.2 (CH), 53.0 (CH), 50.9 (CH3), 38.7 (CH3), 30.0 (CH2), 27.1 (CH3).

MS (EI): m/z = 419.1 [M + H]+.

Anal. Calcd for C₁₉H₂₁N₃O₇·H₂O: C, 55.04; H, 5.54; N, 6.42. Found: C, 54.98; H, 5.48; N, 6.63.

2c-H₄

CHCl₃ was used as the solvent instead of CH₂Cl₂; yield: 93 mg (98%); slightly brown solid; mp 98 °C.

IR (KBr): 3347, 2944, 1636, 1515, 1332, 1261, 743 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.26 (d, J = 8.5 Hz, 2 H), 7.00 (d, J = 8.5 Hz, 2 H), 6.94 (m, 1 H), 6.71 (m, 2 H), 6.61 (m, 2 H), 6.53 (m, 1 H), 4.77 (t, J = 7.2 Hz, 1 H), 4.30 (m, 2 H), 3.09 (dd, J = 13.9, 6.5 Hz, 1 H), 2.99 (dd, J = 13.9, 6.5 Hz, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 172.7 (C), 168.9 (C), 158.4 (C), 155.8 (C), 148.0 (C), 145.7 (C), 143.2 (C), 130.0 (CH), 127.2 (C), 126.9 (C), 125.9 (CH), 124.6 (CH), 120.9 (CH), 120.0 (C), 119.2 (CH), 118.4 (CH), 118.8 (CH), 117.7 (CH), 114.8 (CH), 114.2 (CH), 55.3 (CH), 38.5 (CH3), 37.0 (CH3).

MS (EI): m/z = 440 [M + H]+.


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Yield: 40 mg (43%); brown oil.

IR (KBr): 3402, 2948, 2838, 2806, 1671, 1585, 1462, 1433, 1030 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 8.15–6.50 (22 Harom), 4.72 (m, 2 H), 4.46 (m, 2 H), 3.02 (m, 1 H), 2.15 (s, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 174.8 (C), 166.7 (C), 152.8 (C), 152.6 (C), 146.9 (C), 146.3 (C), 142.3 (C), 142.1 (C), 137.0 (C), double intensity), 136.8 (C), 134.2 (CH, double intensity), 133.7 (CH, double intensity), 133.4 (CH, double intensity), 130.9 (CH, quadrupel intensity), 127.5 (CH, quadrupel intensity), 124.8 (CH), 123.9 (CH, double intensity), 120.5 (CH, double intensity), 120.1 (C), 113.5 (CH), 112.1 (CH), 77.9 (C), 49.4 (CH3), 38.4 (CH3), 27.3 (CH2), 21.8 (CH3).

MS (FAB, DMSO): m/z = 669 [M + H]+.

2e-H₄

Compound 8e (500 mg, 1 equiv) was dissolved in CH₂Cl₂ (15 mL). At 0 °C, BBr₃ (8 equiv) was added and the mixture was stirred for 8 h at 0 °C. MeOH was slowly added to the cooled suspension. The solvents were removed in vacuum, the residue was dissolved in EtOAc and washed with H₂O and brine. The organic phase was dried (MgSO₄) and the solvent was removed under reduced pressure; yield: 364 mg (84%); slightly brown solid; mp 97 °C (dec.).
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**Amino Acid-Bridged Dicatecholate Complexes**

\( ^{13}C \) NMR (130 MHz, CD\(_2\)OD): \( \delta = 175.3 \) (C), 162.9 (C), 151.3 (C), 150.9 (C), 148.9 (C), 146.6 (C), 125.0 (CH), 121.4 (CH), 120.4 (CH), 119.5 (CH), 114.5 (CH), 113.6 (CH), 108.9 (C), 103.8 (C), 58.3 (CH), 38.7 (CH\(_2\)), 29.4 (CH\(_2\)), 26.3 (CH\(_2\)), 25.9 (CH\(_2\)).

MS (ESI): \( m/z = [Na\_2\text{[(2b)\_2(OCH\_3\_2)Ti\_2]}]^{2+} \). Anal. Calcd for C\(_{40}\)H\(_{40}\)Na\(_2\)O\(_{16}\)Ti\(_2\): C, 44.15; H, 4.50; N, 5.77.

K\(_2\)\{[(2b)\_2(OCH\_3\_2)Ti\_2]\} + K\(_2\)\{(2b)\_2(OCH\_3\_2)Ti\_2]\} Red solid.

IR (KBr): 3403, 1639, 1525, 1448, 1254, 1219, 1064, 853, 742, 488 cm\(^{-1}\).

**Deprotection of 9 to 2d-H4**

Compound 9 (22 mg, 0.033 mmol) was dissolved in CH\(_2\)Cl\(_2\) (20 mL) and trifluoroacetic acid (0.2 mL) and trisopropylsilane (1 mL) were added. The mixture was stirred for 2 h at r.t. The precipitate was collected by filtration, washed with CH\(_2\)Cl\(_2\) and dried; yield: 14 mg (ca. 100%); slightly brown solid.

**Diimine Complexes with Methoxide Colligands; General Procedure**

The amino acid-bridged ligand 2-H4 (1 equiv, ca. 0.1 mmol), TiO(acac)\(_2\) (1 equiv) and alkali metal carbonate (1 equiv) were dissolved in MeOH. The mixture was stirred for 20 h and the solvent was removed in vacuum. The residue was dissolved in MeOH and filtered over Sephadex LH20 and the orange red band was collected.

**Li\(_2\)\{[(2a)\_2(OCH\_3\_2)Ti\_2]\}**

Yield: 91%; red solid.

IR (KBr): 3425, 1707, 1633, 1592, 1525, 1451, 1356, 1255, 1022, 931, 801, 744, 664 cm\(^{-1}\).

**Li\(_2\)\{[(2b)\_2(OCH\_3\_2)Ti\_2]\}**

Yield: 91%; red solid.

IR (KBr): 3370, 1707, 1636, 1593, 1525, 1451, 1356, 1255, 1022, 931, 801, 744, 664 cm\(^{-1}\).

**Na\(_2\)\{[(2b)\_2(OCH\_3\_2)Ti\_2]\}**

Yield: 90%; red solid.

IR (KBr): 3408, 1702, 1651, 1591, 1527, 1447, 1252, 1219, 1027, 739, 674, 634 cm\(^{-1}\).

**K\(_2\)\{[(2b)\_2(OCH\_3\_2)Ti\_2]\}**

Yield: quant.; red solid.

Allyloxy-Bridged Complexes

The allyloxy-bridged complexes were prepared as described for the corresponding methoxide derivative, with the exception that all procedures were performed in allyl alcohol.

Li₂(2e)(OCH₂CH=CH₂)₂Ti₂

Yield: 67%; red solid.

IR (KBr): 3041, 2926, 2865, 1639, 1559, 1519, 1488, 1251, 1221, 1059, 1031, 743 cm⁻¹.

1H NMR (300 MHz, DMSO-d₆): δ = 6.16–6.00 (m, 6 H), 5.32–4.90 (m, 2 H), 4.68 (m, 3 H), 3.95 (m, 2 H), 3.48–2.80 (br m, 2 H), 2.30–1.75 (br m, 4 H), 1.06 (t, J = 7.3 Hz, 3 H), 0.98 (t, J = 7.3 Hz, 3 H).

Na₂[(2e)₂(OCH₂CH=CH₂)₂Ti₂] + Na₄[(2e)₃Ti₂] → Li₂[(2e)₂(OCH₂CH=CH₂)₂Ti₂] + Na₄[(2e)₃Ti₂]

Yield: 93%; red solid.

IR (KBr): 3043, 2926, 2865, 1433, 1353, 1254, 1026, 740, 651 cm⁻¹.

1H NMR (300 MHz, DMSO-d₆): δ = 6.42–6.00 (m, 6 H), 5.94 (br s, 1 H), 4.77 (t, J = 14.3 Hz, 1 H), 4.52 (t, J = 14.3 Hz, 1 H), 4.20–3.70 (m, 5 H), 3.00–2.50 (br m, 3 H), 1.70–1.10 (br m, 2 H).

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