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Synthesis and Binding Property of a Novel Tripodal Hexadentate Ligand Having Catechol Moieties

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Abstract:

A novel tripodal hexadentate ligand, consisting of three catechol units, three isobutenyl ether arms, and one aromatic core, was synthesized through four steps, in which the Claisen rearrangement was included as the key step. The hexadentate ligand formed a 1:1 complex with iron(III) trichloride hexahydrate with an equilibrium constant (conditional) of 6.3 x 10^4 M^{-1} in acetonitrile in the presence of 2,4,6-trimethylpyridine.

Keywords: host compound; ionophore; rearrangement; iron and compounds

There have been synthesized a large number of hexadentate ligands, as models of enterobactin, for biological and/or medicinal applications upon mimicking naturally-occurring siderophores. [1-3] Most of the artificial hexadentate ligands have the structural feature of three catechol units connected with a core by three arms of amide linkages, which feature renders the ligands soluble in water. In contrast to the advanced studies on such enterobactin-like, amide-linked hexadentate ligands, [4] there have been few attempts to synthesize a lipophilic tripodal hexadentate ligand, in which three bidentate moieties are attached to a core by stable arms such as carbon-chain and ether linkers, and to apply it to selective extraction and/or transportation.

In this paper we wish to report the synthesis and Fe^{3+}-binding ability of a novel tripodal hexadentate ligand having three catechol units connected with a core by stable ether linkers.

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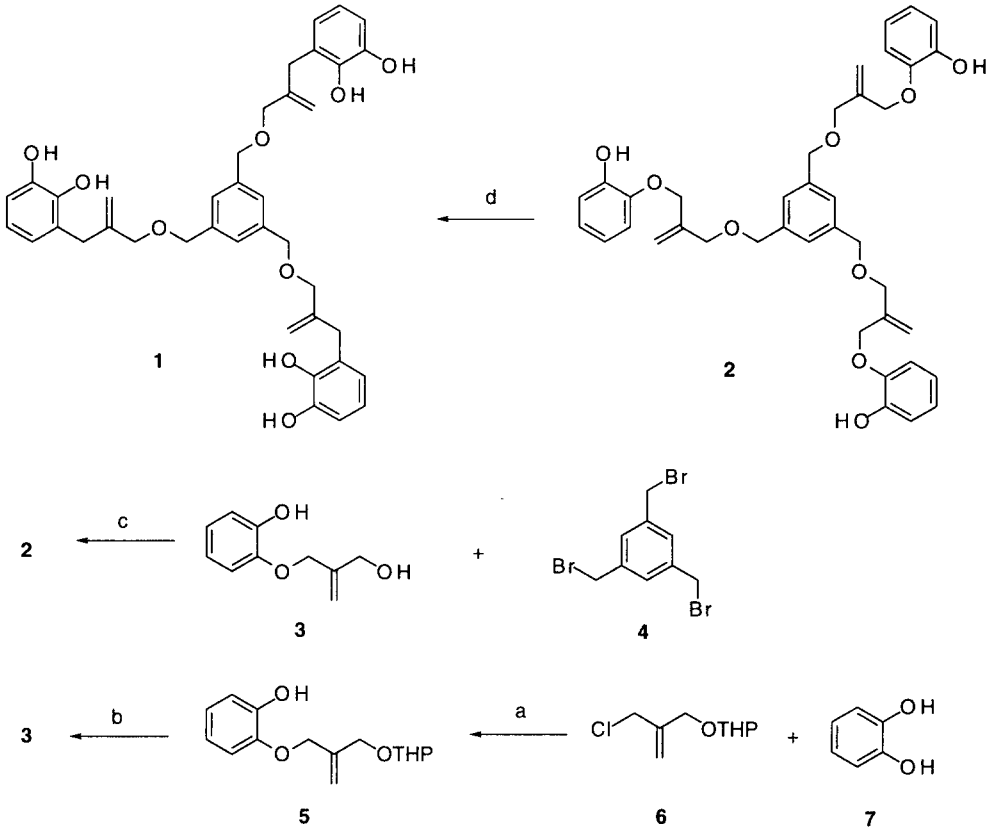
One of the authors has recently reported the synthesis and binding ability of tetradentate ligands having two bidentate units and demonstrated that the Claisen rearrangement was very useful in the construction of such ligands. [5] This success prompted us to similarly apply the Claisen rearrangement to the synthesis of a new tripodal hexadentate ligand. As the tripodal hexadentate ligand, we designed compound **1**, which has both catechol units as binding sites and a mesitylylene derivative as a core.



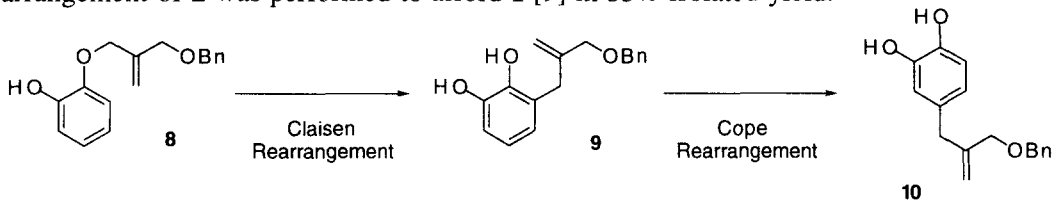
a) K_2CO_3, Acetone, reflux (74 %) b) Amberlyst 15 (H^+), MeOH, rt (81 %) c) NaH, DME, reflux (77 %) d) Et_2AlCl, CH_2Cl_2, reflux (33 %)

For the construction of the target ligand **1** by the Claisen rearrangement, tris(isobutenyl ether) **2** should be a precursor. In order to synthesize precursor **2**, 2-(chloromethyl)-2-propen-1-yl 2-tetrahydropyranyl ether (**6**) is necessary as well as catechol (**7**) and 1,3,5-tris(bromomethyl)benzene (**4**) as the starting materials. Ether **6** [6] was easily prepared from ethyl 2-(hydroxymethyl)acrylate [7] through protection with dihydropyran (quant.), reduction with DIBAL (95% yield), and chlorination with CCl4/Ph3P (84% yield).

The reaction of **6** with two equimolar amounts of **7** in the presence of K2CO3 (equimolar to **7**) proceeded very smoothly to give catechol mono-ether **5** in 74% yield, and the corresponding bis-ether was not detected, indicating that the second Williamson reaction was strongly suppressed probably due to steric hindrance. Hydrolysis of **5** with an acidic ion

exchange resin afforded alcohol **3** (81% yield), the dianion of which was allowed to react with **4** to give precursor **2** [8] in 77% yield.

In order to optimize the reaction conditions for the Claisen rearrangement of **2**, the rearrangement of model compound **8** was carried out. The thermal Claisen rearrangement of **8** at 180 °C for 4 h unfortunately gave a mixture of **9** and further Cope-rearranged product **10** in a ratio of 44:56, although the conversion was satisfactory. In contrast, the rearrangement of **8** proceeded smoothly, when the reaction was carried out by using Et_2AlCl as an activator in dichloromethane under reflux, to give **9** in 69% isolated yield with excellent selectivity (**9**:**10** = 92:8). Under these optimized conditions, the Claisen rearrangement of **2** was performed to afford **1** [9] in 33% isolated yield.



In the next stage, the binding ability of **1**, thus prepared, for trivalent cations was preliminarily examined. Figure 1 shows the UV spectral change upon titrating an acetonitrile solution of $FeCl_3 \cdot 6H_2O$ with a mixture of **1** and 6 equimolar amounts (vs **1**) of 2,4,6-trimethylpyridine in acetonitrile. With increasing the molar ratio of **1**, the peak at 360 nm, which corresponds to the absorption of Fe^{3+}, decreased and a new broad peak appeared at 528 nm, which would correspond to the absorption of complex(es) newly formed. [10] The clear isosbestic points indicate that the complexation of **1** with Fe^{3+} gives only one species of the complex. [10]

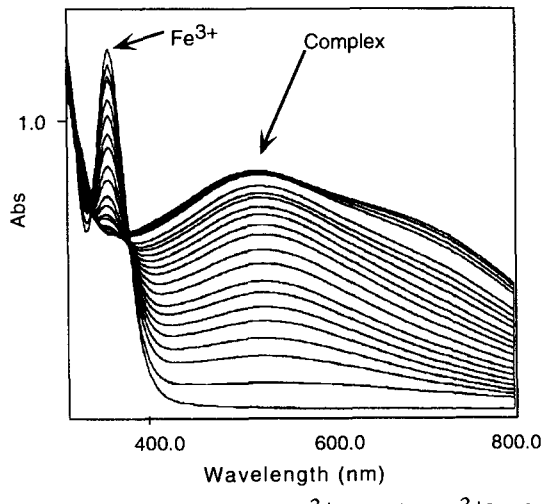


Figure 1. UV titration of Fe^{3+} with **1**. [Fe^{3+}] = 0.2 mM in acetonitrile. Spectra were recorded with increasing the amount of **1** (0.1 equivalent interval from 0.1 to 2.4 equivalents to Fe^{3+}) and 2,4,6-trimethylpyridine (6 equimolar amount to **1** added).

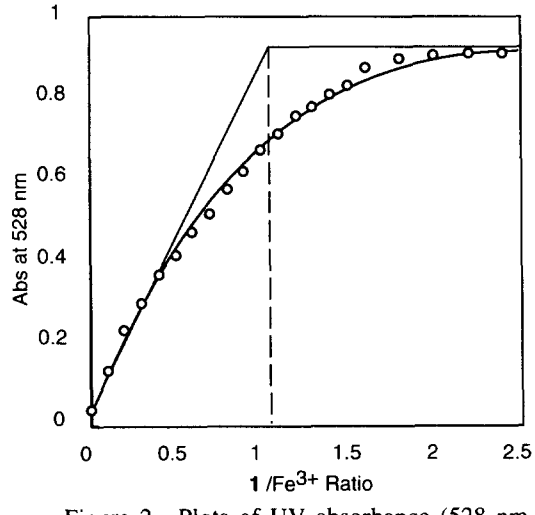


Figure 2. Plots of UV absorbance (528 nm corresponding to the absorbance of **1**·Fe^{3+} complex) vs **1**/Fe^{3+} ratio. The conditions were the same as Figure 1.

Figure 2 shows the plots of UV absorbance vs $\mathbf{1}/Fe^{3+}$ ratio. From this figure, it became clear that the molar ratio of $\mathbf{1}$:Fe^{3+} in the complex formed was 1:1 and that the equilibrium constant (conditional) was $6.3 \times 10^4\ M^{-1}$.

In conclusion, we have synthesized a new type of tripodal hexadentate ligand and found that the ligand formed a 1:1 complex with Fe^{3+}. Further investigations on the complexation of **1** with other metal cations and on selective extraction/transportation are currently in progress.

References and Notes

[1] "*The Biological Chemistry of Iron*," ed by H. B. Dunford, D. Dolphin, K. N. Raymond, and L. Sieker, pp 85-105, D. Reidel Publishing Co., Dordrecht (1981).

[2] "*Handbook of Microbial Iron Chelates*," ed by G. Winkelmann, CRC Press, Boca Raton (1991).

[3] "*The Development of Iron Chelators for Clinical Use*," ed by R. J. Bergeron and G. M. Brittenham, CRC Press, Boca Raton (1992).

[4] M. Akiyama, T. Ikeda, *Chem. Lett.*, 849 (1995) and references cited therein.

[5] a) K. Hiratani, T. Takahashi, K. Kasuga, H. Sugihara, K. Fujiwara, K. Ohashi, *Tetrahedron Lett.*, **36**, 5567 (1995). b) K. Hiratani, K. Kasuga, M. Goto, H. Uzawa, *J. Am. Chem. Soc.*, **1997**, *119*, 12677.

[6] ^{1}H NMR δ 1.5–1.9 (m, 6 H), 3.5–3.6 (m, 1 H), 3.8–3.9 (m, 1 H), 4.07 (d, J = 13 Hz, 1 H), 4.14 (s, 2 H), 4.34 (d, J = 13 Hz, 1 H), 4.66 (t, J = 3 Hz, 1 H), 5.27 (s, 1 H), 5.30 (s, 1 H); ^{13}C NMR 18.8, 25.0, 30.0, 44.7, 61.4, 66.4, 94.0, 115.7, 141.8; IR (neat) 3495, 1743, 1658, 1118, 904.

[7] J. Villieras, M. Rambaud, *Org. Synth. Coll. Vol. 8*, 265.

[8] ^{1}H NMR δ 4.12 (s, 6 H), 4.52 (s, 6 H), 4.60 (s, 6 H), 5.29 (s, 6 H), 6.11 (s, 3 H), 6.88–6.90 (m, 12 H), 7.26 (s, 3 H); ^{13}C NMR 70.8, 71.2, 72.0, 113.9, 115.1, 116.7, 120.0, 122.4, 126.6, 138.0, 140.9, 145.7, 146.6; IR (neat) 3400, 1500, 1460, 1260, 1220; FABMS (M+H) 654.

[9] ^{1}H NMR δ 3.43 (s, 6 H), 4.05 (s, 6 H), 4.53 (s, 6 H), 5.09 (s, 3 H), 5.17 (s, 3 H), 6.07 (s, 3 H), 6.63–6.79 (m, 9 H), 7.29 (s, 3 H), 7.41 (s, 3 H); ^{13}C NMR 34.2, 72.0, 73.8, 113.5, 115.8, 121.2, 121.6, 126.5, 127.9, 137.5, 141.2, 144.0; IR (neat) 3400, 2880, 1480, 1360, 1280, 1080; FABMS (M+H) 654.

[10] The titration of an equimolar mixture of **1** and $FeCl_3 \cdot 6H_2O$ in acetonitrile (0.2 mM) with an acetonitrile solution of 2,4,6-trimethylpyridine showed that 3 equimolar amounts of the base were required for the complexation. The titration gave only a purple solution of the complex (λmax 528 nm, $\varepsilon = 4.5 \times 10^3$) with a clear isosbectic point, and no other complex was formed even though an excess base was added. Thus, the complex formed during titration (λmax 528 nm) would be a neutral complex, where three of the hydroxyl groups in the ligand were deprotonated and the others were protonated.