A Novel Template Method for Preparing Unidirectional Kinetically Inert Metal Complexes

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Received October 16, 1997

Metal complexes may serve as important building blocks for molecular structures because of their unique structural and physiochemical properties.[1] So far, the design of most metal containing structures has relied on symmetric ligands thus preventing applications that rely on vectorial processes. The limited availability of nonsymmetric, unidirectional metal complexes is due to the fact that most of the preparation procedures rely on spontaneous complexations. This results in a random mutual orientation of nonsymmetric ligands leading to formation of mixtures. For example, the complexation of nonsymmetric ligands to octahedral complexes should theoretically result in a 1:3 ratio between the symmetric fac and nonsymmetric mer isomers, but this ratio may shift dramatically toward the mer isomer as a result of the ligand's structure.[2] Since the fac isomer is the desired product, a better control over the ligand's orientation should be developed.

Examples for controlling the ligand's direction by hydrophobic interactions,[3] by the trans effect,[4] and by using two binding sites with different binding affinities[5] have been described. All of these examples rely on the ligand's structure and therefore cannot give a general solution for controlling the ligand's mutual orientation. Since covalent templating has been successfully used for resolving alignment problems and inducing chirality,[6] it may be used for preparing unidirectional metal complexes.

Here we introduce a general approach for preparing inert metal complexes based on the use of a cyclic template for orienting ligand strands (Figure 1). Complexation with a kinetically inert metal ion followed by the template removal affords unidirectional metal complexes. This method is suitable for preparing metal-containing building blocks with complementary functional groups.

The feasibility of this method is demonstrated by preparing octahedral Cr(III) and Ru(II) complexes with nonsymmetric *chiral* binding units carrying amino and carboxylic acid groups on their termini. For octahedral complexes where a second chiral center is formed upon complexation (Δ or Λ), the chirality of the ligand induces preferential formation of a given isomer in the diastereomeric mixture. This enables monitoring of the orientation of the ligand strands by circular dichroism (CD) and allows separation between diastereoisomers. 1,3,5-Tris(hydroxymethyl)-benzene was selected as a template, since it is suitable for condensation with both carboxylic acids and amino groups (after converting to isocyanates) to yield tris benzyl esters and tris benzyl carbamates, respectively. Hydrogenolysis of the latter cleaves the template and regenerates the original functional groups (analogous to the benzyl and benzyloxycarbonyl protecting groups in peptide synthesis).

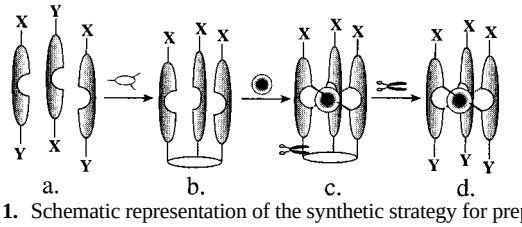
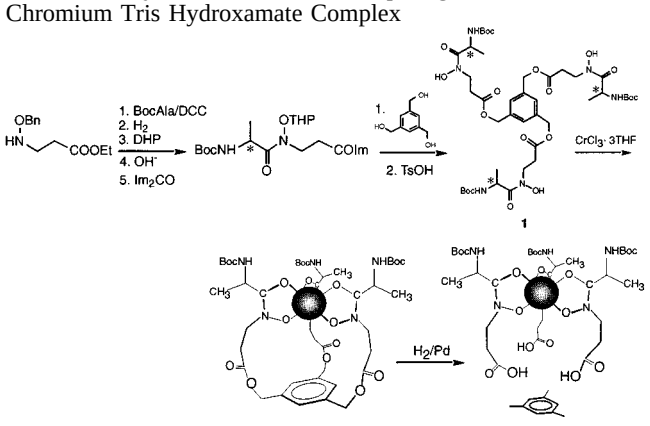


Figure 1. Schematic representation of the synthetic strategy for preparing unidirectional metal complexes. (a) Synthesis of a bifunctional binding strands. (b) Attachment to a template. (c) Binding of kinetically inert metal ion. (d) Template removal.

Scheme 1. Synthetic Scheme for Preparing Unidirectional Chromium Tris Hydroxamate Complex



The ligand for chromium was based on L-alanine-derived hydroxamic acid (**1**, Scheme 1). Complexation of ligand **1** with Cr(lll)[7] produces the **1-Cr-T** complex in which the UV/vis and CD spectra (Table 1) are in agreement with Raymond's published spectra of tris hydroxamate chromium complexes.[8] According to the $\Delta\epsilon$ values, this is a diastreomeric mixture dominated by the Δ isomer. Hydrogenolysis of the complex removed the template to form (**1-Cr-D**) as reflected by the disappearance of the ester IR peak and by the appropriate FAB-MS. The CD spectrum was identical to that of the templated complex. No further separation between the diastroisomers was attempted.

The ligand for Ru(II) is based on 2,2′-bipyridine (bipy) which was modified nonsymmetrically to contain carboxylic acid and a protected amine groups on its 5 and 5′ positions[9] (Scheme 2). A chiral spacer (L-alanine) was introduced between the ligating elements and the template to allow for the flexibility required

† Deceased, March 1997.

(1) Lehn, J. M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995; p 271. Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154−1196. Balzani, V.; Scandola, F. *Supramolecular Photochemistry*; Ellis Horwood: New York, 1991; p 427. Beissel, T.; Powers, R. E.; Raymond, K. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1084−1086. Desmartin, P. G.; Williams, A. F. *New. J. Chem.* **1995**, *19*, 1109−1112. Hasenknopf, B.; Lehn, J. M.; Baum, G.; Fenske, D. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 1397−1400.

(2) Predieri, G.; Vignali, C.; Denti, G.; Serroni, S. *Inorg. Chim. Acta* **1993**, *205*, 145−148.

(3) Lieberman, M.; Sasaki, T. *J. Am. Chem. Soc.* **1991**, *113*, 1470−1471. Ghadiri, M. R.; Case, M. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1594−1597.

(4) Enemark, E. J.; Stack, T. D. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 996−998.

(5) Piguet, C.; Hopfgartner, G.; Bocquet, B.; Schaad, O.; Williams, A. F. *J. Am. Chem. Soc.* **1994**, *116*, 9092−9102. Albrecht, M.; Frochlich, R. *J. Am. Chem. Soc.* **1997**, *119*, 1656−1661.

(6) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 868−870. Guilhem, J.; Pascard, C.; Sauvage, J. P.; Weiss, J. *J. Am. Chem. Soc.* **1988**, *110*, 8711−8713. Murner, H.; von Zelewsky, A. *Inorg. Chem.* **1996**, *35*, 3931−3935. Woods, C. R.; Benaglia, M.; Cozzi, F.; Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1830−1833.

(7) The ligand and equivalent amounts of NaOAc and $CrCl_3$·3THF were refluxed in dry CH_3CN for 1 h. The complex was purified by preparative TLC ($CHCl_3$/6% MeOH), 30% yield.

(8) Leong, J.; Raymond, K. N. *J. Am. Chem. Soc.* **1975**, *97*, 293−296. *Detection, Determination, Isolation, Characterization and Regulation of Microbial Iron Chelates*; Matzanke, B. F., Ed.; CRC Press: Boston, 1991; pp 15−64.

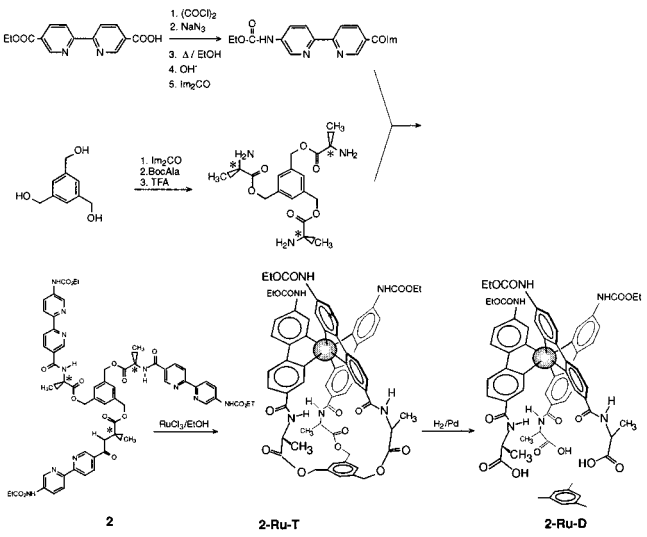
(9) The synthesis was based on 5-ethyl ester 5′-carboxylic acid 2,2′-bipyridine which was converted to carboazide and subsequently rearranged and reacted with EtOH to give the 5-ethyl ester 5′-ethylcarbamate bipyridine. The synthesis of the tripod was found to be more efficient if the triol was first reacted with the amino acid to give the trisamine and then reacted with the bipy unit.

S0002-7863(97)03605-6 CCC: $15.00
Published on Web 02/20/1998

Table 1. Spectroscopic Data for Tripodal Ligands and Their Chromium and Ruthenium Complexes

cmpd	IR (cm^{-1})	UV λ_{max} (ϵ)	CD λ_{ext} ($\Delta\epsilon$)	MS (*m*/*e*)
1	1736, 1707, 1657			943.55
1-Cr-T	1734, 1715, 1596	424 (61) 595 (58)	410 (−0.8), 465 (0), 542 (+1.52), 600 (0), 638 (−0.55)	992.52
1-Cr-D	1700, 1650, 1597	425 (60) 593 (60)	410 (−0.75), 465 (0), 540 (+1.50), 600 (0), 642 (−0.4)	877.26
2	1734, 1701, 1640			1189.24
2-Ru-T Λ	1733, 1701, 1651	314 (67800) 460 (7600)	227 (−58), 290 (−48), 305 (0.0), 320 (+73), 350 (+92), 370 (0.0), 415 (−12.0), 451 (0.0), 468 (+6.0)	1290.50
2-Ru-T Δ	1733, 1701, 1651	314 (67800) 460 (7600)	227 (0.0) 286 (+72), 302 (0.0), 319 (−68), 346 (−100), 366 (0.0), 412 (+12.7), 450 (0.0), 462 (−4.5)	1290.80
2-Ru-D Δ	1700, 1701, 1650	314 (67800) 460 (7600)	227 (0.0), 286 (+68), 300 (0.0), 319 (−84), 346 (−100), 366 (0.0), 412 (+12.7), 450 (0.0), 462 (−7.5)	1176.40

Scheme 2. Synthetic Scheme for Preparing Unidirectional Ruthenium Tris Bipyridine Complex



for Ru(II)−bipy tripod complexes[10] and to permit separation between the Λ and Δ isomers. Separation of the complex to its Δ and Λ components provides the shape and values for the fac orientation. The retention of these values after removal of the template will determine the extent to which the orientation of the complexes has been preserved.

Ligand **2** was complexed with Ru(II)[11] and gave two main products which were separated by preparative TLC to give two diasteriomers (**2-Ru-T** Δ and **2-Ru-T** Λ) as shown by their identical MS, different NMR spectra,[12] and CD Cotton effects (Table 1). The unidirectionality of the strands was reflected by a single set of peaks in the NMR spectrum. Hydrogenolysis of the major product, **2-Ru-T** Δ, resulted in the removal of the template (**2-Ru-D** Δ) as reflected by the disappearance of the aryl and benzyl peaks in the NMR spectrum (s, 7.32 ppm and ABq, 5.08 ppm)[13] and the appropriate MS. The fac symmetry of the complex was conserved as indicated by the symmetric

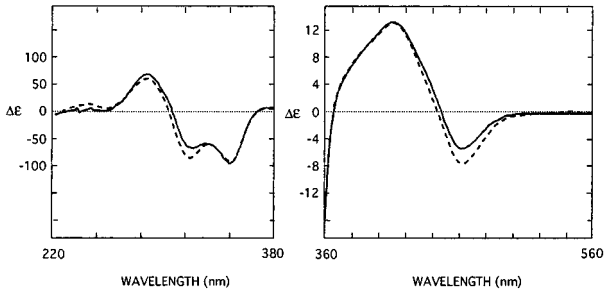


Figure 2. CD spectra of **2-Ru-T** Δ before (−) and after template removal (− − −) in MeOH.

NMR spectrum. The $\epsilon/\Delta\epsilon$ ratio had the same value as prior to the template removal, affirming no isomerization occurred (Figure 2). The complex was stable, and no isomerization was observed even after heating it to 50 °C for several minutes. Because racemization was not observed (Ray-Dutt or Bailar twists did not occur[14]), it can be concluded that the directionality of the complex was preserved.

The template method[15] is the preferred choice for aligning nonsymmetric ligands about inert metal ions, with the advantage of exclusively generating the symmetric isomers, including systems with orthogonal or complemental functional groups. In addition, incorporating chiral centers into the ligating chains,[16] optically pure complexes are easily obtained. Integration of these are best demonstrated with chiral ligands possessing carboxylic acids on one end and amino groups on the other, leading to the formation of the first example of chiral "amino acids" metal-containing building blocks. These building blocks are readily available for stepwise oligomerization and multilayer formation of anisotropic materials with electron and energy transfer properties. Efforts in these directions are currently in progress.

Acknowledgment. This paper is dedicated to the memory of Dr. Jacqueline Libman, whose untimely death was a great loss to her family, to her colleagues, and to science. The authors thank Mr. Peter Oosting for his technical assistance. Support of this work from the US-Israel Binational Science Foundation, Israel Ministry of Science-Tashtyot program and the Minerva Foundation, Munich, Germany is gratefully acknowledged.

Supporting Information Available: NMR spectra (2 pages). See any current masthead page for ordering information and Web access instructions.

JA973605C

(10) Barigelletti, F.; De Cola, L.; Balzani, V.; Belser, P.; von Zelewsky, A.; Vögtle, F.; Ebmeyer, F.; Grammenudi, S. *J. Am. Chem. Soc.* **1989**, *111*, 4662−4668.

(11) Ethanolic solution of $RuCl_3$ hydrate was added dropwise to a refluxed solution of ligand **2** in EtOH and then refluxed for 18 h. The complexes were purified over preparative TLC (8:1:0.35:0.1 CH_3CN/BuOH/H_2O/saturated KNO_3) 20% yield.

(12) **2-Ru-T** Δ (CD_3OD): δ 8.57 (m, 6H, Py), 8.29 (dd, J_1 = 1.9 Hz, J_2 = 8.5 Hz, 3H, Py), 8.13 (d, *J* = 2.3 Hz, 3H, Py), 8.06 (m, 3H, py), 8.01 (d, *J* = 1.5 Hz, 3H, Py), 7.32 (s, 3H, ArH), 5.08 (ABq, *J* = 11.3 Hz, δΔ = 0.38, 6H, ArCH_2), 4.67 (q, *J* = 7.2 Hz, 3H, C_αH), 4.08 (q, *J* = 7.1 Hz, 6H, CH_2{Et}), 1.26 (d, *J* = 7.2 Hz, 9H, $C_\alpha HCH_3$), 1.20 (t, *J* = 7.1 Hz, 9H, CH_3{Et}. **2-Ru-T** Λ (CD_3OD): δ 8.57 (m, 6H, Py), 8.36 (dd, J_1 = 1.9 Hz, J_2 = 8.5 Hz 3H, Py), 8.28 (d, *J* = 2.4 Hz, 3H, Py), 8.08 (dd, J_1 = 2.4 Hz, J_2 = 8.6 Hz, 3H, Py), 7.87 (d, *J* = 1.8 Hz, 3H, Py), 7.42 (s, 3H, ArH), 5.10 (ABq, *J* = 11.8 Hz, δΔ = 0.15, 6H, ArCH_2), 4.67 (q, *J* = 7.2 Hz, 3H, C_αH), 4.10 (q, *J* = 7.1 Hz, 6H, CH_2{Et}), 1.48 (d, *J* = 7.3 Hz, 9H, $C_\alpha HCH_3$), 1.21 (t, *J* = 7.1 Hz, 9H, CH_3{Et}).

(13) **2-Ru-D** Δ (CD_3OD): δ 8.63 (d, *J* = 8.6 Hz, 6H, Py), 8.44 (d, *J* = 8.6 Hz, 3H, Py), 8.24 (d, *J* = 2.1 Hz, 3H, Py), 8.10 (m, 6H, Py), 5.00 (m, 3H, C_αH), 4.11 (q, *J* = 7.1 Hz, 6H, CH_2{Et}), 1.37 (b, 9H, $C_\alpha HCH_3$), 1.22 (t, *J* = 7.1 Hz, 9H, CH_3{Et}).

(14) von Zelewsky A. *Stereochemistry of Coordination Compounds Concepts*; John Wiley & Sons: Chichester, 1996; p 254.

(15) Complexes with different symmetries can be prepared by changing the template symmetry [such as C_2, C_3, C_4]

(16) Libman, J.; Tor, Y.; Shanzer, A. *J. Am. Chem. Soc.* **1987**, *109*, 5880−5881. Shanzer, A.; Libman, J.; Lifson, S. *Pure Appl. Chem.* **1992**, *64*, 1421−1435.