Inorg. Chem. **2004**, *43*, 4817–4819

Inorganic Chemistry
Communication

Chiral Induction in a Ribose-Decorated Metallostar through Intrinsic and Interionic Diastereomeric Interactions

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Received May 10, 2004

A ribose-functionalized bpy ligand has been prepared and shown to give modest diastereomeric excesses of Λ-[FeL$_3$]$^{2+}$ complexes; interconversion of Δ and Λ cations is relatively fast, and in CHCl$_3$, the favored complexes with Δ- or Λ-TRISPHAT counterions are homochiral, $(\Delta_+\Delta_-)$ or $(\Lambda_+\Lambda_-)$. In the case of the Δ-TRISPHAT salt, a single diastereomer is observed (de $\geq$ 96%).

Metallodendrimers and metallostars are versatile and increasingly exploited scaffolds used for the preparation of molecular systems bearing multiple functional units.[1a] We have been particularly interested in metallostars, in which the only formal branching is at the core, and any subsequent structural development is linear.[1] There has been much effort devoted to sugar-functionalized dendrimers ("sugar balls") which have unique physicochemical and biological properties,[2] although few examples of sugar-functionalized metal-containing systems have been reported.[3–6] Pendant chiral-functionality might influence the central Δ or Λ chirality in metallostars based upon {M(bpy)$_3$} motifs. We now describe the synthesis of first generation ribose-functionalized metallostars and demonstrate a modest chiral-induction and a large supramolecular chiral-amplification in this system.

The new electrophilic protected ribofuranose derivative **2** was prepared in 55% yield as a colorless oil by the reaction of 2-bromoethanol with commercially available 1,2,3,5-tetraacetyl-β-D-ribofuranose in the presence of SnCl$_4$.[7] As expected, the substitution proceeded with stereoretention, and the β-configuration at the anomeric center was confirmed by the observation of H^{B1} (see Scheme 1 for ring labeling) as a singlet at δ 5.06. The reaction of **2** with 4,4′-dihydroxy-2,2′-bipyridine in DMF in the presence of K$_2$CO$_3$ gave ribofuranose-functionalized ligand **1** in 86% yield as a pale yellow oil. Ligand **1**[8] reacted immediately with FeCl$_2$·4H$_2$O in CH$_2$Cl$_2$−EtOH to give a bright red solution from which the red complex [Fe(**1**)$_3$][PF$_6$]$_2$ was isolated[9] in 57% yield after treatment with [NH$_4$][PF$_6$] (Scheme 1). The iron(II) complex was fully characterized by conventional spectro-

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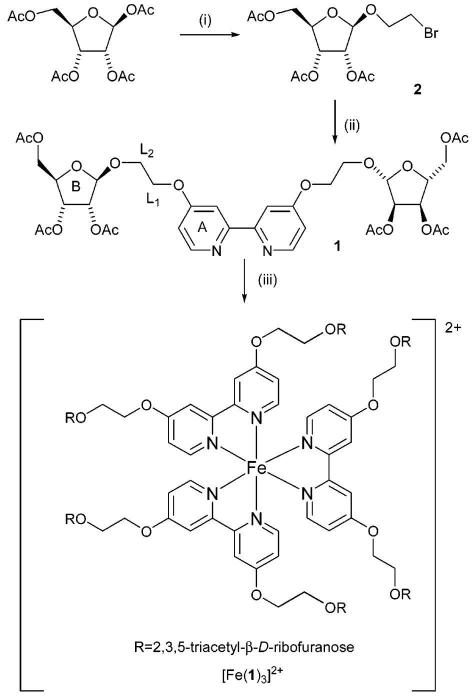
(8) **1**: 4, 4′-Dihydroxy-2, 2′-bipyridine (127 mg, 676 μmol) and K$_2$CO$_3$ (560 mg, 4.06 mmol) were stirred in dry DMF (10 mL) under N$_2$ for 1 h at 75 °C. 2-Bromoethyl-2,3,5-triacetyl-β-D-ribofuranoside (517 mg, 1.35 mmol) dissolved in dry DMF (5 mL) was added and the mixture stirred at 75 °C for 2 h. KI (224 mg, 1.35 mmol) was added, and stirring continued overnight. The solvent was removed in vacuo and the residue suspended in water (10 mL) and extracted with CHCl$_3$ (3 × 20 mL), and the extracts were dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo. The crude reside was purified by column chromatography (SiO$_2$, CH$_2$Cl$_2$/MeOH(4%)) to give **1** as a pale yellow oil (460 mg, 86%). Electrospray HRMS: *m/z* 815.2508 ([M + Na]$^+$, calcd 815.2487). ^{1}H NMR (CDCl$_3$, 500 MHz, 295 K) δ 8.47 (H^{A6}, d, 2H, *J* 5.68 Hz), 7.97 (H^{A3}, d, 2H, *J* 2.46), 6.87 (H^{A5}, dd, 2H, *J* 2.58, 5.66 Hz), 5.34 (H^{B3}, m, 2H), 5.29 (H^{B2}, br d, 2H, *J* 4.9 Hz), 5.12 (H^{B1}, s, 2H), 4.33 (H^{B4}, m, 2H), 4.33 (H$^{B5a/b}$, m, 2H), 4.29 (H^{L2}, t, 4H, *J* 4.5 Hz), 4.18 (H$^{B5b/a}$, dd, 2H, *J* 5.9, 11.24 Hz), 4.09 (H$^{L1A/b}$, m, 2H), 3.86 (H$^{L1b/a}$, m, 2H), 2.11 (OAc, s, 6H), 2.08 (OAc, s, 6H), 2.05 (OAc, s, 6H).

10.1021/ic049392r CCC: $27.50

Scheme 1 [a]



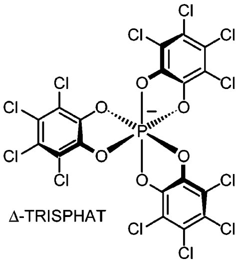
[a] (i) $SnCl_4$, $BrCH_2CH_2OH$, $CH_2Cl_2{-}MeCN$, 55%; (ii) K_2CO_3, 4,4′-$(HO)_2$bpy, DMF, 86%; (iii) $FeCl_2.4H_2O$, $CH_2Cl_2{-}EtOH$, 57%.

scopic methods and the ^{1}H NMR spectrum assigned using COSY and NOESY techniques.

The complex contains a total of 25 stereogenic centers. Of these, the 24 in the sugar substituents have defined *R* or *S* configuration, and only the Δ or Λ configuration at the {Fe(bpy)$_3$}center is undefined. A single investigation into chiral induction at a metal center with a remote hexose-functionalized bpy ligand has been reported;[5] in this case, a 46% diastereomeric excess (Λ: Δ α-anomer; Δ: Λ *β*-anomer) was observed, with the favored configuration at the metal stereogenic center depending upon the α- or *β*-configuration at the hexose. We hoped that by placing the ribose closer to the bpy and the metal center, the chiral induction at the metal would be proportionately greater.

The ^{1}H NMR spectrum of a CD_3CN solution of [Fe(**1**)$_3$][PF$_6$]$_2$ showed a doubling of resonances in the aromatic region as expected if two diastereomers are present. The splitting of peaks was most noticeable for H^{A5}. However, the splitting of the signals was not great, and the diastereomeric excess (estimated from the overlapping signals for the H^{A5} proton in the Δ and Λ diastereomers) was a maximum of 10% (±5%). Although the observation of two signals means that the system is in slow exchange on the ^{1}H NMR time scale (500 MHz, 295 K), ligand exchange is possible in $[Fe(bpy)_3]^{2+}$ systems, which are known to racemize relatively rapidly.[10] This suggested that we might observe a different diastereoselectivity in other solvents in which ion-pairing effects differ.

We hoped that solutions in less coordinating solvents might show greater diastereoselectivity as intramolecular polar interactions would be optimized, but we found that in $CDCl_3$ solution the diastereomeric excess was only slightly higher (de = 20 ± 2% by ^{1}H NMR) than in CD_3CN solution. The addition of CD_3SOCD_3 to the $CDCl_3$ solution results in a coalescence of the signals of the two diastereomers and the appearance of free **1** at high concentrations. We have observed similar ligand dissociation processes in other iron(II) complexes of sugar-functionalized ligands in polar solvents.[11] In $CHCl_3$, the complex exhibits in the CD spectrum a negative Cotton effect at the higher wavelength ($\Delta\epsilon_{580} = -2.7$) corresponding to the MLCT band. Both the CD and electronic spectra of **1** are transparent in this region, and we can assign the band with confidence to an excess of the Λ_+ complex[12] (Δ_+ and Λ_+ refer to the chirality at the cationic center).



The chiral tris(tetrachlorobenzenediolato)phosphate(V) anion, known as TRISPHAT, interacts strongly with aromatic rings such as those found in $[Fe(\mathbf{1})_3]^{2+}$ [13] and has been used as a chiral shift reagent for oligopyridine complexes.[14] In general, a high level of homochiral recognition (Δ_+, Δ_-) is achieved (de ≥ 96%).[14b,c] Its association with diastereomeric $[Fe(\mathbf{1})_3]^{2+}$ moieties was considered, as selective interactions with either Δ_+ or Λ_+ forms of the cationic complex could potentially occur and overcome, or reinforce, the modest Λ_+ preference induced by the sugars. With a TRISPHAT anion of, for instance, Δ_- configuration, if there is a significant thermodynamic difference between the energies of the equilibrating homochiral ($\Delta_+\Delta_-$) and heterochiral ($\Lambda_+\Delta_-$)

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(9) [Fe(**1**)$_3$][PF$_6$]$_2$: Solutions of **1** (12 mg, 15.2 μmol) in $CH_2Cl_2{-}EtOH$ (2 mL, 1:1) and $FeCl_2{\cdot}4H_2O$ (1.0 mg, 5.1 μmol) in EtOH (1 mL) were mixed, and the red solution was stirred at room temperature for 1 h. Treatment with NH_4PF_6 gave a red precipitate which was filtered over Celite, washed with water, and redissolved in MeCN. The solvent was removed in vacuo to give [Fe(**1**)$_3$][PF$_6$]$_2$ as a red solid in 57% yield. [Fe(**1**)$_3$][PF$_6$]$_2$: *m*/*z* 1216.7 $[M - 2PF_6]^{2+}$, 2580.0 $[M - PF_6]^{+}$. ^{1}H NMR (CD_3CN, 500 MHz, 295 K): δ 8.12, 8.11 (H^{A3}, d + d, 6H), 7.25, 7.24 (H^{A6}, d + d, 6H), 6.98, 6.97 (H^{A5}, dd + dd, 6H), 5.17 (H^{B3}, m, 6H), 5.12 (H^{B2}, m, 6H), 5.10, 5.09 (H^{B1}, s + s, 6H), 4.35 (H^{L2}, m, 12H), 4.30 (H^{B4}, m, 6H), 4.28 ($H^{B5a/b}$, m, 6H), 4.10 ($H^{B5b/a}$, m, 6H), 4.05 ($H^{L1a/b}$, m, 6H), 3.84 ($H^{L1b/a}$, m, 6H), 2.06, 2.05 (OAc, s + s, 18H), 2.00 (OAc, s + s, 18H), 1.99, 1.98 (OAc, s + s, 18H). λ_{max}(CH_3CN)/nm (ϵ_{max}/mol^{-1} dm^3 cm^{-1}): 544 (2400), 362 (3400), 293 (17 700), 274 (19 700), 223 (51 700). Elemental analysis calcd for $C_{108}H_{132}O_{54}N_6FeP_2F_{12}{\cdot}0.5NH_4PF_6$: C, 46.19; H, 4.78; N, 3.24. Found: C, 45.70; H, 4.78; N, 3.60%

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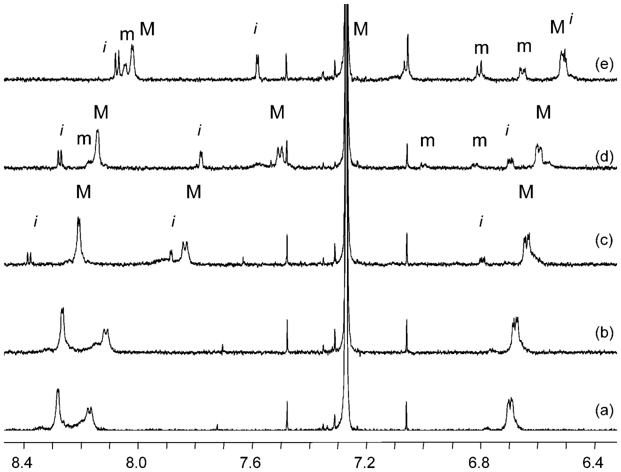

Figure 1. ^{1}H NMR spectra of [Fe(**1**)$_3$][Δ-TRISPHAT]$_2$ in (a) 0%, (b) 2%, (c) 5%, (d) 10%, and (e) 20% CD_3SOCD_3 in $CDCl_3$. Peaks marked M and m refer to major and minor diastereomers, respectively, and the peaks marked *i* are free ligand observed at high % DMSO.

ion pairs, then a classical Pfeiffer effect will occur,[15] and result in an enrichment of one of the two diastereomeric salts. The sense of the stereoselective induction and its magnitude strongly depend on the structure of the diimine ligands and the polarity of the solvent.[16]

The reaction of [Fe(**1**)$_3$][PF_6]$_2$ with [cinchonidinium]-[Δ-TRISPHAT] or [Bu_3NH][Λ-TRISPHAT] followed by chromatography allowed the isolation of pure [Δ-TRISPHAT] and [Λ-TRISPHAT] salts of the complex. The ^{1}H NMR spectrum of a $CDCl_3$ solution of [Fe(**1**)$_3$][Δ-TRISPHAT]$_2$ (Figure 1) exhibited a single solution species (an accidental degeneracy of the signals for the (Δ_+, Δ_-) and (Λ_+, Δ_-) salts in pure chloroform is very unlikely as good NMR differentiation of the diastereomeric salts is observed in the presence of DMSO). Upon the addition of CD_3SOCD_3 to the $CDCl_3$ solution, there is both a shifting of the peaks and the development of two solution species corresponding to a major and a minor diastereomeric ion pair (together with some ligand dissociation at high CD_3SOCD_3 concentrations). This is consistent with a very high diastereoselectivity in $CDCl_3$ through a Pfeiffer effect. We believe that the addition of DMSO results in a weakening of the electrostatic interactions within the ion pair and leads to a mixture of diastereomers. A similar behavior was observed for the salt [Fe(**1**)$_3$][Λ-TRISPHAT]$_2$ with, surprisingly, in this case the presence of the minor diastereomer (15−20%) in $CDCl_3$ only.

Figure 2 shows CD spectra in $CHCl_3$ of the original PF_6^- salt and the salts obtained with Δ- and Λ-TRISPHAT. The TRISPHAT salts have opposite responses at 580 nm, a region in which TRISPHAT itself does not absorb, with a stronger Cotton effect for the salt with Δ anion ($\Delta\epsilon_{580} = +14.0$) than that for Λ anion ($\Delta\epsilon_{580} = -8.6$). Accordingly, we may conclude that in chloroform solutions the diastereomeric ion pairing is sufficiently strong that with [Δ-TRISPHAT] the solution species is only [Δ-Fe(**1**)$_3$][Δ-TRISPHAT]$_2$ (de 96% ± 2%) and with [Λ-TRISPHAT] the solution species is preferentially [Λ-Fe(**1**)$_3$][Λ-TRISPHAT]$_2$ (de 59% ± 2%). We also notice that the Cotton effect value ($\Delta\epsilon_{580} = -2.7$) for salt [Fe(**1**)$_3$][$PF_6$]$_2$ is in complete agreement with the diastereoselectivity measured by NMR. Interestingly, instead of reinforcing the natural preference for a Λ_+ configuration at the metal center imposed by the ribose substituents, Λ-TRISPHAT leads to a lower selectivity than its enantiomer. In the case of the $\Lambda_+\Lambda_-$ homochiral diastereomeric ion pair, we propose that secondary supramolecular interactions between the chiral anion and the sugar substituents result in a destabilization allowing the presence of significantly more $\Delta_+\Lambda_-$ salt at equilibrium.

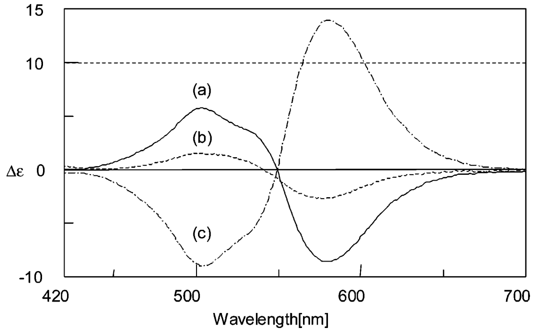

Figure 2. CD spectra in the region of the MLCT bands (λ 420−700 nm) of (a) [(Λ)-Fe(**1**)$_3$][Λ-TRISPHAT]$_2$ (de 59%), (b) [(Λ)-Fe(**1**)$_3$][PF_6]$_2$ (de 19%), and (c) [(Δ)-Fe(**1**)$_3$][Δ-TRISPHAT]$_2$ (de 96%) (1.10×10^{-4} M in $CHCl_3$).

In conclusion, we have prepared a new ribose-functionalized ligand and shown that ribose-decorated metallostars are obtained in a self-assembly reaction with iron(II). The ribose substituents result in a modest chiral induction at the {Fe(bpy)$_3$} center, favoring the Λ_+ diastereomer in the complex [Fe(**1**)$_3$][PF_6]$_2$. As the iron(II) complexes are reasonably labile, supramolecular interactions with TRISPHAT anions in the diastereomeric ion-pairs allow great control over the configuration of the {Fe(bpy)$_3$} through a Pfeiffer effect.

Acknowledgment. We thank the Universities of Basel and Geneva, the Swiss National Science Foundation, the Sandoz Family Foundation, Portland Cement Fabrik, and the EPSRC for support.

Supporting Information Available: NMR spectra in different mixtures of DMSO and $CDCl_3$; CD spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

IC049392R

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