Ion-Pair-Mediated Asymmetric Synthesis of a Configurationally Stable Mononuclear Tris(diimine) – Iron(II) Complex**

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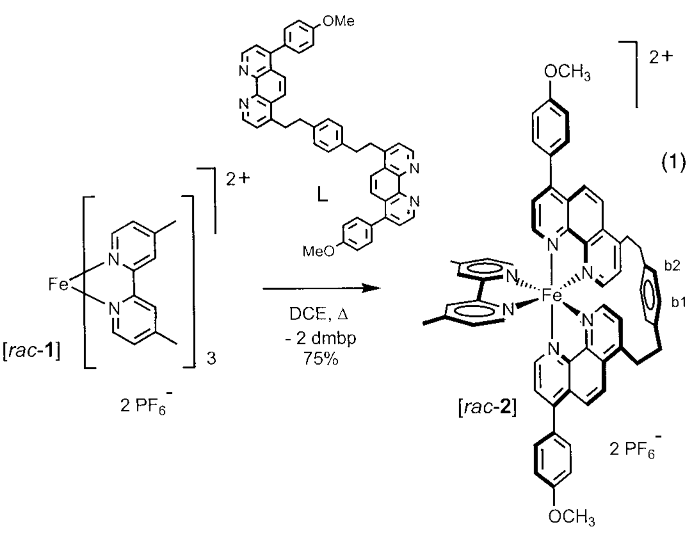
In memory of André Collet

Chiral mononuclear divalent tris(diimine) complexes of first-row transition metals—keystones of coordination chemistry—are notoriously known for their high chemical but low configurational stability.[1] The Δ and Λ enantiomers—right- and left-handed propellers, respectively—can be isolated in good enantiomeric purity by efficient resolution procedures.[1d, 2] However, once dissolved, these derivatives racemize rapidly when no other source of chiral information is present on the ligands[3] or in the reaction medium.[4]

Recently, the synthesis of a bis(1,10-phenanthroline) ligand L that forms octahedral complexes with a well-defined axis was reported: simple treatment of $[Fe(dmbp)_3][PF_6]_2$ ($[\mathbf{1}][PF_6]_2$, 1.0 equiv, dmbp = 4,4′-dimethyl-2,2′-bipyridine) with L (1.0 equiv) in refluxing 1,2-dichloroethane (DCE) afforded $[Fe(dmbp)(L)][PF_6]_2$ ($[\mathbf{2}][PF_6]_2$) in high yield and purity [Eq. (1); for b1 and b2, see Figure 1].[5] Here we report on the unusual configurational stability of **2**, which can be resolved by simple preparative thin-layer chromatography (TLC), and on its direct asymmetric synthesis by using TRISPHAT anions (see below) as noncovalent chiral auxiliaries (diastereomeric ratio, d.r. > 20:1).

The ease of synthesis of **2** and the rapidity of its formation led us to assume a high chemical stability for $[\mathbf{2}][PF_6]_2$. It was then debatable whether an improved chemical stability would also mean an increased configurational stability, so that the Δ and Λ enantiomers might be inert and separable from each other. Previously, the synthesis and resolution of the D_3-symmetric tris(tetrachlorobenzenediolato)phosphate(V) anion (**3**), known as TRISPHAT, was reported.[6] In association with mononuclear ruthenium(II) or iron(II)tris(diimine) complexes, it is an efficient NMR chiral-shift, resolving, and asymmetry-inducing agent.[7] It was therefore foreseen that anion **3** could behave as a NMR chiral-shift reagent for the structurally related complex **2** and possibly lead to its resolution.



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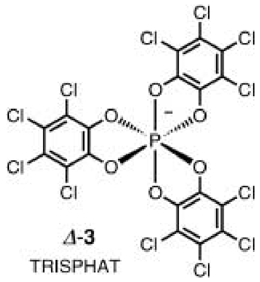

Δ-3
TRISPHAT

Racemic complex **2** was studied in combination with a TRISPHAT salt. In an NMR tube, $[Et_4N][\Delta\text{-}\mathbf{3}]$[8] was added as a solid to a solution of $[rac\text{-}\mathbf{2}][PF_6]_2$ in 10% $[D_6]DMSO/CDCl_3$ (Figure 1, spectra (a) and (b)). Efficient separation of the signals of **2** was achieved with small amounts of chiral-shift reagent (1.0 – 2.5 equiv). Protons H(b1) and H(b2) [see Equation (1)] were most easily monitored, and a rather large difference in chemical shift ($\Delta\delta_{max} \approx 0.15$ ppm) was observed. A 1:1 ratio of Δ and Λ enantiomers could be measured by direct integration of the respective signals. This 1:1 ratio of the diastereomers $[\Delta\text{-}\mathbf{2}][\Delta\text{-}\mathbf{3}]_2$ and $[\Lambda\text{-}\mathbf{2}][\Delta\text{-}\mathbf{3}]_2$ indicated a possible configurational stability of cation **2**. Indeed, it was recently shown that anions **3** act as effective asymmetry inducers on $[Fe(dmbp)_3]^{2+}$ (**1**); when associated with the labile cationic guest, they control its configuration with high diastereoselectivity (d.r. > 49:1 in $CDCl_3$ in favor of $[\Delta\text{-}\mathbf{1}][\Delta\text{-}\mathbf{3}]_2$).[7b] Two hypotheses could then explain the lack of asymmetric induction observed in the NMR titration experiment (Figure 1, spectrum (b)): poor chiral recognition by **3** or high configurational stability of **2**.

We thus decided to attempt an ion-pair chromatographic resolution, as the physical separation of ion pairs $[\Delta\text{-}\mathbf{2}][\Delta\text{-}\mathbf{3}]_2$ and $[\Lambda\text{-}\mathbf{2}][\Delta\text{-}\mathbf{3}]_2$ would prove the second hypothesis to be correct.[9] Under previously reported conditions,[7d, e] solutions of [cinchonidinium]$[\Delta\text{-}\mathbf{3}]$ (2.5 equiv) in acetone and of $[rac\text{-}\mathbf{2}][PF_6]_2$ in CH_2Cl_2 were prepared, mixed, and adsorbed on silica gel plates. Development by elution with CH_2Cl_2 showed a much reduced affinity of salts $[\mathbf{2}][\Delta\text{-}\mathbf{3}]_2$ for silica gel, as they were retained to a much lesser extent than the PF_6^- precursor ($R_f \approx 0$).[10] Two well-separated bands were obtained ($R_f \approx$ 0.94 and 0.84 in analytical TLC), abraded from the glass

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[**] We are grateful for financial support of this work by the Swiss National Science Foundation, the Federal Office for Education and Science (COST D11), the Fondation de Famille Sandoz (JL), the EC, the CNRS, and the MENRT (DP).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

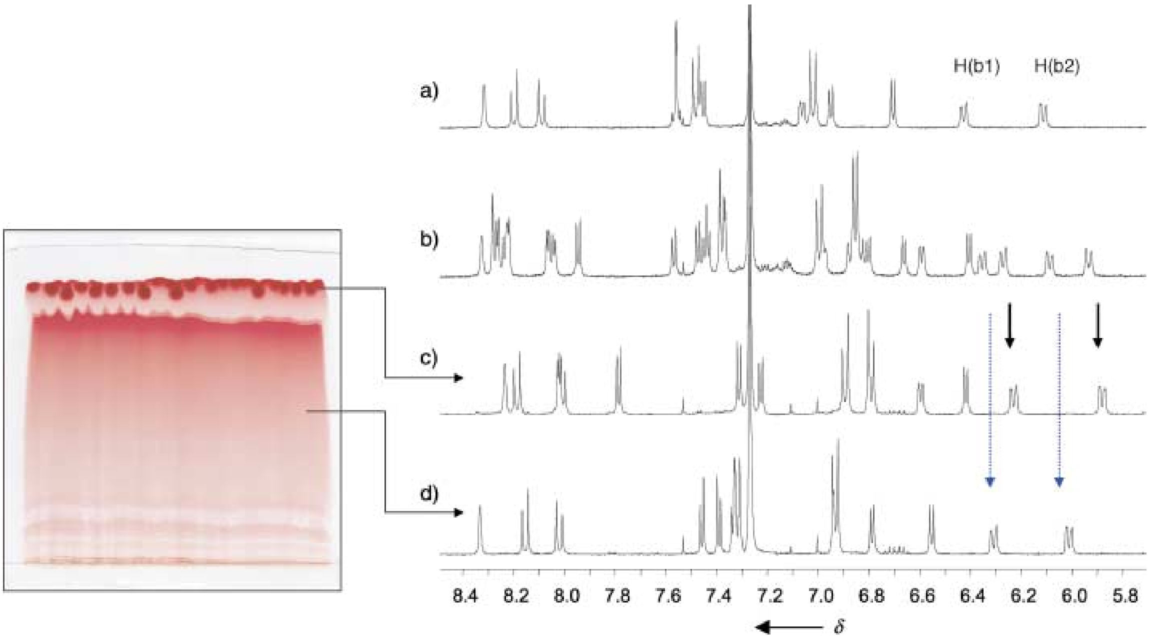


Figure 1. Ion-pair chromatographic resolution of [*rac*-**2**][PF$_6$]$_2$ with [cinchonidinium][Δ-**3**]. ^{1}H NMR spectra ($\delta = 8.50-5.75$) in 10% [D$_6$]DMSO/CDCl$_3$ of a) [*rac*-**2**][PF$_6$]$_2$; b) [*rac*-**2**][PF$_6$]$_2$ + 2.5 equiv of [Et$_4$N][Δ-**3**], d.r. = 1:1; c) [Δ-**2**][Δ-**3**]$_2$, d.r. > 49:1; d) [Λ-**2**][Δ-**3**]$_2$, d.r. > 49:1.

surface, and stirred in CH$_2$Cl$_2$. The resulting suspensions were filtered and concentrated in vacuo. The ^{1}H NMR spectra revealed two completely different sets of signals corresponding to the resolved Λ and Δ enantiomers of the cation **2** (Figure 1, spectra (c) and (d)). Pure separated diastereomeric ion pairs [Δ-**2**][Δ-**3**]$_2$/[Λ-**2**][Δ-**3**]$_2$ were thus obtained in good chemical yields (48 and 45%, respectively). A circular dichroism (CD) spectrum of the more strongly eluted fraction (CH$_2$Cl$_2$, ca. $5 \cdot 10^{-6}$ M) revealed strong exciton coupling in the $\pi-\pi^*$ region ($\Delta\varepsilon_{270} = +73$, $\Delta\varepsilon_{300} = -101\,\text{M}^{-1}\text{cm}^{-1}$) and the visible metal-to-ligand charge transfer (MLCT) transitions also showed opposite Cotton effects ($\Delta\varepsilon_{479} = -16$, $\Delta\varepsilon_{553} = +18\,\text{M}^{-1}\text{cm}^{-1}$). The CD spectrum of the less strongly eluted diastereomer in the 235–600 nm region is essentially the mirror image. These spectra can be assigned to the Δ and Λ configurations of the cationic complex and demonstrate that compounds [Δ-**2**][Δ-**3**]$_2$ and [Λ-**2**][Δ-**3**]$_2$ are the more and less strongly eluted ion pairs, respectively.[11] We believe that the unusual configurational stability of **2**, evidenced by the ^{1}H NMR spectra shown in Figure 1, is attributable to the bis-bidentate nature of L. Racemization of the iron(II) complex implies a complete rearrangement of the system with several decoordination and recoordination steps that result, in particular, in the inversion of the helix formed by L within **2**.[5, 12]

Asymmetric synthesis of configurationally stable mononuclear coordination complexes has recently been the subject of much attention; the classical strategy is the introduction of stereogenic elements on the ligands, which then control—by intramolecular diastereoselective interactions—the configuration around the octahedral metal center.[3, 13] Temporary covalent interactions between a chiral medium (sugars) and designed achiral ligands can also be used and lead to good selectivities, as shown recently by Shinkai et al.[14] Having demonstrated the configurational stability of complex **2**, we reasoned that its asymmetric synthesis could be also possible by using TRISPHAT anions (**3**) as chiral auxiliaries.[15] We imagined that the configurational ordering induced by anions **3** on the labile [Fe(dmbp)$_3$]$^{2+}$ precursor **1** could be partially or fully transferred to complex **2** during synthesis. Treatment of a solution of [**1**][Δ-**3**]$_2$ in refluxing CD$_2$Cl$_2$ [d.r. 7.25:1 in favor of the homochiral ion pair (^{1}H NMR)[16]] with L (0.94 equiv) afforded the desired complex [**2**][Δ-**3**]$_2$ in quantitative yield. Excellent diastereoselectivity (d.r. > 20:1) was obtained, as a single set of signals corresponding to those of diastereomer [Δ-**2**][Δ-**3**]$_2$ could be observed in the ^{1}H NMR spectrum of the crude reaction mixture (Figure 2, spectrum (c)).[17] To our knowledge, this is the first example of high selectivity in the asymmetric synthesis of a stable coordination complex by using diastereoselective interactions restricted to intermolecular forces.

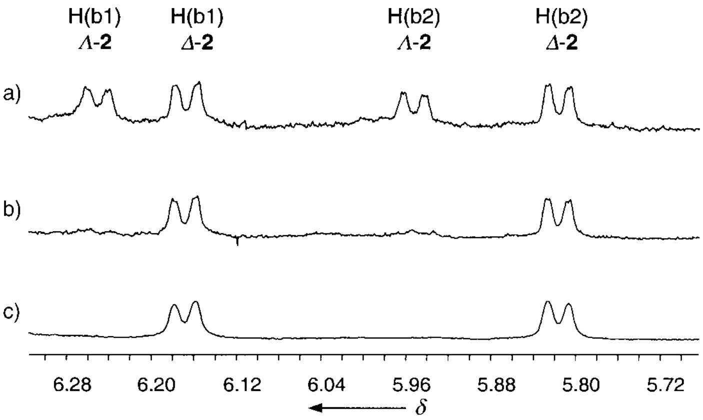
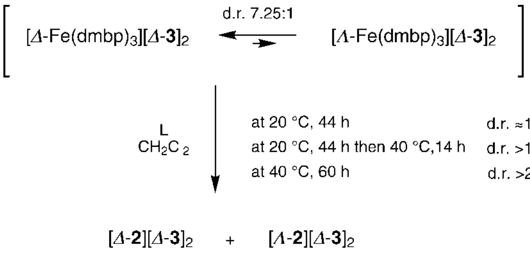


Figure 2. ^{1}H NMR spectra ($\delta = 6.30-5.68$) in 10% [D$_6$]DMSO/CDCl$_3$ of the crude reaction mixture [**1**][Δ-**3**]$_2$ + L. a) After 44 h at 20 °C, d.r. ≈ 1:1; b) after 44 h at 20 °C and 14 h at reflux, d.r. > 10:1; c) after 60 h at reflux, d.r. > 20:1.

It was then of interest to determine the origin—kinetic or thermodynamic—of the selectivity, especially since its value (d.r. > 20:1) is higher than the asymmetric induction of anions **3** on **1** (d.r. = 7.25:1). Several studies were therefore performed to determine the nature of the control. First, pure heterochiral complex [*Λ*-**2**][*Δ*-**3**]$_2$, isolated by chromatographic resolution, was heated to reflux in CD_2Cl_2, and complete transformation into the homochiral diastereomer [*Δ*-**2**][*Δ*-**3**]$_2$ was observed after 18 h.[18] Under similar conditions, no change was monitored for solutions of complex [*Δ*-**2**][*Δ*-**3**]$_2$. These results seemed to indicate thermodynamic control, as the high diastereoselectivity of the synthetic reaction could result from equilibration of the diastereomers at elevated temperature. To test this hypothesis, the asymmetric synthesis was attempted again at room temperature (20 °C) rather than at reflux (40 °C). A rather long reaction time (44 h) was required to achieve replacement of two dmbp ligands by L, and the resulting [**2**][*Δ*-**3**]$_2$ salt was obtained with essentially no selectivity (Scheme 1; d.r. ≈ 1:1, Figure 2, spectrum (a)).



Scheme 1.

When the reaction was carried out for 44 h at 20 °C and then 14 h at 40 °C, a high selectivity was again observed in favor of the homochiral complex [*Δ*-**2**][*Δ*-**3**]$_2$ (d.r. > 10:1, Figure 2, spectrum (b)). All these experiments seem to indicate that the reactions performed at room temperature lead to a poor diastereoselectivity under kinetic control, and that heating is required to induce a high degree of configurational ordering under thermodynamic control. The selectivity of the reaction probably results from the preferred homochiral association of three-bladed propellers **2** and **3**.

In conclusion, we have shown that the configurational stability of a tris(diimine) – iron(II) complex can be unusually high for a carefully designed tetradentate ligand and that its resolution and asymmetric synthesis is feasible by using TRISPHAT anions as noncovalent chiral auxiliaries.

Received: December 6, 2001 [Z18336]

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[18] At room temperature in CD_2Cl_2, no such epimerization was observed by ^1H NMR spectroscopy.