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Phase Transfer of Enantiopure Werner Cations into Organic Solvents: An Overlooked Family of Chiral Hydrogen Bond Donors for Enantioselective Catalysis

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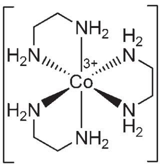
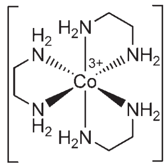
Werner salts of the chiral tris(ethylenediamine)-substituted octahedral cation [Co(en)$_3$]$^{3+}$, and related complexes, have played important historical roles in the development of inorganic chemistry and stereochemistry.[1–3] As originally described in 1912,[2b] the two enantiomers (**I**, **II**) can be separated by recrystallization of the diastereomeric tartrate salts. Chloride anion exchange then affords resolved enantiomers of [Co(en)$_3$]Cl$_3$. An extensive aqueous chemistry of these salts, and analogues with other diamines, was subsequently developed.[4,5] However, despite the ready availability and low cost of these enantiopure building blocks, there have been no applications in enantioselective organic syntheses. Towards this end, we posed the initial question as to whether such Werner salts can be rendered soluble in organic solvents.



I
Λ



II
Δ

A literature survey revealed scant data, the most relevant of which involved the tetraphenylborate salt [Co(en)$_3$](BPh$_4$)$_3$.[6,7] This complex, or the hexakis(ammonia) analogue, was reported as soluble in methanol, acetone, THF, and methanol/CH$_2$Cl$_2$ 1:9.[6b,c,7a] Many salts with more lipophilic diamine ligands—such as *trans*-1,2-cyclohexanediamine—have been described.[5] However, these have largely featured small inorganic anions, and we have not been able to locate any mention of solubility in organic solvents outside of an occasional reference to a light alcohol.[8] Accordingly, we set out to study chiral Werner salts with highly lipophilic anions, and communicate herein our initial results with the tetrakis[(3,5-trifluoromethyl)phenyl]borate or BAr$_f^-$ anion.[9]

As shown in Scheme 1, an orange aqueous solution of Δ-(−)-[Co(en)$_3$]I$_3$·H$_2$O[10] and a colorless CH$_2$Cl$_2$ solution of NaBAr$_f$ (1:3 mol ratio)[9b] were combined and stirred. As illustrated in the photographs, the lower CH$_2$Cl$_2$ phase turned orange, and the upper aqueous phase was nearly decolorized. The solvent was removed from the former to give the anion exchange product Δ-(−)-[Co(en)$_3$](BAr$_f$)$_3$ as an orange powder in 87% yield, which was characterized by NMR (^{1}H, ^{13}C), IR, and UV-visible spectroscopy.[11] Both ^{1}H NMR spectra and elemental analyses showed the product to be a hydrate, for which fourteen water molecules best fit the data (calcd for C$_{102}$H$_{88}$B$_3$CoF$_{72}$N$_6$O$_{14}$ (3081.07): C 39.76, H 2.88, N 2.73; found C 39.87, H 2.77, N 2.66). The hydration level was reproducible, and presumably reflects a labile second-coordination-sphere hydrogen bonding network, which was viewed as an auspicious sign for catalysis (below). Thermogravimetric analyses showed several mass loss regimes, the first two with T_i/T_e values[12] of 37.1/95.7 °C (3.4%, or 5.8 H$_2$O) and 95.8/155.7 °C (13.3% cumulative loss), respectively.

The $[\alpha]^{25}_{589}$ value for Δ-(−)-[Co(en)$_3$](BAr$_f$)$_3$·14 H$_2$O was much smaller than that of the corresponding iodide salt Δ-(−)-[Co(en)$_3$]I$_3$·H$_2$O (−9±1° (CH$_2$Cl$_2$) versus −90° (H$_2$O)[10]). As analyzed elsewhere,[13] this is an expected consequence of the much heavier anion. For idealized salts

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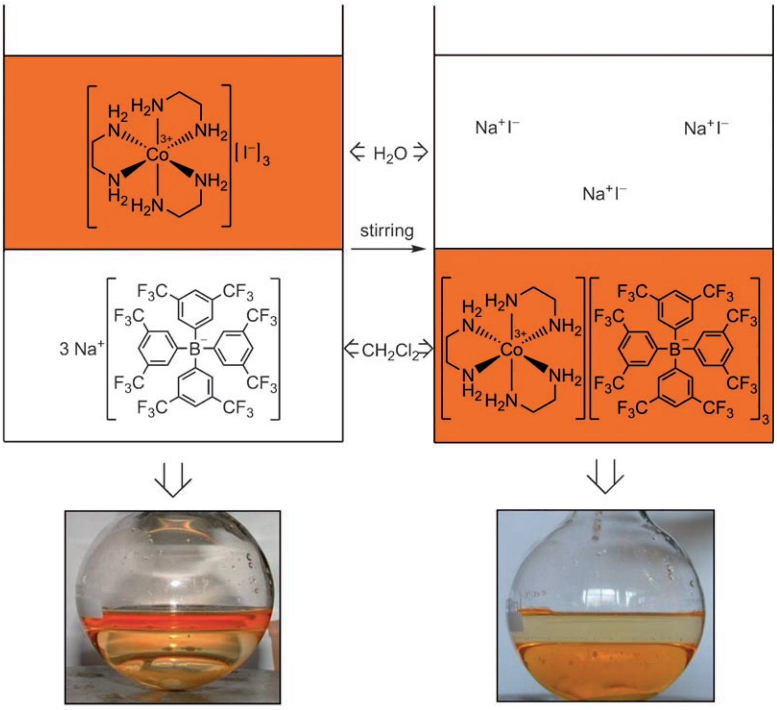


Scheme 1. Synthesis of Δ-(−)-[Co(en)$_3$](BAr$_f$)$_3$·14H$_2$O.

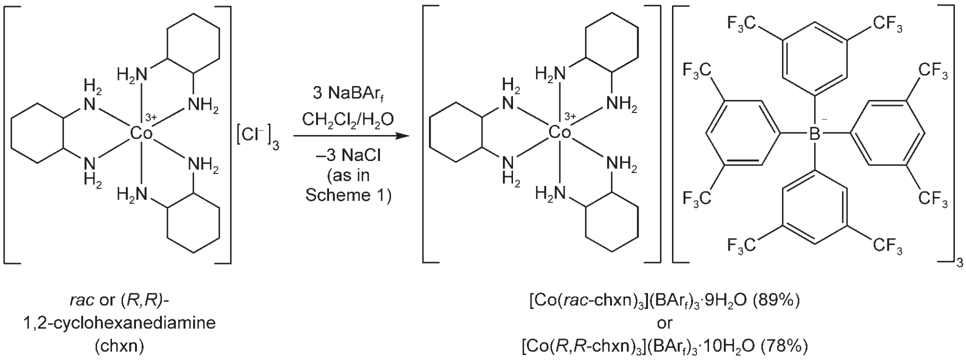
composed of non-interacting cations and anions, a value of −19° would be predicted. Besides CH$_2$Cl$_2$, Δ-(−)-[Co(en)$_3$](BAr$_f$)$_3$·14 H$_2$O was soluble in acetone, ethyl acetate, THF, DMSO, and alcohols. It was sparingly soluble in ether, and insoluble in CHCl$_3$, toluene, and benzene.

To confirm generality, the preceding protocol was applied to two *trans*-1,2-cyclohexanediamine (chxn) complexes, as depicted in Scheme 2. First, an aqueous solution of a salt derived from racemic *trans*-1,2-cyclohexanediamine, [Co(*rac*-chxn)$_3$]Cl$_3$·H$_2$O,[14] was similarly treated with a CH$_2$Cl$_2$ solution of NaBAr$_f$. The aqueous phase decolorized, and an identical workup gave [Co(*rac*-chxn)$_3$](BAr$_f$)$_3$ in 89 % yield as a nonahydrate, as assayed by ^{1}H NMR and microanalysis.[15] Eight stereoisomers are possible (four diastereomers and their enantiomers), which for the starting salt have been independently isolated, characterized, and thermally equilibrated (H$_2$O, 100 °C).[5a] Interestingly, the product exhibited three chxn ^{13}C NMR signals, suggestive of a single diastereomer. Of the two diastereomers that would give only three signals, *lel*$_3$ and *ob*$_3$, the former is much more stable (8.20 kJ mol^{-1} or 1.96 kcal mol^{-1}).[16]

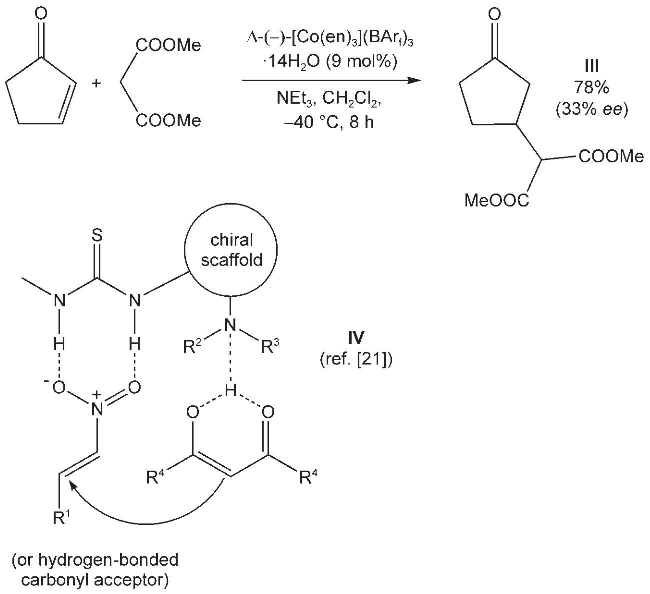
An analogous reaction was conducted with a salt derived from enantiopure *R,R*-chxn, [Co(*R,R*-chxn)$_3$]Cl$_3$·4 H$_2$O,[5a] a system for which only two diastereomers (Δ-*lel*$_3$ and Λ-*ob*$_3$) are possible. Workup gave [Co(*R,R*-chxn)$_3$](BAr$_f$)$_3$ as a decahydrate in 78 % yield.[17] Since only a single set of three chxn ^{13}C NMR signals was observed, the product was tentatively assigned as the more stable Δ-*lel*$_3$ diastereomer. Both [Co(*rac*-chxn)$_3$](BAr$_f$)$_3$·9H$_2$O and [Co(*R,R*-chxn)$_3$](BAr$_f$)$_3$·10H$_2$O exhibited solubility profiles very similar to that of Δ-(−)-[Co(en)$_3$](BAr$_f$)$_3$·14H$_2$O. Hence, it can be confidently extrapolated that all trications of the type [Co(1,2-diamine)$_3$]$^{3+}$ can be solubilized in organic media.

There is currently much interest in chiral hydrogen bond donors as enantioselective catalysts for organic reactions.[18] A variety of literature data suggests that many amine-substituted Werner cations are exceptional donors. For example, hydrogen bonds between the anions and NH protons are present in all of the numerous crystal structures of [Co(1,2-diamine)$_3$]X$_3$ and similar species we have examined. In the case of chiral anions, many chiral recognition phenomena have been documented. For example, diastereomeric salts derived from Δ-*lel*$_3$-[Co(*R,R*-chxn)$_3$]$^{3+}$ or Λ-*lel*$_3$-[Co(*S,S*-chxn)$_3$]$^{3+}$ and the tartrate dianion have been crystallographically characterized, and exhibit multidentate hydrogen bonding motifs.[19] The relative strengths of these interactions have been estimated computationally, and are weaker in the more soluble diastereomer. Similar structural studies have been conducted with diastereomeric tartrate salts of the enantiomeric cations **I** and **II**,[20] per Werner's original resolution.

Thus, we sought to conclude this study with a brief proof of principle. Recently, a variety of chiral thioureas have been found to be effective enantiose-



Scheme 2. Syntheses of *trans*-1,2-cyclohexanediamine complexes.



Scheme 3. Enantioselective catalysis of a Michael addition by a Werner complex.

lective catalysts for Michael additions, activating the acceptor via hydrogen bonding.[21,22] As shown in Scheme 3, the Michael addition of dimethyl malonate to 2-cyclopenten-1-one was attempted in the presence of 9 mol% of Δ-(−)-$[Co(en)_3](BAr_f)_3 \cdot 14H_2O$ in CH_2Cl_2 at −40°C, using a stoichiometric amount of NEt_3. Column chromatography gave the addition product **III** in 78% yield. As described in the Supporting Information, analysis of the corresponding ethylene glycol ketal by chiral HPLC indicated a 33% *ee*.[23] When an aqueous solution of the reaction residue was treated with a CH_2Cl_2 solution of $NaBAr_f$, Δ-(−)-$[Co(en)_3](BAr_f)_3 \cdot 14H_2O$ was recovered in high yield (81% after recrystallization (analytically pure), or 98% with minor amounts of NEt_3/educts/**III**) and reused with similar results.

Since cobalt(III) Werner cations are substitution inert, asymmetric induction must take place via a second-coordination-sphere mechanism, possibly with the participation of hydrogen-bonded water molecules. Although our *ee* value is lower than those obtained with the best thiourea catalysts, the latter normally incorporate a nitrogen base, such that the more highly organized transition state assemblies **IV** (Scheme 3) are possible.[21] Accordingly, efforts to prepare functionalized Werner complexes that feature this and other design elements are in progress and will be reported in due course.[24]

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Keywords: enantioselective catalysis · hydrogen bonds · Michael addition · phase-transfer catalysis · Werner complex

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[11] $[\alpha]_D^{25} = -9 \pm 1$ ($c = 1.05$ in CH_2Cl_2); ^1H NMR (400 MHz, CD_2Cl_2): BAr_f at $\delta = 7.72$ (s, 24H; *o*), 7.58 (s, 12H; *p*); 4.69 (br s, 12H; NH_2), 2.98 (br s, 6H; C*H*H′), 2.76 (s, 30H; 15H_2O), 2.66 ppm (s, 6H; CH*H*′); ^{13}C NMR (100.6 MHz, CD_2Cl_2): BAr_f at $\delta = 161.8$ (q, ^1J(C,B) = 49.9 Hz; *i*), 134.9 (s; *o*), 128.9 (q, ^2J(C,F) = 30.1 Hz; *C*CF_3), 124.7 (q, ^1J(C,F) = 272.5 Hz; CF_3), 117.6 (s; *p*); 45.5 ppm (s; CH_2). IR (thin film): $\nu = 3246$ (NH_2), 1613 (NH_2), 1355, 1274, 1116, 891, 837 cm^{-1}; UV/Vis (EtOH): λ_{max} (ε) = 463 (170), 334 (255), 278 (10702), 269 (13532 $mol^{-1} dm^3 cm^{-1}$).

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[16] To our knowledge, no ^{13}C NMR spectra of any salts of the formula $[Co(\textit{trans}\text{-chxn})_3]X_3$ have ever been reported. However, the stereoisomers of analogous *rac* and *meso*-2,3-butanediamine complexes exhibit distinctive ^{13}C NMR spectra.[3c] The well-established *lel*/*ob* nomenclature refers to the orientation of the $H_2NC{-}CNH_2$ bonds versus the three-fold axis of the CoN_6 core (paral*lel* or *ob*lique). Reference structures with alternative *R*/*S* designations are provided in the Supporting Information.

[17] ^1H NMR (400 MHz, CD_2Cl_2): BAr_f at $\delta = 7.72$ (s, 24H; *o*), 7.57 (s, 12H; *p*); 4.64 (br s, 6H; N*H*H′), 4.09 (br s, 6H; NH*H*′), 2.81 (s, 23H; 11.5 H_2O), chxn at 2.23 (m, 12H), 1.74 (m, 6H), 1.44 (m, 6H),

1.10 ppm (m, 6H); ^{13}C NMR (100.6 MHz, CD_2Cl_2): BAr_f at $\delta = 161.8$ (q, ^1J(C,B) = 50.0 Hz; *i*), 134.9 (s; *o*), 128.9 (q, ^2J(C,F) = 30.1 Hz; *C*CF_3), 124.7 (q, ^1J(C,F) = 272.5 Hz; CF_3), 117.6 (s; *p*); chxn at 61.6 (s; NCH), 33.2 (s; CH_2), 23.3 ppm (s; CH_2); IR (thin film): $\nu = 1611$ (NH_2), 1355, 1272, 1119, 889, 837 cm^{-1}; elemental analysis calcd (%) for $C_{114}H_{98}B_3CoF_{72}N_6O_{10}$: C 43.18, H 3.11, N 2.65; found: C 43.27, H 2.72, N 2.63.

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