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Spontaneous Resolution

Efficient Asymmetry Generation in the Synthesis of Oxo-Rhenium(V) Complex *cis*-$[ReOCl_2\{OCMe_2CMe_2OP(OCMe_2CMe_2O)\}py]$**

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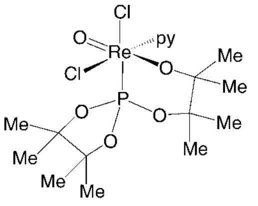
One of the most intriguing challenges of stereochemistry is deracemization and the preparation of homochiral compounds.[1] Despite the great progress in asymmetric organic synthesis, there are only several instances of genuine "absolute" asymmetric preparation of inorganic compounds,[2] these include spontaneous resolution processes too.[3] Thus, a partial photoresolution either in circularly polarized light[4a,b] or a parallel magnetic field[4c] has been observed for the $[Cr(ox)_3]^{3-}$ ion and its derivatives. Gillard and his associates have described the synthesis of the chiral polysulphide $(NH_4)_2[Pt(S_5)(S_6)_2]\cdot 2\,H_2O$.[5] The complex crystallizes spontaneously with one enantiomer in excess. It was obtained from a well-stirred water reaction mixture of K_2PtCl_6 and an excess of $(NH_4)_2S_n$, maintained at pH 9.4. Kondepudi and coworkers have shown that, whereas the crystallization of $NaClO_3$ from unstirred solutions yields a racemic conglomerate of (+)- and (−)-$NaClO_3$ (cubic space group $P2_13$), vigorous stirring triggers spontaneous symmetry breaking and produces almost exclusively crystals of single handedness.[6] Asakura et al. have demonstrated the generation of optically active *cis*-$[CoBr(NH_3)(en)_2]Br_2$ (en = 1,2-ethanediamine) from optically inactive substrates in a stirred suspension by a chiral autocatalysis mechanism.[7] More recently, it has been reported that the crystallization of $NaClO_3$ from a solution irradiated by antiparallel-spin electrons results in dextrorotatory crystals in excess, whereas irradiation by parallel-spin positrons yields crystals with the opposite handedness.[8] Keszthelyi and Szabó-Nagy have described a small enantiomeric excess found in polycrystalline material upon crystallization from racemic solutions of (+)- and (−)-tartrate(2−) with either (+)- and (−)-$[Co(en)_3]^{3+}$ or $[Ir(en)_3]^{3+}$ ions.[9] The authors of the latter two works have claimed that the observed partial deracemization is because of electroweak forces. Clearly, these preparations could only be successful under nonequilibrium conditions involving physical fields and/or autocatalytic chirality-amplification mechanisms. Nevertheless, in the preparation of transition-metal complexes, the generation of chiral asymmetry with substantial optical yields still remains rather rare.

In the course of our research on the coordination capability of the spirophosphorane $HP(OCMe_2CMe_2O)_2$,[10] we synthesized a chiral complex *cis*-$[ReOCl_2\{OCMe_2CMe_2OP(OCMe_2CMe_2O)\}py]$ (*cis*-**1**, py = pyridine) as a racemate.[10a] In addition to monodentate ligands, the six-coordinate complex also contains a chelating phosphite diolato(1−) ligand, a deprotonated tautomeric form of the spirophosphorane $(OCMe_2CMe_2O)POCMe_2CMe_2OH$. The complex appeared to be rigid on the NMR time scale.



cis-**1**
[*OC*-6-52-*C*]

Subsequently, we discovered that, depending on the reaction conditions, some built-in right or left handedness could be obtained, particularly if the synthesis was carried out under vigorous stirring conditions. Thus, the toluene suspension of *trans*-$[ReOCl_2(OEt)py_2]$[11] and a twofold excess of $HP(OCMe_2CMe_2O)_2$,[10a,12] boiled and vigorously stirred, affords the polycrystalline title compound in yields of approximately 70 % with a large excess of one optical isomer. Figure 1 shows the circular dichroism (CD) spectra of the representative samples of the compound prepared with and without stirring and boiling.

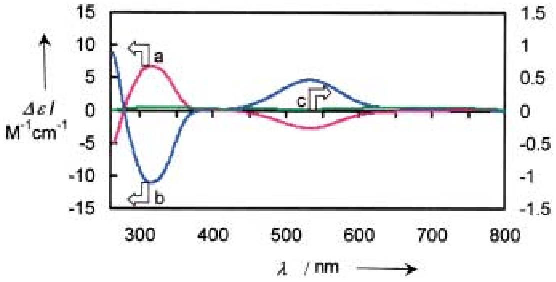


Figure 1. CD spectra for samples of *cis*-**1** in MeCN solution ($c = 1\times10^{-3}$ M, 20 °C, 1 cm cell): a) sample made with excess levorotatory $(-)_{535}$ enantiomer (red), b) sample made with excess dextrorotatory $(+)_{535}$ enantiomer, obtained with stirring (blue), and c) racemic sample obtained without stirring (green).

While the absence of absorption indicates formation of a racemate, certain differences in $\Delta\varepsilon$ intensity at 535 nm and 310 nm, observed for the two congeners, suggest a disparate distribution of enantiomers in these samples.

Figure 2 shows the optical yields (*ee* evaluation, see below) of the product obtained for a number of syntheses under different reaction conditions. The syntheses conducted with stirring and boiling (Figure 2 a) afford products with randomly distributed optical yields. But the residual optical activity or lack of such activity in the CD spectra observed for the samples with no boiling, no stirring (Figure 2 b) implies

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[**] py = Pyridine.

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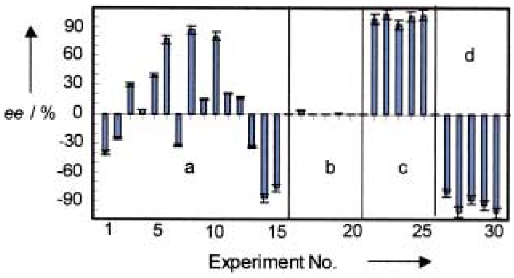

Figure 2. Chiral-symmetry-breaking syntheses of *cis*-**1**. The optical yields *ee* (± max. absolute error) for samples obtained from: a) stirred and boiled reaction mixture, b) neither stirred nor boiled reaction mixture (but at the same reaction temperature as in (a)), c) stirred and boiled reaction mixture seeded with 2 mol% of dextrorotatory $(+)_{535}$ solid sample, d) stirred and boiled reaction mixture seeded with 2 mol% of levorotatory $(-)_{535}$ solid sample.

racemate formation and equilibrium reaction conditions. Furthermore, when the preparations were performed with seeding with a small amount (2 mol%) of the dextrorotatory $(+)_{535}$ or levorotatory $(-)_{535}$ solid sample (from exp. No. 8 and 14, Figure 2a) with sustained stirring and boiling, products related to the *ee* value of the seeds (exp. No. 21, Figure 2c exp. No. 26, Figure 2d) were obtained. Repeated seeding with samples of either handedness from previous preparations (exp. Nos. 22–25, Figure 2c, and exp. Nos. 27–30, Figure 2d) resulted in products of similar, fairly high optical purity (*ee*).

Fortunately, X-ray diffraction studies along with CD studies of different single crystals made it possible to assign the absolute configuration and pertinent CD spectra. The complex *cis*-**1** crystallizes at ambient temperature from acetonitrile solution in an enantiomorphic space group as a conglomerate of either *A* or *C* enantiomers.[13,14] CD studies of the single crystals[15] allowed us to assign CD spectra inherent to the enantiomer *C* ($\Delta\varepsilon_{535} = 5.45(\pm 0.07)$ and $\Delta\varepsilon_{310} = -12.1$ (±0.2 std error) and consequently to evaluate the enantiomeric excess values for all the described preparations (Figure 2). In seeded syntheses the *ee* values appeared to be particularly high, up to 99% (±3% max. absolute error).

Thus, depending on the reaction conditions, the chiral-symmetry-breaking synthesis of *cis*-**1** produces a disparate distribution of $C\,(+)_{535}$ and $A\,(-)_{535}$ enantiomers and the system clearly exhibits chirally autocatalytic behavior (random *ee* distribution, strong chiral seeding effect). This synthesis may involve two processes currently under investigation, both exhibiting autocatalytic phenomena. The first is a spontaneous resolution of conglomerates in stirred crystallization owing to a secondary nucleation mechanism.[16] The second is asymmetric autocatalytic reaction[17] driven by kinetic nonlinear effects[18] and/or agglomerate formation.[19]

Our preliminary studies on racemization allowed us to elucidate some mechanistic aspects of this synthesis. Starting either with a highly enriched dextrorotatory sample (*ee* +99%) or a racemate and similar conditions to those applied for the synthesis, the readily soluble (1.6 g per 100 cm^3 at RT and approximately 8 g per 100 cm^3 at 100 °C in toluene) achiral *trans* complex can be obtained in low yield.[20]. The only species left is the starting, hardly soluble, *cis* complex (*cis–rac* 0.0018 g per 100 cm^3 at 110 °C in toluene) with its optical (*ee*) purity retained.

Furthermore, the *trans*-**1** complex reacts under similar conditions affording *cis*-**1**, either the *rac* complex in 73% yield (it the reaction was not seeded) or the *C* complex with *ee* +48% in 81% yield if seeded with 2% of the *C* complex (Supporting Information). These findings strongly suggest that in solution, the soluble *trans* complex participates as an intermediate in the equilibrium (Figure 3) between the two hardly soluble enantiomers.

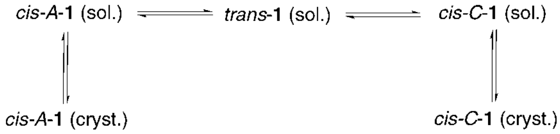

Figure 3. The role of the soluble *trans* complex as an intermediate between the two enantiomers.

Owing to this *cis–trans* isomerization reaction, the equilibrium between the two enantiomers is readily shifted by growth of the available crystals (either formed or added) and the spontaneous resolution is achieved by an autocatalytic secondary nucleation process.

Thus, it appears that the chirally autocatalytic synthesis presented is an example of a highly efficient, spontaneous resolution of the conglomerate during a stirred crystallization while the complex forms, a process rarely observed for coordination compounds.

Experimental Section

Typical procedure for syntheses with stirring*:* *trans*-[ReOCl$_2$(OEt)py$_2$] (0.150 g, 0.315 mmol) was added to a toluene (25 cm^3) solution of HP(OCMe$_2$CMe$_2$O)$_2$ (0.167 g, 0.633 mmol) in a 50-cm^3 Schlenk flask under nitrogen. The flask, equipped with a teflon stirbar (16 × 7 mm), condenser, and oil bubbler, was placed in an oil bath heated to 120 °C. The reaction mixture was boiled and vigorously stirred (ca. 1100 rpm) for 5 h to afford the pink-violet precipitate. After cooling to room temperature, the product was collected by filtration, washed with methanol and ethyl ether and dried under vacuum; yield 0.146 g (0.237 mmol, 75%). The seeded experiments were conducted under the same reaction conditions save for the addition of the seeds (finely ground, 2% (mol Re/mol Re)) from previously obtained samples before the start of the synthesis. For unstirred experiments, similar reaction conditions were applied except for the glassware. A thick-walled round-bottom flask (50 cm^3) equipped with a teflon pressure-release valve was charged with the reagents and toluene, sealed, and immersed entirely in preheated (120 °C) oil bath. After one minute the overpressure was partially reduced, yet reaction-mixture boiling was avoided.

The experiments for mechanistic studies were performed under similar conditions (reactant amounts, stirring, boiling toluene) to those used for syntheses except that previously obtained products were used as substrates (Supporting Information).

CD measurements of the single-crystal samples in solution (six solutions and five crystals in each), together with concentration determination (by means of the UV spectra calibration curve), gave six values of $\Delta\varepsilon_{535} = 5.64$, 5.54, 5.54, 5.46, 5.36, 5.16 (±0.10); and $\Delta\varepsilon_{310} = -13.0$, −12.2, −12.1, −11.9, −11.7, −11.7(±0.16 max. absolute error), respectively. Hence, the mean values: $\Delta\varepsilon_{535} = 5.45(\pm 0.07)$ and $\Delta\varepsilon_{310} = -12.1(\pm 0.2$ std error) for the pure enantiomer C-$(+)_{535}$. The

CD spectra of the products were recorded for acetonitrile solutions in a 1 cm cell at 20 °C with a Jasco J 715 instrument.

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[1] a) E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**; b) A. von Zelewsky, *Stereochemistry of Coordination Compounds*, Wiley, New York, **1996**; c) *Comprehensive Asymmetric Catalysis* (Eds.: E. Njacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[2] a) M. Avalos, P. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios, L. D. Barron, *Chem. Rev.* **1998**, *98*, 2391 – 2404; b) B. L. Feringa, R. A. van Delden, *Angew. Chem.* **1999**, *111*, 3624 – 3645; *Angew. Chem. Int. Ed.* **1999**, *38*, 3418 – 3438; c) M. Avalos, P. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios, *Tetrahedron: Asymmetry* **2000**, *11*, 2845 – 2874.

[3] a) I. Bernal, G. B. Kauffman, *J. Chem. Educ.* **1987**, *64*, 604 – 610; b) J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolutions*, W. Krieger Publishing, Malabar Florida, **1994**.

[4] a) K. L. Stevenson, J. F. Verdieck, *J. Am. Chem. Soc.* **1968**, *90*, 2974 – 2975; b) B. Norden, *Acta Chem. Scand.* **1970**, *24*, 23 – 25; c) G. L. J. A. Rikken, E. Raupach, *Nature* **2000**, *405*, 932 – 935.

[5] a) R. D. Gillard, F. L. Wimmer, J. P. G. Richards, *J. Chem. Soc. Dalton Trans.* **1985**, 253 – 258; b) E. H. M. Evans, J. P. G. Richards, R. D. Gillard, F. L. Wimmer, *Nouv. J. Chim.* **1986**, *10*, 783 – 791.

[6] a) D. K. Kondepudi, R. Kaufman, N. Singh, *Science* **1990**, *250*, 975 – 976; b) D. K. Kondepudi, K. L. Bullock, J. A. Digits, J. K. Hall, J. M. Miller, *J. Am. Chem. Soc.* **1993**, *115*, 10211 – 10216.

[7] a) K. Asakura, K. Kobayshi, Y. Mizusawa, T. Ozawa, S. Osanai, S. Yoshikawa, *Phys. D* **1995**, *84*, 72 – 78; b) K. Asakura, D. K. Kondepudi, R. Martin, *Chirality* **1998**, *10*, 343 – 348; c) K. Asakura, A. Ikumo, K. Kurihara, S. Osanai, D. K. Kondepudi, *J. Phys. Chem.* **2000**, *104*, 2689 – 2694.

[8] S. Mahurin, M. McGinnis, J. S. Bogard, L. D. Hulett, R. M. Pagni, R. N. Compton, *Chirality* **2001**, *13*, 636 – 640.

[9] A. Szabó-Nagy, L. Keszthelyi, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 4252 – 4255.

[10] a) T. Głowiak, W. K. Rybak, A. Skarżyńska, *Polyhedron* **2000**, *19*, 2667 – 2672; b) A. Skarżyńska, W. K. Rybak, T. Głowiak, *Polyhedron* **2001**, *20*, 2667 – 2674.

[11] a) N. P. Johnson, F. J. M. Taha, G. W. Wilkinson, *J. Chem. Soc.* **1964**, 2614 – 2618; b) M. Freni, D. Giusto, P. Romiti, G. Minghetti, *Gazz. Chim. Ital.* **1969**, *99*, 286 – 299; c) A. Guest, C. J. L. Lock. *Can. J. Chem.* **1971**, *49*, 603 – 610.

[12] a) R. R. Holmes, *J. Am. Chem. Soc.* **1974**, *26*, 4143 – 4149; b) R. Burgada, *Bull. Soc. Chim. Fr.* **1975**, 407 – 424.

[13] Crystal structure determination of *cis*-*C*-(+)$_{535}$-[ReOCl$_2${OCMe$_2$CMe$_2$OP(OCMe$_2$CMe$_2$O)}py], $C_{17}H_{29}Cl_2NO_5PRe$, orthorhombic, space group $P2_12_12_1$, $a = 9.988(2)$, $b = 11.655(2)$, $c = 18.301(4)$ Å, $V = 2130.4(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.919$ Mg m^{-3}, $\mu = 6.057$ mm^{-1}, $F(000) = 1208$, $\lambda(\mathrm{Mo}_{K\alpha}) = 0.71073$ Å, $T = 90(1)$ K, crystal dimensions $0.1 \times 0.1 \times 0.15$ mm, $2\theta_{max} = 57.28°$, 14435 reflections collected, 5031 unique; R indices $R_1 = 0.0199$, $wR_2 = 0.0515$ (all data) and Flack parameter 0.024(5). For the opposite absolute configuration A: $R_1 = 0.0501$, $wR_2 = 0.1268$ and Flack parameter 0.973(6). The data collected on KM4CCD camera diffractometer were corrected for Lorentz and polarization effects. Data reduction and analysis were carried out using the Kuma Diffraction (Wrocław) programs. The structure was solved by means of heavy atom methods using SHELXS-97 and refined by the full-matrix least-squares method on all F^2 using SHELXL-97 procedures (G. M. Sheldrick, Universität Göttingen, **1997**). Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included from the $\Delta\rho$ maps and refined with isotropic thermal parameters. CCDC-167174 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[14] Five different individual crystals grown from highly enriched dextrorotatory (+)$_{535}$, polycrystalline products (set c in Figure 2) consistently revealed similar Flack parameters and the same *C* stereochemistry in X-ray analyses, which indicates that there was no racemic twinning of the single crystals and the high optical purity of these polycrystalline products.

[15] The six dextrorotatory-originated crystalline samples, each containing five single crystals, yielded six very similar CD spectra in acetonitrile solution (Experimental Section), corroborating the homochirality of the single crystals and the optical purity of the obtained six crystalline samples.

[16] a) D. K. Kondepudi, J. Laudadio, K. Asakura, *J. Am. Chem. Soc.* **1999**, *121*, 1448 – 1451; b) D. K. Kondepudi, K. Asakura, *Acc. Chem. Res.* **2001**, *34*, 946 – 954.

[17] a) I. Sato, K. Kadowaki, K. Soai, *Angew. Chem.* **2000**, *112*, 1570 – 1572; *Angew. Chem. Int. Ed.* **2000**, *39*, 1510 – 1512; b) K. Soai, T. Shibata, I. Sato, *Acc. Chem. Res.* **2000**, *33*, 382 – 390.

[18] a) C. Girard, H. Kagan, *Can. J. Chem.* **2000**, *78*, 816 – 828; b) D. G. Blackmond, *Acc. Chem. Res.* **2000**, *33*, 402 – 411.

[19] D. G. Blackmond, Ch. R. McMilan, S. Ramdechul, A. Schorm, J. M. Brown, *J. Am. Chem. Soc.* **2001**, *123*, 10103 – 10104.

[20] The *cis* complex, *C* or *rac*, stirred and boiled in toluene for 5 h, affords the *trans* complex in 10.5 % or 17.5 % yields, respectively, and the corresponding *cis* complex with *ee* +99 % (*C*) or *ee* 0 % (*rac*). After another 15 h reaction time, no further conversion was observed within the experimental error (Supporting Information).