

# Enantiomeric enrichment of a nonracemic conglomerate of a chiral oxo-rhenium(v) complex

Witold K. Rybak\* and Anna Skarżyńska

Faculty of Chemistry, University of Wrocław, 50-383, Wrocław, Poland.

E-mail: rybak@wchuwr.chem.uni.wroc.pl; Fax: +48 71 3282 348; Tel: +48 71 3757 348

Received (in Toulouse, France) 16th July 2003, Accepted 24th September 2003

First published as an Advance Article on the web 30th October 2003

The enantiomer being in excess was readily recovered from a nonracemic conglomerate of chiral *cis*-[ReOCl<sub>2</sub>{OCMe<sub>2</sub>CMe<sub>2</sub>O-P(OCMe<sub>2</sub>CMe<sub>2</sub>O)}py] by means of a difference in solubility between the enantiomer and the racemate; subsequently the solubility diagram and the specific optical rotation [ $\alpha$ ]<sub>589</sub> = +1345 (±30 max. absolute error; *c* = 0.05 g per 100 cm<sup>3</sup> in MeCN) for the pure enantiomer of the absolute configuration *C* was also determined.

Since Pasteur's discovery of homochiral crystallization, much research activity has been devoted to deracemization and preparation of single-handed compounds.<sup>1–3</sup> Chiral molecules crystallize to form crystalline racemate that can be a racemic compound (true racemate), a racemic solid solution or a conglomerate (racemic mixture). While the first two racemate forms usually require optically active auxiliary agents to separate the enantiomers (with a number of exceptions<sup>3,4</sup>), the third one, conglomerate, can undergo spontaneous resolution during the course of crystallization, without the aid of any diastereomeric interaction. Perhaps the most spectacular example in coordination chemistry is provided by Werner's complex, *cis*-[Co(en)<sub>2</sub>(NO<sub>2</sub>)<sub>2</sub>]Cl, separated with the aid of a chiral resolving agent<sup>5,6</sup> but proved by Bernal<sup>7</sup> to crystallize as a conglomerate with single crystals as large as 1.5 × 0.7 × 0.5 cm<sup>3</sup>. However, it is known that only a limited number of conglomerates crystallize in hemihedral forms pure and large enough to permit them to be sorted by physical means. More recently, instances of such spontaneous resolution by 'triage' have been reported in connection with the preparation of chiral diphosphane ligands<sup>8</sup> and the synthesis of octahedral metal complexes with tripod N<sub>6</sub>-type donor atom ligands.<sup>9</sup>

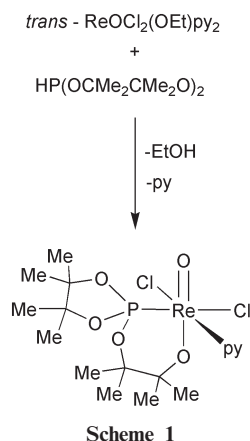
Several procedures have been developed to overcome the practical difficulties in separating enantiomers. One frequently used method implies preferential homochiral crystallization of conglomerates from either solutions or melts due to 'resolution by entrainment'.<sup>1,10</sup> More recently, related spontaneous resolutions including Werner's chiral Co(III) complexes have been described by Kostyanovsky and his associates.<sup>11,12</sup> Further progress in deracemization has been made by imposing far-from-equilibrium conditions on chiral systems,<sup>13–15</sup> which occur for instance in stirred crystallization.<sup>16</sup> Under such conditions, due to asymmetric transformations (both of the first and of the second kind) during the course of crystallization (*e.g.*, secondary nucleation, racemization, formation of agglomerates), chirally autocatalytic preparations have been afforded with a fairly high enantioselectivity. Perhaps the most representative examples include recrystallization of NaClO<sub>3</sub><sup>17</sup> and 1,1'-binaphthyl<sup>18,19</sup> but also the synthesis of *cis*-[CoBr(N-H<sub>3</sub>)(en)<sub>2</sub>]Br<sub>2</sub>.<sup>20</sup> In all these systems the compounds crystallize as conglomerates.

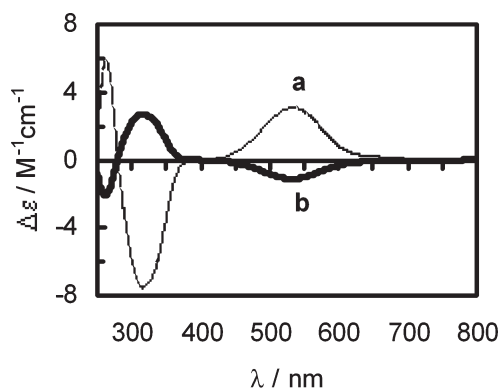
In our studies concerning optical activation in the synthesis of chiral *cis*-[ReOCl<sub>2</sub>{OCMe<sub>2</sub>CMe<sub>2</sub>OP(OCMe<sub>2</sub>CMe<sub>2</sub>O)}py] (**1**)<sup>21</sup> (Scheme 1) we were faced with the question of evaluation the enantiomeric excess (*ee*). Here we report on a simple method for enantiomer separation from a nonracemic conglomerate of the title rhenium complex **1**, based on Werner's primary observation<sup>6</sup> of a large difference in solubility between the enantiomorph complexes and racemates, without the necessity of crystallization. This permitted us to determine the solubility diagram and ultimately the stereochemistry of **1**.

Two enantiomerically impure polycrystalline samples **a** and **b** of the rhenium compound **1** (obtained from a chirally autocatalytic synthesis<sup>21</sup>), discerned in the CD spectra shown in Fig. 1, were tested for complete enantiomeric separation. A visible variance in the Δε absorption at 535 and 310 nm, observed for the two congeners, indicates a disparate distribution of enantiomers in these samples.

Fig. 2 shows the optical activity changes as a result of the number of successive extractions of these two samples with a small amount of acetonitrile (MeCN). The rotation angle and related optical yield of both the saturated solution of the extract (**l**) and the solid residue sample (**s**) were examined. Quite a few of the early samples of the extract solutions exhibit an optical rotation close to zero, characteristic for the racemate. Disparate contents of enantiomers in samples **a** and **b** imply a different number of extractions, which ultimately yield the abundant pure enantiomers, either dextrorotatory (+)<sub>589</sub> or levorotatory (–)<sub>589</sub>, as solid residues (**s** for both **a** and **b** samples, Fig. 2). Solubility data compiled in this way enabled us to construct the solubility diagram, which is presented in Fig. 3.

The shape of the solubility diagram, as well as the single eutectic point E found, confirm that polycrystalline **1** exists as a conglomerate. Indeed, the solubility of the racemate (0.105 g per 100 cm<sup>3</sup>) is almost twice that of the pure enantiomer (0.0531 g per 100 cm<sup>3</sup>) in acetonitrile at room temperature



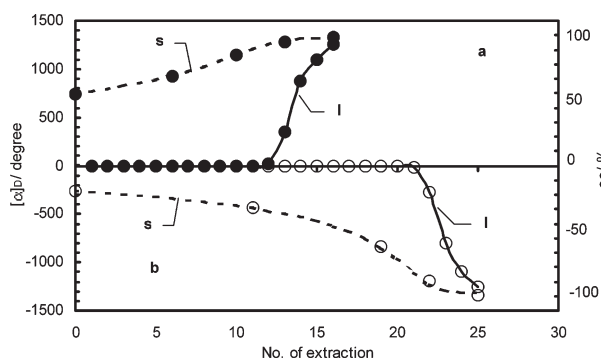


**Fig. 1** CD spectra for acetonitrile solutions of nonracemic solid samples of *cis*-[ReOCl<sub>2</sub>{OCMe<sub>2</sub>CMe<sub>2</sub>OP(OCMe<sub>2</sub>CMe<sub>2</sub>O)}py] used for enantiomeric separation with an excess of (a) dextrorotatory (+)<sub>589</sub> ( $\Delta\epsilon_{535}$  3.13,  $\Delta\epsilon_{310}$  -7.47) and (b) levorotatory (-)<sub>589</sub> ( $\Delta\epsilon_{535}$  -1.12,  $\Delta\epsilon_{310}$  2.67) enantiomers (see Fig. 2).

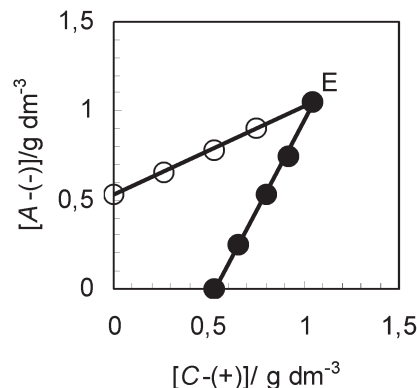
(20 °C), which is consistent with the so-called 'double solubility rule of Meyerhoffer'.<sup>10</sup>

When the recovered sample of the pure dextrorotatory (+)<sub>589</sub> enantiomer was crystallized from acetonitrile, it gave monocrystals (space group *P*2<sub>1</sub>2<sub>1</sub>1, No. 19). X-Ray analysis of the single crystal, by means of the similarity of the Flack parameters, confirmed the absolute configuration *C*; this stereochemistry of the rhenium compound is identical with that already reported.<sup>21</sup> Actually, it also made it possible to assign the specific optical rotation  $[\alpha]_{589} = +1345$  ( $\pm 30$  max. absolute error; *c* = 0.05 g per 100 cm<sup>3</sup>, MeCN, 20 °C) to the pure enantiomer with the absolute configuration *C*.

In summary, this enantiomeric enrichment method is based on the considerable difference in solubility between enantiomorphs and racemates established for conglomerates some time ago<sup>5,6,10</sup> but not appreciated so far. Obviously, only the enantiomer that is in excess can be recovered from a nonracemic mixture if subsequent asymmetric transformations are not available. Therefore, this method is rather rarely presented in the literature<sup>22</sup> and, to the best of our knowledge, has not been used for the resolution of inorganic compounds. Nevertheless, this simple and rapid separation procedure might be sensible and beneficial in some cases. In the case of optical activation reactions, it enables ready identification of situations where the reaction product is a conglomerate. It also makes it possible to prepare seeds for preferential crystallization. It may also



**Fig. 2** Enantiomeric separation of nonracemic solid samples (0.15 g) of *cis*-[ReOCl<sub>2</sub>{OCMe<sub>2</sub>CMe<sub>2</sub>OP(OCMe<sub>2</sub>CMe<sub>2</sub>O)}py] with (part a) dextrorotatory (+)<sub>589</sub> (56.1% ee) and (part b) levorotatory (-)<sub>589</sub> (20.5% ee) enantiomeric excess. Specific optical rotation  $\alpha_{589}$  and ee values vs. number of consecutive extractions with 5 cm<sup>3</sup> portions of MeCN were determined for the extract liquor (curves l) and occasionally for residues of the solid sample (curves s). The pure dextrorotatory and levorotatory enantiomers were recovered in yields of 0.069 g (46%) and 0.018 g (11.9%), respectively.



**Fig. 3** Solubility diagram for *cis*-[ReOCl<sub>2</sub>{OCMe<sub>2</sub>CMe<sub>2</sub>OP(OCMe<sub>2</sub>CMe<sub>2</sub>O)}py] in acetonitrile at 20 °C.

be helpful in the resolution of conglomerates that reveal racemic crystal twinning or epitaxial growth. Crystallization of the recovered pure enantiomer, in contrast to the racemic mixture or a partially enriched sample, may also facilitate the determination of the absolute configuration and stereochemistry for the particular enantiomer by means of X-ray analysis and schiroptical methods.

## Experimental

A centrifuge tube (10 cm<sup>3</sup>) equipped with a small Teflon<sup>®</sup> stir-bar was charged with a finely ground polycrystalline sample of the title compound **1** (0.15 g) and acetonitrile (5 cm<sup>3</sup>). The mixture was stirred at room temperature for 15 min, then centrifuged (6000 rpm) to separate the liquor. The liquor and occasionally solid residues dissolved in MeCN were examined by means of UV spectra and a calibration curve to determine the optical rotation,  $\alpha_{589}$ , and the concentration of the rhenium complex. The evaluation of ee was based on the specific optical rotation value  $[\alpha]_{589} = 1345$  (*c* = 0.05 g per 100 cm<sup>3</sup>, MeCN) of the pure enantiomer.

## References

- 1 J. Jacques, A. Collet and S. H. Wilen, *Enantiomers, Racemates and Resolutions*, W. Krieger Publishing, Malabar, FL, USA, 1994.
- 2 A. von Zelewsky, *Stereochemistry of Coordination Compounds*, Wiley, New York, 1996.
- 3 E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994.
- 4 R. Tamura, H. Takahashi, K. Hirotsu, Y. Nakajima, T. Ushio and F. Toda, *Angew. Chem., Int. Ed.*, 1998, **37**, 2876–2878 and references therein.
- 5 A. Werner, *Chem. Ber.*, 1911, **44**, 1887–1890.
- 6 I. Bernal and G. B. Kauffman, *J. Chem. Educ.*, 1987, **64**, 604–610.
- 7 I. Bernal, *Inorg. Chim. Acta.*, 1985, **96**, 99–110.
- 8 O. Tissot, M. Gouygou, F. Dallemer, J.-C. Daran and G. G. A. Balavoine, *Angew. Chem., Int. Ed.*, 2000, **40**, 1076–1078.
- 9 S. Nagasato, I. Katsuki, Y. Motoda, Y. Sunatsuki, N. Matsumoto and M. Kojima, *Inorg. Chem.*, 2001, **40**, 2534–2540.
- 10 A. Collet, M.-J. Brienne and J. Jacques, *Chem. Rev.*, 1980, **80**, 215–230.
- 11 R. G. Kostyanovsky, V. R. Kostyanovsky, G. K. Kadorkina and V. Y. Torbeev, *Mendeleev Commun.*, 2000, **3**, 83–84.
- 12 R. G. Kostyanovsky, V. Y. Torbeev and K. A. Lyssenko, *Tetrahedron: Asymmetry*, 2001, **12**, 2721–2726.
- 13 M. Avalos, P. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios and L. D. Barron, *Chem. Rev.*, 1998, **98**, 2391–2404.
- 14 B. L. Feringa and R. A. van Delden, *Angew. Chem., Int. Ed.*, 1999, **38**, 3418–3438.
- 15 M. Avalos, P. Babiano, P. Cintas, J. L. Jimenez and J. C. Palacios, *Tetrahedron: Asymmetry*, 2000, **11**, 2845–2874.
- 16 D. K. Kondepudi and K. Asakura, *Acc. Chem. Res.*, 2001, **34**, 946–954.

- 17 D. K. Kondepudi, K. L. Bullock, A. Digits, J. K. Hall and J. M. Miller, *J. Am. Chem. Soc.*, 1993, **115**, 10 211–10 216.
- 18 K. R. Wilson and R. E. Pincock, *J. Am. Chem. Soc.*, 1975, **97**, 1474–1478.
- 19 D. K. Kondepudi, J. Laudadio and K. Asakura, *J. Am. Chem. Soc.*, 1999, **121**, 1448–1451.
- 20 K. Asakura, A. Ikumo, K. Kurihara, S. Osanai and D. K. Kondepudi, *J. Phys. Chem. A*, 2000, **104**, 2689–2694.
- 21 W. K. Rybak, A. Skarżyńska and T. Głowiak, *Angew. Chem., Int. Ed.*, 2003, **42**, 1725–1727.
- 22 A. Horeau, 1972 observation quoted by E. L. Eliel, S. H. Wilen and L. N. Mander, p. 158 in ref. 3.