Resolution of racemates with achiral reagents

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The conditions required for resolving racemates into enantiomers by crystallization involve a deficiency of either the conglomerator or the achiral solubiliser to promote the solubility of the compound to be resolved; in both cases the resolution can also be achieved by internal entrainment, adding a single crystal of the resolvable conglomerate.

L. Pasteur was the first (May 1848) to separate[1] the enantiomorphic levorotatory and dextrorotatory crystals of an entirely racemic conglomerate such as sodium ammonium tartrate **1**·4H_2O. The individual crystals taken from this conglomerate were shown to be optically active[2] as were also the first crystals precipitated from its supersaturated solution.[3–5] The most important consequence of these classical experiments is the possibility to effect homochiral crystallization and, thereby, spontaneous resolution at the level of single crystals.

Independently, theoretical investigation of the meanings of this fundamental phenomena — the possibility of homochiral crystal formation — was begun by O. Bravais in France in the same year 1848 (Bravais crystal lattices) and completed by E. S. Fedorov in Russia and A. Schönflies in Germany (1890–1891). Sixty five of the 230 Fedorov space groups are chiral,† and hence all those chemical compounds which crystallise in these space groups produce crops of homochiral crystals (conglomerates) and are capable of spontaneous resolution into enantiomers by crystallization. However, all the methods developed by Pasteur (manual sorting of conglomerate crystals by a 'chiral' experimenter, separation *via* diastereomers and utilization of enzymes) and his followers (using an optically active seed by Gernez,[6] see also refs. 7–9) implicate the use of either chiral chemical reagents or asymmetric physical fields.[9–12] In particular, a modification of the second Pasteurian method included the use of a chiral resolving reagent in nonstoichiometric quantity.[7] W. Marckwald (1896) applied a half-mole quantity of the alkaloid cinchonine to resolve tartaric acid; W. J. Pope and S. J. Peachey (1899) introduced a neutralization technique for the second moiety of the compound to be resolved.

In the present work, we propose and realise a simple idea for the resolution of conglomerates without the involvement of any chiral reagent (preliminary results[13] were obtained at the 150th anniversary of Pasteur's discovery). (±)-Tartaric acid itself forms heterochiral crystals (space group $P\bar{1}$) whereas the Pasteur salt (±)-**1**·4H_2O containing achiral addends (NaOH, NH_3, H_2O) crystallises as a conglomerate[7] (space group $P2_12_12$). Such addends are called conglomerators (C).

On the onset of crystallization from a supersaturated solution of a conglomerate, the first formed 'left' (L) or 'right' (D) crystal initiates the formation of further crystals of the same type. If the supersaturation is sufficiently great, crystallization of the opposite enantiomer occurs. Such an alternating process (circulatory crystallization[14]) leads to a racemic precipitate. If the same procedure is performed with a deficiency of the conglomerator, after the first enantiomer has crystallised, the second enantiomer in the form of its adduct with the conglomerator is no longer supersaturated (Scheme 1).

† Chiral space groups compatible with a single enantiomer in a crystal: triclinic *P*1; monoclinic *P*2, $P2_1$, *C*2; orthorhombic *P*222, $P222_1$, $P2_12_12$, $P2_12_12_1$, *C*222, $C222_1$, *I*222, $I2_12_12_1$, *F*222; tetragonal *P*4, ($P4_1$, $P4_3$), $P4_2$, *I*4, $I4_1$, *P*422, $P42_12$, ($P4_122$, $P4_322$), ($P4_12_12$, $P4_32_12$), $P4_22_12$, $P4_22_12$, *I*422, $I4_122$; trigonal *P*3, ($P3_1$, $P3_2$), *R*3, *P*312, *P*321, ($P3_112$, $P3_212$), ($P3_121$, $P3_221$), *R*32; hexagonal *P*6, ($P6_1$, $P6_5$), ($P6_2$, $P6_4$), $P6_3$, *P*622, ($P6_122$, $P6_522$), $P6_322$, ($P6_422$, $P6_222$); cubic *P*23, $P2_13$, *I*23, $I2_13$, *F*23, *P*432, ($P4_132$, $P4_332$), $P4_232$, *I*432, $I4_132$, *F*432, $F4_132$ (in brackets, 11 enantiomorphous couples of space groups).

$$\text{Cryst. } (\text{LC})_n \xleftarrow[[\text{C}] \to 0]{} n\text{L} + n\text{D} + n\text{C} \xrightarrow[[\text{C}] \to 0]{} (\text{DC})_n \text{ cryst.}$$

Scheme 1

We found that crystallization of the Pasteur salt from H_2O at 18 °C (1 day) leads to crystals of (±)-**1**·4H_2O in 36% yield. Crystallization under the same conditions, except that a half-mole quantity of Na_2CO_3 was added, gives (–)-**1** (yield 30%, optical purity 55%). The experiment with Na_2CO_3 was then repeated but with the addition of a random crystal of conglomerate (±)-**1**·4H_2O as a seed to the supersaturated solution; this resulted in the formation of crystalline (+)-**1** (yield 35%, optical purity 65%). Such a procedure is essentially a modification of the Gernez method. It does not use any external chiral seed and can be called the internal entrainment procedure. Finally, the optical purity of (+)-**1**·4H_2O was increased to 80% by its crystallization at 30 °C (1 day), separation of the precipitated racemate (±)-**1**·4H_2O and evaporation of the mother liquor. Thus, the temperature conditions for conglomerate formation found by van't Hoff[15] can be used for increasing the optical purity by successive conglomerate–racemate crystallizations.

Racemic coordination complexes were originally resolved by A. Werner (1811) using chiral reagents.[16] Many of these complexes were later shown to form conglomerates,[17,18] *e.g. cis*-$[Co(NO_2)_2(en)_2]Cl$ **2** (space group $P2_1$). We have found that its analogue *cis*-$[Co(NO_2)_2(en)_2]Br$ **3** is also a conglomerate, as follows from the optical activity of its individual crystals. This is confirmed by a single crystal X-ray diffraction study of (±)-**3** (space group $P2_1$). Like **1**, compounds **2** and **3** can be resolved by crystallization from supersaturated solutions upon adding their individual conglomerate crystals as seeds. Bromide **3** is less soluble[19] than chloride **2** by a factor of 3.6, and we succeeded in obtaining optically active bromides (–)-**3** and (+)-**3** (yields 15–30%, optical purity 20–50%) by crystallization from aqueous solutions of chloride (±)-**2** containing a half-mole quantity of NaBr as a conglomerator.

Chiral ammonium salt $Me(Et)N^+(Allyl)PhI^-\cdot CHCl_3$ **4** forms a conglomerate as shown by the observed hemihedrism[20] and optical activity of its single crystals,[21] and confirmed by us by X-ray study (space group $P2_12_12_1$). Obviously, the molecule of $CHCl_3$ in compound **4** is a conglomerator. After evacuation of $CHCl_3$ by a vacuum treatment of rubbed salt **4** (under NMR monitoring), crystallization from EtOH–Et_2O with a half-mole quantity of $CHCl_3$ gave enantiomer (+)-**4** (yield 35%, optical purity 61%). A similar resolution was experimentally observed earlier with a new conglomerate.[22]

The high efficiency of the above method of racemate resolution was illustrated by the salts of α-phenylethylamine, one of the simplest, most easily available and widely used chiral amines.[23] The sulfate,[7] cinnamate[24(a)-(d)] **5**, and succinate[24(e)] **6** of α-phenylethylamine are known conglomerates. Using this fact, D. Kozma *et al.*[25] increased the optical purity of the partly enriched amine, and K. Saigo *et al.*[24(a)] described a classical resolution of (±)-**5** by entrainment. The mixture of cinnamate **5** and hydrochloride (mole ratio ~1:2) containing (+)-**5** as a seed crystallised from H_2O–MeOH (2:3) to give first crystals of (+)-**5** (yield 22%, optical purity 75%). Next, (±)-**5** in a quantity ap-

proximately equivalent to that of the separated crystals and a seed of (–)- **5** were added to the mother liquor; crystals of (–)-**5** were isolated (yield 35%, optical purity 85%).

In our work, no optically active salt **5** was added as a seed which is an essential novelty of our procedure. We repeated Saigo's experiment without the seed and obtained three portions of crystals of alternating sign of optical rotation in total yields of 35% and optical purity up to 95%. We call such a resolution as a single conglomerate method.

Our second approach, called the double conglomerate method, was applied to the crystallization of an equimolar mixture of **5** and **6**. This gave four portions of crystals of (+)-**5** (yield 45%, optical purity 30–54%); (–)-**6** was isolated from the mother liquor (yield 35%, optical purity 40%). Salts **5** and **6** differ in solubility and other properties, and they can be easily identified by NMR spectra. Thus, we can call them quasi-diastereomers. Significantly, the single conglomerate method and the double conglomerate method both provide products of optical purity up to 95.6% after a single crystallization. These methods can be applied to the resolution of amino acids as salts with aromatic sulfonic acids, which are known to be conglomerates.[26]

The idea of using a deficiency of the conglomerator (Scheme 1) was extended to crystallization with a deficiency of the achiral solubiliser promoting the solubility of the compound to be resolved. As mentioned above, Werner complexes **2** and **3** highly differ in solubility, therefore the Cl^- anion can be considered as a solubiliser, and a spontaneous resolution can be expected when crystallising with its deficiency. Indeed, a single crystallization of an equimolar mixture of racemates **2** and **3** leads to the formation of (–)- **3** or (+)-**3** in 15–20% yields with an optical purity of 50–60% .

Another substrate suitable for a similar resolution was found in a structural study of *N*-succinopyridine,[25] $C_5H_5N^+CH(CO_2^-)$-CH_2CO_2H **7**, an adduct of pyridine with maleic acid (space group $P2_12_12_1$), synthesis and the properties of which have not been published. We found that prompt evaporation of the solution of an equimolar mixture of pyridine with maleic acid leads to only pyridinium maleate, whereas the prolonged keeping of the same solution (1–2 weeks) results in formation of bright transparent crystals of adduct **7** (mp 214 °C), and each crystal of which shows optical activity. By crystallization of (±)-**7** from H_2O with a half-mole quantity of pyridine or CF_3CO_2H, enantiomers (–)-**7** and (+)-**7** were obtained (yield 12–15 %, optical purity 40-70%).

We have initiated a systematic search[22,28] and design[29] of conglomerates. Proposed methods can be widely used for spontaneous optical enrichment of new conglomerates, which could be found, under scrutinity, among various chemicals in any laboratory.

Significantly, spontaneous resolution of conglomerates in the presence of nonstoichiometric quantities of either a conglomerator or a solubiliser could be the most natural explanation for the origin of biohomochirality.

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References

1 (*a*) L. Pasteur, *Ann. Phys*., 1848, **24**, 442; (*b*) L. Pasteur, *Compt. Rend. Acad. Sci*., 1848, **26**, 535; (*c*) L. Pasteur, *Lecons de chimie professees en 1860. Soc. Chim. de Paris*, Paris, 1861.

2 L. Pasteur, *Ann. Chim. Phys*., 1850 (3), **28**, 56.

3 L. Pasteur, *Ann. Chim. Phys*., 1852, **34**, 30.

4 G. B. Kauffman and R. D. Myers, *J. Chem. Ed*., 1975, **52**, 777.

5 G. B. Kauffman, I. Bernal and H.-W. Schütt, *Enantiomer*, 1999, **4**, 33.

6 D. Gernez, *Compt. Rend. Acad. Sci*., 1866, **63**, 843.

7 J. Jacques, A. Collet and S. H. Wilen, *Enantiomers, Racemates, and Resolution*, Krieger Publ. Comp., Malabar, Florida, 1994.

8 (*a*) A. Collet, in *Comprehensive Supramolecular Chemistry*, ed. D. N. Reinhoudt, Pergamon, 1996, vol. 10, ch. 5, p. 13; (*b*) A. Collet, *Enantiomer*, 1999, **4**, 157.

9 W. A. Bonner, *Origin Life Evol. Biosphere*, 1994, **24**, 63; (*b*) W. A. Bonner, *Origin Life Evol. Biosphere*, 1995, **25**, 175; (*c*) W. A. Bonner, *Origin Life Evol. Biosphere*, 1996, **26**, 27.

10 (*a*) V. I. Goldanskii, in *The Role of Radiation in the Origin and Evolution of Life*, eds. M. Akaboshi, N. Fujii and R. Gonzales, Kioto University Press, Kioto, Japan, 2000, p. 291; (*b*) V. I. Goldanskii, *Khim. Fiz.*, 1999, **18**, 3 (*Chem. Phys. Rep*., 1999, **18**, 627).

11 M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios and L. D. Barron, *Chem. Rev.*, 1998, **98**, 2391.

12 Y. Inoue, H. Tsuneishi, T. Hakushi, K. Yagi, K. Awazu and H. Onuki, *J. Chem. Soc., Chem. Commun*., 1996, 2627.

13 (*a*) R. G. Kostyanovsky, invited lecture at Paul Walden Symposium, Riga, 1998 [P. Trapencieris, *Khim. Geterotsikl. Soedin*., 1998, 712 (in Russian)]; (*b*) V. R. Kostyanovsky, Diploma, Moscow, 1998; (*c*) R. G. Kostyanovsky, *Abstracts of the Interdisciplinary Symposium on Biological Homochirality*, 1998, Italy, OP20, p. 41; (*d*) R. G. Kostyanovsky, G. K. Kadorkina and V. R. Kostyanovsky, *Abstracts of the V Scientific Conference of N. N. Semenov Institute of Chemical Physics, RAS*, 1999, Moscow, p. 60 (in Russian); (*e*) V. R. Kostyanovsky, *Abstracts of the First Workshop on Organic Chemistry and Catalysis between Russian Academy of Sciences and Bayer AG*, Moscow, 2000, p. 24.

14 G. A. Potter, Ch. Garcia, R. McCague, B. Adger and A. Collet, *Angew. Chem., Int. Ed. Engl*., 1996, **35**, 1666.

15 J. H. van't Hoff and C. M. van Deventer, *Z. Phys. Chem*., 1887, **1**, 165.

16 A. Werner, *Ber.*, 1911, **44**, 1887.

17 I. Bernal and G. B. Kauffman, *J. Chem. Ed*., 1987, **64**, 604.

18 G. B. Kauffman and I. Bernal, *J. Chem. Ed*., 1989, **66**, 293.

19 K. Yamanari, J. Hidaka and Y. Shimura, *Bull. Chem. Soc. Jpn*., 1973, **46**, 3724.

20 (*a*) E. Wedekind, *Zur Stereochemie des fünfwertigen Stickstoffs*, Leipzig, 1899, p. 56; (*b*) A. Fock, *Z. Kristallogr.*, 1902, **35**, 399; (*c*) E. Wedekind, *Ber.*, 1903, **36**, 3793.

21 E. Havinga, *Biochim. Biophys. Acta*, 1954, **13**, 171.

22 R. G. Kostyanovsky, A. P. Avdeenko, S. A. Konovalova, G. K. Kadorkina and A. V. Prosyanik, *Mendeleev Commun*., 2000, 16.

23 E. Juaristi, J. Escalante, J. L. Leon-Romo and A. Reyes, *Tetrahedron: Asymmetry*, 1998, **9**, 715.

24 (*a*) H. Nohira, M. Kai, M. Nohira, J. Noshikawa, T. Hoshiko and K. Saigo, *Chem. Lett*., 1981, 951; (*b*) K. Saigo, H. Kimoto, H. Nohira, K. Yanagi and M. Hasegawa, *Bull. Chem. Soc. Jpn*., 1987, **60**, 3655; (*c*) K. Saigo, Y. Hashimoto, K. Kinbara and A. Sudo, *Proc. Indian Acad. Sci. (Chem. Sci.)*, 1996, **108**, 555; (*d*) K. Kinbara, Y. Hashimoto, M. Sukegawa, H. Nohira and K. Saigo, *J. Am. Chem. Soc*., 1996, **118**, 3441; (*e*) D. Kozma, Z. Bocskei, K. Simon and E. Fogassy, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1883.

25 (*a*) D. Kozma, Z. Madarasz, M. Acs and E. Fogassy, *Chirality*, 1995, **7**, 381; (*b*) D. Kozma and E. Fogassy, *Enantiomer*, 1997, **2**, 51.

26 H. Kimoto, K. Saigo, Y. Ohashi and M. Hasegawa, *Bull. Chem. Soc. Jpn*., 1989, **62**, 2189.

27 M. N. G. James and M. Matsushima, *Acta Crystallogr*., 1976, **B32**, 999.

28 (*a*) R. G. Kostyanovsky, P. E. Dormov, P. Trapenzieris, B. Strumfs, G. K. Kadorkina, I. I. Chervin and I. Ya. Kalvin's, *Mendeleev Commun*., 1999, 26; (*b*) D. A. Lenev, K. A. Lyssenko and R. G. Kostyanovsky, *Izv. Akad. Nauk, Ser. Khim*., 2000, in press.

29 (*a*) R. G. Kostyanovsky, K. A. Lyssenko, G. K. Kadorkina, O. V. Lebedev, A. N. Kravchenko, I. I. Chervin and V. R. Kostyanovsky, *Mendeleev Commun*., 1998, 231; (*b*) R. G. Kostyanovsky, K. A. Lyssenko, Yu. I. El'natanov, O. N. Krutius, I. A. Bronzova, Yu. I. Strelenko and V. R. Kostyanovsky, *Mendeleev Commun*., 1999, 106; (*c*) R. G. Kostyanovsky, K. A. Lyssenko, D. A. Lenev, Yu. I. El'natanov, O. N. Krutius and I. A. Bronzova, *Mendeleev Commun*., 1999, 151; (*d*) R. G. Kostyanovsky, K. A. Lyssenko and D. A. Lenev, *Mendeleev Commun*., 1999, 154; (*e*) R. G. Kostyanovsky, K. A. Lyssenko and V. R. Kostyanovsky, *Mendeleev Commun*., 2000, 44.

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