

## New Optical resolution Method Based On The Formation Of A Solid Solution. Optical Resolution Of Racemic 1-(4-Methylthiophenyl)-2-phenylpropan-1-one By Co-crystallization With (+)-1-(4-Methoxyphenyl)-2-phenylpropan-1-one.

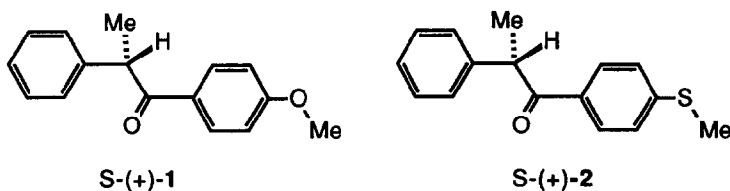
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**Abstract :** Crystallization of ketone *S*-(+)-1 in the presence of a small amount of its sulfur analogue ( $\pm$ )-2 afforded a solid solution containing 8% of *S*-(+)-2; the latter was isolated in enantiomerically pure form by column chromatography. This simple optical resolution procedure may represent an alternative to chiral HPLC for the preparation of small quantities of pure enantiomers, and the determination of their absolute configurations.

Because it implies a perfect organization of symmetry-related species, crystallization is one of the simplest and most efficient molecular recognition process. In general, a given molecule will not allow the presence of foreign species within its crystal lattice, and this property is widely used in the separation and purification procedures based on crystallization. By the same token, homochiral crystals, made of molecules of the same handedness, cannot, in general, accept the incorporation of the opposite enantiomer, and this is one of the reasons why optical purification of partially resolved mixtures can often be effected conveniently by crystallization.<sup>1</sup> On the other hand, molecules having similar structures and sizes may co-crystallize to form solid solutions (sometimes called mixed crystals). When these molecules are chiral, co-crystallization is expected to occur between species having the same handedness.<sup>2</sup> This phenomenon provides the bases for the straightforward optical resolution of ketone 2 described in this communication.



The racemic ketone 1, easily prepared by Friedel-Crafts reaction of hydratropic acid chloride with anisole,<sup>3</sup> has been known for a long time to crystallize as a conglomerate of (+)- and (-)-enantiomers,<sup>1, 4</sup> and hence large quantities of each of these can be obtained by the preferential crystallization method.<sup>5, 6</sup> In connection with spectroscopic studies,<sup>7</sup> we needed a sample of the sulfur substituted analogue 2 in optically active form. Racemic 2 was prepared by the same method as 1, using thioanisole instead of anisole in the Friedel-Crafts reaction.<sup>8</sup> Contrary to ( $\pm$ )-1, compound 2 did not spontaneously resolve on crystallization, and,

apart from chiral chromatography, there is no straightforward optical resolution method for this class of compounds. Given the obvious similarity existing between **1** and **2**, we anticipated that crystallization of (+)-**1** in the presence of a small quantity of ( $\pm$ )-**2** would lead to mixed crystals of (+)-**1** and the enantiomer of **2** having the same handedness.

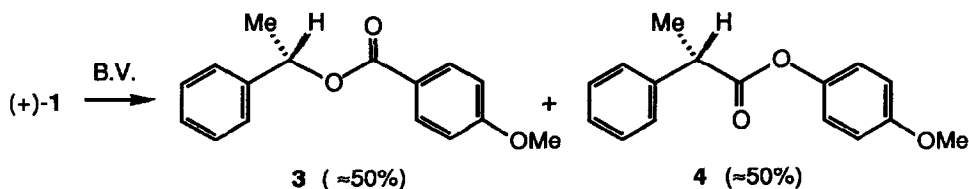
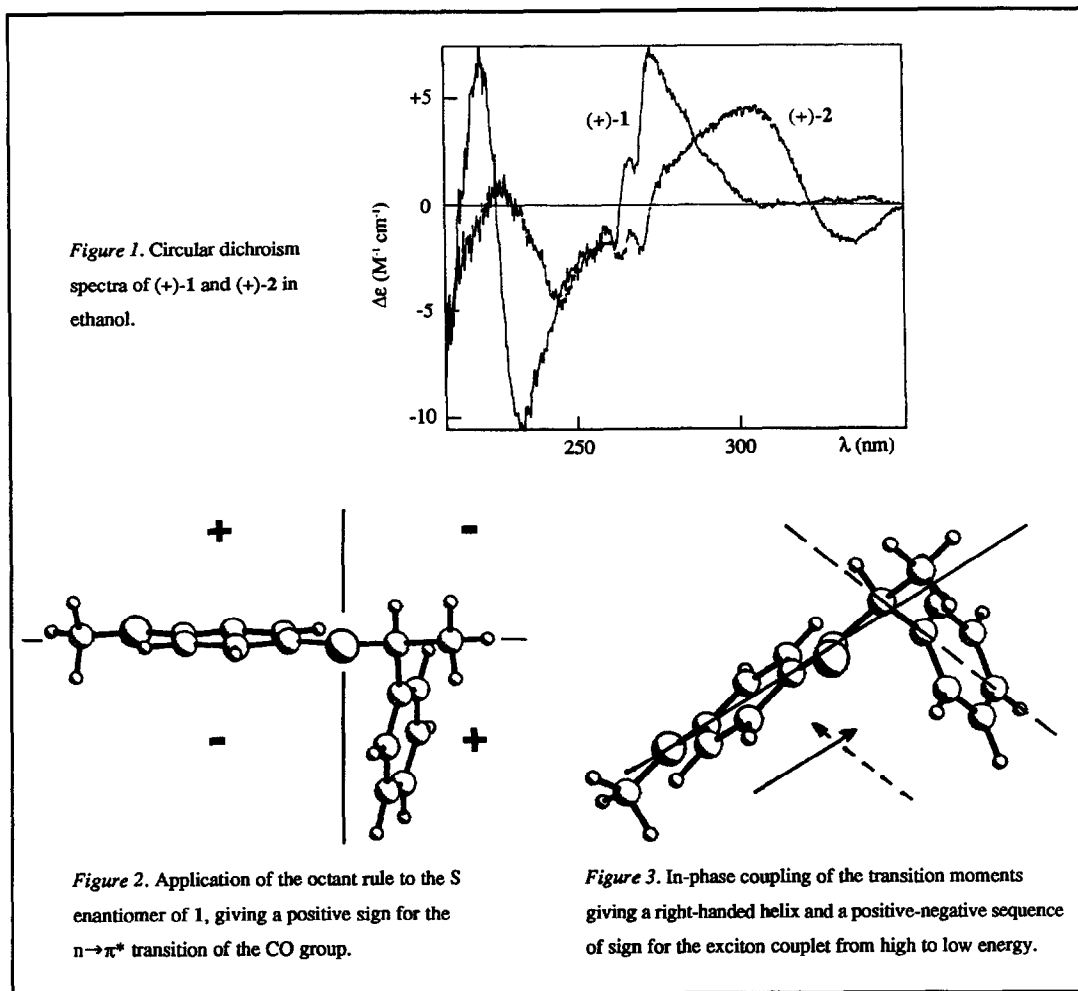
Thus, 400 mg of enantiomerically pure (+)-**1**<sup>3</sup> and 200 mg of ( $\pm$ )-**2** were dissolved in 6 mL of hot methanol, and, after seeding with a small monocrystal of (+)-**1**, the crystallization was allowed to proceed at room temperature. A large crystal was obtained (ca. 20 x 4 x 3 mm, 223 mg); it was carefully washed with a small amount of cold methanol to ensure that its surface was not contaminated by some residual ( $\pm$ )-**2**. The melting of a small fragment (1 mg) was examined by differential scanning calorimetry (DSC). A sharp melting endotherm (mp 75 °C) was observed, and the fact that it was not preceded by any detectable eutectic peak demonstrated that the sample consisted of a single crystal phase.<sup>9</sup> Analysis by TLC and 200 MHz <sup>1</sup>H NMR spectroscopy revealed that the crystal contained 92% of (+)-**1** and 8% of **2**. The two components were separated by column chromatography on silica gel, using dichloromethane/hexane 6:4 (v:v) as the eluant (**1**, R<sub>F</sub> 0.13; **2**, R<sub>F</sub> 0.23); 13.4 mg of **2** (homogeneous by TLC) and 193.6 mg of pure (+)-**1** were isolated. As expected, **2** was optically active, showing  $[\alpha]_{\text{D}}^{25} +67$  (CHCl<sub>3</sub>, c 0.405). It melted sharply at 85 °C (instead of 77 °C for the racemate), and its enantiomeric excess (*ee*) was estimated by the DSC method<sup>10</sup> to be ca. 98% (calculated molar purity *x* in the range of 0.991 to 0.993). Essentially the same results were obtained by fast crystallization of mixtures of (+)-**1** and ( $\pm$ )-**2**, however the *ee* of (+)-**2** obtained in this way was sometimes slightly lower, due to some contamination of the crystalline powder by the racemate contained in the mother liquors (the washing of the crystals was less efficient in this case).

As was anticipated, the configuration of (+)-**2** was found to be identical with that of (+)-**1**. That the (+)-isomers have *S* configuration was established by circular dichroism spectroscopy (CD) and this assignment was confirmed by chemical correlation of (+)-**1** to *S*-(-)-2-phenethyl alcohol. The CD spectrum of (+)-**1** (Fig. 1)<sup>11</sup> displays an exciton couplet (211 nm,  $\Delta\epsilon +7.5$ ; 233 nm,  $\Delta\epsilon -11$ ), which may be ascribed to a coulombic coupling of the <sup>1</sup>L<sub>a</sub> transition of the unsubstituted benzene ring with the  $\pi \rightarrow \text{CO}$  charge transfer transition of the anisoyl group.<sup>12</sup> The sulfur analogue (+)-**2** shows a similar couplet (277 nm, +1.4; 246 nm, -4.9); these couplets are centered on the isotropic UV bands whose maxima are found at 216 nm and 230 nm for **1** and **2**, respectively. In the low energy region both (+)-**1** and (+)-**2** display a positive Cotton effect for the  $n \rightarrow \pi^*$  transition of the carbonyl group at 273 nm (+7.5) and 304 nm (+4.5), respectively, the corresponding UV absorption being found at 279 and 308 nm; (+)-**2** shows an additional negative CD band at 335 nm (-1.7) the origin of which is still unclear. Moreover, both compounds exhibit in the 260 nm region a negative CD pattern which should be ascribed to the <sup>1</sup>L<sub>b</sub> transition of the unsubstituted benzene ring.

The preferred conformation of ketone **1** was determined by molecular mechanics (MMX force field)<sup>13</sup> and was almost superimposable to the conformation observed in the crystal state.<sup>14</sup> Our analysis of the CD of (+)-**1** and (+)-**2** is based on the MMX conformation of the *S* isomer of **1**. Application of the octant rule using this conformation (see Fig. 2) led to the prediction that the *S* isomer would have a positive Cotton effect for the  $n \rightarrow \pi^*$  transition of the carbonyl group, as observed for (+)-**1** and (+)-**2**.

Analysis of the CD observed in the 210-250 nm region in the light of the exciton mechanism<sup>12</sup> led us to the same conclusion. Assuming that the <sup>1</sup>L<sub>a</sub> transition and the  $\pi \rightarrow \text{CO}$  charge transfer transition which coulombically couple to generate the exciton couplet are polarized along the long axis of the benzene rings

(Fig. 3), we would expect for the *S* isomer a positive-negative sequence of signs from high to low energy, as observed in the CD spectra of (+)-1 and (+)-2.



Moreover, ketone (+)-1 was converted via a Baeyer-Villiger (B.V.) reaction (*m*-CPBA,  $\text{CHCl}_3$ ,  $20^\circ\text{C}$ , 30 days, 53%) to a  $\approx 50/50$  mixture of esters 3 and 4. Alkaline hydrolysis of this mixture (6 M NaOH in ethanol,  $20^\circ\text{C}$ , 18 h) and usual workup afforded *S*-(-)-2-phenethyl alcohol (5) that exhibited  $[\alpha]_D^{25} -58$

(CHCl<sub>3</sub>, c 1.7); an authentic sample of enantiomerically pure (-)-5 showed  $[\alpha]_D^{25} -56$  under the same conditions, and, given the precision of the polarimetric measurement, we may consider that the sample of (-)-5 obtained from (+)-1 by the B.V. reaction was enantiomerically pure. If we assume that the migration of the *sec*-phenethyl fragment in (+)-1 occurred with retention of configuration (as usually observed in the B.V. reaction),<sup>15</sup> then the absolute stereochemistry of 1 should be *S*-(+), in agreement with the conclusion based on the chiroptical methods.

In conclusion, the above described optical resolution method, applied to structurally similar substances, may provide a simple alternative to chiral HPLC for the preparation of small quantities of pure enantiomers, and the determination of their absolute configurations. In this respect, it is more simple and more generally applicable than Fredga's method, which rests on the formation of a quasi-racemate between quasi-enantiomers of opposite configuration.<sup>16</sup>

## References and notes

- Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1981.
- For instance, mixtures of *R*-(-)-*o*-chloromandelic acid and *R*-(-)-*o*-bromomandelic acid form solid solutions whereas the pairs of opposite configuration crystallize as eutectics; see Collet, A.; Jacques, J. *Bull. Soc. Chim. France* 1973, 3330. Structurally related molecules of opposite configurations may also form quasi-racemates; see ref. 1, p 100, and ref 16.
- Ketone 1 was originally prepared by reaction of hydratropic acid chloride and anisole in carbon disulfide (see ref. 4). We found that the reaction worked satisfactorily in dichloromethane and we used the following procedure. Aluminium chloride (11 g) was added at 0 °C to a solution of anisole (11 mL, 0.1 mol) in dry dichloromethane (76 mL); this was followed by the dropwise addition of hydratropic acid chloride (9.98 g, 0.059 mol, in 60 mL of dichloromethane). The initially pink solution turned to an orange then deep red colour. After stirring for 5 h at 20 °C, the mixture was poured into ice and 12 M HCl (15 mL), and (±)-1 was extracted in the usual way and recrystallized from methanol; yield 9.5 g (67%), mp 54 °C; *R*<sub>F</sub> 0.61 (dichloromethane, silica gel); 200 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.49 (d, CH<sub>3</sub>, J=6.9 Hz); 3.79 (s, OCH<sub>3</sub>); 4.62 (q, CH, J=6.9 Hz); 6.83 (d, 2 arom. H's, J=8.9 Hz); 7.27-7.16 (m, 5 arom. H's); 7.92 (d, 2 arom. H's, J=8.9 Hz). The enantiomer (+)-1 was obtained by the preferential crystallization method (ref. 5); mp 78 °C,  $[\alpha]_D^{25} + 125$  (CHCl<sub>3</sub>, c 0.46).
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- Collet, A.; Brienne, M.-J.; Jacques, J. *Chem. Rev.* 1980, 80, 215.
- The effect of a sulfide group on the electronic transitions of the benzene chromophore does not seem to be well understood; see: Palmieri, P.; Tullini, F.; Velino, B.; Zauli, C. *Gazz. Chim. Ital.* 1975, 105, 919.
- Ketone (±)-2 was prepared as described above (note 3) using thioanisole instead of anisole; yield 89%, mp 77 °C; *R*<sub>F</sub> 0.84 (dichloromethane, silica gel); 200 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.50 (d, CH<sub>3</sub>, J=6.9 Hz); 2.45 (s, SCH<sub>3</sub>); 4.61 (q, CH, J=6.9 Hz); 7.15 (d, 2 arom. H's, J=8.5 Hz); 7.20-7.27 (m, 5 arom. H's); 7.84 (d, 2 arom. H's, J=8.5 Hz). Anal. Calcd for C<sub>16</sub>H<sub>16</sub>OS: C 74.96; H 6.29; O 6.24; S 12.87. Found: C 74.7; H 6.3; O 6.15.
- A full description of this procedure in terms of phase diagrams will be given in a separate paper.
- The principle of the method is given in ref. 1, p 151. Measurements were done on a Perkin-Elmer DSC7 microcalorimeter. The molar purity *x*, and hence the *ee* of 2 (*ee*=2*x*-1) was calculated from the melting scan (at 2 K/min) by means of the standard purity software provided by the manufacturer.
- CD Spectra were recorded on a Jobin-Yvon Dichrograph V instrument. We are grateful to J. Bolard and L. Faury (Université Paris VI) for these measurements.
- Mason, S.F. *Molecular optical activity and the chiral discriminations*; Cambridge University Press: Cambridge, 1982, and refs therein.
- PCMODEL, from *Serena Software*, P.O. Box 3076, Bloomington, IN 47402-3076. The program was run on an IBM RISC 6000 workstation. We are grateful to C. Andraud for the molecular mechanics studies.
- The crystal structure of 1 was determined by A. Renault (Grenoble) and will be published in a forthcoming paper.
- Lee, J.B.; Uff, B.C. *Quart. Rev.* 1967, 21, 429; Hassal, C.H. *Org. Reactions* 1957, 9, 73.
- See, for example, Fredga, A. *Tetrahedron* 1960, 8, 126.