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New example of spontaneous resolution among aryl glycerol ethers: 3-(2-hydroxyphenoxy)propane-1,2-diol

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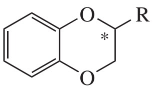
The conglomerate-forming nature of 3-(2-hydroxyphenoxy)propane-1,2-diol was established by IR, DSC, and XRD methods; racemic diol could be resolved by a moderate efficiency preferential crystallization procedure.

2-Substituted 1,4-benzodioxanes **1** have been widely used in the design of therapeutic agents with a pronounced effect of the absolute configuration at the stereogenic C_2 of the dioxane ring on biological response. Popular precursors for their synthesis are enantiomeric 2-hydroxymethyl-1,4-benzodioxanes **2**, which have been obtained through an enzyme-mediated kinetic resolutions of racemate[1] or from other scalemic inters,[2,3] among them 3-(2-hydroxyphenoxy)propane-1,2-diols **3**. Both enantiomers of **3** have been prepared for the first time from (*R*)- and (*S*)-glycidol derivatives.[2]



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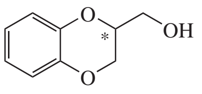

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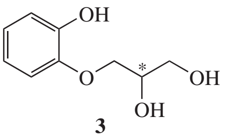

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Here, we consider solid state properties revealing the conglomerate nature of *rac*-diol **3**, and propose a direct resolution procedure for this valuable chiral substance.

Racemic, (*R*)- and (*S*)-**3** have been prepared uniformly by analogy with a published procedure[4] through the reaction of *rac*- , (*S*)- and (*R*)-3-chloropropane-1,2-diols with catechol.[†,‡]

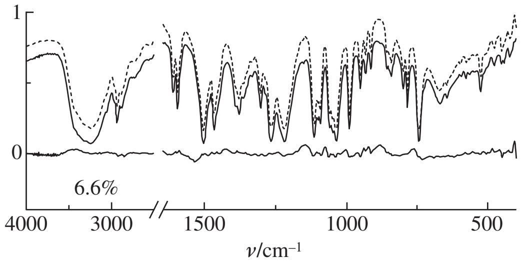

Figure 1 Experimental IR spectra of racemic (solid line) and scalemic (dotted line) 3-(2-hydroxyphenoxy)propane-1,2-diols **3** as well as difference curve (beneath).

Figure 1 shows the IR spectra of both racemic and highly enantiomerically enriched solid samples of **3** along with the normalized difference curve between individual spectra.[§] Excepting minor discrepancies, the spectra are identical. This is a good but not definitive diagnostic for racemic conglomerate formation.

Valuable information on a chiral substance can be obtained by differential scanning calorimetry (DSC). With a knowledge of the temperature and enthalpy of fusion for a racemic and enantiopure sample, it is possible to calculate for enantiomeric **3** the entropy of mixing in the liquid state ΔS_l^m and the free energy of formation ΔG^0 of racemic compound in the solid state.[6,7] Table 1 represents experimental and calculated thermodynamic parameters for diol **3**.[¶] The calculated entropy of mixing is 5.24 J K^{-1} mol^{-1}, which is less but close to the ideal value of 5.77 J K^{-1} mol^{-1} (Rln 2) for conglomerates. The near-zero value of ΔG^0 points to the same crystallization peculiarity.

[†] The NMR spectra were recorded on a Bruker Avance-600 spectrometer in CD_3CN with the signals of the solvent as the internal standard. Optical rotations were measured on a Perkin-Elmer model 341 polarimeter. The value of specific rotation is given in deg cm^3 g^{-1} dm^{-1}, and the concentration of solutions *c* appears in g (100 ml)$^{-1}$. Melting points for general purposes were determined using a Boëtius apparatus and are uncorrected. HPLC analyses of enantiomeric purity were performed on a Shimadzu LC-20AD system controller, and a UV monitor 275 nm was used as a detector. A Chiralcel AD-RH (0.46×15 cm) column from Daicel was used; the column temperature was 21 °C; eluent water–isopropanol (3:1); flow rate, 0.4 ml min^{-1}.

[‡] rac-*3-(2-Hydroxyphenoxy)propane-1,2-diol* (*rac*-**3**): yield 29%, mp 82–83 °C (CH_2Cl_2/hexane) (lit.,[5] mp 82–84 °C).

(S*)-3-(2-Hydroxyphenoxy)propane-1,2-diol* [(*S*)-**3**]: mp 108–109 °C (CH_2Cl_2/hexane) (lit.,[2] mp 106–108 °C); $[\alpha]_D^{20}$ +32.8 (*c* 0.8, EtOH) {lit.,[2] $[\alpha]_D^{20}$ +42.8 (*c* 0.7, EtOH)}; 99.7% ee (HPLC; t_R = 15.6 min). ^{1}H NMR, δ: 2.59 (br. s, 1H, OH), 3.33 (br. s, 1H, OH), 3.64–3.71 (m, 2H, CH_2O), 3.99 (dd, 1H, CH_2O, *J* 9.4 and 6.2 Hz), 4.02–4.05 (m, 1H, CH), 4.10 (dd, 1H, CH_2O, *J* 9.4 and 3.2 Hz), 6.80–6.83 (m, 1H, Ar), 6.87 (d, Ar, *J* 9.4 Hz), 6.96 (d, 1H, Ar, *J* 4.1 Hz), 7.37 (br. s, 1H, OH). ^{13}C NMR (150.864 MHz) δ: 62.87 (CH_2OH), 70.79 (CH_2O), 70.50 (CH), 113.83 (6-C_{Ar}), 115.34 (3-C_{Ar}), 119.97 (4-C_{Ar}), 121.99 (5-C_{Ar}), 146.54 (2-C_{Ar}), 146.70 (1-C_{Ar}).

(R*)-3-(2-Hydroxyphenoxy)propane-1,2-diol* [(*R*)-**3**]: mp 108–109 °C, $[\alpha]_D^{20}$ –33.0 (*c* 0.8, EtOH); 99.8% ee (HPLC; t_R = 13.5 min).

[§] The IR spectra of the polycrystalline samples of *rac*-**3** and (*R*)- or (*S*)-**3** in KBr pellets were recorded on a Bruker IFS-66v Fourier-transform spectrometer. To substantiate the spectra comparison, they were subjected to a procedure of normalization and baseline correction. For this purpose, coefficients that minimize the difference ln $(A_s) - [a_0 + a_1\nu + \ln(A_r)a_2]$, where ln (A_s) and ln (A_r) are the extinctions (transmission logarithms) of the scalemic and racemic samples, respectively; ν is the IR radiation frequency corresponding to *A*, and a_n are the desired regression coefficients, were selected by the least-squares method. It was reasonable to introduce the regression terms $a_1\nu$ to correct the spectral differences caused by the nonspecific (not related to particular absorption bands) interaction of IR radiation with matter (probably, by radiation scatter on heterogeneities of the sample). The ratio between the mean-square deviation of the differential curves and the averaged mean-square deviation of spectral curves for the racemate and scalemate, that is, the ratio of error to variation (%), was used as a quantitative characteristic for differential curves, and this namely quantity is cited in Figure 1.

Table 1 DSC measured melting point T^f and enthalpy of fusion ΔH^f of racemic (subscript *R*) and (*S*)-**3** (subscript *A*), as well as calculated thermodynamic characteristics of 3-(2-hydroxyphenoxy)propane-1,2-diol **3**.

T_A^f/°C	T_R^f/°C	ΔH_A^f/ J mol^{-1}	ΔH_R^f/ J mol^{-1}	ΔG^0/ J mol^{-1}	ΔS_1^m/ J K^{-1} mol^{-1}
107.8	82.6	30790	25720	–14	5.24

From the DSC data for samples of different enantiomeric purity, the melting temperature against composition diagram (binary phase diagram) is depicted in Figure 2. Experimental points in Figure 2 form an obvious single eutectic V-shape curve typical of a racemic conglomerate.[6] Figure 2 presents the theoretical liquidus curve (solid line) deduced for conglomerate from the simplified Schröder–Van Laar equation. Both experimental and theoretical sets correlate quite well, and a calculated value for eutectic melting point (T_{eu} = 82.4 °C) is very close to the experimental T_R^f = 82.6 °C.

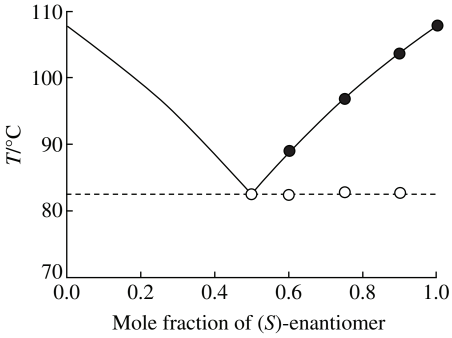

Figure 2 Experimental (circles) and calculated (lines) melting point phase diagram for diol **3**.

Finaly, we studied the crystals of **3** by XRD. To unambiguously establish the absolute configuration for this compound, we have used the direct Flack method for an enantiopure sample with predetermined chiroptical characteristics.[8] As we have only a light atom structure (C,H,N,O), anomalous dispersion effects were small, but the situation was improved using good quality crystals and Cu radiation. The reliability of the absolute structure determination could also be improved using set as many as possible of Friedel pairs in the data, in our case a total number of 1154 was used which is a fraction of 0.68 from possible amount. Refinement leads to good Flack parameters with reasonable standard deviation.[††]

The sample obtained from enantiopure material forms monoclinic crystals, space group $P2_1$. There are two symmetry-independent molecules in the unit cell of this compound, that is Z' = 2; nevertheless, both chiral centres on C(2A) and C(2B) carbons have the same absolute configuration (Figure 3). The Flack parameter for the sample with negative sign of optical rotation is well consistent with *R*-configuration of these C(2) carbon atoms. The crystals grown from racemic **3** solution have had the same habitus and crystallographic characteristics as scalemic ones. Thus, the single crystal X-ray analysis confirms the conglomerate nature of *rac*-**3** established by IR and DSC methods.

Having the same configurations, the independent molecules of **3** have different conformations. If the molecule of **3B** could be characterized by *sc*,*sc*-conformation of the O(1)–C(1)–C(2)–C(3)–O(3) fragment, then for the molecule of **3A** this fragment takes -*sc*,-*sc*-conformation (Figure 4).

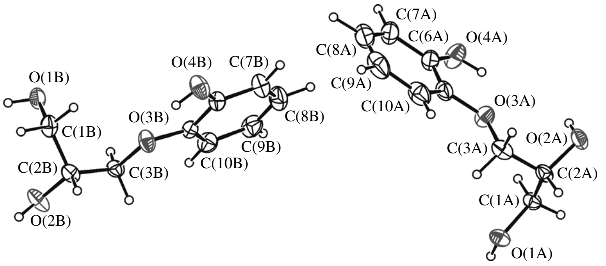

Figure 3 ORTEP drawing of the symmetry independent (*R*)-**3** molecules in crystal.

The existence of three hydroxyls per molecule leads to the development of the elaborated system of hydrogen bonds in the crystals of compound **3**. Owing to H-bonding of glycerol fragments, 2D supramolecular structures arise in the crystals, namely, endless cylinders along existing 2_1 screw axes parallel with 0*b* axis. Alternating sequences of **3A**, **3A′** and **3B**, **3B′** molecules form the H-bond pattern: ···O(2A)–H(20A)···O(1A′)–H(1A′)···O(2B)–H(20B)···O(1B′)–H(1B′)···O(2A″)–H(20A″)···, *etc*. In this aspect, the packing pattern of 3-(2-hydroxyphenoxy)-propane-1,2-diol molecules is close to those of the known chiral drug mephenesin, 3-(2-methylphenoxy)propane-1,2-diol, investigated earlier.[14] The sufficient difference between two packing patterns consists with the presence of phenolic hydroxyl in every molecule of **3**. This group of molecule A takes part in

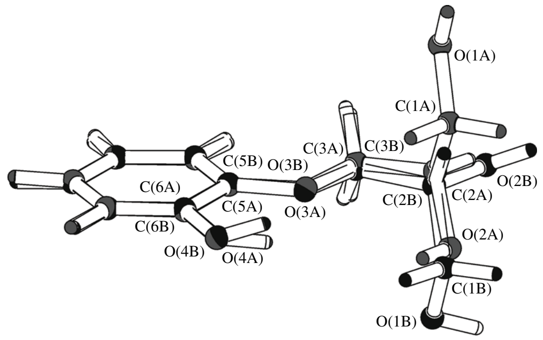

Figure 4 Superposition of two symmetry independent molecules of **3**.

[¶] All thermal measurements were performed on a Perkin–Elmer Diamond DSC model in aluminum pans using a heating rate of 10 K min^{-1}. Mass of the samples amounted to approximately 2.5 mg. Temperature scale and heat flux were calibrated against the data for indium, phenol and naphthalene.

[††] *X-ray diffraction data*. The sample of (–)-3-(2-hydroxyphenoxy)-propane-1,2-diol, (–)-**3**, 99.8% ee, was crystallized from CH_2Cl_2 and was characterized by mp 108–109 °C, $[\alpha]_D^{20}$ –33.0 (*c* 0.8, EtOH); $C_9H_{12}O_4$, *M* = 184.19, monoclinic, space group $P2_1$, *a* = 12.2915(9), *b* = 4.8595(3) and *c* = 15.4607(11) Å, β = 100.165(4)°, *V* = 908.98(11) Å^3, *Z* = 4, d_{calc} = = 1.35 g cm^{-3}, μ(CuKα) = 8.95 cm^{-1}, *F*(000) = 392, 9903 reflections measured, 2781 unique (R_{int} = 0.0445), restraints/parameters = 1/331. Final indices $R_1(F)$ = 0.0365, $wR_2(F^2)$ = 0.1029 using 2693 reflections with $I > 2\sigma(I)$, and $R_1(F)$ = 0.0375, $wR_2(F^2)$ = 0.1041 using all reflections. Goodness-of-fit on F^2 was 0.617, largest difference peak and hole are 0.108 and –0.149 eÅ^{-3}. The Flack parameter is –0.0(2) (absolute structure was established as *R*).

Both enantiopure and racemic diols **3** crystallize in $P2_1$ space group, Z' = 2, having almost identical parameters of crystal unit cell.

Cell parameters and intensities for single crystals were measured at 296 K on a Bruker AXS Kappa Apex diffractometer, using CuKα radiation with graphite monochromator. Data were corrected for the absorption effect using the SADABS[9] program. The structure was solved by a direct method and refined by the full matrix least-squares using the SHELXTL[10] and WinGX[11] programs. All non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were located from difference Fourier maps and all hydrogen atoms refined isotropically. Data collections: images were indexed, integrated, and scaled using the APEX2[12] data reduction package. All figures were made using the PLATON program.[13]

CCDC 717487 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2009.

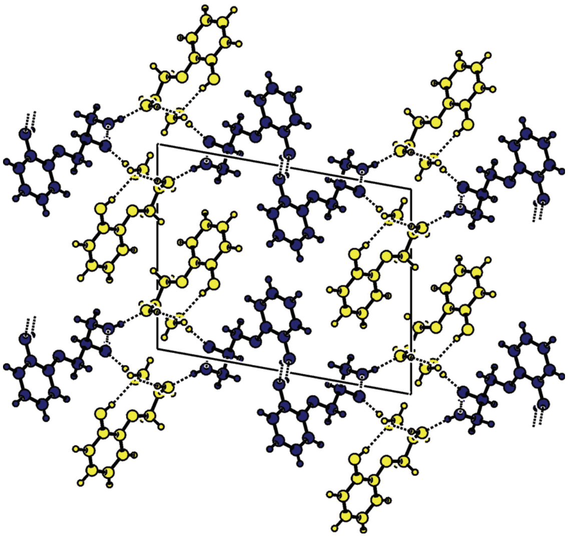

Figure 5 Mutual arrangements of two independent molecules (atoms of molecules B are shown by dark circles) of the compound **3** in the crystal, viewed along the 0*b* axis.

the above 'cylinder' superstructure, bonding with O(1) atom of nearest neighbour molecule A′, whereas the phenolic hydroxyl of molecule B forms H-bond with such a hydroxyl of molecule B′, belonging to another 'cylinder', generating endless zigzag succession O(4B)–H(40B)···O(4B′)–H(40B′)···, taking together supramolecular cylindrical structures. Another interesting feature of the compound **3** packing is an alternating of parallel with the crystallographic 0*ad* plane layers consisting of the molecules of only one sort: either A or B (Figure 5).

Aside from H-bonding, no other clear identifiable bonding interactions, such as π–π and/or π···H tight contacts, for instance, have been detected. In spite of the absence of cavities available for guest molecules, the packing index for crystal lattice of **3** is as low as 69.0%.

All the above-mentioned materials created solid evidence that diol **3** crystallizes as a conglomerate. Thus, the resolution of the racemic mixture *via* a classical entrainment procedure has been tested. In this regard, the choice of a suitable solvent was the main trouble. We have gained the purpose with a moderate success using methylene chloride,[‡‡] but it is obvious that special search would improve the results.

References

1 (*a*) M. D. Ennis and D. V. Old, *Terahedron Lett.*, 1992, **33**, 6283; (*b*) S. Antus, A. Gottsegen, J. Kajtár, T. Kovács, T. S. Tóth and H. Wagner, *Tetrahedron: Asymmetry*, 1993, **4**, 339.

2 A. Delgado, G. Leclerc, C. Lobato and D. Mauleon, *Terahedron Lett.*, 1988, **29**, 3671.

3 C. Bolchi, L. Fumagalli, B. Moroni, M. Pallavichini and E. Valoti, *Tetrahedron: Asymmetry*, 2003, **14**, 3779.

4 R. R. Read and E. Miller, *J. Am. Chem. Soc.*, 1932, **54**, 1195.

5 G. Gellerstedt and J. Gierer, *Acta Chem. Scand.*, 1968, **22**, 2510.

6 J. Jaques, A. Collet and S. H. Wilen, *Enantiomers, Racemates, and Resolutions*, Krieger Publishing Co., Malabar, FL, 1994, pp. 32–57.

7 Z. J. Li, M. T. Zell, E. J. Munson and D. J. W. Grant, *J. Pharm. Sci.*, 1999, **88**, 337.

8 H. D. Flack and G. Bernardinelli, *J. Appl. Crystallogr.*, 2000, **33**, 1143.

9 G. M. Sheldrick, *SADABS, Program for Empirical X-ray Absorption Correction*, Bruker–Nonius, 2004.

10 G. M. Sheldrick, *SHELXTL v.6.12, Structure Determination Software Suite*, Bruker AXS, Madison, Wisconsin, USA, 2000.

11 L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837.

12 *APEX2 (Version 2.1), SAINTPlus. Data Reduction and Correction Program (Version 7.31A, Bruker Advansed X-ray Solutions)*, Bruker AXS Inc., Madison, Wisconsin, USA, 2006.

13 A. L. Spek, *J. Appl. Crystallogr.*, 2003, **36**, 7.

14 A. A. Bredikhin, A. T. Gubaidullin, Z. A. Bredikhina, D. B. Krivolapov, A. V. Pashagin and I. A. Litvinov, *J. Mol. Struct.*, 2009, **920**, 377.

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[‡‡] Racemic 3-(2-hydroxyphenoxy)propane-1,2-diol, *rac*-**3** (0.79 g) and (*S*)-**3** (0.10 g) were dissolved in 180 ml of CH_2Cl_2 at 40 °C. The solution was cooled to 25 °C and seeded with finely pulverized (*S*)-**3** (3 mg). Chiral HPLC was used for monitoring the resolution process. After stirring the mixture for 120 min at 20±0.5 °C, precipitated (*S*)-**3** was collected by filtration (0.16 g after drying; 91% ee). The extra portion of *rac*-**3** (0.16 g) was then dissolved in the mother liquor at 40 °C; the resulting solution was cooled to 25 °C. After addition of (*R*)-**3** (3 mg) as seed crystals to the solution, and stirring the mixture for 100 min at 20±0.5 °C, (*R*)-**3** (0.14 g after drying; 80% ee) was collected by filtration. Further resolution was carried out at 20±0.5 °C by adding amended amounts of *rac*-**3** to the filtrate in a manner similar to that described above. After second cycle, 0.09 g of (*S*)-**3** (92% ee) and 0.07 g of (*R*)-**3** (84% ee) were collected. A high degree of enantiomeric purity of collected diols can be achieved by simple recrystallization from CH_2Cl_2.