Spontaneous resolution of chiral 3-(2,3-dimethylphenoxy)propane-1,2-diol under the circumstances of an unusual diversity of racemic crystalline modifications

Supporting information

Alexander A. Bredikhin,* Dmitry V. Zakharychev, Zemfira A. Bredikhina, Alexey V. Kurenkov, Dmitry B. Krivolapov, Aidar T. Gubaidullin

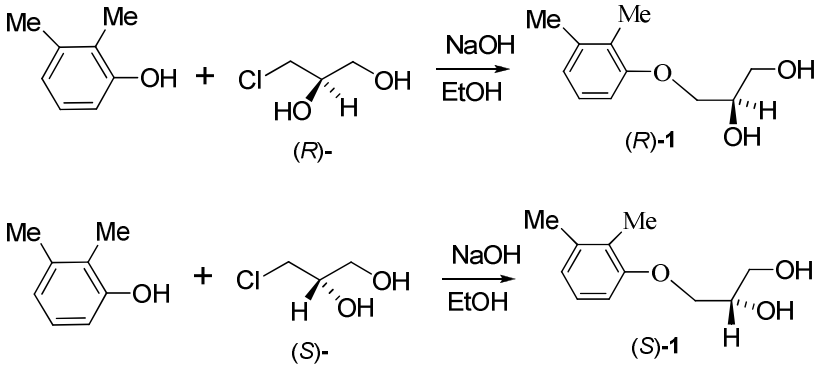
A.E. Arbuzov Institute of Organic and Physical Chemistry of Kazan Scientific Center of Russian Academy of Sciences, Arbuzov St., 8, Kazan 420088, Russian Federation

Corresponding Author: Alexander A. Bredikhin (baa@iopc.ru)

Instrumentation. The NMR spectra were recorded on a Bruker Avance-400 spectrometer (399.9 MHz for ^{1}H and 100.5 MHz for ^{13}C) in $CDCl_3$ with the signals of the solvent as the internal standard. The IR spectra of the polycrystalline samples of *rac*- and (*R*)-diols **1** in KBr pellets were recorded on a Bruker Tensor 27 spectrometer. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter (concentration *c* is given as grams per 100 milliliters). Melting points for general purposes were determined using a Boëtius apparatus. HPLC analyses were performed on a Shimadzu LC-20AD system controller, using UV detector.

Sample preparations. The samples of diol **1** were prepared by reaction of 2,3-dimethylphenol with racemic or enantiopure (*R*)- and (*S*)-3-chloropropane-1,2-diols (Scheme 1) by analogy with published procedure.[1]

Scheme S1. Preparation of enantiopure samples 1



Starting materials. Racemic 3-chloropropane-1,2-diol (99%) was purchased from Acros Organics. 2,3-Dimethylphenol (99%), (*R*)-3-chloropropane-1,2-diol (97%, 98% *ee*) and (*S*)-3-chloropropane-1,2-diol (98%, 98% *ee*), were purchased from Alfa Aesar.

*Racemic 3-(2,3-dimethylphenoxy)propane-1,2-diol, rac-**1**.* Racemic diol *rac*-**1** was prepared by analogy with published procedure.[1] To a solution of 2,3-dimethylphenol (9.21 g, 75.5 mmol) in ethanol (20 ml), a solution of NaOH (3.78 g, 94.4 mmol) in water (7 ml) was added and the resulting mixture was stirred and heated under reflux for 3 h. A solution of racemic 3-chloropropane-1,2-diol (10 g, 90.6 mmol) in ethanol (15 ml) was then added dropwise and the mixture was further stirred and heated at reflux for 12 h. After cooling, the volume of the resulting mixture was reduced to about one third followed by the addition water (100 ml) and extraction with EtOAc (4 × 70 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed. The crude diol **1** was purified by recrystallization from light petroleum ether/ EtOAc (2:1) to afford solid *rac*-**1.3** sample. Yield 11.4 g, 77 %; mp 81.5-90 ^{o}C (*rac*-**1.3**)

[lit.[2] mp 82.5-83 °C (ligroin; benzene)]; R_f = 0.1 [hexane/EtOAc (6:4)]. ^{1}H NMR δ: 2.15 (s, 3H, 2′-CH_3), 2.27 (s, 3H, 3′-CH_3), 2.74 (t, J = 5.7 Hz, 1H, CH_2*OH*), 3.12 (d, J = 4.8 Hz, 1H, CH*OH*), 3.77 (m, J = 11.5, 5.7, 5.7 Hz, 1H, C*H*$_2$OH), 3.86 (ddd, J = 11.5, 5.7, 3.8 Hz; 1H, C*H*$_2$OH), 4.01 (d, J = 5.4 Hz, 2H, OCH_2), 4.10-4.16 (m, 1H, *CH*OH), 6.71 (d, J = 8.1 Hz, 1H, $C^6_{Ar}H$), 6.81 (d, J = 7.6 Hz, 1H, $C^4_{Ar}H$), 7.05 (t, J = 7.9 Hz, 1H, $C^5_{Ar}H$). ^{13}C NMR δ: 11.7 (2-CH_3), 20.0 (3-CH_3), 63.9 (CH_2OH), 69.5 (OCH_2), 70.7 (CHOH), 109.3 (C^6_{Ar}), 123.0 (C^4_{Ar}), 125.2 (C^2_{Ar}-ipso), 125.9 (C^5_{Ar}), 138.1 (C^3_{Ar}-ipso), 156.3 (C^1_{Ar}-ipso).

*(R)-3-(2,3-Dimethylphenoxy)propane-1,2-diol (R)-**1*** was obtained from the (*R*)-3-chloropropane-1,2-diol (1.0 g, 9.1 mmol) and 2,3-dimethylphenol (0.92 g, 7.5 mmol) as described for racemic diol. Yield 0.89 g (60 %); mp 101-102.5 °C (light petroleum ether/ EtOAc); R_f = 0.1 [hexane/EtOAc (6:4)]; $[\alpha]_D^{20}$ = +1.4 (*c* 1.0, EtOH), $[\alpha]_{365}^{20}$ = +3.7 (*c* 1.0, EtOH), $[\alpha]_D^{20}$ = +13.4 (*c* 1.1, MTBE), $[\alpha]_{365}^{20}$ = +43.0 (*c* 1.1, MTBE) {lit.[3] $[\alpha]_D^{25}$ = +1.44 (*c* 1.0, EtOH) 96.6 % *ee*}; 99.3 % *ee* [chiral HPLC analysis; eluent: hexane/2-propanol (8:2); t_R = 11.2 min]. NMR spectra were identical with those cited above for *rac*-**1**.

*(S)-3-(2,3-Dimethylphenoxy)propane-1,2-diol (S)-**1*** was synthesized analogously from the (*S*)-3-chloropropane-1,2-diol as described for diol (*R*)-**1**. Yield 0.86 g (58 %); mp 101.5-103 °C; R_f = 0.1; $[\alpha]_D^{20}$ = –1.0 (*c* 1.1, EtOH), $[\alpha]_{365}^{20}$ = –1.9 (*c* 1.1, EtOH), $[\alpha]_D^{20}$ = –13.5 (*c* 1.0, MTBE), $[\alpha]_{365}^{20}$ = –43.2 (*c* 1.0, MTBE), $[\alpha]_D^{20}$ = +2.3 (*c* 1.1, $CHCl_3$), $[\alpha]_{365}^{20}$ = +9.9 (*c* 1.1, $CHCl_3$) {lit.[4] mp 104–105 °C (EtOH); $[\alpha]_D^{25}$ = +4.25 (c 1.0, $CHCl_3$)}; 99.9 % *ee* (chiral HPLC analysis; t_R = 13.0 min). NMR spectra were identical with those cited above for *rac*-**1**.

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Some detailes of crystal organisation of (*S*)-1.

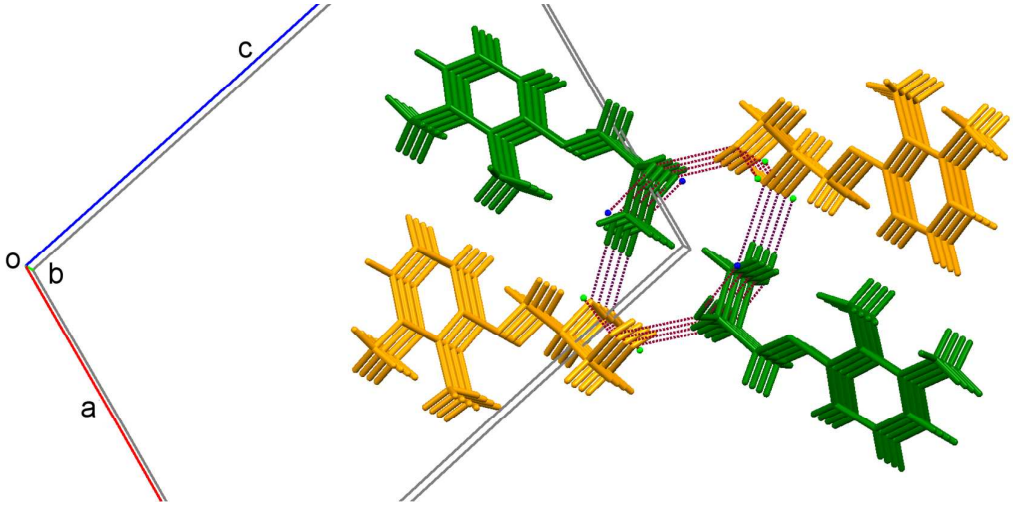

Figure S1. Detail of crystal packing in *S*-**1** crystals: 1D column along *0b* direction. Independent A molecules are denoted by orange color, B molecules are denoted by green; red dashed lines denote intermolecular H-bonds.

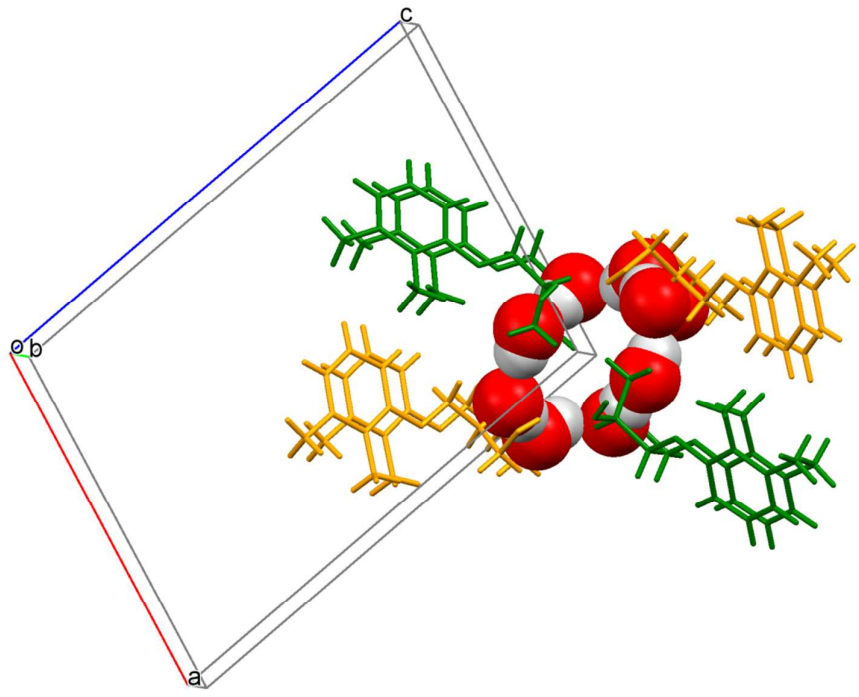

Figure S2. Detail of crystal packing in *S*-**1** crystals: one full pitch of endless *M*-helix of intermolecular H-bonds within 1D-column.

Additional DSC measurement details.

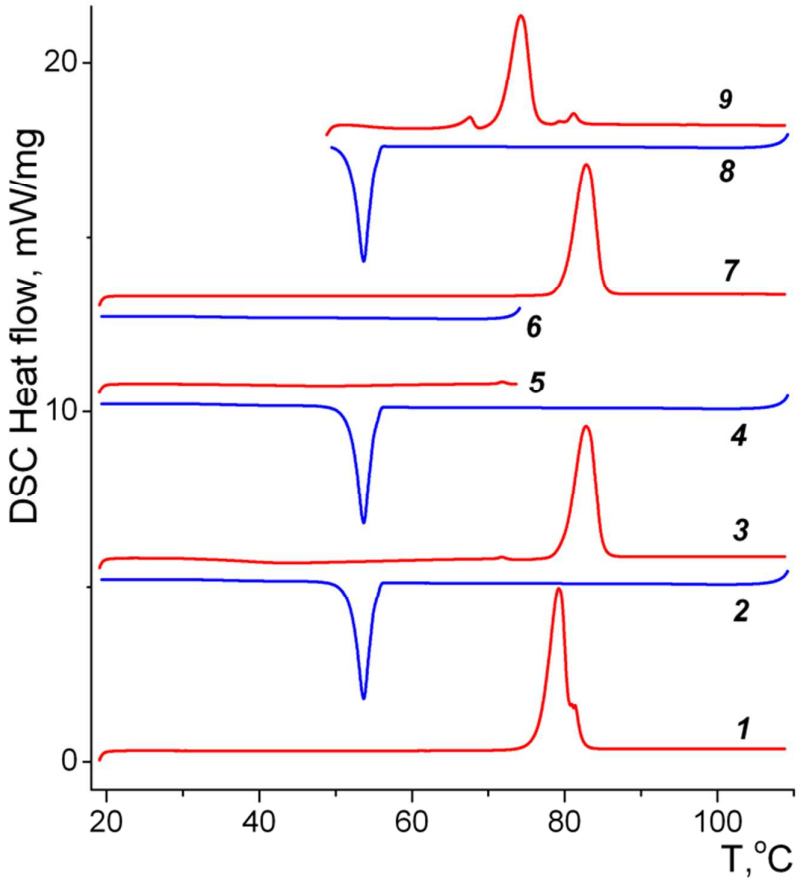

Figure S3. Scheme of the DSC experiments during the study of phase transformations of samples **1** obtained by crystallization from melt.

1 - Melting of the initial sample represented by the predominant *α-rac* phase.

2 - Crystallization of the sample upon cooling to 20 °C. The observed enthalpy of crystallization (~ 17 kJ/mole) is much less than the melting enthalpy.

3 - Melting of the solid phase obtained in the previous step. The parameters of the melting peak correspond to the *β-rac* phase. Before the melting peak, the thermogram exhibits a time-stretched exo-effect, interpreted as the recrystallization of the phase, formed in the primary crystallization, into *β-rac* phase.

4 - Cooling of the sample, obtained on the step 3, and its crystallization. Identical to cycle **2**.

5 - Heating the sample to a temperature of 72 °C to complete the recrystallization processes without melting the sample.

6 - Cooling the sample to 20 ^{o}C.

7 - Melting of the completely recrystallized sample. On the thermogram, the only thermal effect

is the *β-rac* phase melting.

8 - Cooling the sample to the end of crystallization, i.e., to 50 °C.

9 - Heating the sample immediately after crystallization of the melt. The thermogram shows a small peak at 66 ^{o}C, interpreted as the melting of the residual amounts of the primary crystallization product (the *δ-rac* phase), preceding a small, time-stretched exo-effect, interpreted as the recrystallization of *δ-rac* to *γ-rac* phase. The main component of the thermogram is the melting peak of *γ-rac* phase at 71.5 °C. The minor peaks at higher temperatures are interpreted as a fusion of the trace amounts of *β-rac* and conglomerate phases.

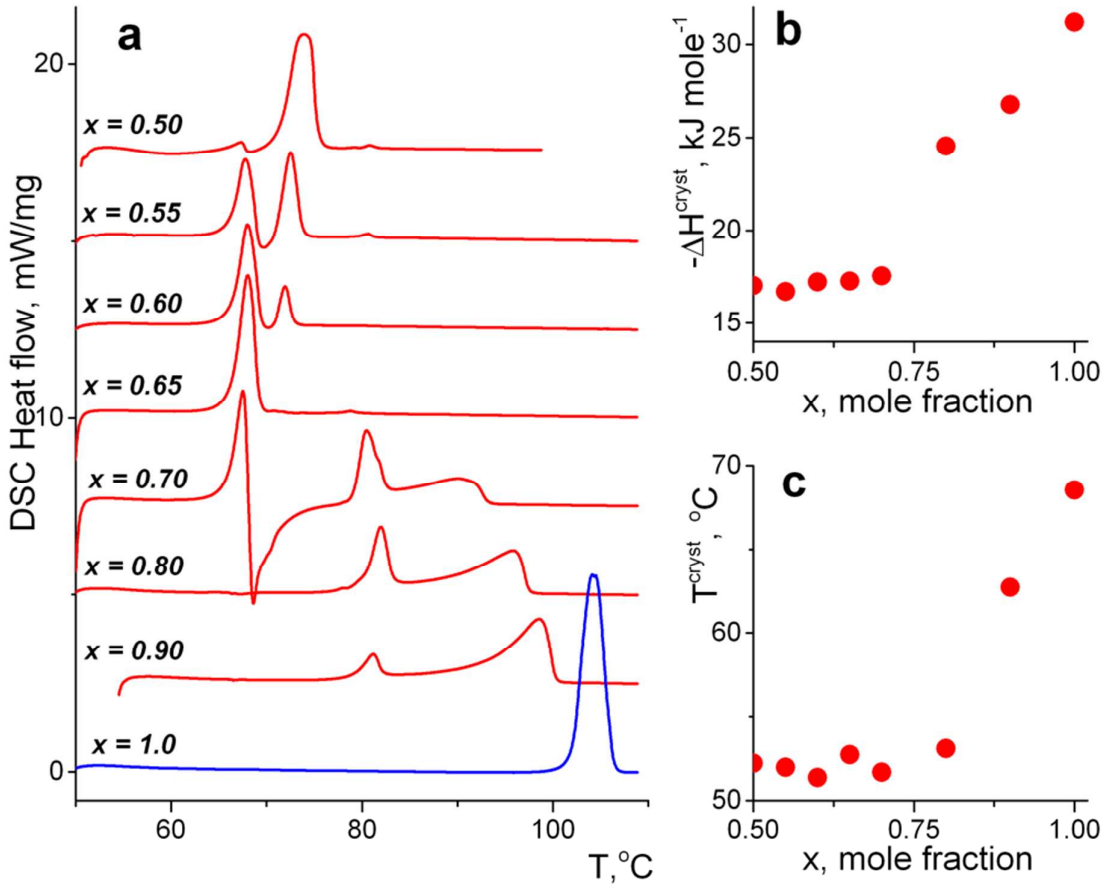

Figure S4. (**a**) DSC traces obtained immediately after the crystallization of the pre-melted sample for mixtures of enantiomers with a predominant enantiomer content (x = mole fraction; from below upwards) 1, 0.9, 0.8, 0.7, 0.65, 0.6, 0.55 and 0.5. (**b, c**) Dependence of the enthalpy (**b**) and temperature (**c**) of crystallization of the melt on the content of the predominant isomer.

For a number of diol **1** samples with different enantiomeric composition, upon transition to heating immediately after crystallization, melting of individual metastable phases can be detected (Figure S4a). Based on these thermograms, it is possible to make some assumptions about the nature of the short-lived metastable *γ- rac* and *δ-rac* phases.

Thus, when the composition is changed up to x = 0.7 (x - mole fraction of the predominant enantiomer), the stability of the *δ-rac* phase somewhat increases, and at x = 0.7 it is possible to observe an individual melting peak of this phase, corresponding to the enthalpy value previously determined from the crystallization peak. For this composition, corresponding to the presence in the system of 40% of enantiopure component, a single melting peak corresponding to the *δ-rac* phase is observed, and no subsequent thermal effects are observed which could correspond to the

transition to the liquid phase of the excess of the enantiopure diol. This allows us to conclude that the enantiopure component is not present in the system as an individual phase, but is included in the *δ-rac* phase. In other words, this is equivalent to the assumption that this last phase is a *solid solution*. It can be seen from Figure S4a, that the melting temperature and the enthalpy of crystallization of the *δ-rac* phase practically do not vary in the entire region of the enantiomeric compositions of the binary mixture, where the melting peak of this phase can be observed. This can serve as an indication that the metastable δ-rac phase is close to an *ideal solid solution*.

The position of the melting peak of the *γ-rac* phase also does not depend on the composition, but the existence of two ideal solid solutions, transformable one into another, is hardly possible. Most likely, the *γ-rac* phase is an independent unstable racemic compound, a precursor of the *β-rac* phase.

The shape of thermograms, corresponding to further increase in the content of the predominant stereoisomer, as well as the dependence of the temperature and enthalpy of crystallization on the composition (Figure S4b-c) can be explained by the fact that at x = 0.8, the crystallization of the phase of individual enantiomer begins to compete with the crystallization of the *δ-rac* phase. At higher enantiomeric excesses, only the peak of melting of β-rac and the subsequent melting of the excess of the enantiophase phase are recorded on thermograms.