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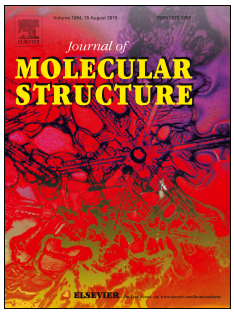

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New example of spontaneous resolution among aryl glycerol ethers: 3-(2,6-dichlorophenoxy)propane-1,2-diol

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ABSTRACT: Using a set of simple tests, based on the properties of ideal conglomerate phase diagrams, it has been suggested to the conglomerate-formative nature of 3-(2,6-dichlorophenoxy)-propane-1,2-diol **1**. Additional arguments have been drawn during the study of a single crystal X-ray diffraction study of the compound. The crystal packing details have been evaluated and discussed. Racemic **1** have been resolved into individual (*S*)- and (*R*)-components by a preferential crystallization procedure.

Keywords: Aryl glycerol ethers; Racemic conglomerate; Preferential crystallization; Solubility; Single crystal X-ray analysis; Crystal packing

HIGHLIGHTS

- Crystallization features of 3-(2,6-dichlorophenoxy)propane-1,2-diol are investigated.
- The crystal, selected from *rac*-diol, was solved in the trigonal Sohncke space groups $P3_2$.
- A right-hand bilifar helix (“double *P*-helix") is the principal supramolecular motif in *S*-diol crystals.
- Direct resolution of *rac*-3-(2,6-dichlorophenoxy)propane-1,2-diol was realized by entrainment procedure.

Introduction

Terminal aromatic glycerol ethers having the general formula Ar-O-$CH_2CH(OH)CH_2OH$ (TAGE) are closely related in its chemical structure to biogenic lipids molecules, and this makes them a grateful object of research. *Firstly*, it was long being established [1,2] that many representatives of TAGE exhibited a variety of biological activity, and some (for example, chlorphenesin [3(a)], guaifenesin [3(b)], mephenesin [3(c)]) acted as active pharmaceutical

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ingredients (APIs). Glycerol ethers are used as synthetic precursors in the preparation of other APIs, such as β-blockers [4,5] myorelaxants [6], antiarrhythmics [7], etc. *Secondly*, the amphiphilic lipid-like character of the TAGE molecules in conjunction with the presence of two free hydroxyl groups allows them to act as a low-molecular gelators [8,9,10] and thermotropic liquid crystals [11,10]. Pronounced ability to a supramolecular association makes them also interesting from a crystallographic point of view [12,13]. *Thirdly*, the TAGE molecules are chiral, and taking into account this fundamental feature provides additional interests both for structural as well as biological characteristics of these substances.

The object of this study is the terminal phenyl ether of glycerol carrying two chlorine atoms in the *ortho* positions of the phenyl ring, 3-(2,6-dichlorophenoxy)propane-1,2-diol **1** (Chart 1). It is known that the racemic form of the diol possesses antibacterial and antifungal activities [1]. Any information about enantiopure forms of compound **1** is absent in the literature. It is also known that *ortho* halogen-substituted phenyl ethers of glycerol are useful precursors in the synthesis of 1,4-benzodioxanes [14], and the benzodioxanes by themselves exhibit biological activity which is different for different enantiomers [15].

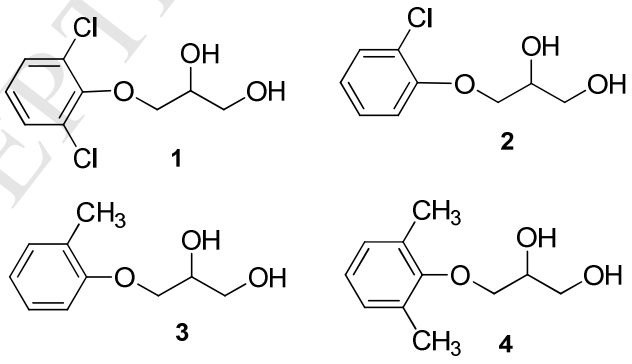


Chart 1. Compounds mentioned in the paper

An obtaining of **1** in the enantiopure form has had for us also noticeable structural interest. The closest analogue of diol **1**, mono-*ortho*-chlorosubstituted phenyl glycerol ether **2** crystallizes from racemic feed material as a normal conglomerate [16], that is, it shows a tendency to spontaneous resolution during crystallization [17]. From the standpoint of the structural requirements (shape of

the substituent and its size) chlorine atom has much in common with a methyl group. It is not surprising that the API mephenesin **3** is a normal conglomerate too [18]. But with all the similarity of the molecular structure of compounds **2** and **3**, despite the fact that both prone to spontaneous resolution upon crystallization, their crystal structures are very different. Chlorophenyl glycerol ether **2** crystallizes with one symmetry independent molecules in the unit cell (Z'= 1), and the primary crystal formative motif in this case is one of archetypal for the TAGE family, namely 2D bilayer *guaifenesin-like* motif [16]. Mephenesin **3** crystallizes with two independent molecules (Z '= 2), which form the 1D columns of another archetypal *mephenesin-like* crystal formative motif [19].

In a molecule of 2,6-dimethylsubstituted diol **4** the phenyl fragment can no longer save the typical to simple alkyl phenyl ethers flat conformation and it turns nearly orthogonal to the plane of $\angle C_{Ar}OC_{Alk}$ valence angle. Despite this drastic change in the geometry, diol 4 inherits from mephenesin 3 the ability to spontaneous resolution. This property has been used by us for direct resolution of racemic diol 4 into the individual enantiomers, which in its turn has become the key step in the synthesis of the API mexiletine in the single enantiomeric forms [7].

An interest to direct methods of racemates resolutions, which do not require for its realization any enantiopure auxiliaries or materials, is growing [20, 21]. For their wide practical application, it is necessary to expand the list of chiral compounds, the abilities of which to spontaneous resolution are reliably proved. In general, such materials are quite rare among chiral organic substances. It is noticed however, that there are the families of organic compounds, for which the frequency of conglomerates appearance significantly exceeds the average expectation. The problem of the existence of such "clusters of conglomerates" has been exemplified and discussed in a recent book [22]. The obvious structural similarity of compound **1** and compounds **2-4** allows to expect, that it can crystallize in the form of a conglomerate. It can serve as an additional argument for inclusion TAGE family to the list of known clusters of conglomerates.

The peculiarity of the family of compounds **2-4** is that small changes in the nature of substitution are accompanied by radical changes in the crystal packing. Therefore, an additional

interest in the nature of crystallization of compound **1** arises due to a question - whether this trend is maintained in this case.

Experimental

Instrumentation

The NMR spectra were recorded on a Bruker Avance-500 (500.13 MHz for ^{1}H and 125.75 MHz for ^{13}C) in $CDCl_3$ or $(CD_3)_2C=O$ with the signals of the solvent as the internal standard. The IR spectra of the polycrystalline samples of *rac*- and (*R*)-diols **1** under investigations 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 g/100 ml). Melting points for general purposes were determined using a Boëtius apparatus and are uncorrected. The melting curves were measured on a NETZSCH 204 F1 Phoenix DSC differential scanning calorimeter in sealing aluminum pans with the rate of heating of 10 $^{o}C \cdot min^{-1}$. The mass of the samples amounted to approximately ~1 mg and was controlled with Sartorius CPA2P balance. Temperature scale and heat flux were calibrated according standard procedure and verified by naphthalene sample.

The elemental composition was determined using a EuroVector EA3000 CHN analyzer. Thin-layer chromatography was performed on Silufol UV-254 plates using EtOAc-hexane (2:3) as eluent; TLC plates were visualized under UV irradiation or by treatment with iodine vapor. HPLC analyses were performed on a Shimadzu LC-20AD system controller, UV monitor 275 nm was used as detector. The column used, from Daicel Inc., was Chiralcel OD (0.46 x 25 cm); column temperature 20 ^{o}C; eluent: hexane/2-propanol = 9:1; flow rate: 1 mL/min. For the determination of enantiomeric compositions, the column was calibrated against the racemic compound.

Materials

Racemic 3-chloropropane-1,2-diol (99+%) was purchased from Acros Organics; 2,6-dichlorophenol (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.

Diols **1** were prepared by analogy with published procedure [23]. To a solution of 2,6-dichlorophenol **5** (2.46 g, 15.1 mmol) in ethanol (10 ml), a solution of NaOH (0.76 g, 18.9 mmol) in water (5 ml) was added and the resulting mixture was stirred and heated under reflux for 3 h. A solution of racemic or scalemic 3-chloropropane-1,2-diol **6** (2 g, 18.1 mmol) in ethanol (8 ml) was then added dropwise and the mixture was further stirred and heated at reflux for 20 h. After cooling, the volume of the resulting mixture was reduced to about one third followed by the addition water (50 ml) and extraction with EtOAc (4 × 50 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 (7:3).

***rac*-3-(2,6-Dichlorophenoxy)propane-1,2-diol, *rac*-1.**

White needles; yield 76 %; mp 79.5-80.5 ^{o}C (lit. [24]: mp 80.5-81 ^{o}C (petroleum ether; benzene)); R_f = 0.1. ^{1}H NMR ($CDCl_3$) δ: 2.36 (t, *J* = 6.1 Hz, 1H, CH_2OH), 3.08 (d, *J* = 4.7 Hz, 1H, CHO*H*), 3.80-3.85 (m, 1H, CH_2OH), 3.87-3.91 (m, 1H, CH_2OH), 4.13 (dd, *J* = 8.3, 6.1 Hz, 1H, OCH_2), 4.15-4.19 (m, 1H, C*H*OH), 4.21 (dd, *J* = 8.3, 2.8 Hz,1H, OCH_2), 7.03 (t, *J* = 8.1 Hz, 1H, $C^4{}_{Ar}H$), 7.31 (d, *J* = 8.1 Hz, 2H, $C^{3,5}{}_{Ar}H$).

(*R*)-3-(2,6-Dichlorophenoxy)propane-1,2-diol, (*R*)-1.

White needles; yield 76%, mp 102-102.5 ^{o}C; R_f = 0.1; $[\alpha]_D^{20}$ = +6.5 (*c* 1.0, EtOH); $[\alpha]_{365}^{20}$ = +23.3 (*c* 1.0, EtOH); $[\alpha]_D^{20}$ = +7.3 (*c* 1.0, MTBE), $[\alpha]_{365}^{20}$ = +23.6 (*c* 1.0, MTBE); 99.4 % ee [chiral HPLC analysis; t_R = 13.5 min]. ^{1}H NMR spectrum was identical with that given above for *rac*-**1**. ^{13}C NMR ($(CD_3)_2C$=O) δ: 63.3 (CH_2OH), 71.0 (OCH_2), 75.0 (CHOH), 125.6 ($C^4{}_{Ar}$), 129.0 ($C^{2,6}{}_{Ar}$), 129.2 ($C^{3,5}{}_{Ar}$), 151.5 ($C^1{}_{Ar}$). Anal. Calcd for $C_9H_{10}Cl_2O_3$: C, 45.59; H, 4.25; Cl, 29.91. Found: C, 45.99; H, 3.90; Cl, 30.10.

(*S*)-3-(2,6-Dichlorophenoxy)propane-1,2-diol, (*S*)-1.

White needles; yield 75%, mp 101.5-102.5 ^{o}C; R_f = 0.1; $[\alpha]_D^{20}$ = – 7.0 (*c* 1.0, MTBE); 99.9 % ee [chiral HPLC analysis; t_R = 10.9 min]. NMR spectra were identical to those reported above for *rac*- and (*R*)-**1**.

Solubility Measurements

Enantiomeric composition of saturated solutions of **1** in cyclohexane (analytical grade) was determined chromatographically. In preliminary experiments the upper limit of solubility of *rac*-**1** and *scal*-**1** was estimated by sequential addition of weighted portions of the substance to a given volume of the solvent (~ 1 mL) with stirring until a stable turbid suspension was formed. Thus, it was found that at room temperature the solubility of each component was less than 2 mg/ml.

Subsequently, the mixtures of rac-1 and scal-1 of various compositions were prepared so that the amount of any component substantially exceeded the solubility threshold. Samples (~ 10 mg) were placed in glass vials of 5 ml, the solvent (3 mL) and magnetic stirring bar was added thereto. The vessel was sealed and the system was stirred continuously overnight at a temperature of 20 ± 1 °C, after which the vessel was held for 2-3 hours without stirring to allow the sedimentation of the excess solid. An aliquot of the liquid phase was collected by a syringe; the solution was filtered by displacement from one syringe to another. Chromatographic analysis conditions were described above. As the numerical characteristics of the enantiomeric composition of the equilibrium liquid phase a corresponding chromatographic peak area was used directly.

Filters Millipore 0.45 μm PTFE hydrophilic were used for the samples filtering. Micro syringes Hamilton (precision within ±1%) were used for analytical sampling and for adding fixed volumes of solvent. The mass of the samples was controlled with Sartorius CPA2P balance (accuracy ±1 μg).

X-ray analysis

The crystals of *rac*-**1** for single crystal X-ray diffraction analysis were prepared by slow evaporation of the saturated solution of the corresponding sample in cyclohexane. The X-ray data for the single crystal, selected at random from a sample of polycrystalline *rac*-**1**, are shown in Table 1; there and hereinafter this crystal is designated as *S*-**1**.

The X-ray diffraction data for the crystal of *rac*-**1** were collected on a Bruker Smart Apex II AXS Apex II CCD diffractometer in the ω-scan mode using graphite monochromated Mo Kα (λ

0.71073 Å) radiation at 296(2) K. The crystal data, data collection, and the refinement parameters are given in Table 1.

Data were corrected for the absorption effect using SADABS program [25]. The structures were solved by direct method and refined by the full matrix least-squares using SHELX [26] and WinGX [27] programs. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were inserted at calculated positions and refined as riding atoms except the hydrogen atoms of OH groups which were located from difference maps and refined isotropically. The absolute structure of the investigated single crystal of glycerol ether **1** was determined based on the Flack parameter [28,29].

All figures were made using Mercury program [30]. Molecular structures and conformations were analyzed by PLATON [31]. Crystallographic data for the structure of (*S*)-**1** reported in this paper were deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1450144. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

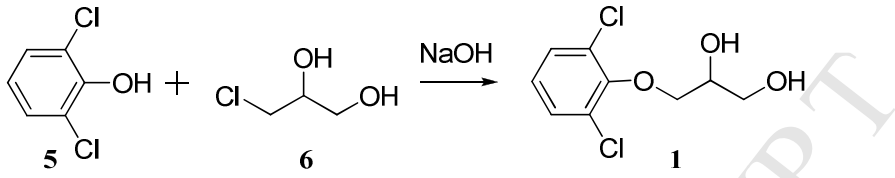
Table 1. Crystallographic data for diol (*S*)-**1**.

Compound	*S*-**1**
Formula	$C_9H_{11}Cl_2O_3$
M (g/mol)	238.08
Temperature, K	296(2)
Crystal class	Trigonal
Space group	$P3_2$
Crystal size	0.25x0.05x0.05 mm^3
Z, Z´	3, 1
Cell parameters	*a* = 14.446(12) Å, *c* = 4.319(4) Å
V, $Å^3$	780.6(14)
F(000)	369

ρ_{calc} g/cm^3	1.519
μ, cm^{-1}	6.01
θ range, deg	2.82 – 25.975
Reflections measured	5369
Independent reflections / R(int)	1901/ 0.1411
Number of parameters / restraints	131/ 1
Reflections [I>2σ(*I*)]	763
Flack parameter	0.06(17)
R_1 / wR_2 [I>2σ(*I*)]	0.0619/ 0.1311
R_1 / wR_2 (all reflections)	0.1599/ 0.1587
Goodness-of-fit on F^2	0.787
ρ_{max}/ρ_{min} (e$\AA^{-3}$)	0.291 / -0.222

Results and discussion

The samples of diol **1** necessary for the initial study were prepared by reaction of 2,6-dichlorophenol **5** with racemic or enantiopure 3-chloropropane-1,2-diol **6**.



*Diagnostic of conglomerate nature of diol **1***

The behavior of a chiral substance during the crystallization from melt or solution is determined by its phase diagram (PD). The most important features of the phase diagram of the normal conglomerate are, *firstly*, the presence of the single eutectic which composition adheres to the racemic ($ee_{eu} \equiv 0$). *Secondly*, the eutectic (in this case – racemate) always melts below than any of its component (in this case - pure enantiomers). Thirdly, by definition, the eutectic for normal racemic conglomerate is a mechanical mixture of homochiral (enantiopure, *ee* = 1) phases (usually crystalline), formed by opposite enantiomers.

Since the construction of the exact phase diagram requires specific equipment and considerable effort, the chemical practice has developed some techniques ("tests") allowing, explicitly or implicitly relying on the particular PD features, by available means in express mode, with a greater or lesser reliability to reveal the "conglomerate nature" of the substance. Let us consider under this angle some experimentally observed properties of compound **1**.

According to the second feature of PD, a comparison of the melting point of racemic and enantiopure chiral samples of the substance belongs to the simplest to implement and the most commonly used tests for the detection of normal conglomerates. The temperature (T^f) and the enthalpy (ΔH^f) of melting for diol **1** samples were determined by DSC and totaled 101.3 ^oC and 34.8 kJ·mole^{-1} for sample (*R*)-**1** and 80.1 ^oC and 32.4 kJ·mole^{-1} for sample *rac*-**1**; thus, racemic sample melts more than 20 degrees lower than scalemic. The substitution of the thermochemical

parameters of enantiopure sample melting in the known (simplified) Schröder-Van Laar equation [32]

$$\ln x = \frac{\Delta H_A^f}{R}\left(\frac{1}{T_A^f} - \frac{1}{T_x^f}\right)$$

allows one to estimate the melting point of the hypothetical ideal conglomerate (T^f_{cong}) as the intersection for two Schröder-Van Laar liquidus curves. The melting point of normal conglomerate calculated on this basis was 79.5 °C, which is in satisfactory agreement with the experimental value of the melting point of the racemic sample, $T^f_{cong} \approx T^f_{rac}$. So it is possible to conclude that the system has only one eutectic (the *first feature* of the phase diagram) and to expect that the system crystallizes as a normal conglomerate.

If the crystals of the enantiomers were formed in the same conditions, then the possibility of their existence as different polymorphs, if not eliminated, but was unlikely. Accordingly, scalar properties of these crystals, for example, their vibrational spectra, should match one another. For conglomerate compounds this means that the vibrational spectra of polycrystalline racemic sample, which is a mixture of homochiral crystals (*third PD feature*), and a polycrystalline sample of pure enantiomer must be the same. Experimental IR spectra for crystalline samples of *rac*-**1** and (*R*)-**1** in KBr tablets are shown in Figure 1a.

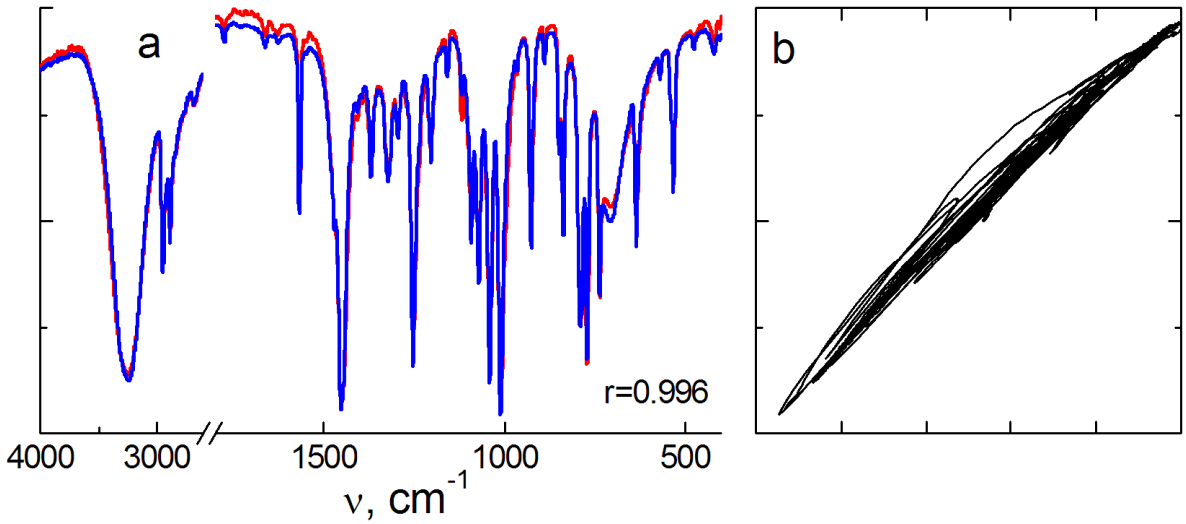


Fig 1. (a) IR spectra of polycrystalline samples of racemic (red curves) and enantiopure (blue curves) **1** and (b) correlation characteristics between them.

Visual examination shows that these spectra are at least similar. In order to give a quantitative character to similarities and differences of the spectra, we have proposed to use the Pearson correlation coefficient for the pair of discrete numerical arrays corresponding to the experimental spectral curves "*rac*-**1**".vs."(*R*)-**1**" [33]. In our case this value is sufficiently high, **r** = 0.996. The similarities and differences in the spectra are even more obvious during a direct comparison of spectra in mutual coordinates of the relative intensity of transmission or absorption [10]. Thus obtained "correlation trajectory" *rac*-**1**".vs."(*R*)-**1**" is shown in Figure 1b. Location of the array of points along the main diagonal and dense nature of the array demonstrates no significant differences between the spectra.

Obviously, the diagnostic value of this test should not be exaggerated. It is apparently inapplicable to substances that form continuous solid solutions of enantiomers. The test may give uncertain results in the case of normal racemic compound formation, if the chiral substance has no expressed intermolecular interactions involving polar bonds. Even the presence of the latter does not lead to a noticeable differentiation of the spectra if the supramolecular crystal-formative motifs for enantiopure and racemic samples coincide.

The first feature of the conglomerate phase diagram, namely its eutectic nature and racemic composition of the eutectic, is rarely used for preliminary testing. Meanwhile, identification of these fundamental features of PD of chiral substance can be regarded as sufficient proof of its conglomerate nature. Recently, we have proposed and have tested on different systems [10,34,35] the fast and efficient test based on the determination of the eutectic composition in solution, which is in equilibrium with the solid sample having intermediate enantiomeric composition, $0 < ee < 1$. The basis of the test consists with the fundamental assumptions that in an equilibrium state the activities of the components of a multicomponent system in the solid and liquid phases are equal; and activity coefficients for both enantiomers dissolved in achiral solvent are also equal [10]. Another way to substantiate our test is the analysis of the graphical representation of the ternary phase diagram of the normal conglomerate [35].

The test to the composition of the ternary phase diagram eutectic for compound **1** was conducted in cyclohexane. There were two sets of experiments with different solid phase enantiomeric composition (mole fractions of *R*-enantiomer amounts 0.35 and 0.80). In all experiments the composition of the eutectic, determined by the ratio of enantiomers in the liquid phase, saturated with respect to each of the solid components, was identical in the limits of measurement accuracy and equal x_{eu} = 0.502 ± 0.005. This indicates that the system studied is eutectic in nature, and eutectic composition corresponds to racemate. In its turn, these facts indicate the crystallization of racemic 2,6-dichlorophenyl ether of glycerol in the form of racemic conglomerate.

Thus, according to the preliminary tests, 2,6-dichlorophenyl glycerol ether is prone to spontaneous resolution, and from this point of view does not fall out from the family of *ortho*-substituted TAGEs shown in Chart 1.

Single crystal X-ray investigations

The compound **1** crystals grown from enantiopure (Fig. 2a) and racemic (Fig. 2b) feed material look very similar to each other, except that on average the last noticeably thinner than the first.

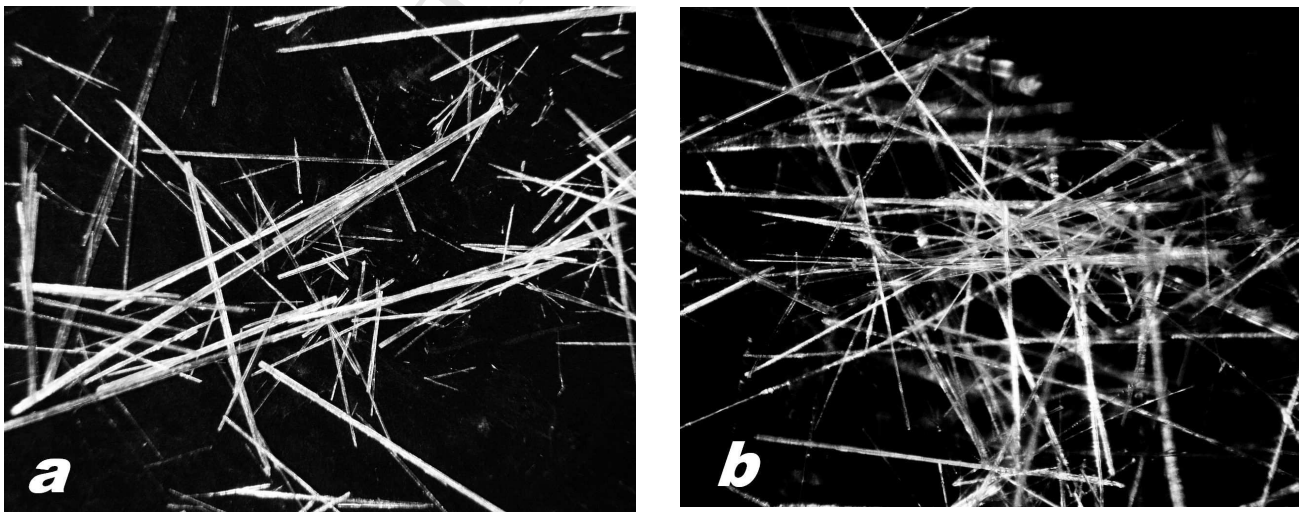


Fig. 2. Appearance of the crystals of **1** grown from enantiopure (***a***) and racemic (***b***) feed material.

The X-ray data for the single crystal, selected at random from a sample of polycrystalline *rac*-**1**, are shown in Table 1, where this crystal is designated as *S*-**1**. The crystal was solved in the

trigonal Sohncke space groups $P3_2$. In the crystal the only symmetry independent molecule, namely *S*-enantiomer, is present. The correctness of the choice of configuration is confirmed by Flack parameter, however, this correspondence cannot be considered as the ascertainment of the absolute configuration of **1**, because no chiroptical characteristics were known for the randomly selected single crystal. The crystallization of a racemate in Sohncke space group with sole symmetrically independent molecule ensures an enantiomeric purity of ideal single crystal (third feature of the conglomerate phase diagram), and in this sense, is the conclusive evidence of spontaneous resolution.

The only independent molecule (and the numbering scheme adopted in the article) is shown in Figure 3.

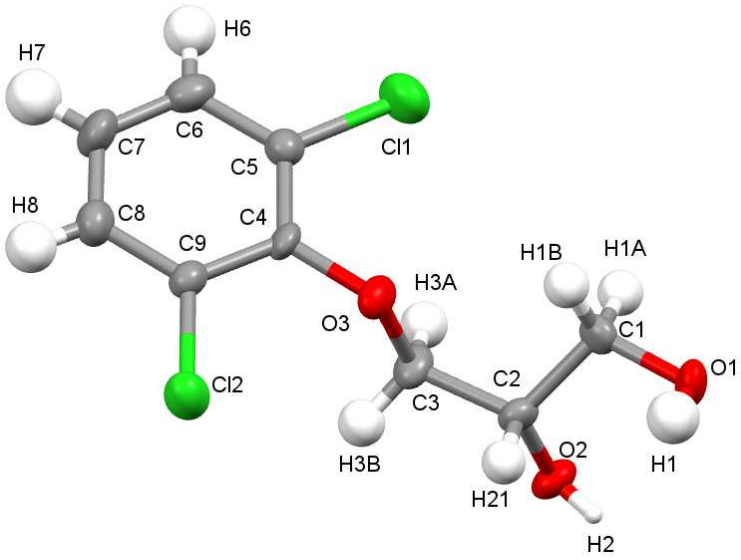


Fig. 3. Geometry of the symmetry independent *S*-molecule in the crystal picked from *rac*-**1** polycrystalline sample. Non-hydrogen atoms are represented by probability ellipsoids of thermal vibrations (p = 30%), hydrogen atoms – by spheres of arbitrary radii.

Detail of *S*-**1** crystal packing is shown in Figure 4. It can be seen that the primary supramolecular motif in the crystal lattice are 1D columns, formed by a continuous system of intermolecular hydrogen bonds O–H···O around the screw axes 3_2 and oriented along the shortest crystallographic axis *0c*. In the 3D structure these columns are packed by dispersion interactions of hydrophobic periphery with six similar adjacent columns (Figure 4, the adjacent columns are marked by spacefill style).

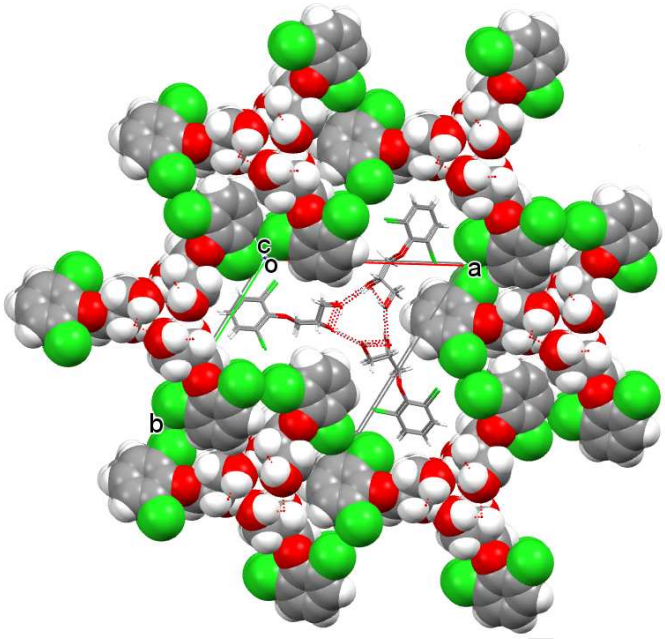


Fig. **4**. Detail of the crystal packing of 1: 1D column of the supramolecular primary motif ("caped sticks") surrounded by six similar adjacent columns ("spacefil").

Within the crystalline space of *S*-**1** the continuous sequence of the intermolecular hydrogen bonds binds the primary hydroxyl group of one molecule with secondary hydroxyl group of a second molecule, then the primary hydroxyl group of the following molecule, and so forth. One possible “monomeric unit" for such a sequence, ··[·O1-H1···O2-H′2·]··, consists of two fragments belonging to two different molecules. This unit is different from other possible monomer unit, ··[·O2-H2···O1-H′1·]··, which in its turn generates another infiniteintermolecular hydrogen bonds sequence. Thus, the overall system of intermolecular hydrogen bonds, forming 1D columns in *S*-**1** crystals, is a right-hand bilifar helix (“double *P*-helix", Fig. 5).

The space group $P3_2$ is one of the few really chiral space groups, herewith the space group $P3_1$ acts as its enantiomorph. It is understood that *R*-enantiomers of diol **1** crystallize in this last group and form the same, but oppositely oriented left-hand double *M*-helix. This, in principle, trivial consequence has been previously confirmed by us by the example of 3-(2,6-dimethylphenoxy)propane-1,2-diol **4**, the crystal structure of which repeats every detail of the structures we see in Figures 4 and 5 [7].

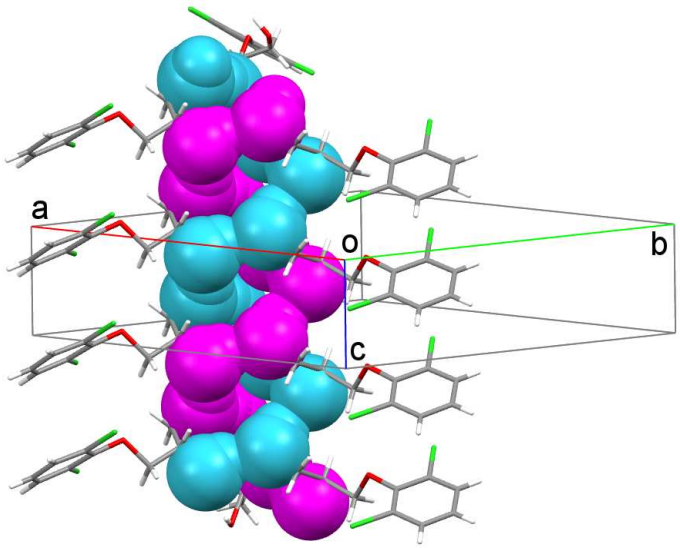


Fig. 5. The H-bound 1D column structure (double *P*-helix in "space-fill" style) in the *S*-**1** crystal picked from racemate. The atoms and hydrogen bonds belonging to the different HB sequences are designated by different colors;

Thus, 1D double helix formed around the screw axes of the third order, 3_1 or 3_2, by two chains of molecules held together by intermolecular hydrogen bonds, can be considered as the third, along with guaifenesin-like and mephenesin-like, archetypal for TAGE supramolecular primary motif. Table 2 compares the main torsion angles characterizing the conformation of the molecules in crystals **1**-**4**.

As follows from the Table, the corresponding specifications for *o*,*o'*-dichloro and *o*,*o'*-dimethyl derivatives **1** and **4** are virtually identical: the maximum difference between them is less than 7.5° (ω1). At the same time, these torsion angles are markedly different from those of *o*-monochloro and *o*-monomethyl derivatives **2** and **3**, for which, respectively, the typical guaifenesin-like and mephenesin-like motifs are realized.

Table 2. Selected torsion angles in molecules in the investigated crystalline 3-aryloxypropane-1,2-diols **1**-**4** (Chart 1).
Adopted in this study numbering scheme is shown in Fig. 2. In all the cases for uniformity the torsion angles are provided for *R*-enantiomers.

Compound (molecule)	Torsion angles							**Formula** τ_1, τ_2, (τ_{22}), τ_3, τ_4, ω_1, ω_2
	O1C1C2C3 τ_1	**C1C2C3O3** τ_2	**O2C2C3O3** (τ_{22})	**C2C3O3C4** τ_3	**C3O3C4C5** τ_4	**H1O1C1C2** ω_1	**H2O2C2C3** ω_2	
(*S*)-**1**[a]	-172.9	55.4	178.4	-175.8	82.7	60.3	160.3	*ap,sc,(ap),ap,ort,sc,ap*
(*S*)-**2**[b]	52.0	53.3	176.9	175.5	176.9	130.2	149.0	*sc,sc,(ap),ap,ap,ac,ap*
(*R*)-**3** (A)[c]	-60.5	-59.6	64.1	-175.0	-179.8	-178.4	-78.7	*-sc,-sc,(sc),ap,ap,ap,-sc*
(*R*)-**3** (B)[c]	60.6	65.3	-172.6	-175.1	-177.9	97.8	151.2	*sc,sc,(ap),ap,ap,ort,ap*
(*S*)-**4**[d]	-172.1	53.2	174.9	179.5	81.6	67.6	159.1	*ap,sc,(ap),ap,ort,sc,ap*

a. This work.
b. Ref. [16].
c. Ref. [18,19].
d. Ref. [7].

*Direct resolution of rac-**1** by entrainment procedure*

Discovering the new conglomerate formative compound in the family of aryl glycerol ethers we have decided to examine its ability to preferential crystallization by entrainment. Before starting the resolution of diol **1**, we have studied in benzene and water the solubility of *rac*-**1** and (*R*)-**1**, as well as the reverse process of crystallization from solution. The difference between the dissolution and crystallization temperature ("thermal gap", ΔT) of *rac*-**1** in benzene was about 7 °C, and for (*R*)-**1** about only 4 °C (Table. 3). This means that the crystallization in benzene goes too fast, making it difficult to control the process of resolution, which occurs in time. In water ΔT is about 20 °C for *rac*-**1** and from 12 ° C to 31 ° C for enantiopure (*R*)-**1**, depending on the degree of initial supersaturation of the solution. For samples of **1** with 0 < *ee* <1 ΔT falls within this range (Table.3). Consequently, water is found to be a suitable solvent for developing a method of stereoselective crystallization of diol **1**.

Table 3. The solubility and crystallisatioin of diol **1** in benzene and water.

Solvent	Sample	Concentration, mg/ml	T sol., °C	T cryst., °C	Δ T, °C
C_6H_6	*rac*-**1**	10.3	23	-	-
		20.3	32	24.8	7.2
		31.0	37	29.5	7.5
	(*R*)-**1**, 99 % ee	10.2	32.5	30.5	2
		20.4	44	40	4
		30.3	48	45.5	2.5
	(*R*)-**1**, 10% ee	20.4	32	28	4
H_2O	*rac*-**1**	10	58.5	38	20.5
	(*R*)-**1**, 99 % ee	2.6	51.5	20.5	31
		5.0	59	37	22
		7.6	65	53	12
	(*R*)-**1**, 10% ee	8.1	54	40	14

In the experiment, which demonstrates the possibility of direct resolution of 3-(2,6-dichlorophenoxy)propane-1,2-diol **1**, the initial concentration of slightly enriched (~ 5% ee) *rac*-**1** was 7.5 mg/mL, and the crystallization temperature was maintained not higher than 39 °C. Over the course of the resolution a supersaturated solution of diol *rac*-**1** (1.035 g), including a moderate excess of (*R*)-**1** (0.041 g), was prepared by heating the mixture in 138 ml of H_2O at 56 ^oC. The solution was cooled to ~ 40 ^oC and a small amount (5 mg) of finely pulverized seed crystals of (*R*)-**1** was added. The stirred solution was allowed to crystallize for about 85 min at 39 ^oC.

For monitoring the entrainment process during seed-induced crystallization of oversaturated slightly nonracemic solutions we have used chiral HPLC analysis of mother liquor aliquots. As seen in Figure 6, during the precipitation an enantiomeric excess of diol **1** remaining in solution is changing, passing through zero. The crystallization process was interrupted when the rate of change of the enantiomeric composition of mother liquor significantly slowed down.

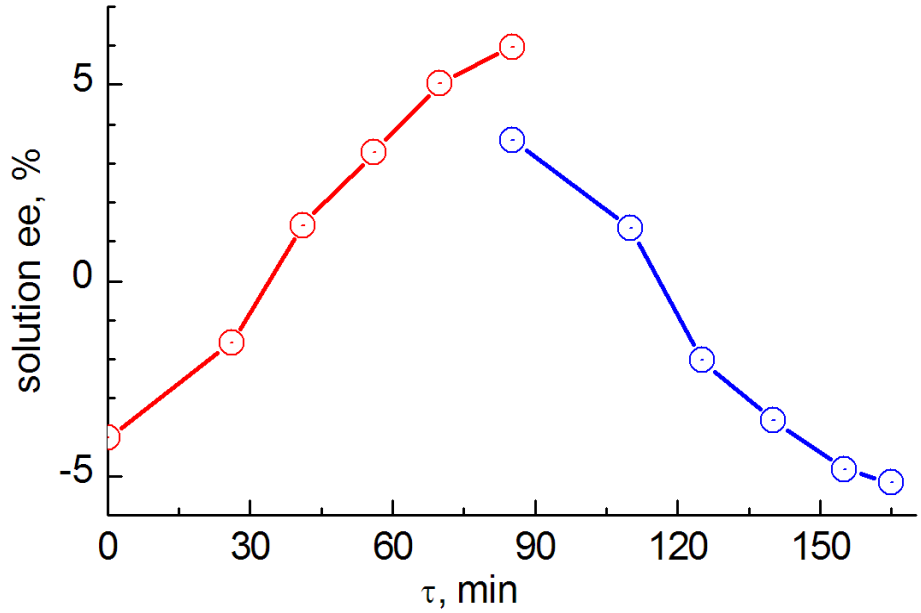


Fig. 6. Mother liquor enantiomeric excess vs. time of preferential crystallization of diol **1** (one cycle, two runs). In place of rupture curves the sedimentation of one enantiomer was interrupted; see text for comments.

Precipitated (*R*)-**1** was collected by filtration. The weight of (*R*)-**1** obtained after first filtration (0.116 g after drying; 93.5 % ee) was more than the common weight of the initial excess of the (*R*)-enantiomer and seed added. The extra portion of *rac*-**1** (0.111 g) was then dissolved in the mother

liquor at 56 ^{o}C in order that the overall quantity of **1** in the solution could be recovered. The mixture was heated until the solid was completely dissolved and then cooled to ~ 40 ^{o}C. After the addition of (*S*)-**1** (5 mg) as seed crystals to the solution, and stirring the mixture for 80 min at 39 ^{o}C, (*S*)-**1** (0.100 g after drying; 94.5 % ee) was collected by filtration.

A high degree of enantiomeric purity of collected diols can be achieved by simple recrystallization. Making sure that compound **1** is quite capable of preferential crystallization we made no attempts to optimize experimental conditions for the resolution.

Conclusions

The representative of TAGE (terminal aromatic esters of glycerol) series, 3-(2,6-dichlorophenoxy)propane-1,2-diol **1**, is in obvious structural relationship with 3-(2-chlorophenoxy)propane-1,2-diol **2** on the one hand and with 3-(2,6-dimethylphenoxy)propane-1,2-diol **4**, on the other. Since both compounds **2** and **4** have a tendency to spontaneous resolution to individual enantiomers during crystallization, it was logical to explore this capacity for compound **1**. A variety of tests designed to identify some essential features of the phase diagrams inherent to ideal conglomerate was examined by the example of this compound. Tests based on thermochemical characteristics, as well as a study of the equilibrium solubility of nonracemic samples showed that crystallization of *rac*-**1** was eutectic in nature, with the eutectic composition of virtually no different from racemic. Comparison of the vibrational spectra of crystalline racemic and scalemic samples, as well as X-ray diffraction study of a single crystal, selected at random from a racemic sample, confirmed the homochiral nature of the components of the eutectic. Finally, a sample of racemic **1** was able to be divided into individual enantiomers by a direct approach, namely resolution by entrainment. Taken together, the test results indicate the ability of the diol **1** to spontaneous resolution.

X-ray diffraction experiment revealed that the primary supramolecular crystal formative motif in the crystals of **1** is a double helix formed by two sequences of identical enantiomers bonded through chains of classical intermolecular hydrogen bonds O–H···O. This motif has been already met in the series of TAGE and can be considered as the archetypal for this family.

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