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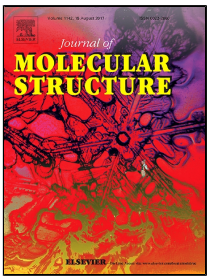

Crystallization features and spontaneous resolution of 3-(2,6-dimethoxyphenoxy) propane-1,2-diol: the case of stable conglomerate and metastable solid solution

Alexander A. Bredikhin, Zemfira A. Bredikhina, Olga A. Antonovich, Dmitry V. Zakharychev, Dmitry B. Krivolapov

PII:	S0022-2860(17)30702-0
DOI:	10.1016/j.molstruc.2017.05.091
Reference:	MOLSTR 23832
To appear in:	*Journal of Molecular Structure*
Received Date:	17 February 2017
Revised Date:	12 May 2017
Accepted Date:	18 May 2017

Please cite this article as: Alexander A. Bredikhin, Zemfira A. Bredikhina, Olga A. Antonovich, Dmitry V. Zakharychev, Dmitry B. Krivolapov, Crystallization features and spontaneous resolution of 3-(2,6-dimethoxyphenoxy)propane-1,2-diol: the case of stable conglomerate and metastable solid solution, *Journal of Molecular Structure* (2017), doi: 10.1016/j.molstruc.2017.05.091

HIGHLIGHTS

- Crystalline 3-(2,6-dimethoxyphenoxy)propane-1,2-diol was investigated by X-ray, IR, and DSC techniques.
- The crystal, selected from racemate, belongs to orthorhombic Sohncke space groups $P2_12_12_1$.
- Racemic 3-(2,6-dimethoxyphenoxy)propane-1,2-diol was resolved by entrainment procedure.
- Along with stable conglomerate, metastable solid solution is formed during a kinetically controlled crystallization.

Crystallization features and spontaneous resolution of 3-(2,6-dimethoxyphenoxy)propane-1,2-diol: the case of stable conglomerate and metastable solid solution

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ABSTRACT: Phase behavior of 3-(2,6-dimethoxyphenoxy)propane-1,2-diol **1** was investigated by IR spectroscopy, X-ray diffraction, and DSC methods. Racemic diol **1** prone to spontaneous resolution and has been resolved into (*S*)- and (*R*)-enantiomers by a preferential crystallization procedure. Separation takes place, but it gives crystalline precipitates with moderate (60-70%) enantiomeric excess values. The plausible reason is the formation of metastable phase of solid solution during the crystallization.

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

1. Introduction

For a wide practical application of direct methods of racemate resolution, that do not require for its implementation any enantiopure auxiliary substances and materials [1], it is necessary to expand the range of chiral compounds, for which the ability to spontaneous resolution is reliably proven [2]. The object of this work is the terminal phenyl glycerol ether carrying two methoxy groups in the *ortho* positions of the phenyl ring, 3-(2,6-dimethoxyphenoxy)propane-1,2-diol **1** (Chart 1). This diol is in obvious structural relationship with the mono-*ortho*-methoxy diol **2**, the well-known drug guaifenesin. Our recent structural studies have shown that the introduction of such substituents as methoxy or methyl group or a chlorine atom at the *ortho* position of the benzene ring in glycerol ethers **2-6** combines them into a common group according the type of their crystallization: all of them exhibit spontaneous resolution property during crystallization of the racemic material [3-6].

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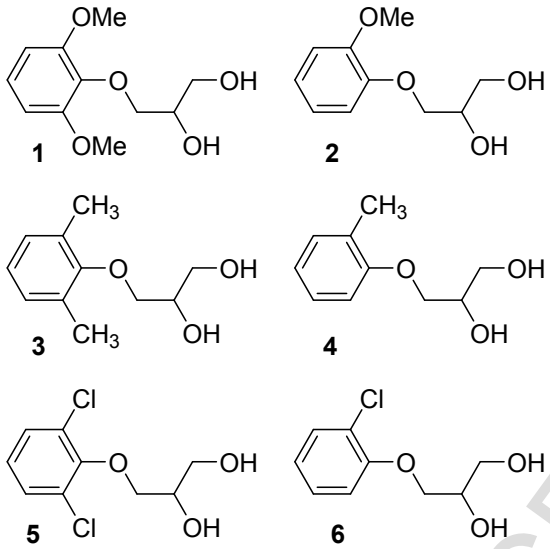


Chart 1. Mono- and di-*ortho*-substituted phenyl glycerol ethers **1**-**6**.

Diol **1** acts as a precursor in the synthesis of compound **7**, a close analog of the α_1-adrenoceptor antagonist WB4101 [7], belonging to the class of 1,4-benzodioxanes (Chart 2). It is known that its *S* enantiomer possess remarkably higher affinity toward α_1-adrenoceptors than the *R* enantiomer [8]. In this connection, the efficient production of single enantiomeric diols **1** is gaining, along with academic, in practical importance.

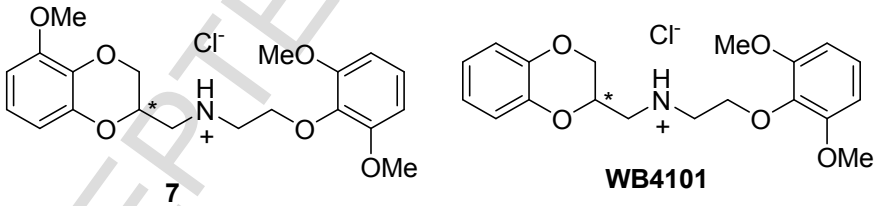


Chart 2. 1,4-Benzodioxanes, exhibiting a pronounced affinity toward α_1-adrenoceptors.

According to the literature, the difference in melting temperatures between enantiopure (73-74°C) [7] and racemic (52-53.5°C) [9] diols **1** is ~ 20 °C. This suggests that the diol **1**, like other members of the family of **1**-**6**, crystallizes in the form of a normal conglomerate, which creates prerequisites for its production in enantiopure forms by direct methods.

2. Experimental

2.1. 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** under investigations in KBr pellets were recorded on a Bruker Tensor 27 spectrometer. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter. 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 5 °C·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. HPLC analyses were performed on a Shimadzu LC-20AD system controller, UV monitor 275 nm was used as detector. The columns used, from Daicel Inc., were Chiralcel OJ or OD (0.46 x 25 cm); eluent hexane: isopropanol = 4:1 v/v; flow rate: 1 ml·min^{-1}.

2.2. Materials

Racemic 3-chloropropane-1,2-diol (99+%), and 2,6-dimethoxyphenol (99%) were purchased from Acros Organics; (*R*)-3-chloropropane-1,2-diol (97%, 98% *ee*), and (*S*)-3-chloropropane-1,2-diol (98%, 98% *ee*) were purchased from Alfa Aesar.

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

Racemic diol *rac*-**1** was prepared by analogy with published procedure [10]. A solution of 2,6-dimethoxyphenol (25 g, 0.16 mol) in 45 ml of absolute ethanol was added to a solution of metal sodium (3.7 g, 0.16 mol) in 80 ml of absolute ethanol. The suspension was stirred for 30 min warming to 70 °C, then 3-chloropropane-1,2-diol (23.2 g, 0.21 mol) was added under argon atmosphere. The reaction mixture was refluxed for 4-5 h and filtered. The filtrate was distilled, and the fraction boiling at 175-195 °C (0.8 mm) (19 g, 52%) was crystallized from Et_2O/n-

pentane to afford 9.9 g (27%) of *rac*-**1**: white solid, mp 50–53 °C (50.7 °C, DSC); {lit. [9]: mp 52-53.5 °C}. ^{1}H NMR, δ: 3.04 (br. s, 2H, OH), 3.70 (approx. dd, J = 11.4, 3.9 Hz; 1H, CH_2OH), 3.78 (approx. dd, 1H, J = 11.4, 2.4 Hz; 1H, CH_2OH), 3.88 (s, 6H, OCH_3), 3.93-4.00 (m, 2H, OCH_2), 4.22-4.27 (m, 1H, CH, C*H*OH), 6.61 (d, J = 8.4 Hz, 2H, $C^{2,4}{}_{Ar}H$), 7.03 (t, J = 8.4 Hz, 1H, $C^5{}_{Ar}H$). ^{13}C NMR δ: 56.1 (2 CH_3O), 63.5 (CH_2), 70.4 (CH), 75.9 (OCH_2), 105.2 ($C^{3,5}{}_{Ar}$), 124.1 ($C^4{}_{Ar}$), 136.9 ($C^1{}_{Ar}$-ipso), 153.2 ($C^{2,6}{}_{Ar}$-ipso).

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

Compound (*R*)-**1** used hereinafter as seed crystals was obtained from (*R*)-3-chloropropane-1,2-diol (*R*)-**9** (0.93 g, 8.4 mmol) and 2,6-dimethoxyphenol (1 g, 6.5 mmol) as described for racemic diol. The reaction mixture was refluxed for 4 h and then filtered. The volume of the resulting filtrate was reduced to about one third followed by the water addition (20 ml) and extraction with EtOAc (3 × 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed. The resulting oil 1.42 g (89%) was purified by column chromatography (silica gel, eluent: light petroleum/EtOAc = 4:1) to afford diol (*R*)-**1** as a colorless oil (0.29 g, 19.6 %.) Diol was crystallized from Et_2O/n-pentane to afford analytically pure (*R*)-**1** (0.15 g, 9%); white solid, mp 72-73 °C (71.9 °C, DSC), $[\alpha]_D^{20}$ = –13.2 (*c* 1; EtOH); $[\alpha]_D^{20}$ = -19.6 (*c* 1; MTBE), $[\alpha]_{365}^{20}$ = -62.4 (*c* 1; MTBE); {lit.[7]: mp 73-74 °C, $[\alpha]_D^{25}$ = –13.3 (*c* 1, EtOH)}; > 99% *ee* {for reliable *ee* determination the crude diol was transformed into a diastereromeric mixture of cyclic sulfites via reaction between (*R*)-**1** (1 equiv) and $SOCl_2$ (1.1 equiv) in CH_2Cl_2 at 0 °C. The procedure of analysis is described in detail and illustrated by the example of nitro substituted phenyl glycerol ethers in our previous work [11]. Chiral HPLC analysis of the reaction mixture: Daicel Chiralcel OD column; column temperature 25 °C; t_R = 12.3 min (major), t_R = 13.0 min (minor); t_R = 13.7 min (major), t_R = 15.2 min (minor]}. NMR spectra for (*R*)-**1** were identical to those cited above for *rac*-**1.**

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

Diol (*S*)-**1** used as seed was obtained from (*S*)-3-chloropropane-1,2-diol (*S*)-**3** (1.97 g, 18 mmol) and 2,6-dimethoxyphenol (2 g, 13 mmol) as described for diol (*R*)-**1**. The resulting thick oil (0.74 g, 25%) was crystallized from ether/pentane to afford analytically pure (*S*)-**1 (**0.35 g, 12%); white solid, mp 72-73 °C (71.8 °C, DSC), $[\alpha]_D^{20}$ = +13.1 (*c* 1; $EtOH_{abs.}$), $[\alpha]_D^{20}$ = +19.5 (*c* 1; MTBE), $[\alpha]_{365}^{20}$ = +62.2 (*c* 1; MTBE); {lit. [7]: mp 73-74 °C, $[\alpha]_D^{25}$ = +11.9 (*c* 1, EtOH)}; 99% *ee* [chiral HPLC analysis, Chiralcel OJ column, column temperature 10°C; t_R = 23.5 min (minor), t_R = 24.8 min (major)]. NMR spectra were identical to those cited above for *rac*-**1.**

2.3. 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 mixture of diethyl ether/pentane. A single crystal, selected at random from the racemic polycrystalline sample, which was kept in long contact with the mother liquor, was used for X-ray analysis; hereinafter this crystal is designated as *R*-**1**.

The X-ray diffraction data for this crystal were collected on a Bruker Smart Apex II AXS Apex II CCD diffractometer in the ω-scan and φ-scan modes 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 [12]. The structures were solved by direct method and refined by the full matrix least-squares using SHELX [13] and WinGX [14] 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. All figures were made using Mercury program [15]. Molecular structures and conformations were analyzed by PLATON [16].

Crystallographic data for the structure of (*R*)-**1** reported in this paper were deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1529709.

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 *R*-**1**.

Compound	*R*-**1**
Formula	$C_{11}H_{16}O_5$
M (g/mol)	228.24
Temperature, K	296(2)
Crystal class	Orthorhombic
Space group	$P2_12_12_1$
Crystal size	0.30x0.30x0.05 mm^3
Z, Z′	4, 1
Cell parameters	*a* = 4.984(3) Å, *b* = 12.826(7) Å, *c* = 18.071(9) Å
V, Å^3	1155.1(10)
F(000)	488
ρ_{calc} g/cm^3	1.312
μ, cm^{-1}	1.04
θ range, deg	1.947 – 25.981
Reflections measured	11448
Independent reflections / R(int)	2249/ 0.0451
Number of parameters / restraints	151/ 0
Reflections [I>2σ(*I*)]	1627
R_1 / wR_2 [I>2σ(*I*)]	0.0567 / 0.1267
R_1 / wR_2 (all reflections)	0.0829/ 0.1397
Goodness-of-fit on F^2	1.001
ρ_{max}/ρ_{min} (eÅ^{-3})	0.290 / -0.200

*2.4. Resolution of racemic 3-(2,6-dimethoxyphenoxy)propane-1,2-diol rac-**1** by preferential crystallization (resolution by entrainment)*

Experiments on the stereoselective crystallization of *rac*-**1** were performed in a two-necked flask equipped with a magnetic stirrer, water condenser and thermometer placed in a water bath at a controlled temperature. During the resolution small portions of the mother liquor were taken through a syringe equipped with Teflon filter and were analyzed by polarimetry (cell path length 100 mm; wavelength 365 nm; 20 °C).

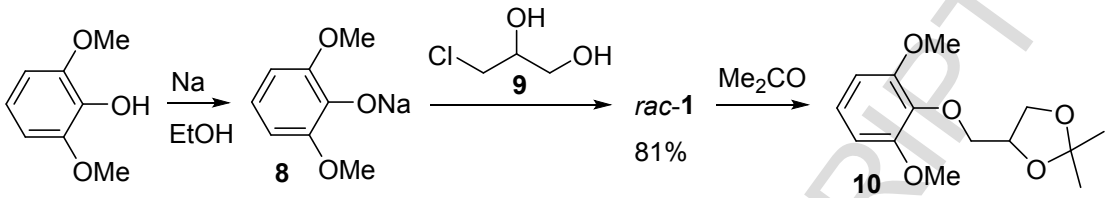
Example of the resolution by entrainment of rac-3-(2,6-dimethoxyphenoxy)propane-1,2-diol ***1*** *in MTBE without the initial enantiomeric enrichment of a starting mixture*: 2.52 g of *rac*-**1** was dissolved in 50 ml of MTBE at 34-35 °C and was cooled with stirring to 14 °C. Then a portion of finely ground crystalline seeds of (*R*)-**1** (10 mg, 0.4% by weight) was added. The solution was stirred and incubated at a temperature of 14 ± 0.5 ° C for 90 min. The precipitate was filtered, collected and dried to obtain 130 mg of (*R*)-**1** (62% *ee*). To the filtrate, which remained after separation of the precipitate, 120 mg of *rac*-**1** was added, and the system was heated to 34-35 °C until full homogenization after which it was cooled to 14 °C, and seeded with finely ground crystals of (*S*)-**1** (10 mg). The solution was stirred at a temperature of 14 ± 0.5 °C, and filtered after 150 min; 204 mg of (*S*)-**1** (59 % *ee*) were obtained. Likewise, the cycle was repeated several times, each time adding the lacking amount of racemic diol. Details of subsequent runs No. 3-6 are shown in Table 2. A high degree of enantiomeric purity of collected diols can be achieved by recrystallization from Et_2O/hexane. For example: a portion of (*R*)-**1** (0.57 g, 67 % *ee*) was crystallized from 20 ml of ether/hexane ~6/1 and then from 7 ml of ether; 0.19 g (33%) of (*R*)-**1** {$[\alpha]_D^{20}$ = -13.1 (*c* 1; EtOH), 99% *ee*} was obtained as result. Similarly, after recrystallization of combined portions of (*S*)-enantiomer (0.59 g, 63 % *ee*), pure (*S*)-**1** {0.18 g; $[\alpha]_D^{20}$ = +12.2 (*c* 1; EtOH), 94% *ee*} was obtained.

3. Results and discussion

3.1. Synthesis

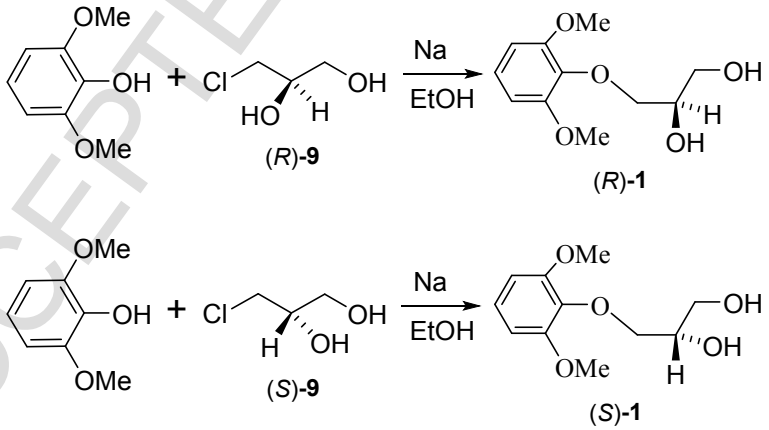
Reaction of sodium 2,6-dimethoxyphenolate **8** with chloropropane diol **9** was used in the literature [9,10] for synthesis of racemic diol **1**. Note that the authors of [9] point out that the

desired product is difficult to purify by distillation. In the cited paper, to prepare the analytically pure diol **1**, the oily crude product was converted into dioxolan **10**, from which, after distillation and acid hydrolysis, *rac*-**1** was recovered as a solid (mp 52-53.5 °C) in an overall yield of about 35 %.



We were able to crystallize *rac*-**1** from a mixture of diethyl ether and pentane immediately after distillation of crude reaction mixture without conversion of the product to acetonide **10**. After further recrystallization the yield of analytically pure *rac*-**1** was 27%.

In the paper [7] enantiopure 3-tosyloxy-1,2-propanediol acetonide was used as a source of chirality for enantiopure diol **1** production. The total yield of the diol starting from tosylate was about 28%. In this paper, to obtain small amounts of enantiopure diol for research purposes, and to use as enantiopure crystal seeds in the future, we have used commercially available enantiopure (*R*)- and (*S*)-3-chloropropane-1,2-diols (*see Experimental Part*).



*3.2. Single-crystal X-ray diffraction data for diol **1***

With prolonged (more than a week) maintaining of crystalline precipitate of racemic diol **1** in contact with the mother liquor the well-shaped needle-like crystals arise. The single crystal selected at random from this racemic polycrystalline sample was investigated by X-ray

diffraction analysis (Table 1). It turned out that its unit cell belongs to Sohncke space group *P* $2_12_12_1$ and contains a single symmetrically independent molecule having, in this particular case, (*R*)-configuration of a chiral center. This means that during equilibrium crystallization of racemic **1** a spontaneous resolution of the racemate into its enantiomers is realized, and in this respect the *ortho*,*ortho*-dimethoxy substituted phenyl glycerol ether does not fall out of the total series of compounds **1**-**6** (Chart 1). However, a more detailed study of its molecular and crystal structure revealed substantial differences inherent to this compound.

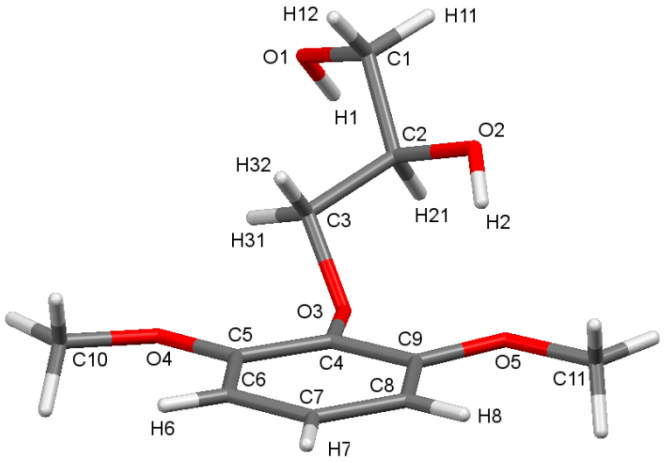


Fig. 1. Molecular structure of diol *R*-**1** and the numbering of the atoms, adopted in this paper.

Figure 1 shows the structure of molecules **1** in *R*-**1** crystals. From the figure, it is immediately evident that the atoms adjacent to the aromatic ring of the molecule, O3-O5, C4-C11 and H6-H8 lie in a common plane (maximum deviation from which is 0.107 Å for the O3 atom). But, unlike the prototype molecules **3** and **5**, the alkoxy moiety in compound **1** is not orthogonal to the plane and is in anticlinal conformation (dihedral angle C9C4O3C3 is about -120°). The cause (or effect) of this is the formation of a stable *intramolecular* hydrogen bond O2-H2···O5 (∠ OHO = 172°, d (O···O) = 2.967 Å). In turn, the formation of a strong intramolecular H-bond deprives of the secondary hydroxyl group of the molecule the possibility to participate in the formation of intermolecular hydrogen bonds (IMHB) and thus the opportunity to form a primary supramolecular crystal-formative motif.

In every currently investigated enantiopure terminal aromatic ethers of glycerol the indispensable element of such supramolecular motif was a single or double helix, formation of which requires the participation of both of the vicinal hydroxyl groups. The primary motif, which is realized in scalemic **1** crystals, is a one-dimensional ribbon, organized around the screw axis 2_1, parallel to the direction *0a* (Fig. 2).

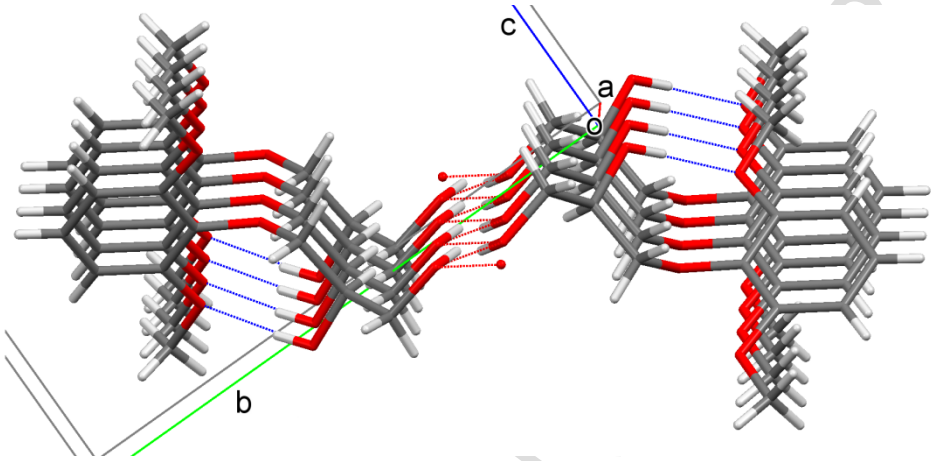


Fig. 2. Primary crystal-formative supramolecular motif in *R*-**1** crystals; blue dotted line marks intramolecular, and red dotted line - intermolecular hydrogen bonds O-H···O'.

Molecules that form the 1D arrays (in this case - enantiomers *R*-**1**) bonded to each other by zigzag sequence of strong IMHBs O1-H1···O1' (∠ OHO = 165°, d (O···O) = 2.876 Å). Integration of the primary 1D elements into 3D crystal packing is shown in Fig. 3.

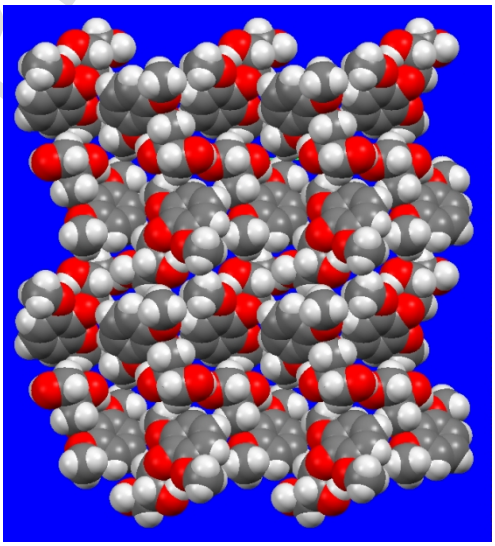


Fig. 3. Detail of crystal packing; view along *0a* axis.

Formed in such a way homochiral packing is sufficiently dense (PI = 68.2%) and in equilibrium conditions of crystal growth is more stable than an ordered packing of heterochiral racemic compound. At the same time the *R*-**1** packing has a visible porous structure. Perhaps this "not ideality" of the lattice, tolerated to a certain freedom during its formation, in other crystallization conditions allows to realize different type of crystalline organization. This topic will be discussed further.

*3.3. Other data on the nature of diol **1** stable solid phase*

Differential scanning calorimetry method was used to determine temperature and enthalpy of melting for enantiopure (*ee* = 0.994) and equilibrium racemic samples of diol **1**. The values of these variables are, respectively, T^A_f = 71.5 °C, ΔH^A_f = 29.6 kJ/mole, and T^R_f = 50.7 °C, ΔH^R_f = 27.1 kJ/mole. Substitution of the data for enantiopure sample in Schroeder - van Laar equation [17] ($T^R_f = -\Delta H^A_f \frac{T^A_f}{\ln(0.5)RT^A_f - \Delta H^A_f}$) enables to evaluate the melting point for eutectic of pure enantiomers of 51.1 °C. This value is in good agreement with the experimental value of the racemate melting point (50.7 °C), which again indicates a high probability of crystallization of diol **1** stereoisomers in the form of normal racemic conglomerate.

This fact is also confirmed by the high degree of similarity (Fig. 4) of the IR spectra of crystalline samples of racemic and enantiopure **1**. Details of the quantitative comparison of the spectra are described in our previous papers [18].

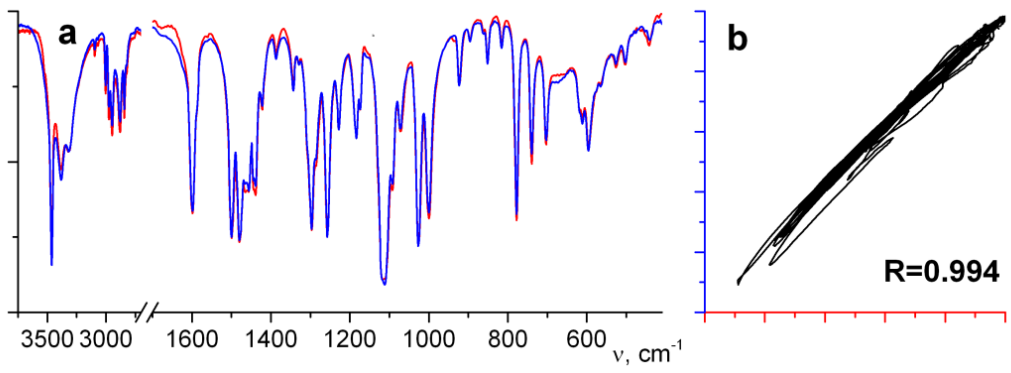


Fig. 4. IR spectra of racemic (red curves) and enantiopure (blue curves) samples of diol **1** (a) and a graphical representation of the correlation between them (b).

In conjunction with the above X-ray diffraction results, these data suggest that at room temperature stable crystalline form of racemic diol **1** is normal conglomerate.

*3.4. Direct resolution of rac-**1** by entrainment*

Crystallization of the racemic 2,6-dimethoxyphenoxypropane-1,2-diol as a normal conglomerate is a favorable factor to resolve it into individual enantiomers by entrainment approach. Preliminary tests showed that at room temperature *rac*-**1** solubility is practically unlimited in ethyl acetate, methylene chloride, chloroform, fairly soluble in lower alcohols, water, and benzene. Quantitatively, the solubility of *rac*-**1** at 22 °C was 29.2, 23.4 and 18.0 $mg \cdot ml^{-1}$ in toluene, methyl *tert*-butyl ether (MTBE), and CCl_4, respectively. Of these three solvents the reverse to dissolution process, that is, effective spontaneous crystallization, was observed only in MTBE. Therefore, a more detailed study of the solubility and crystallization of both racemic and enantiopure **1** was carried out in MTBE.

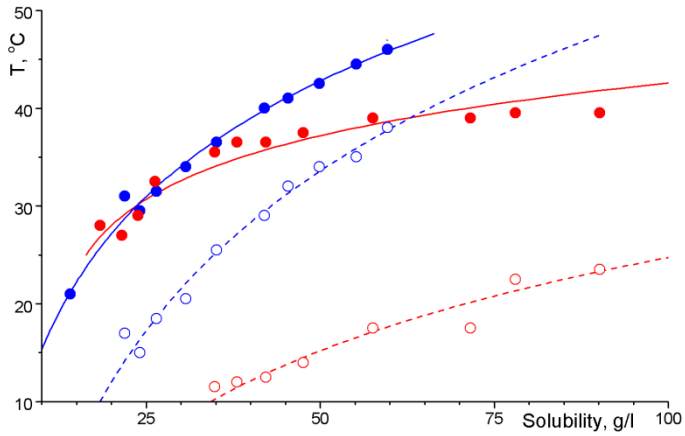


Fig. 5. Temperature dependence of solubility (per single enantiomer, solid lines) and for onset of crystallization (dotted lines) of *rac*-**1** (red) and (*S*)-**1** (blue) in MTBE.

Figure 5 shows the temperature dependence of the solubility of diol **1** stereoisomers in MTBE. The solid red circles identify the end of dissolution, and the red hollow circles - the starting points of crystallization for the racemic samples. Similarly, the behavior of enantiopure diol in the "dissolution-crystallization" cycle is characterized in blue. Concentration values for racemate are given per individual stereoisomer (i.e., the real values of racemate concentration are halved). From the data obtained it follows that the width of metastable zone for *rac*-**1** is about 22 °C, while for (*S*)-**1** this value is about 11 °C. From the charts analysis, it can also be concluded

that, with increasing temperature, the experimental points, corresponding to the process of dissolution of enantiopure and racemic samples, no longer lie on a single curve. That is, when the temperature is above 30 ± 5 °C, Meyerhoffer's rule, stating that the solubility of the racemate is twice as high as that of the pure enantiomer [19], is no longer verified. In turn, this means that the dissolution process for diol **1** is complicated by concentration and solvation effects. Meyerhoffer's coefficient high values are associated with a decrease of the metastable zone width and, consequently, with reduced spontaneous resolution efficiency [1]. This means that the process of direct resolution should be preferably conducted at concentrations of the individual stereoisomer lower than 30 $g \cdot l^{-1}$ and, accordingly, at temperature below 25 °C.

Table 2

Resolution by entrainment (3 circles, 6 runs) of *rac*-**1** in MTBE (50 ml, 10 mg of crystal seeds on every run, crystallization temperature 14 ± 0.5 °C).

Run	Added amount of *rac*-**1**, (mg)	Operation amount of enantiomers, (mg)		Resolution time, min	(*R*)-**1** and (*S*)-**1** obtained			
		(*R*)-**1**	(*S*)-**1**		Yield, mg	*ee*, %	*YE*[a],	
							mg	%
1	2520	1260	1260	90	(*R*) 130	62	71	5.6
2	120	1225	1295	150	(*S*) 204	59	110	8.5
3	194	1280	1240	120	(*R*) 180	70	116	9.1
4	170	1222	1298	120	(*S*) 203	62	116	8.9
5	194	1280	1240	150	(*R*) 166	70	106	8.3
6	156	1227	1293	150	(*S*) 152	63	86	6.6

[a] *YE*: Yield enantiomer; *YE*(mg) = [Yield(mg) × *ee* (%)]/100 – 10; *YE*(%) = [*YE*(mg) ×100] / Operation amount of (*R*)- or (*S*)-**1**(mg)

Table 2 presents the stereoselective crystallization of racemic diol **1** without preliminary enantiomeric enrichment in MTBE at the above conditions. Technical details of the process are given in the experimental part. In Fig. 6 the same process of *rac*-**1** resolution is illustrated through changes in mother liquor optical rotation values (red lines and circles). The solid circles indicate the values of optical rotation at which the process was interrupted and the precipitate

was filtered off. Then the compensating amounts of *rac*-**1** and the solvent were added to preheated mother liquor, and the process was repeated (see Experimental section).

From Table 2 it is clear, that the separation process is carried out with moderate values of the enantiomeric purity of the crystalline solid (60-70%). Nevertheless, initially moderate yield of pure enantiomer (5.6% in the first stage) is increasing to 9.8%. At the same time, despite the moderate efficiency characteristics of the process, each separation step creates the required enantiomeric enrichment of the mother liquor with the opposite enantiomer.

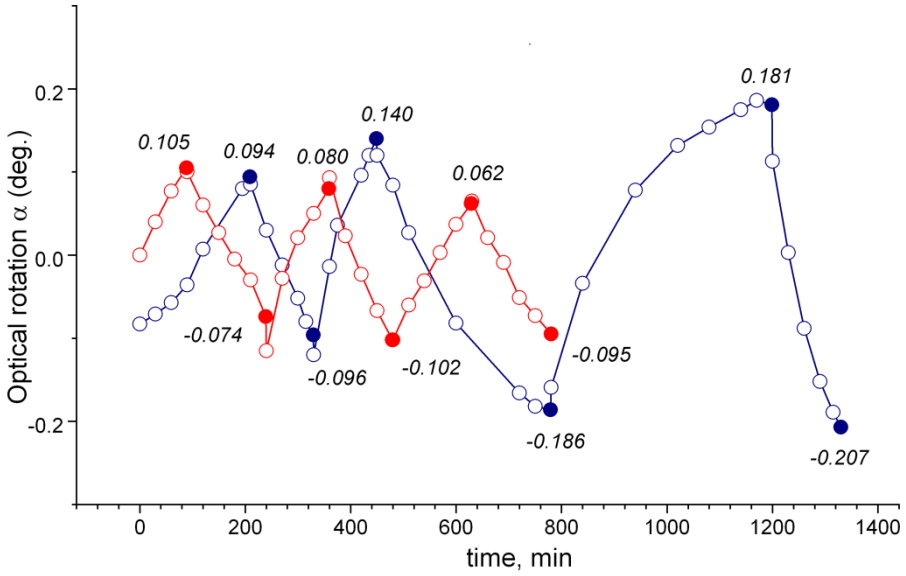


Fig. 6. Mother liquor optical rotation (T = 20 °C; cell length 100 mm; λ = 365 nm) vs time of preferential crystallization of racemic (red) and slightly enantiomerically enriched diol **1** (navy blue). Closed circles represent the values of optical rotation, on reaching which the process was interrupted.

We have tried to increase the separation efficiency through the creation of a small enantiomeric enrichment (~ 3% *ee*) in the first separation stage. The experimental results are shown in Table 3 and Fig. 6. The diagram (Fig. 6, blue lines and circles) depicts the entire separation process. In this experiment, the precipitate is filtered off at a time when the value of specific rotation of the mother liquor reaches the maximum value with the opposite sign and then stops growing (blue solid circles). In each run, the temperature was gradually decreased during crystallization (the table lists the temperature interval between the onset of crystallization and its end). The table shows that the yield of pure enantiomer always increases compared with the

previous one and reaches the value of 15% (Table. 3), but the enantiomeric excess of the filtered crystals in the two versions (cf. Table 2) are in the general range of 58-70%. In carrying out the resolution with even greater initial enrichment of the starting solution (~ 11% *ee*), the yield of single enantiomers increases to 25%, but an enantiomeric purity of the precipitate (64% *ee*) is retained substantially the same. This constancy made us suspect that under kinetically controlled crystallization, another metastable phase(s) could be formed with an enantiomeric composition which differs from that of a normal conglomerate. It is obvious that such a phenomenon can complicate the process of spontaneous resolution and reduce its effectiveness.

Table 3

Resolution by entrainment of slightly enriched **1** in MTBE (50 ml, 10 mg of crystal seeds on every run, crystallization temperature 12 ± 2 °C).

Run	Added amount of *rac*-**1**, (mg)	Operation amount of enantiomers, (mg)		T, °C	Resolution time, min	(*R*)-**1** and (*S*)-**1** obtained			
		(*R*)-**1**	(*S*)-**1**			Yield, mg	*ee*, %	*YE*[b],	
								mg	%
1	2000[a]	1070	1008	15-12	210	(*R*) 178	64	104	9.7
2	168	1018	1060	13-12	120	(*S*) 194	58	103	9.7
3	184	1069	1009	13-11	120	(*R*) 241	68	154	14.4
4	232	993	1086	12-11	330	(*S*) 247	70	163	15.0
5	237	1074	1003	13-11	420	(*R*) 204	69	131	12.3
6	194	1009	1069	12-10.5	130	(*S*) 203	60	112	10.5

[a] Additional amount of (*R*)-**1** 78 mg (80 % *ee*).
[b] *YE*: Yield enantiomer; *YE*(mg) = [Yield(mg) × *ee* (%)]/100 – 10; *YE*(%) = [*YE*(mg) ×100] / Operation amount of (*R*)- or (*S*)-**1**(mg)

*3.5. Re-investigation of the nature of diol **1** crystallization*

For the analysis of the phase behavior of the system in the metastable region DSC thermograms were obtained for the samples of diol **1** of different enantiomeric composition recorded directly after the crystallization of the sample under conditions close to those of a spontaneous separation (MTBE, ~ 15 °C) (red curves in Fig. 7). The obtained thermograms have

been compared with thermograms for the same samples, but subjected to a procedure of thermodynamic equilibration, i.e. slurring in hexane for about 24 hours (blue curves).

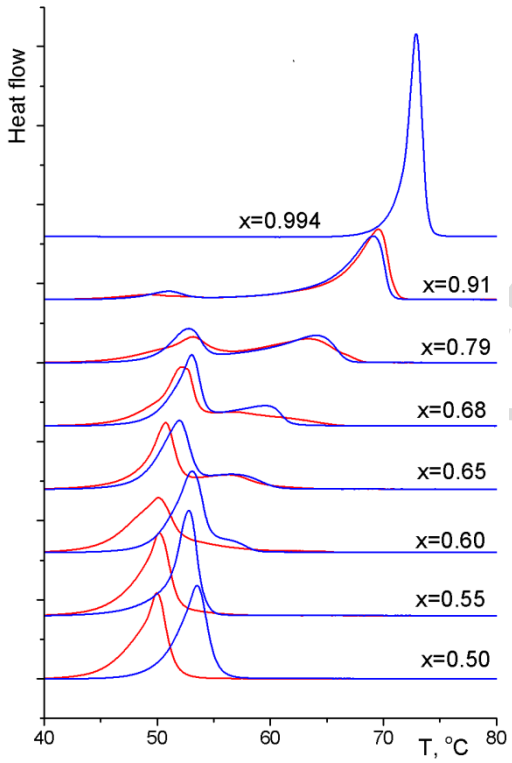


Fig. 7. DSC thermograms of equilibrium (blue lines) and metastable (red lines) samples of diol **1** of different enantiomeric composition; x = mole fraction of the dominant enantiomer.

From the figure, it is clear that immediately after crystallization a metastable solid phase is formed which thermochemical properties significantly differ from those of equilibrium samples. In particular, the thus obtained racemic sample has a lower melting point (47.6 °C vs T^R_f = 50.7 °C), its melting enthalpy well below than that of equilibrium sample (26.3 kJ/mole vs ΔH^R_f = 27.1 kJ/mole). One could also note, that IR spectra of the racemic metastable phases do not differ from enantiopure sample spectra and (stable) normal conglomerate. This fact, although indirectly, indicates the isomorphic character of stable and metastable crystalline phases. Unequivocally identify the nature of the latter only on the basis of data available is hardly possible, and its metastable character makes it difficult to use other methods. However, certain assumptions in this regard can be made.

In Fig. 8 the characteristic temperatures of the DSC thermograms are imposed on the theoretical phase diagram (built on the basis of Schroder – van Laar equation and numerical data for enantiopure substance) under the assumption that the binary system of stereoisomers exists as a normal racemic conglomerate. Obviously, the behavior of the equilibrated samples corresponds well to this model, while the specimens immediately after precipitation look like metastable and thermodynamically nonequilibrium entities.

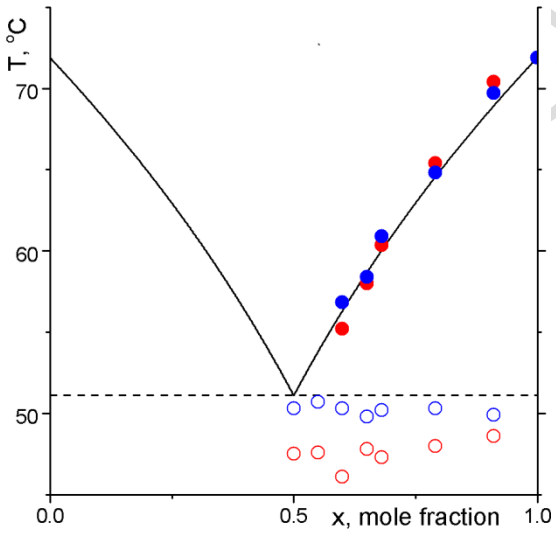


Fig. 8. The binary phase diagram for compound **1**. Solid black legs - liquidus, calculated on the basis of Schroeder - van Laar model; dotted line - solidus. Blue and red hollow circles - experimental values of the melting onset for equilibrium and metastable samples, respectively; solid circles - experimental temperature values of the end of melting.

From Fig. 7 it follows, that the qualitative nature of the thermograms for the stable and metastable systems is similar. Initially, the peak is observed, which can be identified as the eutectic melting peak followed by post-eutectic melting process. Therefore, we can assume that the metastable system in itself is a conglomerate. Further attention is drawn to significant reduction, in comparison with the equilibrium model, of the eutectic melting peak on the thermogram for the composition x = 0.91. Such system behavior can be explained if we assume that the metastable phase is a *conglomerate of limited solid solutions of enantiomers*.

For a long time, the formation of solid solutions of enantiomers was considered as rare phenomenon, represented by no more than 1% of the total number of chiral compounds [20]. In

recent years, such solid solutions are increasingly becoming the subject of research [21-24]. Along with a simple registration of zone of solid solution in the phase diagram of chiral substances, appear special [21,25] and generalizing [26] works, in which the mechanism of formation of this specific phase and its genetic link with the crystal organization of enantiopure substance and/or racemic compound are discussed. It is also shown that the ability of a chiral substance, prone to spontaneous resolution, to form a (metastable) solid solution has a negative effect on the results of its direct separation into individual enantiomers [27,28].

4. Conclusions

Like other studied to date 2,6-disubstituted phenyl ethers of glycerol, 3-(2,6-dimethoxyphenoxy)propane-1,2-diol **1** crystallizes by type of racemic conglomerate. Nevertheless, its crystal structure differs from the previously studied terminal aromatic glycerol ethers (TAEG) by the fact, that one of the hydroxyl groups of the glycerol moiety is involved in the formation of a strong intramolecular hydrogen bond with the methoxy substituent and does not participate in the formation of crystal-formative supramolecular motif. In all of the TAEG conglomerates this motif represents a single or double helix, organized around a screw or a simple rotation axis of symmetry. In the case of **1**, the primary motive, though arranged around the screw axis 2_1, is a one-dimensional ribbon bound with zigzag sequence of intermolecular hydrogen bonds.

Another feature of the phase behavior of racemic diol **1** is the formation during a kinetically controlled crystallization of the metastable phase (presumably limited solid solution of the enantiomers), isomorphic with normal conglomerate. Evidently, this characteristic property complicates the process and lowers the efficiency of resolution of racemic **1** into individual enantiomers by entrainment technique. Isomorphism of metastable solid solution and enantiopure substance explains, firstly, the initiation of solid solution crystallization by enantiopure seeds and, secondly, why the results of resolution are essentially independent of the seed amount. At the same time, the initial formation of a solid solution (with smaller than for

normal conglomerate enantiomeric purity) determines the final composition of the resultant precipitate in the separation process. This unfavorable ratio of enantiomers in the solid solution is preserved and subsequently, when during the process of "aging" precipitated metastable phase is decomposed and changed into the thermodynamically stable normal conglomerate.

Acknowledgment

The authors thank Dr. A.V. Pashagin for valuable assistance with chiral HPLC analysis and Prof. A.T. Gubaidullin for valuable help with the X-ray data.

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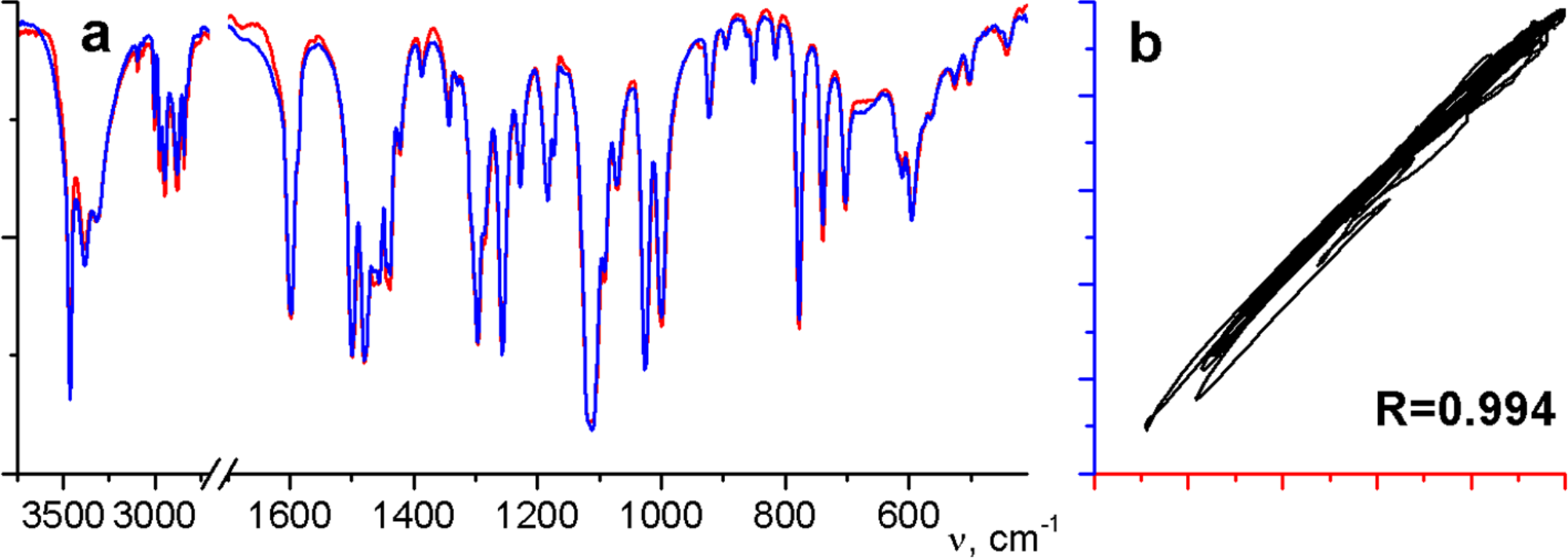
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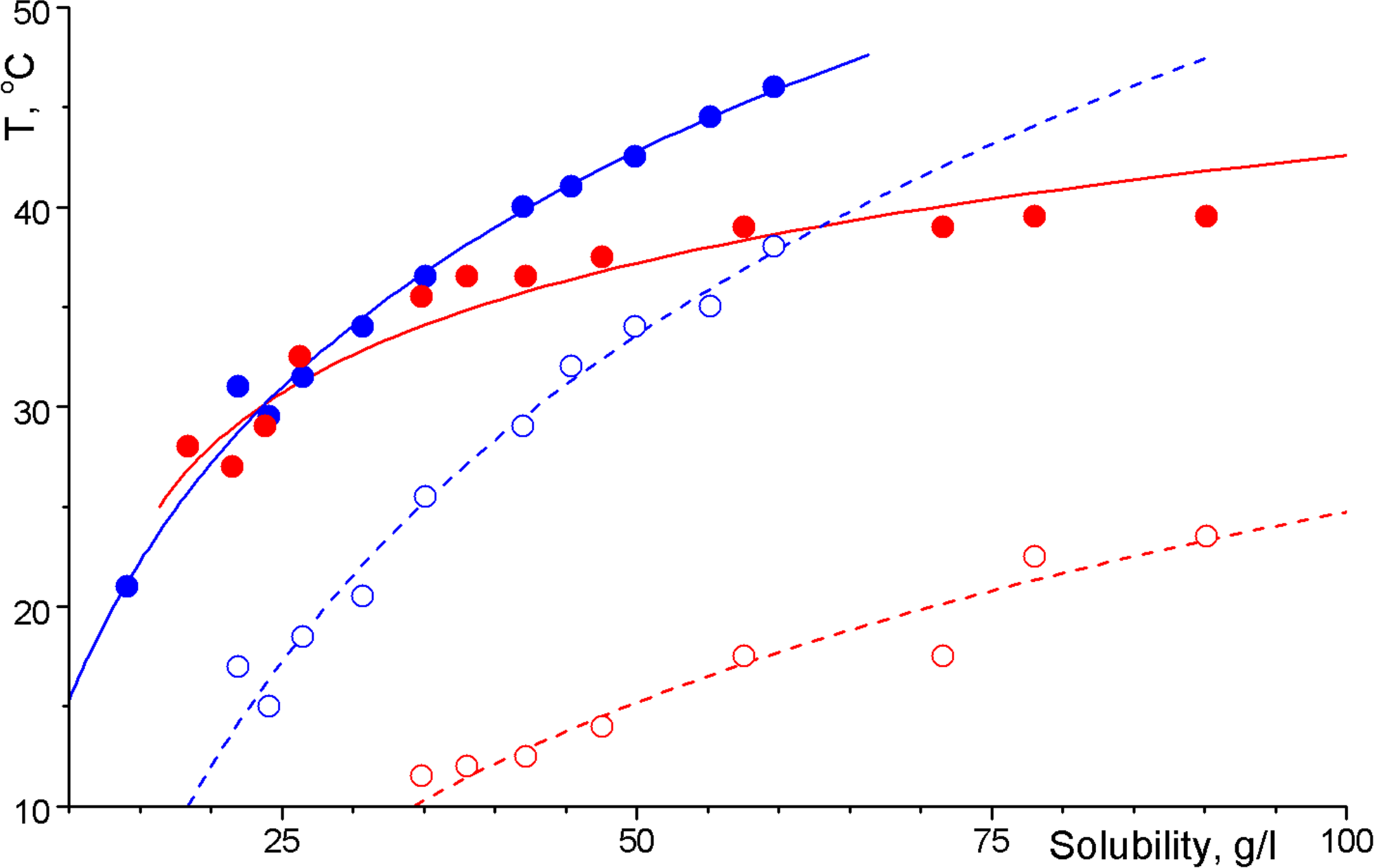
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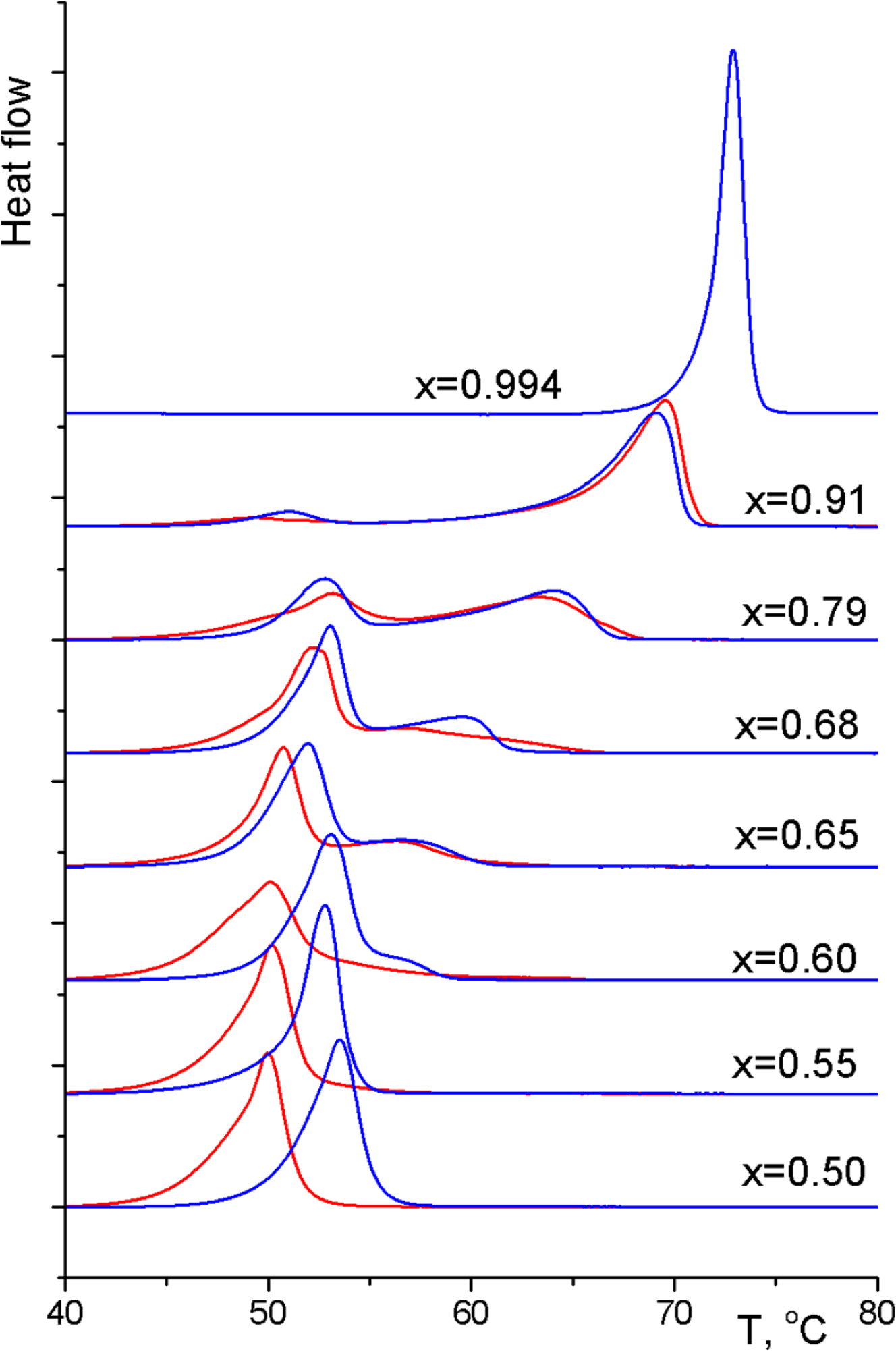
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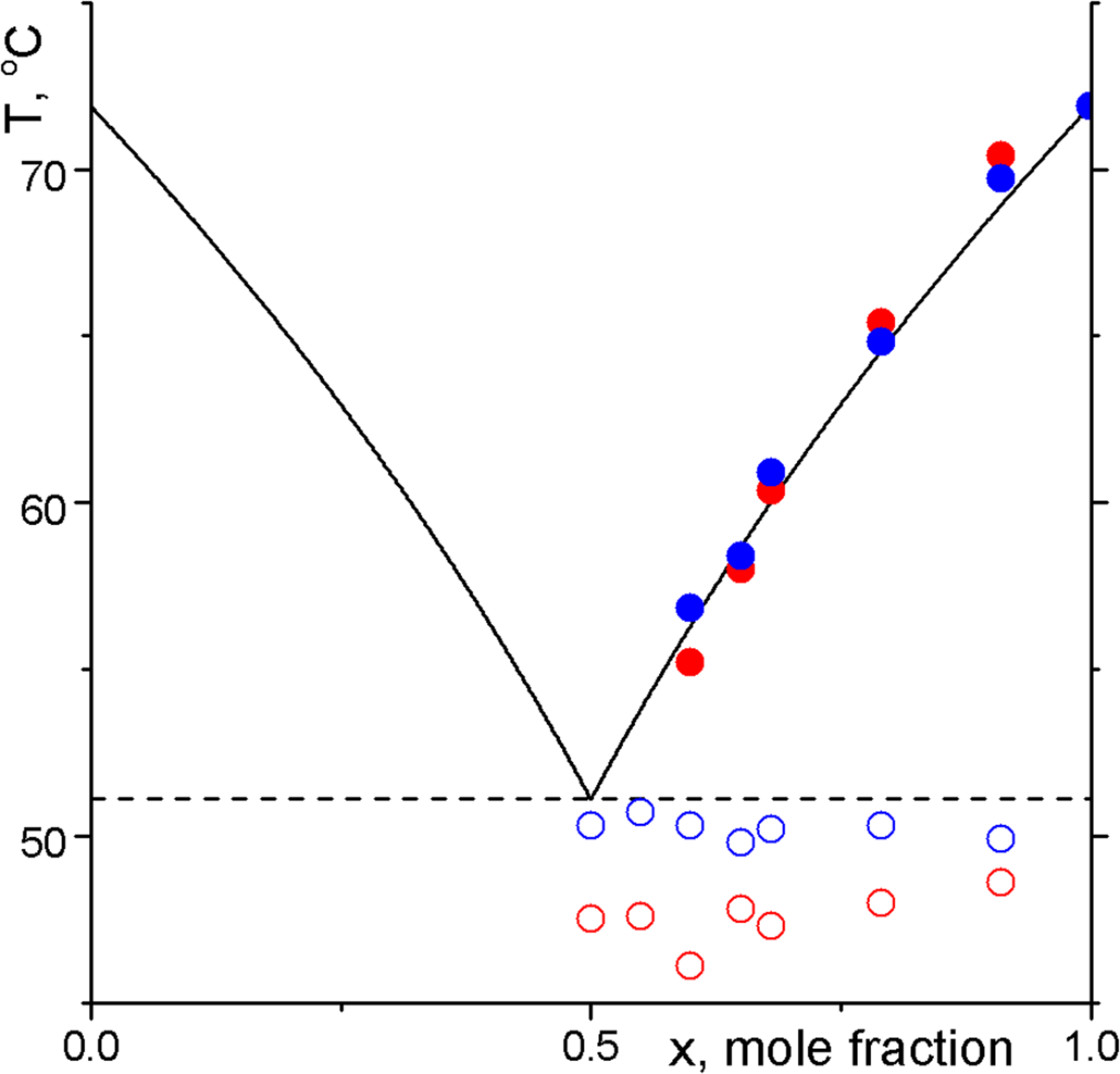
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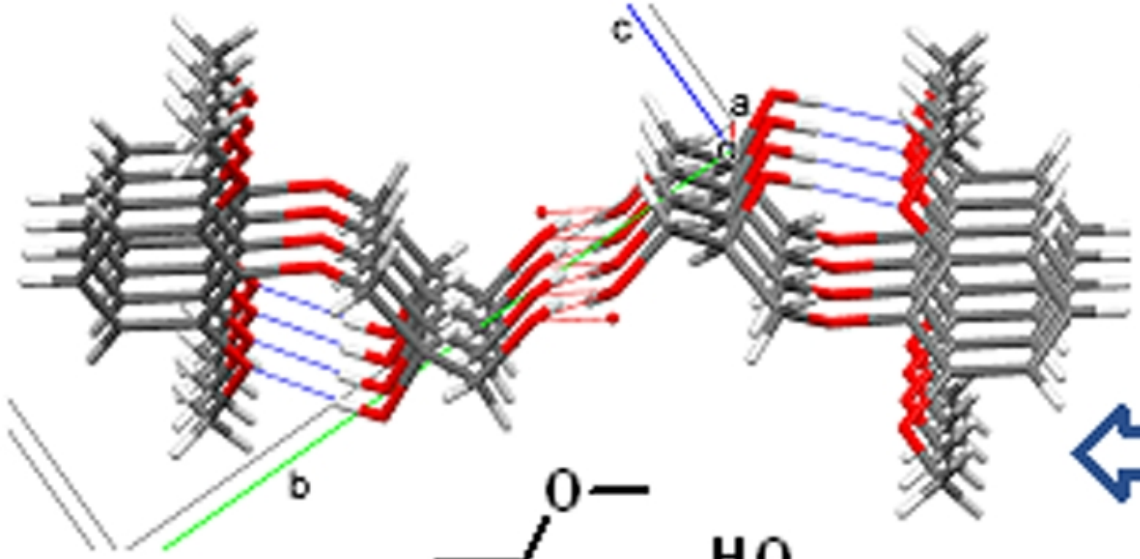
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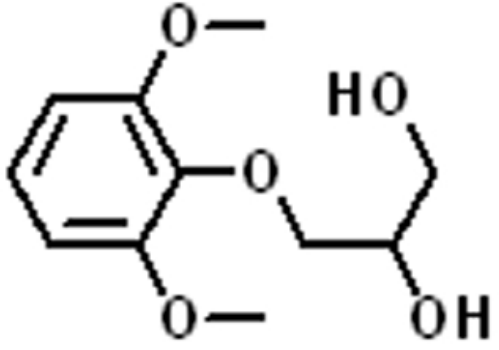
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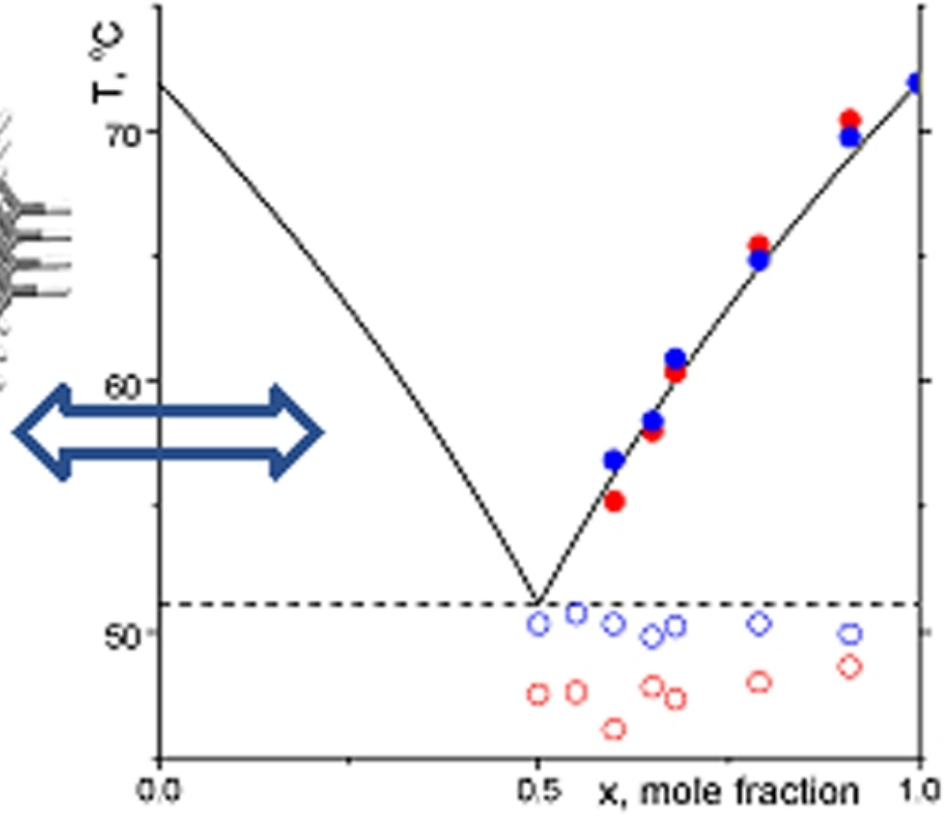
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