Three Different Types of Chirality-Driven Crystallization Within the Series of Uniformly Substituted Phenyl Glycerol Ethers

ALEXANDER A. BREDIKHIN,* ZEMFIRA A. BREDIKHINA, VICTORINA G. NOVIKOVA, ALEXANDER V. PASHAGIN, DMITRY V. ZAKHARYCHEV, AND AIDAR T. GUBAIDULLIN

A.E. Arbuzov Institute of Organic and Physical Chemistry, Russian Academy of Sciences, Kazan, Russian Federation

Dedicated to the 160th Anniversary of Louis Pasteur's Discovery

ABSTRACT Seven chiral arylglycerol ethers 2-R-C_6H_4-O-$CH_2CH(OH)CH_2OH$ (R = H, Me, Et, Allyl, *n*-Pr, *i*-Pr, *tert*-Bu) were synthesized in racemic and scalemic form. The IR spectra, melting points, and enthalpies of fusion for racemic and scalemic samples of every species were measured, the entropies of enantiomers mixing in the liquid state and Gibbs free energies of a racemic compound formation were derived and binary phase diagrams were reconstructed for the whole family. Solid racemic compounds stabilities were ranked for the four substances. Spontaneous resolution was established for the registered chiral drug mephenesin and its ethyl analogue. Metastable anomalous conglomerate, forming crystals having three independent *R** and one independent *S** molecules in the unit cell, is formed during solution crystallization of *tert*-butyl derivative; metastable phase transforms slowly into traditional racemic conglomerate. *Chirality 20:1092–1103, 2008.*

KEY WORDS: spontaneous resolution; anomalous conglomerate; thermochemistry; X-ray diffraction; preferential crystallization; mephenesin

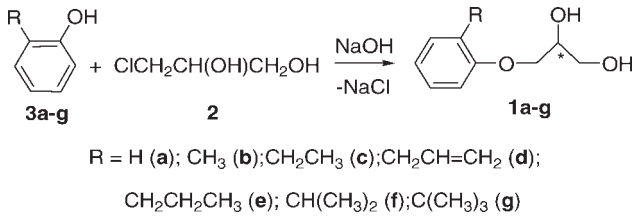
INTRODUCTION

Louis Pasteur's observation of spontaneous resolution of the tartaric acid particular salt followed by triage separation of its enantiomers, in his great 1848 experiment[1], laid the groundwork for the modern science of stereochemistry. Up to now the nature of spontaneous resolution remains something of an enigma, and according to Lluīsa Perez-Garcia and David Amabilino "the understanding and prediction of spontaneous resolution ... remains one of the true challenges for science in the 21st century".[2] Not only has an unquenchable thirst for knowledge made spontaneous resolution so attractive, the practical reasons are every bit as important as the abstract ones. Based on this phenomenon, direct methods for production of single enantiomers, as for instance resolution by entrainment,[3,4] refer to natural limits of resolution effectiveness because of no need of chiral auxiliaries and specialized equipment.

There are different ways to study spontaneous resolution, tracking the little chemical structure variations accompanying the crystallization in the series of closely related chiral compounds is one possibility. The members of such a series must be selected in such a way that every compound would have minimal but regular distinctions from each other. In addition, it would be desirable to have not only qualitative categories like the "conglomerate" or "racemic compound" for characterization of crystalline type, but to introduce a quantitative measure allowing us to rank the observed properties. For this measure one can use the Gibbs free energy changes, ΔG^0, accompanied by the reaction of the racemic compound formation from the enantiopure components, and the values of entropy of mixing of enantiomers in the liquid state, ΔS_1^m. The Gibbs free energy of formation is always negative for a racemic compound, if it can exist, while for a racemic conglomerate this value must be (but not always is) close to zero. So obtained the entropy of mixing has no clear interpretation, but for ideal conglomerate this value must be equal to $R\ln 2$ or 5.75 J K^{-1} mol^{-1}. Both of these thermodynamic characteristics could not be measured directly, but could be calculated on the basis of the chiral substances melting point temperatures and fusion enthalpies T^f and ΔH^f.[3,5] The method of choice for experimental T^f and ΔH^f determination is differential scanning calorimetry (DSC).[6]

As regards the choice of the chemical objects, our recent interests deal with the terminal aryl glycerol ethers $ArO—CH_2CH(OH)CH_2—OH$. The reasons must be pointed out. Firstly, the glycerol ethers and esters are rather common in the family of lipids. Lipids (fats, plasmalogenes, membrane forming glycerolipids, and the like) form the third class, after proteins and carbohydrates, of "life molecules," hence a spontaneous resolution among the lipid-like compounds could be related to the problem of origin of life homochirality.[7] Secondly, many physiologi-

Contract grant sponsor: Russian Fund of Basic Research; Contract grant numbers: 06-03-32508, 07-03-12070
*Correspondence to: A. A. Bredikhin, A.E. Arbuzov Institute of Organic and Physical Chemistry, Arbuzov st., 8, Kazan, 420088, Russia.
E-mail: baa@iopc.knc.ru
Received for publication 7 March 2008; Accepted 20 June 2008
DOI: 10.1002/chir.20648
Published online 2 September 2008 in Wiley InterScience (www.interscience.wiley.com).



Scheme 1. Synthesis of the chiral *ortho*-substituted phenyl glycerol ethers **1a-g**.

cally active substances, including registered drugs like fungicide chlorphenesin,[8] expectorant guaifenesin,[8] muscle relaxant mephenesin,[8] belong to the series of aryl glycerol ethers, possibly because of their similarity to lipids. Thirdly, the terminal aryl glycerol ethers by simplest chemical manipulations could be transformed to another drugs, in particular to β-adrenoblockers of vast ArO—CH_2-CH(OH)CH_2—NHR family.[9,10] Last, fourthly, it is relatively easy to prepare both racemic and scalemic samples of the aryl glycerol ethers needed for experiments.

Recently, we have studied the crystallization peculiarities in the series of *ortho*-halogen and *ortho*-alkoxyphenyl glycerol ethers.[11,12] The present study is carried out to examine the chirality-driven crystallization of a series of ortho-substituted phenyl glycerol ethers, where the substituent is the hydrogen atom or a hydrocarbon moiety. The availability of both enantiomers of 3-chloropropane-1,2-diol **2** by Jacobsen kinetic hydrolytic resolution of a racemic epichlorohydrin[13] makes it possible to obtain all the series of glycerol ethers **1a–g** through the use of a single process (Scheme 1).

The purposes of this work are to study the melting of the substituted phenyl glycerol ethers as enantiomers, as racemates, and in some cases as mixtures of intermediate compositions by means of DSC; to evaluate stabilities of racemic compounds under experiment; to compare the crystallization peculiarities with the substitution pattern; and to investigate the abilities of conglomerate forming compounds to be resolved by entrainment procedure.

MATERIALS AND METHODS

General

The NMR spectra (600 MHz for ^{1}H and 150.864 MHz for ^{13}C) were recorded on a Bruker Avance-600 spectrometer in $CDCl_3$ with TMS or the signals of the solvent as the internal standard. The IR spectra of the polycrystalline samples of *rac*- and *scal*-compounds under investigations in KBr pellets were recorded on a Bruker IFS-66v Fourier-transform spectrometer.

The X-ray single crystal experiments were carried out on Bruker AXS Smart Apex II and Kappa Apex II diffractometers. Powder X-ray diffraction (PXRD) data were collected on a Bruker *D*8 Advance diffractometer equipped with an Vantec linear PSD, using graphite monochromated Cu Kα (λ 1.54184 Å) radiations, (40 kV, 40 mA).

Optical rotations were measured on a Perkin-Elmer model 341 polarimeter. Throughout the paper the value of specific rotation is given in deg mL g^{-1} dm^{-1}, and the concentration of solutions *c* appears in g (100 ml)$^{-1}$.

Enantiomeric purity was checked by HPLC analysis performed on a Shimadzu LC-20AD system controller, and UV monitor 275 nm was used as a detector. The column used, from Daicel, Inc., was Chiralcel AD-RH (0.46 cm × 15 cm).

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 ~2.5 mg. Temperature scale and heat flux were calibrated against the data for indium, phenol, and naphthalene.

Racemic epichlorohydrin (99%) and 3-(2-methylphenoxy)-propane-1,2-diol (98%) were purchased from Alfa Aesar®; 3-chloropropane-1,2-diol (99+%), phenol (99+%), *o*-cresol (99+%), 2-ethylphenol (99%) were purchased from Acros Organics®; 2-propylphenol (97%), 2-isopropylphenol (98%), 2-*tert*-butylphenol (99%), and 2-allylphenol (98%), were purchased from Lancaster; methyl-*tert*-butyl ether (MTBE, 99.5%) was obtained from Fisher Scientific.

Preparation of 3-Aryloxypropane-1,2-diols

Racemic and enantiopure diols **1a–g** were synthesized by analogy with a published procedure[14] from corresponding phenol **3a–g** and racemic or scalemic 3-chloropropane-1,2-diols, *rac*-**2** and *scal*-**2**, respectively. (−)-(*R*)-**2** {$[\alpha]_D^{20}$ −6.4 (*c* 5, H_2O)} and (+)-(*S*)-**2** {$[\alpha]_D^{20}$ +6.1 (*c* 4.8, H_2O)} were prepared through Jacobsen kinetic hydrolytic resolution of *rac*-epichlorohydrin without modifications.[13]

General procedure. To the solution of corresponding phenol **3a–g** (10 mmol) in ethanol (6 ml) a solution of NaOH (0.5 g, 12.5 mmol) in water (2 ml) was added and the resulting mixture was stirred and heated under reflux for 30 min. Then a solution of 3-chloropropane-1,2-diol **2** (1.3 g, 12 mmol) in ethanol (1 ml) was added, and the mixture was further stirred and heated at reflux for 3 h. After cooling, the mixture was concentrated under reduced pressure followed by addition of water (6 ml) and extraction with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed. The crude diols **1a–g** were usually purified by recrystallization from hexane; (*S*)-aryloxypropanediols were obtained from (+)-(*S*)-**2**, and (*R*)-aryloxypropanediols were obtained from (−)-(*R*)-**2**.

***rac*-3-Phenoxypropane-1,2-diol, *rac*-1a.** Yield: 1.3 g (80%), mp 58–59°C (Ref. 11: mp 56–60°C). An analytical sample was obtained by slow crystallization of crude *rac*-**1a** from a hexane-ether (1:1) mixture. ^{1}H NMR, δ: 2.55 (br.s, 2H, 2 OH), 3.75 (dd, J = 11.7, 5.5 Hz, 1H, 1CH_2O), 3.84 (dd, J = 11.7, 3.8 Hz, 1H, 1CH_2O), 3.99–4.04 (m, 2H, CH_2O), 4.08–4.15 (m, 1H, CHO), 6.91 (dd, J = 8.4, 1.0 Hz, 2 H, $C^{2,6}_{Ar}$ *H*), 6.98 (t, J = 7.4 Hz, 1H, C^{4}_{Ar} *H*), 7.29 (td, J = 7.4, 1.4 Hz, 2H, $C^{3,5}_{Ar}$ *H*). ^{13}C NMR, δ: 63.83 (CH_2OH), 69.28 (CH), 70.57 (CH_2O), 114.71 ($C^{3,5}_{Ar}$), 121.48 (C^{4}_{Ar}), 129.70 ($C^{2,6}_{Ar}$), 158.55 (C^{1}_{Ar}).

(*R*)-3-Phenoxypropane-1,2-diol, (*R*)-1a. Yield: 1.2 g (71%), mp 68–69°C (Ref. 15: mp 62.5–64.5°C); $[\alpha]_D^{20}$ –10.1 (*c* 1, EtOH), $[\alpha]_D^{20}$ −9.7 (*c* 1.0, MeOH) {Ref. 15: $[\alpha]_D^{20}$ −9.5 (*c* 0.5, MeOH), 98.9% ee}, $[\alpha]_D^{20}$ +4.2 (*c* 1, hexane/EtOH, 4:1), $[\alpha]_D^{20}$ + 2.0 (*c* 1, MTBE); 99.6% ee [HPLC; column temperature 29°C; eluent: water/isopropanol = 3.75/1; flow rate 1.0 ml/min; t_R(major) = 7.4 min]; t_R (minor) = 9.6 min]. NMR spectra were identical with spectra of *rac*-**1a**.

(*S*)-3-(2-Methylphenoxy)-propane-1,2-diol, (*S*)-1b. Yield: 1.4 g (77%), mp 90–91°C (Ref. 16: mp 91–92°C); $[\alpha]_D^{20}$ −19.3 (*c* 1.2, hexane/i-PrOH, 4:1) {Ref. 17: $[\alpha]_D^{20}$ −19.3 (*c* 0.9, hexane/i-PrOH, 4:1)}, $[\alpha]_D^{20}$ −12.8 (*c* 1.1, MTBE); 99.8% ee [HPLC; column temperature 40°C; eluent: water/isopropanol = 3/1; flow rate 1.0 ml/min; t_R(major) = 8.3 min]. ^{1}H NMR (600 MHz) δ = 2.20 (br.s, 1H, OH), 2.23 (s, 3H, CH_3), 2.70 (br.s, 1H, OH), 3.78 (dd, *J* = 11.8, 6.1 Hz, 1H, 1CH_2), 3.85 (dd, *J* = 11.8, 3.7 Hz, 1H, 1CH_2O), 4.04–4.07 (m, 2H, CH_2O), 4.11–4.14 (m, 1H, CH), 6.82 (d, *J* = 7.9 Hz, 1H, C^6_{Ar} *H*), 6.88 (t, *J* = 7.4 Hz, 1H, C^4_{Ar} *H*), 7.13–7.15 (m, 2H, $C^{3,5}_{Ar}$ *H*).

(*R*)-3-(2-Methylphenoxy)-propane-1,2-diol, (*R*)-1b. Yield: 1.4 g (77%), mp 90–91°C; $[\alpha]_D^{20}$ +19.3 (*c* 1.2, hexane/i-PrOH, 4:1) {Ref. 17: $[\alpha]_D^{20}$ +19.8 (*c* 0.9, hexane/i-PrOH, 4:1)}, $[\alpha]_D^{20}$ +12.8 (*c* 1.1, MTBE); 99.9% ee [HPLC; column temperature 40°C; eluent: water/isopropanol = 3/1; flow rate 1.0 ml/min; t_R(major) = 7.1 min].

***rac*-3-(2-Ethylphenoxy)-propane-1,2-diol, *rac*-1c.** Yield: 1.5 g (76%), mp 51–53°C (Ref. 18: mp 56–57°C). ^{1}H NMR, δ: 1.23 (t, *J* = 7.6 Hz, 3H, CH_3), 2.67 (2H, *J* = 7.6 Hz, C$H_2$$CH_3$), 3.30 (br.s, 1H, OH), 3.53 (br.s, 1H, OH), 3.78 (dd, *J* = 11.5, 6.3 Hz, 1H, 1CH_2O), 3.87 (dd, *J* = 11.5, 3.7 Hz, 1H, 1CH_2O), 4.01–4.05 (m, 2H, CH_2O), 4.03–4.07 (m, 1H, CH), 6.76 (d, *J* = 8.4 Hz, 1H, C^6_{Ar} *H*), 6.85 (t, *J* = 7.3 Hz, 1H, C^4_{Ar} *H*), 7.06–7.09 (m, 2H, $C^{3,5}_{Ar}$ *H*). ^{13}C NMR, δ: 14.20 (CH_3), 23.22 (*C*$H_2$$CH_3$), 63.93 ($CH_2$OH), 69.03 (CH), 70.71 ($CH_2$O), 111.41 ($C^6_{Ar}$), 121.18 ($C^4_{Ar}$), 126.90 ($C^5_{Ar}$), 129.09 ($C^3_{Ar}$), 132.66 ($C^2_{Ar}$), 156.14 ($C^1_{Ar}$).

(*S*)-3-(2-Ethylphenoxy)-propane-1,2-diol, (*S*)-1c. Yield: 1.3 g (68%), mp 68–70°C; $[\alpha]_D^{20}$ −14.5 (*c* 1, hexane/EtOH, 4:1); $[\alpha]_D^{20}$ −12.3 (*c* 1.0, MTBE); 99.9% ee [HPLC; column temperature 29°C; eluent: water/isopropanol = 3/1; flow rate 1.0 ml/min; t_R(major) = 18.1 min]. NMR spectra were identical with spectra of *rac*-**1c**.

(*R*)-3-(2-Ethylphenoxy)-propane-1,2-diol, (*R*)-1c. Yield: 1.4 g (72%), mp 68–70°C; $[\alpha]_D^{20}$ +11.9 (*c* 1.0, MTBE); 99.3% ee [HPLC; column temperature 29°C; eluent: water/isopropanol = 3/1; flow rate 1.0 ml/min; t_R (major) = 15.6 min].

***rac*-3-(2-Allylphenoxy)-propane-1,2-diol, *rac*-1d.** Yield: 1.6 g (75%), mp 41–43°C (hexane) (Ref. 9: mp 43–44°C).

(*S*)-3-(2-Allylphenoxy)-propane-1,2-diol, (*S*)-1d. Yield: 1.4 g (70%), mp 57–58° (hexane); $[\alpha]_D^{20}$ −2.7 (*c* 0.6, EtOH); $[\alpha]_D^{20}$ −7.2 (*c* 1.0, MTBE); {Ref. 9: mp 47–49°C; $[\alpha]_D^{20}$ −2.1 (*c* 2.8, EtOH)}; 99.9% ee [HPLC; column temperature 29°C; eluent: water/isopropanol = 3/1; flow rate 0.6 ml/min; t_R (minor) = 28.2 min, t_R(major) = 33.4 min]. ^{1}H NMR δ: 2.63 (broad s, 1H, OH), 3.03 (broad s, 1H, OH), 3.34–3.42 (m, 2H, —CH_2—CH=), 3.73 (dd, *J* = 11.5, 5.5 Hz, 1H, CH_2O), 3.81 (dd, *J* = 11.4, 3.3 Hz, 1H, CH_2O), 4.01–4.08 (m, 2H, CH_2O), 4.11–4.19 (m, 1H, CH), 4.98–5.05 (m, =CH_2), 5.92–6.02 (m, 1H, =CH), 6.82 (d, *J* = 8.1 Hz, 1H, C^6_{Ar} *H*), 6.92 (t, *J* = 7.3 Hz, 1H, C^4_{Ar} *H*), 7.12–7.19 (m, 2H, $C^{3,5}_{Ar}$ *H*). ^{13}C NMR δ: 34.58 (*C*H_2—CH=), 63.87 (OCH_2), 69.38 (OCH_2), 70.78 (CH), 111.82 (C^6_{Ar}), 115.30 (CH=*C*H_2), 121.27 (C^4_{Ar}), 127.54 (C^5_{Ar}), 130.20 (C^3_{Ar}), 137.27 (*C*H=CH_2), 128.73 (C^2_{Ar}), 156.34 (C^1_{Ar}).

***rac*-3-(2-Propylphenoxy)-propane-1,2-diol, *rac*-1e.** Yield: 1.6 g (76%), mp 52.5–53.5°C (hexane); (Ref. 19: mp 52–53°C). ^{1}H NMR, δ: 0.97 (t, 3H, CH_3, *J* = 7.3 Hz), 1.61–1.65 (m, 2H, C$H_2$$CH_3$), 2.61 (t, *J* = 7.3 Hz, 2H, C$H_2$$CH_2$), 2.80 (br.s, 2H, OH), 3.69 (dd, *J* = 11.5, 5.8 Hz, 1H, CH_2O), 3.78 (dd, *J* = 11.5, 3.7 Hz, 1H, CH_2O), 3.95–3.98 (m, 2H, CH_2O), 4.03–4.07 (m, 1H, CH), 6.73 (d, *J* = 7.8 Hz, 1H, C^6_{Ar} *H*), 6.83 (dd, *J* = 6.8, 7.3 Hz, 1H, C^4_{Ar} *H*), 7.04–7.07 (m, 2H, $C^{3,5}_{Ar}$ *H*). ^{13}C NMR, δ: 14.07 (CH_3), 23.07 (CH_2), 32.24 (OCH_2), 63.90 (CH_2O), 69.07 (CH_2O), 70.71 (CH), 111.46 (C^6_{Ar}), 121.04 (C^4_{Ar}), 126.94 (C^5_{Ar}), 130.06 (C^3_{Ar}), 131.08 (C^2_{Ar}), 156.22 (C^1_{Ar}).

(*R*)-3-(2-Propylphenoxy)-propane-1,2-diol, (*R*)-1e. Yield: 1.5 g (71%), mp 67–69°C (hexane); $[\alpha]_D^{20}$ +14.9 (*c* 1, hexane/ EtOH, 4:1); $[\alpha]_D^{20}$ = +11.9 (*c* 1.0, MTBE); 99.9% ee [HPLC; column temperature 28°C; eluent: water/isopropanol = 3/1; flow rate 1.0 ml/min; t_R(major) = 28.9 min, t_R(minor) = 33.2 min]. NMR spectra were identical with spectra of *rac*-**1e**.

***rac*-3-(2-Isopropylphenoxy)-propane-1,2-diol, *rac*-1f.** Yield: 1.8 g (88%), mp 80–81°C (hexane). ^{1}H NMR, δ: 1.16 (d, 6H, CH_3, *J* = 6.8 Hz), 2.20 (br. s, 2H, OH), 3.20–3.25 (m, 1H, CH), 3.71 (dd, *J* = 11.5, 5.6 Hz, 1H, CH_2O), 3.80 (dd, *J* = 11.5, 3.7 Hz, 1H, CH_2O), 3.98–4.01 (m, 2H, CH_2OH), 4.05–4.09 (m, 1H, CH), 6.77 (d, *J* = 8.1 Hz, 1H, C^6_{Ar} *H*), 6.89 (t, *J* = 7.3 Hz, 1H, C^4_{Ar} *H*), 7.08 (t, *J* = 7.3 Hz, 1H, C^5_{Ar} *H*), 7.15 (d, *J* = 7.3 Hz, 1H, C^3_{Ar} *H*). ^{13}C NMR, δ: 22.70 (CH_3), 26.87 (CH), 63.89 (OCH_2), 69.29 (CH_2O), 70.64 (CH), 111.54 (C^6_{Ar}), 121.37 (C^4_{Ar}), 126.20 (C^5_{Ar}), 126.68 (C^3_{Ar}), 137.00 (C^2_{Ar}), 155.47 (C^1_{Ar}).

(*R*)-3-(2-Isopropylphenoxy)-propane-1,2-diol, (*R*)-1f. Yield: 1.6 g (76%), mp 71–72°C (petroleum); $[\alpha]_D^{20}$ +13.7 (*c* 1, hexane/i-PrOH, 4:1); $[\alpha]_D^{20}$ +10.7 (*c* 1.0, MTBE) {Ref. 14: $[\alpha]_D^{20}$ +14.1 (*c* 1, hexane/i-PrOH, 4:1)}; 99.0% ee [HPLC; column temperature 21.5°C; eluent: water/isopropanol = 3.75/1; flow rate 0.8 ml/min; t_R(major) = 67.2 min, t_R(minor) = 86.1 min]. NMR spectra were identical with spectra of *rac*-**1f**.

***rac*-3-(2-*tert*-Butylphenoxy)-propane-1,2-diol, *rac*-1g.** Yield: 1.4 g, 63%, mp 68–71°C (hexane/benzene). (Ref. 20: mp 56°C). ^{1}H NMR, δ: 1.41 (s, 9H, CH_3), 2.35 (br.s, 2H, OH), 3.82 (dd, *J* = 11.5, 6.0 Hz, 1H, CH_2O), 3.92 (dd, *J* = 11.5, 3.7 Hz, 1H, CH_2O), 4.07–4.12 (m, 2H, OCH_2), 4.21–4.24 (m, 1H, CH), 6.91 (d, *J* = 7.8 Hz, 1H, C^6_{Ar} *H*), 6.95 (dd, *J* = 7.3, 7.8 Hz, 1H, C^4_{Ar} *H*), 7.20 (t, *J* =

TABLE 1. Resolution by entrainment of *rac*-mephenesin 1b (500 cm^3 H_2O, 25 mg crystal seeds on every run, crystallization temperature 25°C ± 0.5°C)

Run	Added amount of (*R,S*)-**1b**, (g)	Operation amount of (*R*)- and (*S*)-**1b**[a], (g)		Resolution time (min)	(*R*)- and (*S*)-**1b** obtained		
		(*R*)-**1b**	(*S*)-**1b**		Yield (g)	ee (%)[b]	YE (g)[c]
1	9.0[d]	5.50	4.50	95	(*R*) 1.82	97.0	1.77
2	1.80	4.63	5.37	80	(*S*) 1.66	95.4	1.60
3	1.64	5.41	4.59	75	(*R*) 1.50	98.5	1.47
4	1.48	4.68	5.32	80	(*S*) 1.55	92.7	1.48
5	1.53	5.39	4.61	75	(*R*) 1.62	95.0	1.56
6	1.60	4.63	5.37	85	(*S*) 1.54	97.0	1.50

[a]The operation amounts in even runs 2–6 were calculated based on the results in odd runs 1–5, respectively.
[b]ee: enantiomeric excess (HPLC).
[c]YE: Yield of enantiomer; YE (g) = [Yield (g) × ee (%)]/100 − 0.025 (seed weight).
[d]Additional amount of (*R*)-**1b** 1.0 g.

7.3 Hz, 1H, C^5_{Ar} *H*), 7.32 (d, *J* = 7.8 Hz, 1H, C^3_{Ar} *H*). ^{13}C NMR, δ: 30.16 (CH_3), 34.93 (*C*Me_3), 64.12 (OCH_2), 69.15 (CH_2O), 70.95 (CH), 112.42 (C^6_{Ar}), 121.10 (C^4_{Ar}), 126.97 (C^5_{Ar}), 127.28 (C^3_{Ar}), 138.24(C^2_{Ar}), 157.34 (C^1_{Ar}).

(*S*)-3-(2-*tert*-Butylphenoxy)-propane-1,2-diol, (*S*)-1g. Yield: 1.5 g (67%), $[\alpha]^{20}_D$ −10.5 (*c* 1, hexane/EtOH, 4:1); $[\alpha]^{20}_D$ −9.5 (*c* 1.0, MTBE). 99.3% ee [HPLC; column temperature 21°C; eluent: water/isopropanol = 3/1; flow rate 0.8 ml/min, t_R(major) = 50.5 min]. NMR spectra were identical with spectra of *rac*-**1g**.

(*R*)-3-(2-*tert*-Butylphenoxy)-propane-1,2-diol, (*R*)-1g. mp 94–95°C (hexane); $[\alpha]^{20}_D$ +10.5 (*c* 1, hexane/EtOH, 4:1); $[\alpha]^{20}_D$ +9.5 (*c* 1.0, MTBE). 99.7% ee [HPLC; column temperature 21°C; eluent: water/isopropanol = 3/1; flow rate 0.8 ml/min, t_R (major) = 46.3 min].

Resolution of Racemic 3-(2-Methylphenoxy)-propane-1,2-diol (Mephenesin, rac*-1b) by Preferential Crystallization (Entrainment)*

Racemic mephenesin *rac*-**1b** (9.0 g) and (*R*)-**1b** (1.0 g) was dissolved in 500 ml of water at 53–55°C. The solution was cooled to 28°C and seeded with finely pulverized (*R*)-**1b** (25 mg). After stirring the mixture for 95 min at 25°C ± 0.5°C, precipitated (*R*)-**1b** was collected by filtration (1.82 g after drying; 97% ee) (Table 1, run 1). The extra portion of *rac*-**1b** (1.80 g) was then dissolved in the mother liquor at 55°C; the resulting solution was cooled to 28°C. After the addition of (*S*)-**1b** (25 mg) as seed crystals to the solution, and stirring the mixture for 80 min at 25°C ± 0.5°C, (*S*)-**1b** (1.66 g after drying; 95% ee) was collected by filtration (run 2). Further resolution was carried out at 25°C ± 0.5°C by adding amended amounts of *rac*-**1b** to the filtrate in a manner similar to that described above. The detailed conditions are given in Table 1. A high degree of enantiomeric purity of collected diols can be achieved by simple recrystallization. For example, a portion of (*R*)-**1b** (1.62 g, 95% ee) was dissolved in the boiling hexane (64 ml). After cooling the solution to −2°C, the crystallized (*R*)-**1b** was collected by filtration (yield 1.24 g; 99.5% ee).

*Resolution of Racemic 3-(2-Ethylphenoxy)-propane-1,2-diol (*rac*-1c) by Preferential Crystallization*

Racemic diol *rac*-**1c** (1.0 g) and (*S*)-**1c** (0.1 g) was dissolved in 115 ml of water at 53–55°C. The solution was cooled to 25°C and seeded with finely pulverized (*S*)-**1c** (2.5 mg). After stirring the mixture for 70 min at 20°C ± 0.5°C, precipitated (*S*)-**1c** was collected by filtration (0.20 g after drying; 90% ee). The extra portion of *rac*-**1c** (0.2 g) was then dissolved in the mother liquor at 55°C; the resulting solution was cooled to 25°C. After the addition of (*R*)-**1c** (2.5 mg) as seed crystals to the solution, and stirring the mixture for 80 min at 20°C ± 0.5°C, (*R*)-**1c** (0.18 g after drying; 89% ee) was collected by filtration.

*X-ray Diffraction Experiments for 3-(2-*tert*-Butylphenoxy)-propane-1,2-diols, 1g*

The X-ray diffraction data for crystals of compounds *rac*-**1g** and (*S*)-**1g** were collected on a Bruker AXS Smart Apex II and Kappa Apex II [(*S*)-**1g**] diffractometers in the ω and φ-scan modes, using graphite monochromated Mo *K*α λ 0.71073 Å (*rac*-**1g**) and Cu Kα λ 1.54184 Å [(*S*)-**1g**] radiations. Data were corrected for the absorption effect using SADABS program.[21] The structures were solved by direct method and refined by the full matrix least-squares using SHELXTL[22] and WinGX[23] programs. All nonhydrogen atoms were refined anisotropically. The positions of hydrogen atoms were located from the Fourier electron density synthesis and were included in the refinement in the isotropic riding model approximation. Illustrations were made using PLATON.[24]

Crystallographic data (excluding structure factors) for the structures reported in this article have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 691121 for *rac*-**1g**, and 691122 for (*S*)-**1g**. Copies of the data can be obtained free of charge upon application to the CCDC (12 Union Road, Cambridge CB2 1EZ U.K. Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

Room-temperature powder X-ray diffraction data were collected in the Bragg–Brentano mode with a flat-plate

sample. The sample was lightly ground and loaded into a standard sample holder, which was kept spinning (30 rpm) throughout the data collection. Patterns were recorded in the 2θ range between 3° and 50°, in 0.008° steps, with a step time of 2 sec. Five powder patterns were collected and summed for each sample.

Crystallographic Data for (S)*-3-(2-*tert*-Butylphenoxy)-propane-1,2-diol,* (S)*-1g*

The single crystal picked out from the crop of the aforementioned *scal*-**1g** with a specific rotation value of $[\alpha]_D^{20}$ −9.5 (c 1.0, MTBE) was used for single crystal experiment. Formula $C_{13}H_{20}O_3$, colorless prism of dimensions 0.35 × 0.24 × 0.14 mm^3, formula weight 224.29 g mol^{-1}, monoclinic, a = 26.5455(8), b= 6.9990(3), c= 16.6275(6) Å, β = 124.359(2)°, V = 2550.23(16) $Å^3$, T = 293 K, space group C 2 (No. 5), Z 8, μ(Cu-K_α) 6.57 cm^{-1}, F(000) = 976, d_{calc} = 1.168 g cm^{-3}, 4917 reflections measured, 2106 unique (R_{int} = 0.0673), 1961 observed with Fo > 4σ (Fo), 378 parameters. The final R1(F^2) was 0.0480 (>2σI) and wR2(all data) = 0.1291. Goodness-of-fit on F^2 was 1.025, largest diff. peak and hole are 0.203 and −0.194 e·$Å^3$. The final value −0.10(3) of Flack enantiopole parameter[25,26] proved the expected *S* absolute configuration.

The finely pulverized portion from the same bulk sample was used for PXRD experiments.

Crystallographic Data for rac*-3-(2-*tert*-Butylphenoxy)-propane-1,2-diol,* rac*-1g*

The single crystal picked out from the crop of freshly crystallized *rac*-**1g** was used for determination of crystal and molecular structure of primary racemate. The eutectic character of the crop and the metastability of this crystal modification (see text) are the important reasons precluding the high quality crystal growth. Nevertheless the experiment with this crystal enables us to evaluate some important features of primary racemate structure. Formula $C_{13}H_{20}O_3$, colorless prism of dimensions 0.70 × 0.46 × 0.12 mm^3, formula weight 224.29 g mol^{-1}, triclinic, a = 6.6876(11), b = 14.659(2), c = 14.648(2) Å, α = 70.083(2)°, β = 76.777(2)°, γ = 76.785(2)°, V = 1296.3(4) $Å^3$, T = 293 K, space group P 1 (No. 1), Z 4, μ(Mo Kα) 0.80 cm^{-1}, d_{calc} = 1.149 g cm^{-3}, F(000) = 488, 10,227 reflections measured, 9387 unique (R_{int} =0.0173), 3565 observed with Fo > 4σ (Fo), 556 parameters. The final R1(F^2) was 0.0900 (>2σI) and wR2 (all data) = 0.2970. Goodness-of-fit on F^2 was 0.927, largest diff. peak and hole are 0.343 and −0.223 e·$Å^3$.

The finely pulverized portion from the same bulk sample was used for PXRD experiments.

RESULTS AND DISCUSSION

IR Spectroscopy Investigations of the Racemic and Scalemic Samples of the Compounds 1a–g

For initial evaluation of the crystallization type of our compounds, we compared the IR spectra of the racemic

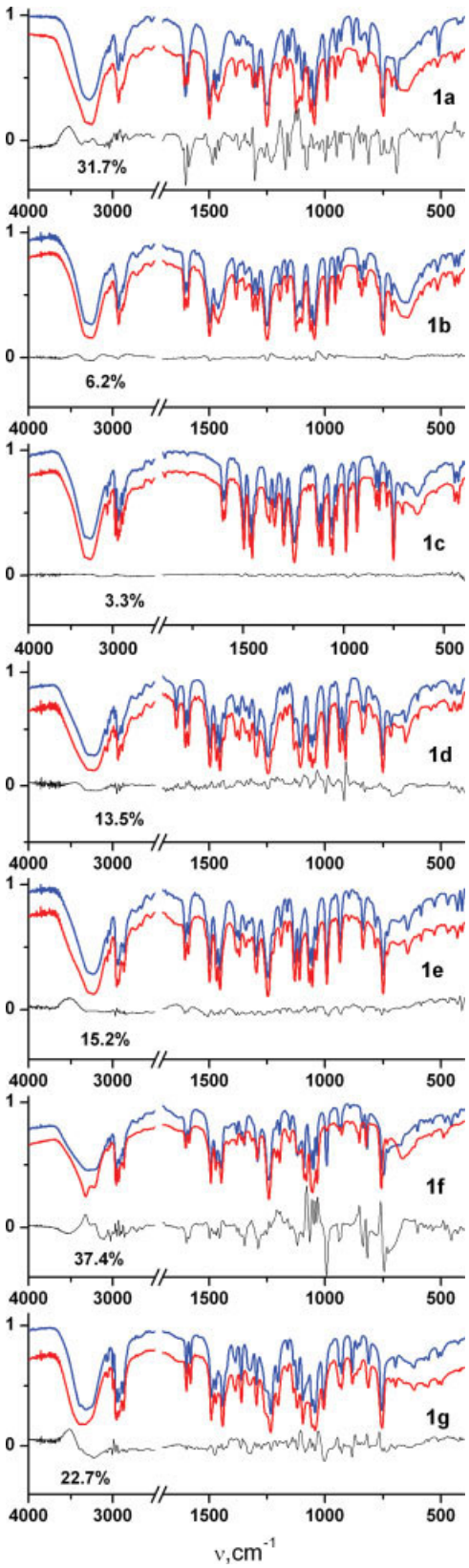


Fig. 1. IR spectra of the crystalline samples **1a–g**. Red curves—racemates, blue curves—scalemates, black curves are differential curves (see text). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE 2. DSC measured melting point (T^f) and enthalpy of fusion (ΔH^f) of racemic (low index R) and enantiopure (low index A) compounds 1a–f and calculated thermodynamic characteristics for these substances, calculated and measured eutectic (low index eu) fusion temperature and eutectic enantiomeric composition (x mole fraction of a predominant enantiomer)

Comp.	T^f_A (°C)	T^f_R (°C)	ΔH^f_A (KJ mol^{-1})	ΔH^f_R (KJ mol^{-1})	T^f_{eu}, calc. (°C)	T^f_{eu}, exp. (°C)	x_{eu}	ΔS^m_1 (J K^{-1} mol^{-1})	ΔG^0 (J mol^{-1})
1a	68.3	58.5	31.8	28.0	56.5[a]	56.3	0.68	2.59	−994
1b	91.0	70.6	34.4	32.2	70.1[b]	70.6	0.50	5.42	−51
1c	68.9	50.9	35.0	34.8	50.7[b]	50.9	0.50	5.68	−21
1d	58.0	41.7	28.8	27.8	41.3[a]	41.7	0.58	4.44	−389
1e	67.3	53.3	31.9	29.5	52.6[a]	53.0	0.60	3.89	−561
1f	71.8	80.5	30.6	31.5	67.5[a]	67.7	0.87	−2.22	−2765

[a]Calculated as intersection for Schröder-Van Laar and Prigogine-Defay curves branches.
[b]Calculated as intersection for two Schröder-Van Laar curves branches.

and highly enantiomerically enriched crystalline samples of **1a–g** in KBr pellets, since the IR spectra of an optically active and the racemic form should be identical for the normal conglomerate formative compounds. To substantiate this comparison, the spectra 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). It should be noted that the use of polynomials of higher powers (quadratic and cubic) for the generation of differential spectra does not improve the statistical parameters characterizing regression. 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 quantities are cited in Figure 1.

Figure 1 shows good coincidence between the pairs of spectra for compounds **1b** and **1c** under visual comparison; the same is almost true for the allyl and normal propyl derivatives **1d,e**, whereas the spectra of racemic and enantiopure crystalline samples for unsubstituted compound **1a**, isopropyl, and *tert*-butyl substituted phenyl glycerol ethers **1f,g**, differ noticeably. A similar pattern can be observed for the differential curves: for compounds **1b** and **1c**, and to a certain extent for compounds **1d,e**, differences between the spectra of the racemate and enantioenriched sample are about the same level as instrumental background. At the same time they are rather substantial for compounds **1a,f,g**. Thus, IR-test is consistent with the conglomerate nature of mephenesin **1b**; and the great probability exists that normal racemic conglomerate is also formed by ethyl derivative **1c**. The question of crystalline type for other investigated compounds needs further consideration.

Thermochemical Investigations and Phase Behavior of the Compounds 1a–f

The results obtained for the temperature (T^f) and the enthalpy of fusion (ΔH^f) of the pure enantiomers (low index A) and the pure racemates (low index R) of aryl glycerol ethers **1a–f** are presented in Table 2.

In the idealized case, to construct the liquidus of the binary melting phase diagram in the region of a pure component fusion, it is enough to have data on the fusion temperature and enthalpy of fusion for an enantiomerically pure sample. In this case the liquidus line is described by Schröder-Van Laar equation, which is usually used in the simplified form[3]

$$\ln x = \frac{\Delta H^f_A}{R}\left(\frac{1}{T^f_A} - \frac{1}{T^f}\right) \quad (1)$$

where x is the mole fraction of one of the enantiomers in the mixture (the mole fraction of another enantiomer is $x' = 1 - x$); R is the universal gas constant ($R = 8.3170$ J K^{-1} mol^{-1}). The liquidus lines of the phase diagrams for the compounds **1a–f**, which were calculated by eq. 1 using experimental data for enantiomerically pure diols, are presented in Figure 2 (blue lines). The same figures show the experimentally obtained liquidus points drawn by circles. For samples of diols with an intermediate enantiomeric composition, the experimental DSC thermograms contain additional peaks with the almost constant temperature T^f_{eu} which corresponds to the melting point of the eutectics. These experimental characteristics are put on the plot as solid circles too. It is significant that for the compounds **1b** and **1c** experimental liquidus points, including points for racemates, practically fall on the Schröder-Van Laar curves.

The experimental data for racemates, T^f_R and ΔH^f_R, allow to construct another type of a theoretical curve describing liquidus line for congruent melting of binary molecular compounds.

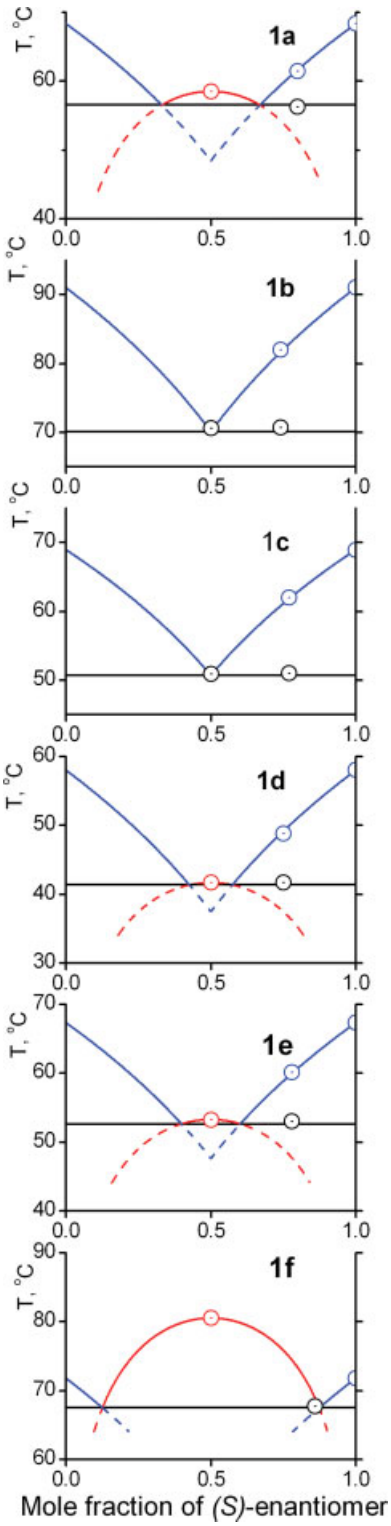


Fig. 2. Experimental (circles) points and calculated (solid lines fragments) binary melting phase diagrams for compounds **1a–f**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

In this case, the liquidus line obeys the Prigogine–Defay equation, which is usually used in the simplified form[3]

$$\ln 4x(1-x) = \frac{2\Delta H^{f}_{R}}{R}\left(\frac{1}{T^{f}_{R}} - \frac{1}{T^{f}}\right) \quad (2)$$

The liquidus lines of the phase diagrams for the compounds **1a–f**, which were calculated by eq. 2 using experimental data for racemic diols, are presented in Figure 2 by red lines.

From Figure 2 it will be obvious that the end of fusion temperatures (colored circles position) for compounds **1a, d–f** are accurately and completely described by combination of theoretical curves of both types. Hence, complete melting phase diagrams could be reproduced by solid liquidus lines fragments with the addition of probable solidus lines (black straight lines which are drawn parallel to the *x*-axis).

Inspecting the forms of so-built phase diagrams one can suppose that the methyl and ethyl substituted phenyl glycerol ethers **1b,c** crystallize as racemic conglomerates, whereas the unsubstituted phenyl glycerol ether **1a** and its allyl and propyl derivatives **1d–f** forms solid racemic compounds. There are other points in favor of this distribution of the crystallization types, we mean the calculated values of entropy of mixing for the liquid enantiomeric compounds, ΔS^{m}_{l}, and the free energy of formation of racemic compounds in the solid state, ΔG^{0}.

Based on a thermodynamic cycle involving the solid and liquid phases of the enantiomers and racemic species, formulas for the ΔG^{0} and ΔS^{m}_{l} calculations were proposed by Grant and coworkers.[5]

$$\Delta G^{0}_{T^{f}_{R}} = -\frac{(T^{f}_{R} - T^{f}_{A})\Delta H^{f}_{A}}{T^{f}_{A}} - T^{f}_{R} R \ln 2 \quad (\text{if } T^{f}_{R} - T^{f}_{A} < 0) \quad (3a)$$

$$\Delta G^{0}_{T^{f}_{A}} = -\frac{(T^{f}_{R} - T^{f}_{A})\Delta H^{f}_{R}}{T^{f}_{R}} - T^{f}_{A} R \ln 2 \quad (\text{if } T^{f}_{R} - T^{f}_{A} > 0) \quad (3b)$$

$$\Delta S^{m}_{l} = \frac{\Delta H^{f}_{R}}{T^{f}_{R}} - \frac{\Delta H^{f}_{A}}{T^{f}_{A}} - \frac{\Delta H^{f}_{R} - \Delta H^{f}_{A}}{T^{f}_{R} - T^{f}_{A}} \ln \frac{T^{f}_{R}}{T^{f}_{A}} \quad (4)$$

The values of ΔS^{m}_{l} and ΔG^{0} calculated by the formulas (3) and (4) are presented in Table 2. The entropy of mixing for enantiomers **1b** and **1c** in the liquid state is equal to 5.42 and 5.67 J K^{-1} mol^{-1}, which is slightly less but close to the value of 5.75 J K^{-1} mol^{-1} (Rln2) for an ideal conglomerate. The near zero value for ΔG^{0} also points on the same feature of chiral **1b** and **1c**.[3,5] The relatively high negative value for ΔG^{0} for unsubstituted and isopropyl derivatives **1a** and **1f** is a good diagnostic for a stable racemic compounds formation in the crystalline state.[5] The intermediate ΔS^{m}_{l} and especially ΔG^{0} values for diols **1d** and **1e** exclude a conglomerate formation, and are compatible with the assumption of (rather unstable) racemic compound formation.

Further information about the compounds under investigation could be picked up by inspection of the binary phase diagram characteristics. The case at hand is the composition of the eutectic. The last is the special point on the binary (or

ternary) phase diagram where the three phases, liquid (melt or solution) and two solid (either two individual enantiomers or enantiomer and racemic compound) exist in equilibrium. If the enantiomeric excess of the eutectic point (ee_{eu}) is exactly equal to zero, we are dealing with a conglomerate forming compound. For this compound the direct resolution approaches could be realized and enantiomeric composition of any scalemic (nonracemic) sample could be enriched to any desirable degree by fraction crystallization. If the eutectic ee lies between 0 and 1 ($0 < ee_{eu} < 100\%$), we are dealing most likely with a racemic compound forming substance. For this system, the standard direct resolution is impossible, but if the ee of the starting sample is lower than ee_{eu}, the predominant enantiomer can be enriched in the liquid phase (mother liquor) to the eutectic ee extent, whereas the precipitate will tend to be racemate. If the solution of the starting material has an ee higher than the ee_{eu}, a pure predominant enantiomer or mixtures of enantiomers with an ee higher than the eutectic ee can be crystallized out. Equilibrium crystallization of the sample with ee = ee_{eu} could not change its enantiomeric composition in either the precipitate or in the filtrate form.

The eutectic compositions for the glycerol ethers **1a–f** are presented in Table 1. From this it follows that the sample could be enantioenriched by crystallization provided that an enantiomeric excess of it is about or more than 74% (**1f**), 36% (**1a**), and 20% (**1e**). For the allyl derivative **1d** the ee $\geq$ 6% is sufficient for enantioenrichment, and at last for methyl and ethyl derivatives a sample could be racemic for the purpose; in other words, the compounds **1b** and **1c** could be potentially resolvable by direct methods. We have particularly inspected this possibility.

Resolution of Racemic 3-(2-Methylphenoxy)-propane-1,2-diol (Mephenesin, rac*-1b) and 3-(2-ethylphenoxy)-propane-1,2-diol (*rac*-1c) by Entrainment Procedure*

The entrainment effect, that is the preferential crystallization of an enantioenriched crop induced by seeding with enantiopure crystals of the oversaturated solution of a conglomerate forming (almost) racemic chiral compound, was first discovered by Pasteur's student Gernez.[27,28] Racemates resolution by entrainment[4] is a gratifying labor since success allows one to obtain easily both enantiomers without resorting to any enantiopure auxiliaries. But even in the case of conglomerate forming substances it is not always easy to use the benefits of a spontaneous resolution. Coquerel and coworkers[4,29] are of the opinion that almost half of conglomerate forming compounds would demonstrate poor entrainment characteristics.

Discovering two new conglomerates in the family of aryl glycerol ethers we decided to examine their abilities for preferential resolution. This task was all the more interesting since *rac*-3-(2-methylphenoxy)-propane-1, 2-diol, *rac*-**1b** is a well-known skeletal muscle relaxant, mephenesin.[8] We used water for the resolution as the most cheap and "green" solvent, and by analogy with our own successful effective entrainment procedure for another chiral drug, guaifenesin.[10]

In the case of ethyl derivative **1c** we have just demonstrated entrainment effect. As shown earlier, two runs (one cycle) are sufficient to obtain from 1.2 g racemate (*R*)- and (*S*)-**1c** samples of about 0.2 g each. The quality of both specimens are good enough, and making sure that the compound **1c** is quite capable of preferential crystallization we made no attempts to improve sample enantiopurity and to optimize experimental conditions for the resolution.

For monitoring the entrainment abilities of mephenesin **1b** during seed-induced crystallization of oversaturated slightly nonracemic water solutions we have used mother liquor enantiomeric composition. Unfortunately, the optical rotation of water mephenesin solutions is too low to use polarimetry for these purposes. So we made use of chiral liquid chromatography for monitoring this process. During the course of crystallization we have collected the aliquots (10 μl) of mother liquor at regular intervals. The aliquots were mixed with 1 ml of Pr^iOH, and portions of 20 μl of the solutions were analyzed with the Chiralcel AD-RH column. All investigated solutions of mephenesin of different initial concentrations but of equal starting enantiomeric enrichment behave uniformly in the main features. During the crystallization process primary enantiomeric excess of solute (~9%) decreased to zero, changed sign, and mounted to initial absolute value (even exceeded this value for high initial concentrations). The mother liquor enantiomeric composition (and the composition of deposited crystals as well) then asymptotically tended to racemic. Varying initial concentration, temperature gap, and crystallization time we have adopted the conditions for the satisfactory resolution of racemic mephenesin. An example of successful resolution of near racemic **1b** is illustrated in Table 1.

Over the course of the resolution a supersaturated solution of *rac*-**1b**, including a small excess of (*R*)-**1b**, was prepared by heating, and then cooling to 25°C. A small amount of seed crystals of (*R*)-**1b** was added and the stirred solution was allowed to crystallize for about 85 min. The weight of (*R*)-**1b** obtained after filtration was more than the common weight of the initial excess of the (*R*)-enantiomer and seed added. *rac*-**1b** was added to the mother liquor in order that the overall quantity of **1b** in the solution could be recovered. The mixture was heated until the solid was completely dissolved and then cooled to 25°C. After the solution had been seeded with (*S*)-**1b** and stirred for about 85 min, precipitated (*S*)-**1b** was collected in a similar manner. The cycle was repeated several times.

As evident from Table 1, three cycles (six runs) of entrainment resolution using ordinary laboratory equipment and no resolving agents are sufficient enough to obtain from ~17 g of *rac*-**1b** (*R*)- and (*S*)-**1b** samples of about 5 g each. The quality of each nonracemic specimen is good enough, and single recrystallization is sufficient to obtain (*R*)- and (*S*)-**1b** diols with enantiomeric excess higher than 99%.

*Crystallization Features of 3-(2-*tert*-Butylphenoxy)-propane-1,2-diol 1g*

Both racemic (Fig. 3, curve 1, Fig. 4, curve 1) and enantiopure (Fig. 4, curve 5) polycrystalline samples of 3-(2-*tert*-butylphenoxy)-propane-1,2-diol **1g** obtained by crystal-

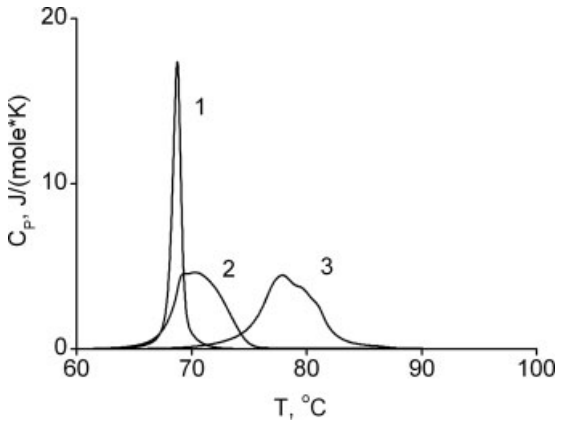


Fig. 3. DSC traces for the racemic samples of 3-(2-*tert*-butylphenoxy)-propane-1,2-diol **1g**; 1—"primary racemate" obtained by solution crystallization of racemic **1g**; 2—the same sample after several weeks aging; 3—artificial recemate obtained by mixing of approximately equal amounts of (*R*)- and (*S*)-**1g**.

lization from the solutions of corresponding composition are melted reproducibly giving the single narrow DSC traces with good linear fronts. This fact provides a way of estimating the temperature and the enthalpy of fusion for the pure enantiomer and the pure racemate of *tert*-butyl derivative **1g** as $T^{f}_{A} = 94.5^{\circ}$, $\Delta H^{f}_{A} = 32.2$ KJ mol^{-1}, $T^{f}_{R} = 67.9^{\circ}$C, $\Delta H^{f}_{R} = 19.3$ KJ mol^{-1}. The first pair of the experimental characteristics allows reconstructing Schröder-Van Laar branches of the phase diagram and estimating (as the position of their intersection) the fusion temperature of hypothetical conglomerate, $T^{f}_{congl.} = 72.2^{\circ}$C. This value is sufficiently above the experimental one for racemate. In the control experiment the racemic sample prepared by mixing of (almost) equal amounts of the pure enantiomer crystals has begun melting at near theoretical temperature T^{f}_{congl} (Fig. 3, curve 3). After several weeks aging of the sample of "primary racemate" (obtained by direct crystallization from a racemate solution) at an ambient temperature, its DSC melting trace splits, and a higher melting component could be observed (Fig. 3, curve 2), while no changes were detected in the melting of pure enantiomer samples of the same age.

The anomalous behavior of the "primary racemate" sets one thinking about additional metastable crystal forms in the system under investigation.[30] The shapes of the DSC traces for intermediate enantiomeric purity samples prepared by drying the solutions of proper composition (Fig. 4) provide support for this conclusion.

Thermograms for the mixtures of intermediate compositions (Fig. 4, curves 2–3) show simultaneous presence of three melting peaks. The low temperature one is identical by appearance and position to the melting of "primary racemate." The peak is traceable in a wide range of compositions; the peak characteristic temperature is therewith kept constant. This suggests that no individual compound but some eutectic mixture melting is the thermoinitiated process behind the low temperature peak appearance. This eutectic is not coincident with the above studied traditional racemic conglomerate formed by enantiopure crystals, and is formed by some other metastable (with respect to a homochiral) solid phase(s).

It can be inferred that all the facts under discussion are understood by reference to so-called anomalous racemate[3,31] formation during the (solution) crystallization of the racemic or the intermediate composition samples of **1g**. According to Jacques et al.,[3] anomalous racemate is an addition molecular compound in which crystals contain two enantiomers with a stoichiometry differing from the usual 1:1 ratio. We have anticipated that the above discussed "primary racemate" of *tert*-butylphenyl glycerol ether **1g** is in fact the racemic conglomerate formed by enantiomeric crystals of such anomalous racemate. To all appearance, despite the fact of less thermodynamic stability, the formation of this crystal modification is kinetically favorable. Therefore, during the racemate crystallization from a solution only the "anomalous conglomerate" (this is a more accurate expression for this case and the other examples of the sort than "anomalous racemate") precipitates.

If a solution contains an excess of one of enantiomers, the precipitate, alongside with anomalous conglomerate, contains individual enantiomer crystals. The presence of this phase manifests itself by appearance of the third high temperature peak on the DSC traces (Fig. 4). However, the possibility of the stable enantiopure solid phase generation from the metastable phase(s) immediately in the course of thermoscanning must not be ruled out. For the high enantiomeric purity samples ($x > 0.8$) the anomalous racemate melting peak virtually goes to level (Fig. 4, curve 4). Evidently in this case two crystal phases present in the sample, namely, one enantiomorph of the anomalous racemate and a pure enantiomer.

Bearing all these facts in mind we embarked on a series of control experiments using X-ray diffraction approaches. First of all we have established the molecular and crystal structure of *scal*-**1g** crystallized from an enantiopure (by HPLC) sample of the *tert*-butylphenyl glycerol ether by

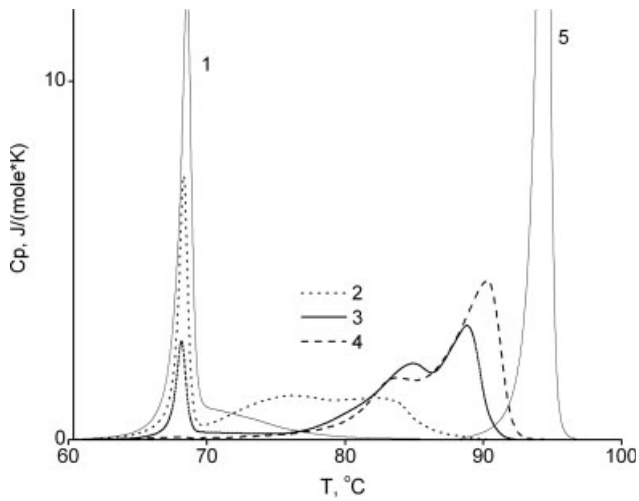


Fig. 4. DSC traces for the varying composition samples of 3-(2-*tert*-butylphenoxy)-propane-1,2-diol **1g**; $x = 0.6$ (1); $x = 0.7$ (2); $x = 0.8$ (3); $x = 0.9$ (4); $x = 1.0$, pure enantiomer (5). Here x—mole fraction of a predominant enantiomer.

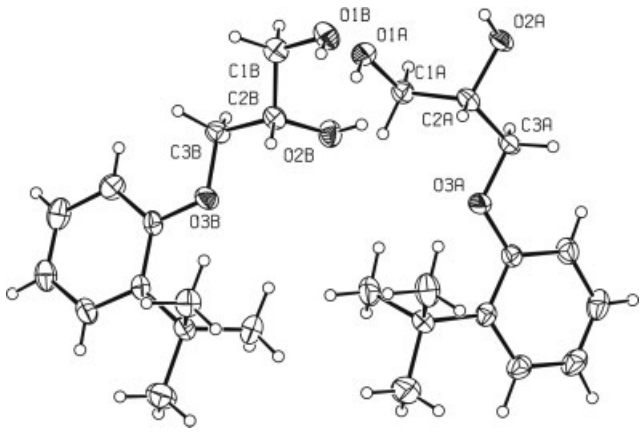


Fig. 5. ORTEP drawing of the independent part of the unit cell for (*S*)-**1g** crystal. Displacement ellipsoids are drawn at the 50% probability level; H atoms are represented by circles of arbitrary size.

single crystal X-ray analysis. Leaving out the details, we will point to Figure 5 where the independent part (two molecules) of the unit cell of *scal*-**1g** is depicted. The powder X-ray diffractogram has been simultaneously obtained from the bulk sample of the *scal*-**1g** (Fig. 7d); the experimental PXRD pattern has coincided completely with the theoretical one (Fig. 7c).

When a single crystal picked up from the bulk sample of "primary racemate" was examined by X-ray diffraction analysis two possibilities for interpretation of the experimental diffraction pattern were aroused. The automatically offered one fitted with achiral space group *Iba*2 (No. 45) with a sufficiently disordered position of all OH groups and low refinements parameters. The disorder could be diminished by lowering the crystal symmetry as far as *P*1 space group. In this case the unit cell consists of four independent molecules with the first three of them having an opposite configuration than the fourth one has. There are no crystallographic reasons to decide between these two possibilities. We have yielded to chiral *P*1 group based on the foregoing thermodynamic arguments. The case of achiral group presumes the existence of an individual racemic compound in the solid primary racemate and consequently the lowering of a fusion temperature of the sample after the enantiopure component was added owing to new eutectic formation. This is not the case as it was established in the experiments (see Fig. 4). On the contrary the case of noncentrosymmetrical *P*1 group presumes the crystallization of the *rac*-**1g** primary racemate as a mixture of enantiomorphous crystals having triple excess of one or another enantiomer. This mixture constitutes a eutectic by itself, and owing to this fact has a possibility to keep a constant melting temperature with the advent of additional component.

Figure 6 demonstrates an independent part of the *P*1 unit cell for the crystal picked up from the primary racemate bulk sample. The calculated PXRD pattern for this cell as well as for an experimental one for the freshly crys-

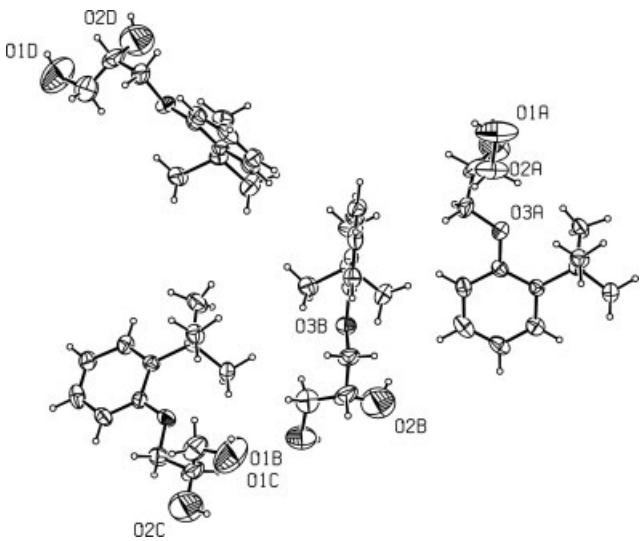


Fig. 6. ORTEP drawing of the independent part of the unit cell for *rac*-**1g** crystal. Displacement ellipsoids are drawn at the 30% probability level; H atoms are represented by circles of arbitrary size.

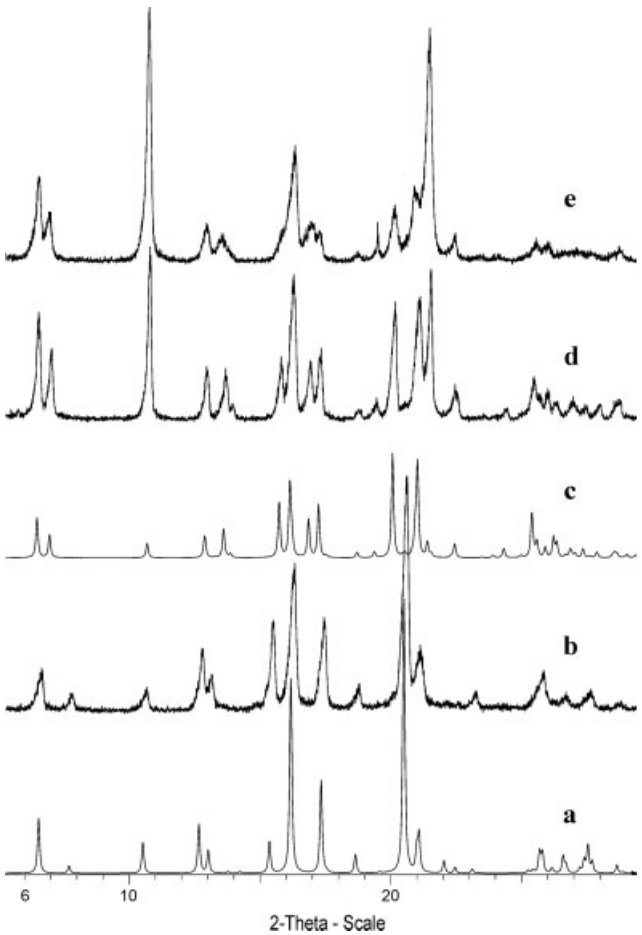


Fig. 7. Powder X-ray diffractograms for compound **1g**: (**a**) calculated from single crystal X-ray data based upon *P*1 unit cell parameters of primary racemate; (**b**) experimental pattern of freshly crystallized primary racemate; (**c**) calculated from single crystal X-ray data for enantiopure crystal; (**d**) experimental pattern for bulk enantiopure sample; (**e**) experimental pattern of bulk racemic sample after 2 months of aging.

tallized bulk sample of *rac*-**1g** are reproduced in Figure 7 (a and b correspondingly); both patterns are coincident with one another. Figure 7e demonstrates the PXRD pattern for the same *rac*-**1g** bulk sample after ~2 months of aging under ambient temperature. It will readily be seen that this curve coincides almost completely with the above discussed curve (Fig. 7d) for the enantiopure sample. And this is direct evidence of solid phase change from metastable primary crystals (anomalous conglomerate) to stable normal conglomerate formed by enantiopure components.

CONCLUSIONS

The seven aryl glycerol ethers **1a–g** studied in this work have very close chemical structure and differ only in the uniformly positioned (*ortho* phenoxyl position) far removed from the chiral centers substituents. All the substituents, hydrogen atom, alkyl, or allyl groups, are alike in polarity, are not capable of strong hydrogen bond formation, and are distinguishable mainly in size and conformational properties. Nevertheless these seemingly second-order distinctions were found to be sufficient for considerable changes in the crystallization characteristics of the different racemic members of the family.

Thus, three racemates out of the series of seven, H-, *n*-Pr-, and *i*-Pr-derivatives **1a,e,f**, crystallize as typical racemic compounds if not identical in thermodynamic characteristics. Allyl derivative **1d** forms rather unstable racemic compound. It is not improbable that the change of crystallization conditions will change the crystallization type in this case. Two substances **1b** and **1c** turn out to be typical conglomerates. The property of their spontaneous resolution could be used as the basis for an effective production of these compounds in a single enantiomer form. This is particularly of importance because one of these substances, **1b**, is the registered drug mephenesin.

Finally, the series is closed by the *tert*-butyl derivative **1g**, a racemate of which manifests rare if not unique types of spontaneous resolution. It seems reasonable to say that the metastable form, resulting during solution crystallization, and the stable form, to which metastable one transforms as times goes by, both are the eutectic mixtures of scalemic crystals. Metastable eutectic, i.e. the conglomerate of enantiomorphous crystals enriched with one or another enantiomer, arising as a result of spontaneous resolution of the anomalous racemate, turns into the eutectic of enantiopure crystals.

Thus, in this work the queer character of a spontaneous resolution has been demonstrated once again, the number of known conglomerate forming substances has been enlarged, and the uncommon variant of spontaneous resolution of metastable anomalous racemate has been found out.

LITERATURE CITED

1. Pasteur L. Sur les relations qui peuvent exister entre la forme cristalline, la composition chimique et le sens de la polarisation rotatoire. Ann Chim Phys 1848;24:442–460.
2. Perez-Garcia L, Amabilino DB. Spontaneous resolution, whence and whither: from enantiomorphic solids to chiral liquid crystals, monolayers and macro- and supramolecular polymers and assemblies. Chem Soc Rev 2007;36:941–967.
3. Jacques J, Collet A, Wilen SH. Enantiomers, racemates and resolutions. Malabar, FL: Krieger Publishing; 1994. 447 p.
4. Coquerel G. Preferential crystallization. Top Curr Chem 2007;269:1–51.
5. Li ZJ, Zell MT, Munson EJ, Grant DJW. Characterization of racemic species of chiral drugs using thermal analysis, thermodynamic calculation, and structural studies. J Pharm Sci 1999;88:337–346.
6. Höhne GWH, Hemminger WF, Flammersheim H-J. Differential scanning calorimetry. Berlin-Heidelberg-New York: Springer Verlag; 2003. 298 p.
7. Avalos M, Babiano R, Cintas P, Jimenez JL, Palacios JC. Symmetry breaking by spontaneous crystallization—is it the most plausible source of terrestrial handedness we have long been looking for?—A reappraisal. Orig Life Evol Biosphere 2004;34:391–405.
8. O'Neil MJ, editor. The Merck Index, 14th ed. Whitehouse Station, NJ: Merck and Co; 2006.
9. Bredikhina ZA, Savel'ev DV, Bredikhin AA. Cyclic sulfites—the key intermediates in the synthesis of 1-alkylamino-3-aryloxypropan-2-ols from glycidol. Russ J Org Chem 2002;38:213–219.
10. Bredikhina ZA, Novikova VG, Zakharychev DV, Bredikhin AA. Solid state properties and effective resolution procedure for guaifenesin, 3-(2-metoxyphenoxy)-1,2-propanediol. Tetrahedron: Asymmetry 2006;17:3015–3020.
11. Zakharychev DV, Lazarev SN, Bredikhina ZA, Bredikhin AA. Crystallization of chiral compounds 3. 3-Phenoxypropane-1,2-diol and 3-(2-halophenoxy)propane-1,2-diols. Rus Chem Bull Int Ed 2006;55:230–237.
12. Bredikhin AA, Bredikhina ZA, Zakharychev DV, Konoshenko LV. Spontaneous resolution among chiral glycerol derivatives: crystallization features of *ortho*-alkoxysubstituted phenyl glycerol ethers. Tetrahedron: Asymmetry 2007;18:1964–1970.
13. Schaus SE, Brandes BD, Larrow JF, Tokunaga M, Hansen KB, Gould AE, Furrow ME, Jacobsen EN. Highly selective hydrolytic kinetic resolution of terminal epoxides catalyzed by chiral (salen)Co^{III} complexes. Practical synthesis of enantioenriched terminal epoxides and 1,2-diols. J Am Chem Soc 2002;124:1307–1315.
14. Egri G, Kolbert A, Balint J, Fogassy E, Novak L, Poppe L. Baker's yeast mediated stereoselective biotransformation of 1-acetoxy-3-aryloxypropan-2-ones. Tetrahedron: Asymmetry 1998;9:271–283.
15. Kitaory K, Furukawa Y, Yoshimoto H, Otera J. CsF in organic synthesis. Regioselective nucleophilic reaction of phenols with oxiranes leading to enantiopure β-blockers. Tetrahedron 1999;55:14381–14390.
16. Bredikhin AA, Bredikhina ZA, Lazarev SN, Savel'ev DV. Systematic search for conglomerates among glycerol aromatic monoethers: guaifenesin and mephenesin are the cases. Mendeleev Commun 2003;13:104–105.
17. Theil F, Weidner J, Ballschuh S, Kunath A, Schick H. Kinetic resolution of acyclic 1,2-diols using a sequential lipase-catalyzed transesterifications in organic solvents. J Org Chem 1994;59:388–393.
18. Lambooy JP. Physiologically active substituted α-glyceryl phenyl ethers. J Am Chem Soc 1951;73:349–350.
19. Yale HL, Pribyl EJ, Braker W, Bergeim FH, Lott WA. Muscle-relaxing compounds similar to 3-(*o*-toloxy)-1,2-propanediol. I. Aromatic ethers of polyhydroxy alcohols and related compounds. J Am Chem Soc 1950;72:3710–3716.
20. Auzou G, Rips R, Derappe C, Peyroux J. Anxiolytic activity derived from a myorelaxant structure. *tert*-Butylphenol derivatives. Eur J Med Chem Chim Ther 1974;9:548–554.
21. Sheldrick GM. SADABS, Program for empirical X-ray absorption correction. Bruker-Nonius, 2004.
22. Sheldrick GM. SHELXTL v.6.12, Structure determination software suite, Bruker AXS, Madison, WI, 2000.

23. Farrugia LJ. WinGX 1.64.05. An integrated system of Windows programs for the solution, refinement and analysis of single crystal X-ray diffraction data. J Appl Crystalogr 1999;32:837–838.
24. Spek AL. Single-crystal structure validation with the program *PLATON*. J Appl Cryst 2003;36:7–13.
25. Flack HD. On enantiomorph polarity estimation. Acta Crystallogr Sect A 1983;39:876–881.
26. Flack HD, Bernardinelli G. Reporting end evaluating absolute structure and absolute configuration determination. J Appl Crystallogr 2000;33:1143–1148.
27. Gernez. Séparation des tartrates gauches et des tartrates droits à l'aide des solutions sursaturées. Compt Rend 1866;63: 843.
28. Gernez. Verfahren zur Scheidung rechtsdrehend- und linksdrehendweinsaurer Salze. Ann Chem Pharm 1867;143:376.
29. Dufour F, Perez G, Coquerel G. A Priori assessment of the maximum possible entrainment effect attainable during preferential crystallization. The case of the simultaneous resolution of (±)-ephedrine and (±)-mandelic acid. Bull Chem Soc Jpn 2004;77:79–86.
30. Coquerel G. Review on the heterogeneous equilibria between condensed phases in binary systems of enantiomers. Enantiomer 2000;3:481–498.
31. Levkin PA, Torbeev VY, Lenev DA, Kostyanovsky RG. Homo- and heterochirality in crystals. Top Stereochem 2006;25:81–134.