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Enthalpic changes on mixing two couples of *S*- and *R*-enantiomers of heptane-2-ol, octane-2-ol, nonane-2-ol, 3-chloro-propane-1,2-diol, 2-methyl-1,4-butanediol at 298.15 K

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Abstract

Enthalpies of mixing of (*R*)- and (*S*)-enantiomers of liquid chiral compounds such as heptane-2-ol, octane-2-ol, nonane-2-ol, 3-chloro-propane-1,2-diol and 2-methyl-1,4-butanediol have been measured over a range of mole fractions at 298.15 K, albeit very small values. Mixing of heterochiral liquids of heptane-2-ol, octane-2-ol, nonane-2-ol, 3-chloro-propane-1,2-diol, realized enthalpic destabilization over the whole range of mole fractions, whereas that of 2-methyl-1,4-butanediol realized enthalpic stabilization over entire compositions. The maximum values of enthalpies of mixing and the intermolecular interaction of cohesive energy density and entropy of vaporization showed a linear correlation except for the compounds having two chiral centers and others.

Keywords: (*R*)- and (*S*)-enantiomers; Chiral compound; Enthalpy of mixing; Heptane-2-ol; Heptane-2-ol; Octan-2-ol; Nonane-2-ol; 3-Chloro-propane-1,2-diol, 2-methyl-1,4-butanediol

1. Introduction

Stereospecific intermolecular interactions arising from the asymmetric structures of molecules play a significant roll in biochemical reactions. It is very important to understand the mechanisms of reactions undergone by enzymes. Takagi et al. [1,2] discovered in 1966 that the small enthalpies of mixing of two enantiomers of the same compounds are measurable by microcalorimetry. Thereafter, the influences of stereospecific interactions and densities in the liquid state have been evaluated by others [3–9].

In our previous papers [10,11], enthalpies of mixing of six systems of (*R*)- and (*S*)-enantiomers were reported. All measured systems showed a very small enthalpy change. Two systems were slightly exothermic showing slight enthalpic stabilization, whereas four systems were endothermic, showing a small enthalpic destabilization on mixing at 298.15 K.

In order to reveal the origin of chiral discrimination, enthalpies of mixing of (*R*)- and (*S*)-enantiomers of chiral compounds such as heptane-2-ol, octane-2-ol, nonane-2-ol, 3-chloro-propane-1,2-diol and 2-methyl-1,4-butanediol were measured at 298.15 K by precise solution microcalorimetry over the whole range of mole fractions at 298.15 K.

2. Materials and methods

Each enantiomer of the compounds heptane-2-ol, octane-2-ol, nonane-2-ol, 3-chloro-propane-1,2-diol and 2-methyl-1,4-butanediol (AZmax, GR) was fractionally distilled over freshly activated molecular sieves 4A which had been evacuated at 453 K for 12 h under 10^{-2} to 10^{-3} Pa. Their chemical purities, obtained from gas chromatography by using each 2 m column of 10% SE-30 on chromosorb and 20% PEG-1000 on celite 545 with FID on a Yanagimoto G180FP, were more than 99.9%. Water contents obtained by a coulometric Karl–Fischer method on a Moisturemeter (Mitsubishi Chemical Ind., CA-02) are listed in Table 1. Densities of the samples measured by a vibrating-tube

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Table 1
Purities and densities at 298.15 K of the enantiomers used

Samples	Enantiopurity (mol%)	Water content[a] (mol%)	Density (g cm^{-3})
(*R*)-(−)-heptane-2-ol	99.8	0.005	0.95612
(*S*)-(+)-heptane-2-ol	96.3	0.008	0.95609
(*R*)-(+)-octane-2-ol	99.9	0.031	1.06215
(*S*)-(−)-octane-2-ol	90.5	0.024	1.06209
(*R*)-(+)-nonane-2-ol	99.9	0.006	0.84441
(*S*)-(−)-nonane-2-ol	93.3	0.003	0.84439
(*R*)-(+)-3-chloro-propane-1,2-diol	98.8	0.008	0.87312
(*S*)-(−)-3-chloro-propane-1,2-diol	99.9	0.004	0.87311
(*R*)-(+)-2-methyl-1,4-butanediol	99.9	0.005	1.1085
(*S*)-(−)-2-methyl-1,4-butanediol	99.8	0.005	1.1087

[a] Determined by the coulometric Karl–Fisher method.

densimeter (Anton Paar DMA60) at 298.15 ± 0.001 K are also listed in Table 1. The details of densimetric procedures were the same as those described previously [12].

Enantiopurities of each sample were determined on a polarimeter (Horiba SEPA-200). Specific rotations of more than seven different mole fractions of (*R*)- and (*S*)-enantiomers for each compound and their single enantiomers were measured. Enantiopurities were calculated from the correlation between mole fractions of (*S*)-enantiomers and the specific rotations as reported previously [10]. The enantiopurities of samples are listed in Table 1.

A twin-microcalorimeter of the heat-conduction type, Thermal Activity Monitor (Thermometric AB, Järfälla, Sweden) with 0.8 cm^3 volume of mixing vessels, which had been modified by the present authors [13,14], was used for the measurements of excess enthalpies at 298.15 K over the whole range of mole fractions. Less than 10 g of each chiral material was required for the whole concentration measurements.

A reliability test of the microcalorimeter system and the procedures used had been performed using binary mixtures of $(1-x)$1,4-dimethybenzene + x1, 3-dimethylbenzene and $(1-x)$1,4-dimethylbenzene and x1,2-dimethylbenzene as reported previously [13] for exothermic and endothermic systems.

3. Results and discussion

The experimental results for enthalpies of mixing of (*R*)- and (*S*)-enantiomers of heptane-2-ol, octane-2-ol, nonane-2-ol, 3-chloro-propane-1,2-diol and 2-methyl-1,4-butanediol are summarized in Table 2 and Fig. 1. They were fitted to Eq. (1) by the method of least squares

$$H^{\mathrm{E}}\ (\mathrm{J\,mol^{-1}}) = (1-x)xA \tag{1}$$

The coefficients *A* of Eq. (1) and the standard deviations of fits s_{f}:

$$s_{\mathrm{f}} = \left[\frac{\sum_{i=1}^{n}\{H^{\mathrm{E}}(\mathrm{obs.}) - H^{\mathrm{E}}(\mathrm{calc.})\}^2}{n-1}\right]^{1/2} \tag{2}$$

are given in Table 3. The enthalpies of mixing of (*R*)- and (*S*)-enantiomers of propane-1,2-diol are also shown in Fig. 1 for comparison. The mixing of (*R*)- and (*S*)-enantiomers of all chiral compounds measured caused absorption of a small quantity of heat over the whole range of mole fractions at 298.15 K except the mixtures of (*R*)- and (*S*)-2-methyl-1,4-butanediol.

Enthalpies of mixing of (*R*)- and (*S*)-3-chloro-propane-1,2-diol showed the largest destabilization on mixing in this work. Compared with other enantiomers which have two hydroxyl groups, enthalpies of mixing of (*R*)- and (*S*)-propane-1,2-diol and those of (*R*)- and (*S*)-2-methyl-1,4-butanediol showed exothermic interactions, however, those of 3-chloro-propane-1,2-diol showed large endothermic enthalpies on mixing. When a chlorine atom was introduced into propane-1,2-diol, the enthalpy of mixing (*R*)- and (*S*)-3-chloro-propane-1,2-diol showed large destabilization of 29 J mol^{-1} at equimolar mixture than that of (*R*)- and (*S*)-propane-1,2-diol. It was six times the destabilization than the enthalpy of mixing of (*R*)- and (*S*)-propane-1,2-diol. The large destabilization might be caused by less stabilization, by means of dipole–dipole interactions between heterochiral compounds. The molecular surface of 3-chloro-propane-

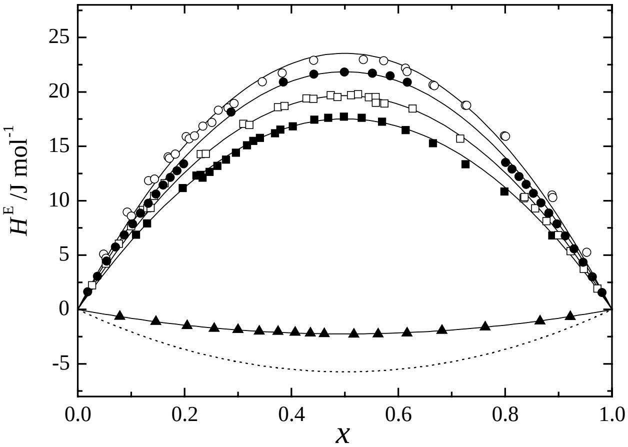

Fig. 1. Excess enthalpies of (*R*)- and (*S*)-enantiomers at 298.15 K: (○) 3-chloro-propane-1,2-diol; (●) nonane-2-ol; (□) octane-2-ol; (■) nonane-2-ol; (▲) 2-methyl-1,4-butanediol; (···) propane-1,2-diol.

Table 2
Excess enthalpies of mixing of $(1-x)(R)$-enantiomer and $x(S)$-enantiomer at 298.15 K

x	H^E (J mol^{-1})	x	H^E (J mol^{-1})	x	H^E (J mol^{-1})
3-Chloro-1,2-propandiol					
0.04852	5.086	0.2185	15.65	0.6133	21.98
0.05294	4.704	0.2343	16.96	0.6165	22.22
0.09255	7.946	0.2512	17.30	0.6647	21.32
0.1006	8.588	0.2631	17.93	0.6677	20.66
0.1327	11.84	0.2813	18.62	0.7255	18.76
0.1436	11.49	0.2925	19.23	0.7282	18.77
0.1694	14.03	0.3453	20.82	0.7986	15.46
0.1713	13.90	0.3876	22.14	0.8007	15.41
0.1828	13.59	0.4491	23.32	0.8880	9.512
0.2032	15.70	0.5371	23.27	0.8893	9.284
0.2087	15.28	0.5801	22.51	0.9587	3.756
2-Methyl-1,4-butanediol					
0.07897	−0.6578	0.3751	−2.037	0.6163	−2.190
0.1464	−1.126	0.4069	−2.109	0.6816	−1.956
0.2046	−1.505	0.4356	−2.177	0.7626	−1.623
0.2554	−1.758	0.4616	−2.243	0.8653	−1.069
0.3001	−1.872	0.5170	−2.283	0.9222	−0.6726
0.3397	−2.010	0.5623	−2.268		
Heptane-2-ol					
0.1089	6.863	0.2959	14.41	0.4982	17.72
0.1299	7.904	0.3169	15.08	0.5316	17.61
0.1965	11.16	0.3284	15.48	0.5697	17.25
0.2222	12.31	0.3412	15.77	0.6137	16.49
0.2300	12.36	0.3694	16.20	0.6651	15.28
0.2339	12.12	0.3793	16.54	0.7259	13.34
0.2468	12.64	0.4028	16.83	0.7989	10.84
0.2613	13.20	0.4427	17.45	0.8882	6.813
0.2775	13.78	0.4688	17.62		
Octane-2-ol					
0.02701	2.216	0.3213	16.95	0.5742	18.93
0.05260	4.202	0.3747	18.59	0.6269	18.47
0.07688	6.045	0.3869	18.70	0.7160	15.70
0.1000	7.643	0.4283	19.39	0.8345	10.23
0.1219	9.137	0.4410	19.36	0.8363	10.33
0.1303	9.318	0.4734	19.70	0.8563	9.291
0.1363	9.323	0.4863	19.53	0.8773	8.124
0.1428	10.44	0.5119	19.70	0.8994	6.823
0.1627	11.60	0.5248	19.79	0.9226	5.358
0.2305	14.29	0.5451	19.50	0.9470	3.730
0.2399	14.30	0.5576	19.53	0.9728	1.918
0.3101	17.07	0.5580	19.00		
Nonane-2-ol					
0.01867	1.622	0.1859	12.76	0.8260	12.21
0.03666	3.044	0.1983	13.38	0.8393	11.49
0.05400	4.440	0.2869	18.14	0.8530	10.67
0.07072	5.732	0.3847	20.91	0.8672	9.794
0.08687	6.852	0.4420	21.62	0.8818	8.855
0.1025	7.876	0.4992	21.81	0.8970	7.856
0.1175	8.834	0.5514	21.72	0.9126	6.769
0.1321	9.757	0.5849	21.47	0.9289	5.578
0.1462	10.61	0.6168	20.88	0.9457	4.335
0.1599	11.43	0.8007	13.52	0.9631	2.992
0.1731	12.13	0.8132	12.90	0.9812	1.558

1,2-diol is less delocalized than other chiral liquids, which have two hydroxyl groups.

The enthalpies of mixing of (*R*)- and (*S*)-enantiomers of alkane-2-ols were endothermic and increased with increasing size of alkyl chain. There are two explanations in terms of the difference of enthalpy changes observed upon mixing of the two enantiomers. One is the effect of molecular packing in the liquid state; i.e., the change of molar volumes between the homochiral liquid and the heterochiral one on mixing. The contraction in volume on mixing of two

Table 3
Best-fit values for the coefficients A of Eq. (1) and the calculated standard deviations of the fit s_f

System	A	S_f ($\mathrm{J\,mol^{-1}}$)
Heptane-2-ol	70.07	0.23
Octane-2-ol	78.60	0.36
Nonane-2-ol	87.40	0.25
3-Chloro-propane-1,2-diol	93.92	0.36
2-Methyl-1,4-butanediol	−8.986	0.038

compounds leads to enthalpic stabilization, and vice versa except in some special cases. The other is a difference in interaction energy between a homochiral molecular assembly and a heterochiral one. This difference may arise from the intermolecular interaction by three-point contacts, i.e., face to face contacts of polyhedra [15,16]. In order to consider the non-polar interaction term of heterochiral and homochiral interaction in aliphatic alcohols, non-polar attraction forces are assumed to proportionate to $(1/r)^6$, that is $(1/V^2)$. Here molecules are assumed to be spherical. Also, the cohesive energy density $\delta = (\Delta_{\mathrm{vap}}H/V)^{1/2}$ explains all the interaction terms in a pure liquid state for each chiral compound. Correlation between both interaction terms and excess enthalpy at equimolar concentration of heterochiral molecules aliphatic alcohols showed a linear relation as shown in Fig. 2. A major effect on the excess enthalpies of mixing of these aliphatic alcohols might be non-polar interaction. When the van der Waal's attraction force is large, in other words, when $1/V^2$ is large, heterochiral molecular interactions show less endothermic and less unfavorable interactions. Also, a large cohesive energy density induced less endothermic (less unfavorable) interactions. This means the hydroxyl group in aliphatic-2-ols from heptane-2-ol to nonane-2-ol might not give a large effect on excess enthalpies.

Intermolecular dipole–dipole stabilization energies associated with the interaction, entropy of vaporization and cohesive energy densities were calculated and are listed in Table 4. Geometry optimization of the molecular shapes of these enantiomers and physicochemical properties were carried out by calculations using with Gaussian method [17] and Molecular Modeling Pro [18]. Ab initio calculations on molecules have been performed at the RHF/6-311G level of theory. The difference in enthalpy between molecular assembly of the same enantiomers and that of the antipodal two enantiomers was evaluated precisely.

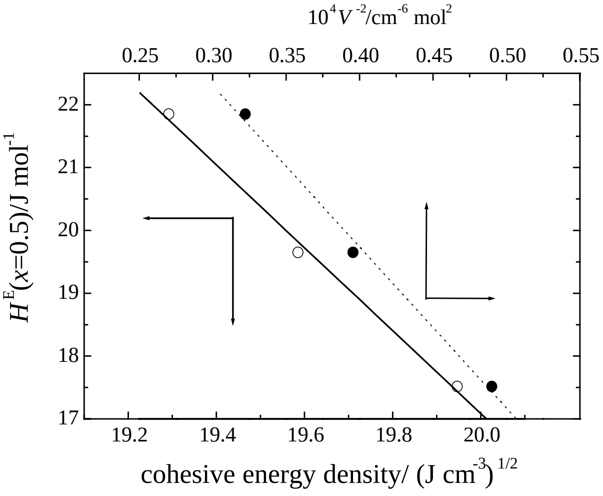

Fig. 2. Correlation between enthalpy of mixing at equimolar concentration and cohesive energy density and $1/V^2$.

A correlation between the maximum and minimum enthalpies of mixing of the enantiomers, and entropies of vaporization of pure enantiomers, are shown in Fig. 3 with previously reported results [10,11]. Entropies of vaporization of enantiomers measured were shown to be larger than Trouton's rule. Enthalpies of mixing were decreased with increasing entropies of vaporization except for five enantiomers (2,6,6-trimethyl-bicyclo[3.1.1]hept-2-ene, 4-isopropenyl-1-methyl-cyclohexene, 3-chloro-propane-1,2-diol, 2-hydroxy-propionic acid and 5-isopropenyl-2-methyl-cyclohex-2-enone). The enantiomers of 2,6,6-trimethyl-bicycle-[3.1.1]hept-2-ene and 4-isopropenyl-1-methyl-cyclohexene have two chiral centers but other enantiomers

Table 4
Excess enthalpies at equimolar mixtures of the two enantiomers and physicochemical properties of chiral molecules

System	H^E ($x = 0.5$) ($\mathrm{J\,mol^{-1}}$)	$\Delta_{\mathrm{vap}}S$ ($\mathrm{J\,K^{-1}\,mol^{-1}}$)	δ ($\mathrm{J\,cm^{-3}})^{1/2}$
Heptane-2-ol	17.52	99.8	19.95
Octane-2-ol	19.65	98.9	19.59
Nonane-2-ol	21.85	98.3	19.29
3-Chloro-propane-1,2-diol	22.54	105.0	30.11
2-Methyl-1,4-butanediol	−2.25	95.7	26.08
2,2-Dimethyl-[1,3]dioxolan-4-yl-methanol[a]	6.77	104.8	23.45
2,6,6-Trimethyl-bicyclo[3.1.1]hept-2-ene[a]	7.24	86.0	17.66
4-Isopropenyl-1-methyl-cyclohexene[a]	1.07	86.2	19.71
2-Hydroxy-propionic acid methylester[a]	13.28	107.6	33.43
Propane-1,2-diol[a]	−5.73	112.8	28.78
5-Isopropenyl-2-methyl-cyclohex-2-enone[a]	−2.11	95.7	26.08

$\Delta_{\mathrm{vap}}S$: entropy of vaporization of chiral liquid; δ: cohesive energy density of chiral liquid.

[a] Cited from [10,11].

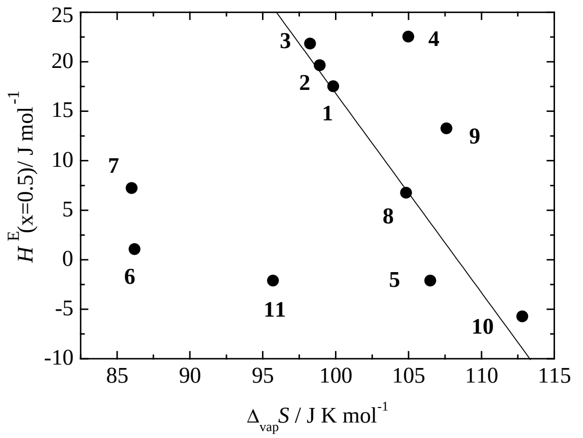

Fig. 3. Correlation between excess enthalpy of mixing at equimolar concentration and entropy of vaporization: **1**, heptane-2-ol; **2**, octan-2-ol; **3**, nonane-2-ol; **4**, 3-chloro-propane-1,2-diol; **5**, 2-methyl-1,4-butanediol; **6**, 2,2-dimethyl-[1,3]dioxolan-4-yl-methanol; **7**, 2,6,6-trimethyl-bicycle-[3.1.1]-hept-2-ene; **8**, 4-isopropenyl-1-methyl-cyclohexene; **9**, 2-hydroxy-propionic acid methylester; **10**, propane-1,2-diol; **11**, 5-isopropenyl-2-methyl-cyclohex-2-enone.

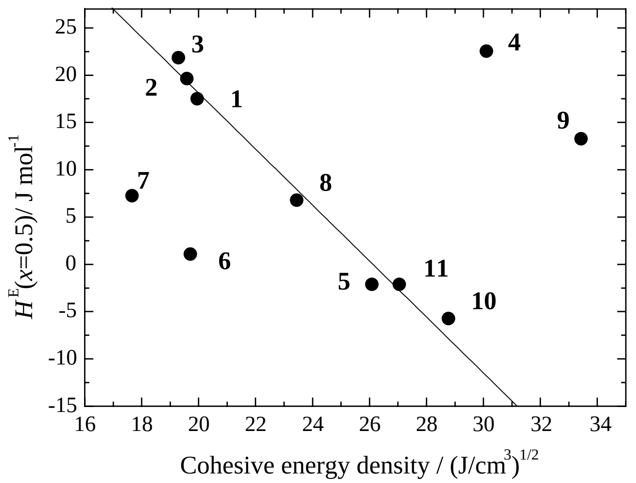

Fig. 4. Correlation between excess enthalpy of mixing at equimolar concentration and cohesive energy density: **1**, heptane-2-ol; **2**, octan-2-ol; **3**, nonane-2-ol; **4**, 3-chloro-propane-1,2-diol; **5**, 2-methyl-1,4-butanediol; **6**, 2,2-dimethyl-[1,3]dioxolan-4-yl-methanol; **7**, 2,6,6-trimethyl-bicycle-[3.1.1]-hept-2-ene; **8**, 4-isopropenyl-1-methyl-cyclohexene; **9**, 2-hydroxy-propionic acid methylester; **10**, propane-1,2-diol; **11**, 5-isopropenyl-2-methyl-cyclohex-2-enone.

measured have one chiral center. The correlation was fitted to Eq. (3):

$$\Delta H^{\mathrm{E}}\,(\mathrm{J\,mol^{-1}}) = 218.1 - 2.013\Delta_{\mathrm{vap}}S \qquad (3)$$

The result is shown in Fig. 3 (standard deviation of the fit s_{f} and correlation coefficient r were 3.4 J mol^{-1} and 0.97, respectively). A large entropy of vaporization shows that molecular motion in the liquid state is inhibited by intermolecular interaction.

This showed that homochiral interactions of the pure enantiomer liquid, which has a large entropy of vaporization, is preferable to contact of the homochiral pair. Thus, enthalpies of mixing of enantiomeric liquids which have large entropies of vaporization, are more unstable than those of liquids with lower entropies of vaporization.

In order to know the whole interaction energy of the contact site on the molecular surface of the chiral molecule, cohesive energy densities of chiral compounds were calculated by the Gaussian method. Correlation between cohesive energy densities of chiral molecules and enthalpies of mixing at equimolar concentration showed good linearity as shown in Fig. 4 except four enantiomers (2,6,6-trimethyl-bicyclo[3.1.1]hept-2-ene, 4-isopropenyl-1-methyl-cyclohexene, 3-chloro-propane-1,2-diol and 2-hydroxy-propionic acid). The correlation was fitted with Eq. (4):

$$\Delta H^{\mathrm{E}}\,(\mathrm{J\,mol^{-1}}) = 76.8 - 2.93\delta \qquad (4)$$

where $s_{\mathrm{f}} = 1.7\,\mathrm{J\,mol^{-1}}$ and $r = 0.99$. The linear line of Eq. (4) is shown in Fig. 4. All enantiomers measured have polar groups and relatively strong polar interactions except 2,6,6-trimethyl-bicyclo[3.1.1]hept-2-ene and 4-isopropenyl-1-methyl-cyclohexene which have two chiral centers. Those enantiomers can have strong inter- and/or intra-molecular hydrogen bonding. The enantiomers have same physicochemical properties except polarization degree. The interactions between homochiral molecules in pure liquid must be proportional to the cohesive energy density. Enthalpic stabilization might be increased with increasing cohesive energy density of the enantiomer when it is same interaction mechanism as shown in Fig. 2. It is clear that surface polarity of chiral liquid molecules plays an important role in the intermolecular interaction between the antipodal two enantiomers. The mixtures of 3-chloro-propane-1,2-diol and 2-hydroxy-propionic acid might have different interaction mechanisms or large volume change on mixing than other systems.

References

[1] S. Takagi, K. Amaya, in: Abstracts of the Second Japanese Conference on Calorimetry and Thermal Analysis, Tokyo, 17–19 November 1966, pp. 1–5.

[2] S. Takagi, R. Fujishiro, K. Amaya, J. Chem. Soc., Chem. Commun. (1968) 480.

[3] J.-P. Guetté, D. Boucherot, A. Horeau, Tetrahedron Lett. 29 (1973) 465–468.

[4] Z. Atik, M.B. Ewing, M.L. McGlashan, J. Phys. Chem. 85 (1981) 3300–3303.

[5] Z. Atik, M.B. Ewing, M.L. McGlashan, J. Chem. Thermodyn. 15 (1983) 159–163.

[6] L. Lepori, M. Mengheri, V. Mollica, J. Phys. Chem. 87 (1983) 3520–3525.

[7] A. Horeau, J.-P. Guetté, Tetrahedron 30 (1974) 1923–1931.

[8] V.R.J. an den Oord, N.J. Breonese, L.J.F. Hermans, J.J.M. Beenakker, J. Chem. Phys. 85 (1986) 2193–2196.

[9] L. Lepori, B. Koppenhoefer, J. Phys. Chem. 98 (1994) 6862–6864.

[10] T. Kimura, T. Ozaki, S. Takagi, Chirality 10 (1998) 722–725.

[11] T. Kimura, T. Ozaki, S. Takagi, Enantiomers 6 (2001) 5–17.

[12] T. Kimura, Y. Usui, S. Nishimura, S. Takagi, J. Fac. Sci. Technol. Kinki Univ. 25 (1989) 109–116.
[13] T. Kimura, T. Matsushita, K. Ueda, K. Tamura, S. Takagi, J. Thermal Anal. Calo. 64 (2001) 149–155.
[14] T. Kimura, T. Ozaki, Y. Nakai, K. Takeda, S. Takagi, J. Thermal. Anal. 54 (1998) 285–296.
[15] K. Amaya, Bull. Chem. Soc. Jpn. 34 (1961) 1689–1693.
[16] K. Amaya, Bull. Chem. Soc. Jpn. 34 (1961) 1803–1806.
[17] Gaussian 03, Revision B.03, Gaussian, Inc., Pittsburgh, PA, 2003.
[18] Molecular Modeling Pro, NorGwyn Montgomery Software Inc.