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ENTHALPIC CHANGES ON MIXING TWO COUPLES OF *S*- AND *R*-ENANTIOMERS WHICH CONTAINED AMINO GROUPS AT 298.15 K

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Enthalpies of mixing of *R*- and *S*-enantiomers of liquid chiral compounds such as 2-aminohexane, 2-aminoheptane, 2-aminooctane, 2-aminononane, 1-(4-chlorophenyl)-ethylamine, 1-(4-fluorophenyl)ethylamine, 2-amino-butane-1-ol have been measured over the whole range of mole fractions at 298.15 K. Mixing of heterochiral liquids observed, realized enthalpic destabilization over entire compositions.

The extreme values of enthalpies of mixing and the intermolecular interaction obtained by the molecular mechanics calculations showed a linear correlation, except the few compounds measured.

Keywords: *2-aminobutan-1-ol, 2-aminoheptane, 2-aminohexane, 2-anminononane, 2-aminooctane, chiral compound, 1-(4- chlorophenyl)ethylamine, enthalpy of mixing, 1-(4-fluorophenyl)-ethylamine, R- and S-enantiomers*

Introduction

Physicochemical studies of model compounds in liquid state are fundamental importance in understanding intermolecular interactions in liquids. In the present time chiral study has generated lots of interest due to their practical applications in various fields. Many researchers are actively involved in studying chiral interaction in aqueous and mixed solvent. Stereospecific intermolecular interactions arising from the asymmetric structures of molecules are playing really significant roll for biochemical reactions. It is very important to understand the mechanisms of reactions undergone by enzymes. Takagi *et al.* [1] 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 on cohesive energies and densities of liquid state have been evaluated by others [2–5]. Our laboratory is engaged in the study of chiral compounds for quiet some time. Previous work of our laboratory includes measurement of enthalpies of mixing for binary liquid chiral systems to understand the chiral discrimination and structural properties of the liquids in the mixture.

In our previous paper [6–10], enthalpies of mixing of 25 systems of (*R*)- and (*S*)-enantiomers were reported. All measured systems showed very small enthalpy change. For nine systems, enthalpies change were very small and slight exothermic, showing slight enthalpic stabilization, whereas the other 16 systems were endothermic ones showing 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 which contained amino groups such as 2-aminohexane(1), 2-aminoheptane(2), 2-aminooctane(3), 2-aminononane(4), 1-(4-chlorophenyl)-ethylamine(5), 1-(4-fluorophenyl)-ethylamine(6), 2-amino-butan-1-ol(7) (Fig. 1) were measured at 298.15 K by precise solution microcalorimetry over the whole range of mole fractions at 298.15 K.

Materials and methods

Each enantiomer of 1, 2, 3, 4, 5, 6 and 7 (Alfa Aesar) 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–vapor phase chromatography by using each 2 m column of 10% SE-30 on chromosorb and 20% PEG-1000 on celite 545 with FID on Yanagimoto G180FP are more than 99.9%. Water contents obtained by a Coulometric Karl-Fischer's method on a Moisturemeter (Mitsubishi Chemical Ind., CA-02) are listed in Table 1. Densities of the samples measured by a vibrating-tube densimeter (Anton Paar D60) at (298.15±0.001) K are also listed in Table 1. The details of densimetric procedures were the same as those described previously [11].

Enantiopurities of each sample were determined on a polarimeter (Horiba SEPA-200). Specific rota-

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

Samples	enantiopurity/ mol %	water[a] / mol %	density/ g cm^{-3}
(–)-(*R*)-2-aminohexane	96	0.003	0.74862
(+)-(*S*)-2-aminohexane	99	0.003	0.74861
(–)-(*R*)-2-aminoheptane	98	0.003	0.75915
(+)-(*S*)-2-aminoheptane	99	0.002	0.75913
(–)-(*R*)-2-aminooctane	99	0.003	0.76779
(+)-(*S*)-2-aminooctane	99	0.002	0.76781
(–)-(*R*)-2-aminononane	98	0.002	0.77536
(+)-(*S*)-2-aminononane	98	0.002	0.77535
(+)-(*R*)-1-(4-chlorophenyl)ethylamine	98	0.003	1.10688
(–)-(*S*)-1-(4-chlorophenyl)ethylamine	98	0.003	1.10686
(+)-(*R*)-1-(4-fluorophenyl)ethylamine	98	0.003	1.05195
(–)-(*S*)-1-(4-fluorophenyl)ethylamine	98	0.004	1.05196
(–)-(*R*)-2-amino-butane-1-ol	98	0.003	0.94528
(+)-(*S*)-2-amino-butane-1-ol	99	0.003	0.94527

[a] Determined by the coulometric Karl-Ficher method

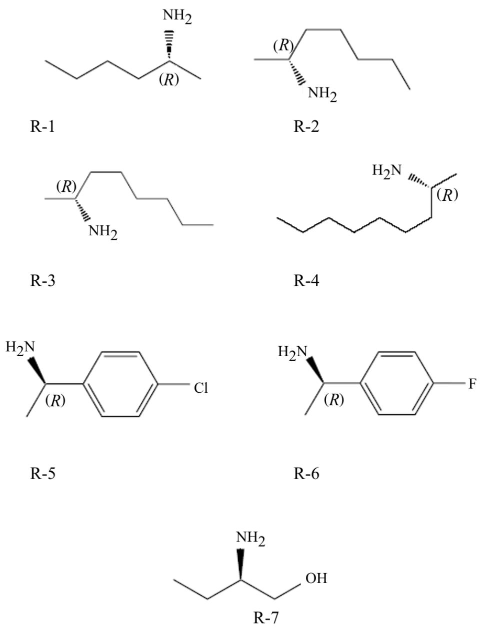

Fig. 1 Molecular structure of enantiomers(*R*-form): R-1, (–)-(*R*)-2-aminohexane; R-2, (–)-(*R*)-2-aminoheptane; R-3, (–)-(*R*)-2- aminooctane; R-4, (–)-(*R*)-2-amino-nonane ; R-5, (+)-(*R*)-1-(4-chlorophenyl)ethylamine; R-6; (+)-(*R*)-1-(4-fluorophenyl)ethylamine; R-7, (–)-(*R*)-2-aminobutan-1-ol

tions 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 [6]. 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 [12, 13], was used for the measurements of excess enthalpies at 298.15 K over the whole range of mole fractions. Each chiral material of only less than 5 g was required for the whole measurements.

A reliability test of the microcalorimeter system and the procedures used had been performed using a binary mixture of (1–*x*)1,4-dimethylbenzene+ *x*1,3-dimethylbenzene and (1–*x*)1,4-dimethybenzene and *x*1,2-dimethylbenzene as reported previously [14] for exothermic and endothermic system.

Results and discussion

The experimental results for enthalpies of mixing of (*R*)- and (*S*)-enantiomers of 1, 2, 3, 4, 5, 6 and 7 are summarized in Table 2 and Fig. 2. They were fitted with Eq. (1) by the method of least squares.

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

The coefficients *A* of Eq. (1) and the standard deviations of fits s_f:

$$s_f=\left[\sum_{i=1}^{n}(H^E_{obs}-H^E_{\mathrm{calc}})^2/(n-1)\right]^{1/2} \qquad (2)$$

were given in Table 3.

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

x	H^E /J mol^{-1}	x	H^E/ J mol^{-1}	x	H^E /J mol^{-1}	x	H^E /J mol^{-1}
2-aminohexane							
0.08815	0.3494	0.3671	1.098	0.5106	1.171	0.6761	1.034
0.1620	0.6457	0.4036	1.127	0.5369	1.165	0.7229	0.9491
0.2248	0.8449	0.4361	1.146	0.5660	1.157	0.7767	0.8263
0.2789	0.9713	0.4653	1.163	0.5985	1.133	0.8392	0.6270
0.3259	1.032	0.4915	1.162	0.6349	1.103	0.9125	0.3707
2-aminoheptane							
0.08927	0.6543	0.3703	1.952	0.5051	2.026	0.6712	1.799
0.1639	1.089	0.4069	2.009	0.5314	2.017	0.7184	1.634
0.2272	1.408	0.4395	2.043	0.5606	1.999	0.7728	1.394
0.2816	1.661	0.4687	2.055	0.5932	1.966	0.8362	1.079
0.3289	1.834	0.4950	2.061	0.6298	1.909	0.9108	0.6670
2-aminooctane							
0.08894	0.9209	0.3694	2.623	0.5065	2.794	0.6724	2.511
0.1634	1.510	0.4059	2.715	0.5327	2.788	0.7195	2.314
0.2265	1.957	0.4385	2.783	0.5619	2.756	0.7738	2.013
0.2808	2.264	0.4677	2.819	0.5945	2.701	0.8369	1.578
0.3280	2.473	0.4940	2.827	0.6310	2.633	0.9112	0.9422
2-aminononane							
0.08857	0.9065	0.3683	2.676	0.5072	2.941	0.6731	2.557
0.1627	1.529	0.4048	2.766	0.5335	2.922	0.7202	2.317
0.2257	2.000	0.4374	2.838	0.5627	2.871	0.7743	2.023
0.2799	2.292	0.4665	2.895	0.5952	2.804	0.8373	1.569
0.3270	2.514	0.4928	2.924	0.6318	2.687	0.9115	0.9291
1-(4-chlorophenyl)ethylamine							
0.09020	3.799	0.3730	10.94	0.4993	11.54	0.6660	10.24
0.1655	6.392	0.4097	11.33	0.5256	11.50	0.7137	9.399
0.2293	8.192	0.4423	11.58	0.5549	11.39	0.7687	8.167
0.2840	9.451	0.4715	11.73	0.5876	11.16	0.8329	6.362
0.3314	10.33	0.4979	11.80	0.6243	10.80	0.9089	3.747
1-(4-fluorophenyl)ethylamine							
0.09122	4.423	0.3759	12.69	0.5034	13.63	0.6697	12.04
0.1672	7.429	0.4127	13.11	0.5297	13.58	0.7170	11.02
0.2314	9.574	0.4454	13.37	0.5589	13.43	0.7716	9.548
0.2865	11.04	0.4746	13.51	0.5915	13.16	0.8352	7.430
0.3342	12.03	0.5009	13.55	0.6282	12.73	0.9102	4.367
2-amino-butan-1-ol							
0.04554	2.807	0.2258	11.19	0.6321	14.87	0.8530	8.065
0.05496	3.409	0.2504	11.78	0.6886	13.65	0.8571	8.041
0.08711	5.149	0.3043	13.44	0.7200	12.71	0.8730	7.533
0.1042	5.874	0.3623	14.76	0.7500	12.12	0.8856	6.802
10.1252	7.135	0.4164	15.63	0.7684	11.21	0.9000	6.047
0.1273	7.230	0.4584	15.83	0.7746	11.06	0.9037	5.801
0.1486	7.835	0.4741	15.98	0.7826	11.03	0.9207	4.922
0.1603	8.578	0.5005	16.05	0.7947	10.48	0.9474	3.494
0.1926	9.946	0.5339	15.91	0.8182	9.866	0.9494	3.465
0.2226	10.80	0.5789	15.64	0.8228	9.531	0.9587	2.916

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 /J mol^{-1}
2-aminohexane	4.709	0.013
2-aminoheptane	8.178	0.027
2-aminooctane	11.27	0.02
2-aminononane	11.57	0.03
1-(4-chlorophenyl) ethylamine	46.42	0.10
1-(4-fluorophenyl)ethylamine	54.23	0.06
2-aminobutane-1-ol	64.12	0.17

H^E/J mol^{-1}=(1–x)xA

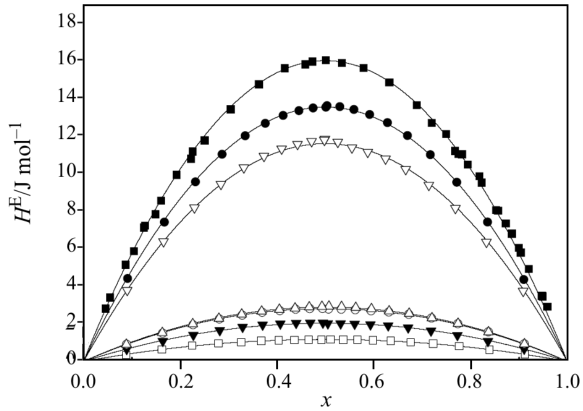

Fig. 2 Excess enthalpies of mixing of (1–x) *R*-enantiomer+*xS*-enantiomer at 298.15 K: □– 2-aminohexane; ▼ – 2-aminoheptane; ○– 2-aminooctane; △ – 2-aminononane; ▽ – 1-(4-chlorophenyl)ethylamine; ● –1-(4-fluorophenyl)ethylamine; ■ – 2-aminobutan-1-ol

The mixing of *R*- and *S*-enantiomers of all chiral compounds measured caused absorption of small heat over the whole range of mole fractions at 298.15 K.

Thus, the difference in enthalpy between molecular assembly of the same enantiomers and that of the antipodal two enantiomers was evaluated precisely. With respect to 1, 2, 3, 4, 5, 6 and 7 mixtures of two enantiomers becomes enthalpically less stable than the corresponding single enantiomers. The extent of destabilization by mixing increases in the following order; 1 < 2 < 3 < 4 < 5 < 6 <7. Thus, 7 showed the largest enthalpic destabilization on mixing of the two enantiomers, while 1 showed the smallest amount of enthalpic destabilization.

Excess endothermic enthalpies of mixing of enantiomers were increased with increasing chain length within the homologous amines as shown in Fig. 2. There are two explanations in terms of the difference in the sign of enthalpy changes observed upon mixing of 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 compounds leads to enthalpic stabilization, and vice versa except some special cases. The other is a difference in interaction energy between homochiral molecular assembly and heterochiral one. This difference may arise from the intermolecular interaction by three-point contacts, i.e., face to face contacts of polyhedra [15, 16]. The attraction forces of the non-polar interaction term of heterochiral and homochiral interaction in aliphatic compounds might be assumed to proportionate to $(1/r)^6$ that is $(1/V^2)$. Here molecules are assumed to be spherical. The radii of hypothetical spherical molecules were estimated from densities in Table 1. Excess enthalpy of chiral aliphatic alcohols were linearly decreased with decreasing attraction force as showed in previous paper [8, 9]. Furthermore correlation between interaction terms of attraction and excess enthalpy at equimolar concentration of heterochiral molecules aliphatic amine showed a linear relation as shown in Fig. 3 except 2-aminononane. The relation were fitted with following Eqs (3) and (4)

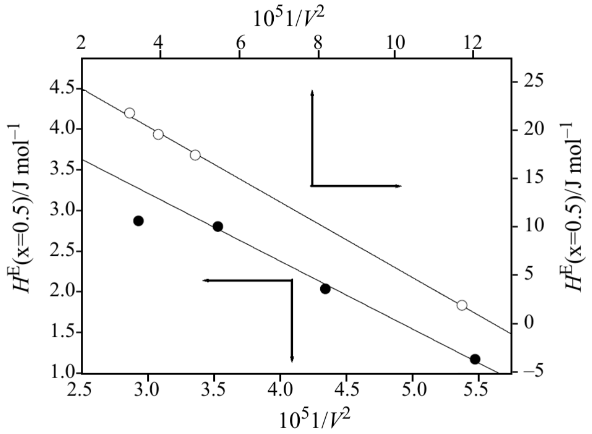

Fig. 3 Correlation between enthalpy of mixing at equimolar concentration and $1/V^2$: ● – amine systems; ○ – alcohol systems

$$H^E \text{ (amine)/ J mol}^{-1}=5.748–8.389\cdot10^4\ V^{-2},\quad s_d=0.069 \text{ J mol}^{-1} \tag{3}$$

$$H^E \text{ (alcohol)/ J mol}^{-1}=28.94–2.2976\cdot10^5 V^{-2},\quad s_d=0.29 \text{ J mol}^{-1} \tag{4}$$

A major effect on the excess enthalpies of mixing of these aliphatic amines might be non-polar interaction. When the Van der Waal's attraction force is large, in other words, when $1/r^6 \propto 1/V^2$ is large, heterochiral molecular interactions show less endothermic, that is, decreased unfavorable interactions. The increasing attraction force of chiral aliphatic

Table 4 Observed excess enthalpies of equimolar mixtures of the two enantiomers and physicochemical properties of chiral molecules

system	H^E(x=0.5)/J mol^{-1}	$\Delta_{vap}S$/J K^{-1} mol^{-1}	δ/J K^{-1} mol^{-1}
2-aminohexane	1.18	91.1	16.19
2-aminoheptane	2.05	91.4	15.88
2-aminooctane	2.82	91.6	15.42
2-aminononane	2.89	92.1	15.20
1-(4-chlorophenyl)ethylamine	11.65	92.7	18.14
1-(4-fluorophenyl)ethylamine	13.51	92.0	17.85
2-aminobutane-1-ol	16.06	106.9	22.59
benzyl-(1-phenyl-ethyl)-amine [a)]	–4.26	88.8	39.21
1-phenylethylamine [a)]	9.06	97.8	35.82
1-phenyl-ethanol [a)]	10.81	90.1	45.62
butyric acid oxiranylmethyl ester [a)]	10.88	106.6	27.05
4-methyl-[1,3]dioxolan-2-one [a)]	–8.49	110.1	27.20
2-chloromethyloxirane [a)]	11.91	101.6	21.22
3-hydroxy-isobutyric acid methyl ester [a)]	–6.40	106.7	26.73
2-hydroxypropionicacidmethylester [b)]	13.28	107.6	33.43
propane-1,2-diol [b)]	–5.73	112.8	28.78
heptane-2-ol[d)]	17.52	99.8	19.95
octan-2-ol [d)]	19.65	98.9	19.59
nonane-2-ol [d)]	21.85	98.3	19.29
3-chloro-propane-1,2-diol [d)]	22.54	105.0	30.11
2-methyl-1,4-butanediol [d)]	–2.25	95.7	27.05
(2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol[c)]	6.77	104.8	23.45
2,6,6-trimethyl-bicyclo[3.1.1]hept-2-ene[c)]	7.24	86.0	17.66
4-isopropenyl1methylcyclohexene[c)]	1.07	86.2	19.71
5-isopropenyl-2-methyl-2-cyclohexanone [c)]	–2.12	95.7	26.08

[a)] Cited from [9], [b)] Cited from [10], [c)] Cited from [11], [d)] Cited from [12], $\Delta_{vap}S$ – Entropy of vaporization; δ – cohesive energies density

amines was linearly decreasing enthalpy of mixing and had a big contribution towards the less favorable interaction. Excess enthalpy of the system of 2-aminononane was 0.4 J mol^{-1} lower than the correlation of Eq. (3), might be due to conformation effect on chiral 2-aninononane in solution. Here all volume of aliphatic amines was calculated as *trans-trans* conformation. When conformation of 2-aninononane was trans-trans form, accessible volume of 2-aninononane was 626 Å^3. However when the conformation of 2-aninononane took *gauche-gauche* form, accessible volume became 535 Å^3. If molecular conformation of 2-aminononane took *gauche-gauche* form, 2-aminononane was more close to the line of Eq. (3). Furthermore, dipole-moment of amines observed were not increased with increasing the number of methylene group, especially for that of 2-aminononae as shown in Table 4. The effect of stabilization to excess enthalpy by dipole-dipole interaction of chiral compounds might be influenced. Because the dipole-dipole interaction energy of pair molecules [17] were shown as :

$$u_{12} = -\frac{2\mu_1^2\mu_2^2}{3\,r^6kT} \tag{5}$$

where μ, *r* and *k* are dipole moment, distance between molecules and Boltzman coefficient, respectively. Here heterochiral compounds have a same dipole-moment, so u_{12} should be proportion to μ^4. A non-linearity of dipole-moment of amines as shown in Table 4 might be an effective reason for non-linearty of excess enthalpies. Compared to the slope of Eqs (3) and (4), the slope of alcohols was three times larger than that of amines. It might be large intermolecular interaction for each heterochiral alcohols, because dipole-moment, solubility parameter and entropy of vaporization of chiral alcohols were larger than those of amines. Entropies of vaporization of enantiomers measured were shown to be larger than Trouton's rule. This showed that homochiral interactions of the

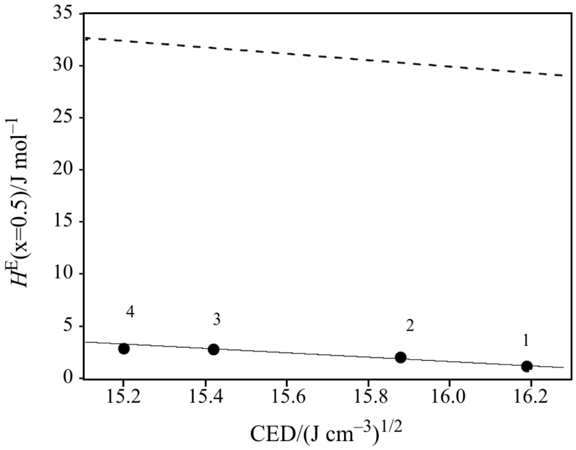

Fig. 4 Correlation between excess enthalpy of mixing at equimolar concentration and cohesive energy density(CED): 1 – 2-aminohexane; 2 – 2-aminoheptane; 3 – 2-aminooctane; 4 – 2-aminononane; broken line, previous results [9]

pure enantiomer liquid, which has a large entropy of vaporization, is preferable to that of the heterochiral pair interaction. However, enthalpies of mixing of enantiomeric liquids of amines which have large entropy of vaporization, showed more unstable than those of liquids of lower entropy of vaporization. Stabilization of liquid by means of association in homochiral liquid state might be decreased by contacts of heterochiral molecules. As a result, the entropies of vaporization of amines were increased with increasing the size of aliphatic group. However those of alcohols were decreased with increasing size of aliphatic groups. Furthermore size dependence of those was larger than those of amines. Those two effects were accelerated the slope of Eq. (3). Here, intermolecular dipole-dipole stabilization energies associated with the interaction of bond dipole moments of the enantiomers were calculated. Geometry optimization of molecular shapes of these enantiomers and physicochemical properties were carried out by calculations using with Gaussian method [18, 19] and Molecular Modeling Pro [20]. Ab initio calculations on molecules have been performed at RHF/6-311G level of theory. Cohesive energy densities were also calculated and are listed in Table 4. The cohesive energy density $\delta=(\Delta_v H/V)^{1/2}$ explains all the interaction terms in a pure liquid state for each chiral compound. From correlation between cohesive energy densities and excess enthalpies as shown in Fig. 4, excess enthalpies of mixing of enantiomers were decreased with increasing cohesive energy densities of pure enantiomer. The system of 2-aminononane showed little difference from correlation between cohesive energy densities and excess enthalpies of other 2-amino-alkane as shown in Fig. 4. The system was less unfavorable than other 2-amino-alkane. To compare with previous results of chiral compounds [9], correlations between δ and H^E of previous results were plotted in Fig. 4. The slopes of cohesive energy density dependence were not so difference between amine system and previous ones, even cohesive energy densities of amines were very small than other chiral compounds. But intercept of previous results was twice larger than that of amine. That means chiral amine systems were less unstable than other chiral compounds. There might be an effect like volume contraction on mixing which contributes to stabilization of amine.

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