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Effect of Molecular Chirality on Racemate Stability: α-Amino Acids with Nonpolar R Groups

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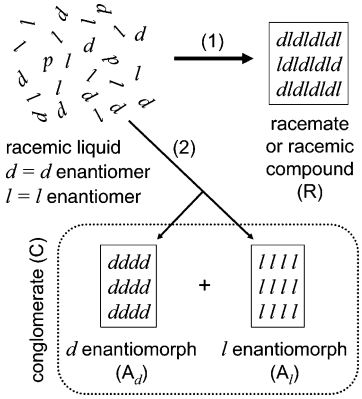
Abstract: A racemate of two opposite and resolvable enantiomers is generally assumed to be more stable than the corresponding conglomerate. Demonstrating this structure−stability relation, however, has proved difficult owing to a sampling bias (data available only for systems whose racemates are stable enough to exist) and a possible kinetic bias (racemates may be easier to crystallize than conglomerates from racemic media). As a new approach to studying the relation, we determined how the relative stability of the conglomerate and the racemate changes with the molecule's degree of chirality in a series of α-amino acids with nonpolar R groups. We found that the excess energy of the conglomerate over the racemate, ($E_C - E_R$), increases with the size of the R group, a measure of the molecule's chirality. If valid in general, this relation demonstrates a tendency for chiral molecules to form racemates rather than conglomerates. Because of the entropy effect on crystal stability, however, the excess free energy of the conglomerate over the racemate, ($G_C - G_R$), shows no simple relation with the degree of chirality at the temperatures of study (−3 to 180 °C).

Introduction

A longstanding subject of chemical research is the relationship between the racemic and chiral crystals of two opposite and resolvable enantiomers (*d* and *l*).[1,2,3] Of interest here are three crystal forms (Scheme 1): the racemate or racemic compound (R), a crystal containing both *d* and *l* in the same unit cell; the enantiomorph (A_d or A_l), a chiral crystal of *d* or *l*; and the conglomerate (C), an equal-molar physical mixture of the *d* and *l* enantiomorphs. By symmetry, A_d, A_l, and C have the same molar energy, entropy, density, and other properties. One commonly assumed relation between these crystal forms is that R is generally more stable than C, or expressed thermodynamically, $G_C = G_A > G_R$, where *G* is molar free energy. This relation is of interest to crystal structure prediction and chiral resolution by crystallization. Demonstrating this relation experimentally as a property of chiral molecules, however, has proved difficult. By the current arguments, the relation holds because (*i*) a racemic solution of *d* and *l* enantiomers tends to crystallize as R (path 1 in Scheme 1) rather than C (path 2) and (*ii*) experimental values of ($G_C - G_R$) generally show R is more stable than C.[2,4,5] Both arguments, however, are open to challenges.[3] Concerning (*i*), it may be kinetics, not just thermodynamics, that causes R to crystallize preferentially from a racemic liquid, for it should be kinetically easier for the racemic liquid to crystallize as R (a crystal of the same composition as the liquid) than as C (two crystals each of different composition from the liquid). Concerning (*ii*), any experimental measurement of ($G_C - G_R$) requires a sample of C (or equivalently one of A_d or A_l) and a sample of R. Whereas a sample of C, A_d, or A_l can generally be obtained,[6] a sample of R is obtainable only if R is sufficiently stable to exist. Thus, data on ($G_C - G_R$) are available only for racemate-forming systems; nonracemate-forming systems, which may have different ($G_C - G_R$), are not represented by the sampling. This

Scheme 1. Crystals and Crystallization of Chiral Molecules[a]



[a] Relations between molar properties: $Q_{Ad} = Q_{Al} = Q_C$, where $Q = E$ (energy), *S* (entropy), *G* (free energy), *d* (density), and others; Wallach's Rule[1] is $d_R > d_A$.

(1) Wallach, O. *Liebigs Ann. Chem.* **1895**, *286*, 90−143. Wallach's Rule states that racemic crystals tend to be denser than their chiral counterparts.
(2) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions.* Krieger Publishing Company: Malabar, FL, 1991.
(3) Brock, C. P.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811−9820.
(4) Li, Z. J.; Grant, D. J. W. *J. Pharm. Sci.* **1997**, *10*, 1073−1078.
(5) Reutzel, S.; Russell, V.; Yu, L. *J. Chem. Soc., Perkin Trans. 2* **2000**, 913−924.

(6) The enantiomorphs (A_d and A_l) can be obtained by first separating the opposite enantiomers and then separately crystallizing the enantiomers. If C is sufficiently stable, it may crystallize from a racemic liquid outright; otherwise, it can be obtained by physically mixing A_d and A_l.

Table 1. Amino Acids $^{+}H_3NCHRCO_2^{-}$ with Nonpolar R Groups

amino acid	R group	$V - V_H$,[a] cm³/mol	$\|[\alpha]_D\|$[b]
glycine	H	0	0°
alanine	CH_3	10.2	2.8°
valine	$CH(CH_3)_2$	30.7	6.4°
norvaline	$CH_2CH_2CH_3$	30.7	7.0°
leucine	$CH_2CH(CH_3)_2$	40.9	10.8°
isoleucine	$CH(CH_3)(CH_2CH_3)$	40.9	11.3°

[a] Reference 11. $V_H = 3.45$ cm³/mol. [b] From ref 12, except for norvaline (ref 13). Solvent is water.

sampling bias, which is analogous to the survival bias encountered in analyzing the historic performance of stock markets,[7] may lead to inaccurate conclusions. The same sampling bias may affect other structure−property studies; for example, are hydrated crystals inherently less soluble than their anhydrous counterparts or only appear so because they are the stable ones isolated for measurement?

Given the weakness of the current arguments for the relative stability of the racemate to the conglomerate, it is desirable to seek further evidence for the validity of this important structure−stability relation. In this work, we adopted the concept of chirality measures[8−10] and collected quantitative thermodynamic data to determine whether the relative stability of the racemate to the conglomerate increases with the degree of chirality for a homologous series of molecules. We studied a series of α-amino acids (Table 1) whose α-carbons are connected to aliphatic groups of increasing sizes (measured by their van der Waals volumes V[11]). Chemical intuition and theoretical analysis[9,10] suggest that as V increases, the *d* and *l* enantiomers become more dissimilar and the molecule's degree of chirality increases. Because chirality measures have not been standardized and "there remains the daunting challenge of bridging the gap between the results of chiral shape analysis and the world of experimental observables",[8] we used the simple function $V - V_H$, where V_H is the van der Waals volume of H, to rank the chirality of the amino acids. This function meets the requirement that it is zero for the achiral member glycine. The order of $V - V_H$ approximately agrees with that of the absolute values of the specific rotations of these amino acids (Table 1),[12,13] another property that might correlate with the degree of chirality. On going from glycine to later members in the series, the tendency of racemate formation increases. Glycine, an achiral molecule, can crystallize as a racemate [polymorph α ($P2_1/n$)] or a conglomerate [polymorph γ ($P3_2$ or $P3_1$) or β ($P2_1$), each being a mixture of crystals of opposite chirality],[14] whereas the later members, all resolvable chiral molecules, crystallize only as racemates from racemic solutions. We inquired in this study whether, with the increase of the degree of chirality, the relative stability of the racemate to the conglomerate also increases. If this relation holds in general (for other homologous series), the tendency for chiral molecules to form racemates can be demonstrated and perhaps better characterized.

Since the approach just described also requires sampling, an immediate question to be answered is whether it too suffers from the sampling bias that over-represents racemate-forming systems. Clearly all quantitative data on the relative stability of the racemate and the conglomerate must still come from racemate-forming systems. However, nonracemate-forming systems may be "sampled" in the following sense. Consider a series of molecules similar to that of Table 1 and assume its first member is not a racemate-former and hence yields no quantitative data on the relative stability of the racemate and the conglomerate. If, with the increase of the degree of chirality, the later members of the series become racemate-formers, then the structure−stability relation is supported by a sampling of the whole series (including the first member). For this reason, the approach adopted here should be less sensitive to sampling bias than a direct survey of the relative properties of racemates and conglomerates.

The relative stability of the racemate to the conglomerate has been studied by comparing their densities[1,3] on the assumption that crystal stability correlates with packing density (the Close Packing Principle).[15] Such analysis is informative, but limited because density proves to be a poor indicator of crystal stability. For example, the stability order of two enantiotropic polymorphs changes at some temperature, but their density order may not change at the same temperature or at any temperature.[16,17] For resorcinol, the more stable polymorph at room temperature is less dense than the less stable polymorph.[18] To rigorously assess the relative stability of crystal forms, it is necessary to rely on quantitative thermodynamic data. At 1 atm, the stability of the racemate relative to the conglomerate is measured by their energy difference, ($E_C - E_R$), at low temperature, and by their free-energy difference, ($G_C - G_R$), at high temperature. We measured both properties for each amino acid studied through a eutectic-melting method.[19] The otherwise applicable melting method[20] was not used because amino acids decompose on melting. We also obtained ($G_C - G_R$) from the aqueous solubility of *l* and *dl* amino acids at 4 and 21 °C. Our results show that the excess energy of the conglomerate over the racemate, ($E_C - E_R$), increases with the degree of chirality. Because of the entropy effect on crystal stability, however, the excess free energy of the conglomerate over the racemate, (G_C

(7) The central question posed here is whether stocks inherently yield better returns on investment than bonds or only appear so because surviving stocks are used for analysis. Brown, S. J.; Goetzmann, W. N.; Ross, S. A. *J. Finance* **1995**, *50*, 853−873.
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(12) Lide, D. R., Ed. *CRC Handbook of Chemistry and Physics, Internet Version 2005*, <http://www.hbcpnetbase.com>; CRC Press: Boca Raton, FL, 2005.
(13) Otey, M. C.; Greenstein, J. P.; Winitz, M.; Birnbaum, S. *J. Am. Chem. Soc.* **1955**, *77*, 3112−3114.
(14) Each molecule in the crystals of glycine is in a chiral conformation. Each single crystal of the α polymorph contains mirror-related conformers of opposite chirality. Each single crystal of the β or γ polymorph contains conformers of the same chirality ("left-handed" or "right-handed"). A sample of many crystals of the β or γ polymorph is a mixture of crystals of opposite chirality or a conglomerate. In addition to α, β, and γ, two high-pressure polymorphs of glycine (δ, $P2_1/a$; ϵ, Pn) are known (Dawson, A.; Allan, D. R.; Belmonte, S. A.; Clark, S. J.; David, W. I. F.; McGregor, P. A.; Parsons, S.; Pulham, C. R.; Sawyer, L. *Cryst. Growth Des.* **2005**, *5*, 1415−1427).
(15) Kitaigorodsky, A. I. *Molecular Crystals and Molecules*; Academic Press: New York, 1973.
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(17) Schodel, H.; Nather, C.; Bock, H.; Butenschon, F. Trimorphism of 2,2′-Dipyridylamine: Structures, Phase Transitions and Thermodynamic Stabilities. *Acta Crystallogr.* **1996**, *B52*, 842−853.
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$- G_R$), shows no simple relation with the degree of chirality at the temperatures of study ($-$ 3 to 180 °C).

Experimental Section

Materials. Amino acids (*l* and *dl* alanine, valine, leucine, isoleucine, norvaline, and norleucine) were obtained from ACROS Organics. Dulcitol, D-mannitol, I-erythritol, and xylitol were obtained from Sigma-Aldrich and used as eutectic additives. Deionized water was used as both a liquid eutectic additive and the solvent for solubility measurement.

Differential Scanning Calorimetry (DSC). DSC was performed with a TA Instruments Q1000 under a 50 mL/min N_2 purge. Amino acid−alditol mixtures were scanned at 0.5 °C/min in crimped Al pans. Amino acid−ice mixtures were scanned at 0.1 °C/min in hermetic Al pans. The temperature and heat flow were calibrated using indium. The eutectic-melting data reported were the average of 2−3 measurements. The melting temperatures were the onsets of melting endotherms. Estimated standard errors were ±0.05 °C for temperatures and ±0.1 kJ/mol for heats. The eutectic-melting method for determining the free-energy difference between crystal forms was described previously.[19] Equal-weight mixtures of amino acid and alditol were used for DSC analysis to facilitate liquid mixing at eutectic melting. Amino acid−ice mixtures were prepared by freezing saturated aqueous solutions prepared at 22 °C that contained excess amino acid crystals. The free-energy difference between the conglomerate and the racemate ($G_C - G_R$) was calculated by:[19]

$$x_{eR}[(G_C - RT\ln 2) - G_R]_{TeA} = \Delta H_{meR}\,(T_{eR} - T_{eA})/T_{eR} + \Delta C_{peR}\,[T_{eA} - T_{eR} - T_{eA}\ln(T_{eA}/T_{eR})] + RT_{eA}\{x_{eR}\ln(x_{eA}/x_{eR}) + (1 - x_{eR})\ln[(1 - x_{eA})/(1 - x_{eR})]\} \quad (1)$$

where G_R is the molar free energy of the racemate and $G_C = (G_d + G_l)/2$ is the molar free energy of the conglomerate (0.5 mol of the *d* enantiomorph and 0.5 mol of the *l* enantiomorph). The other terms in eq 1 have been defined in ref 19.

Thermogravimetric Analysis (TGA). TGA was conducted at 10 °C/min in open Al pans using a TA Q600 SDT unit. The temperature was calibrated using indium and the weight using TA-supplied standard weights and verified against sodium tartrate desolvation.

Powder X-ray Diffractometry (PXRD). PXRD was performed with a Bruker D8 X-ray diffractometer, which was equipped with a Cu Kα source ($\lambda = 1.540\,60$ Å) operating at a tube load of 40 kV and 40 mA. The divergence slit size was 1 mm, the receiving slit, 1 mm, and the detector slit, 0.1 mm. Data were collected by a solid-state (sol-X) detector. Each sample was scanned between 5° and 50° (2θ) with a step size of 0.02° and a maximum scan rate of 1 s/step.

Solubility Measurement. Solubility was measured by a weighing method. Amino acid−water slurries in sealed vials were vigorously shaken in 22.5 °C or 4.2 °C water bath for 24 h. The 22.5 °C vials were then kept at room temperature (21 ± 1 °C) for 30 h before supernatants were drawn for analysis. The 4.2 °C vials were kept in a cold room (4.0 ± 0.5 °C) for 30 h before supernatants were drawn. The room temperature and cold room temperature were monitored using a thermal couple. 3−10 mL of the saturated solutions were drawn and weighed with a microbalance. The solutions were then completely dried in a 45 °C oven for ca. 50 h followed by another ca. 15 h in a 40 °C vacuum oven. Dried crystals were weighed, and the solubilities were calculated from the weights of the saturated solution and the corresponding dried crystals. TGA was used to confirm the dryness of crystals. The remaining crystals in the slurries were later filtered, dried, and tested by PXRD to make sure they remained the same crystal form. The solubility data reported were the average of 2−4 measurements. We used eq 2 to calculate ($G_C - G_R$) from solubility data:

$$G_C - G_R = RT\ln(x_l/x_R) + RT\ln 2 \quad (2)$$

Table 2. Crystal Structures of the Amino Acids Studied Retrieved from CSD[21]

amino acid REFCODE	space group; *a*, *b*, *c* in Å; α, *β*, *γ* in deg; density in g/cm^3
γ glycine GLYCIN18	$P3_1$; 7.037, 7.037, 5.478; 90, 90, 120; 1.592
α glycine GLYCIN28	$P2_1/n$; 5.106, 11.979, 5.463; 90, 111.75, 90; 1.607
l alanine LALNIN01	$P2_12_12_1$; 6.032, 12.343, 5.784; 90, 90, 90; 1.374
dl alanine DLALNI01	$Pna2_1$; 12.026, 6.032, 5.829; 90, 90, 90; 1.399
l valine LVALIN	$P2_1$; 9.710, 5.270, 12.060; 90, 90.80, 90; 1.261
dl valine VALIDL	$P2_1/c$; 5.210, 22.100, 5.410; 90, 109.20, 90; 1.323
l leucine LEUCIN01	$P2_1$; 14.666, 5.324, 9.606; 90, 94.06, 90; 1.165
dl leucine DLLEUC	$P\bar{1}$; 14.120, 5.190, 5.390; 111.10, 86.40, 97.00; 1.191
l isoleucine LISLEU	$P2_1$; 9.750, 5.320, 14.120; 90,95.80, 90; 1.196
dl isoleucine DLILEU	$P\bar{1}$; 14.660, 5.390, 5.270; 109.20, 114.00, 85.20; 1.215
l norleucine LNLEUC10	*C*2; 9.550, 5.260, 15.377; 90, 95.60, 90; 1.133
dl norleucine DLNLUA01	$P2_1/a$; 9.907, 4.737, 16.382; 90, 104.68, 90; 1.172

where x_l and x_R are the solubility of *l* and *dl* amino acids in mole fraction. The term *RT* ln 2 is necessary in eq 2 because the *l* enantiomorph contains one component but the *dl* crystal (racemate) contains two.

Results and Discussion

Before calorimetric analysis, the amino acid crystals were characterized by PXRD and TGA. The PXRD patterns observed were compared with those calculated from the structures retrieved from the Cambridge Structural Database (CSD).[21] Table 2 shows the CSD structures that matched the crystals used in this study. The CSD had no record of *l* norvaline, and its record of *dl* norvaline (ZZZODU) did not match our sample.[22] The PXRD patterns of our *l* and *dl* norvaline samples[23] were sufficiently different from each other to indicate that they were a pair of enantiomorph and racemate. TGA was performed to ensure that all samples used were free of solvents of crystallization (0.04−0.13%).

Table 3 shows the eutectic melting data of the amino acids with different additives. The data on α and *γ* glycine have been reported.[19] *β* glycine was excluded from this work because it transformed to α under our experimental conditions. *dl* norleucine was similarly excluded because it underwent a reversible solid-state transformation at 117 °C (Figure 1), making its eutectic-melting data obtainable only with xylitol and ice.

Table 4 shows the solubilities of several amino acids measured at 4 and 21 °C. These data were collected only to validate the results of the eutectic-melting method, and only selected (less expensive) amino acids were analyzed because the measurement required significantly more material than that of eutectic melting by DSC. We had initially relied on the solubilities in the CRC Handbook of Chemistry and Physics[12] but found the CRC data differed significantly from ours. For example, the solubility of *l* valine is 8.8 g/100 g of water at 21 °C in the CRC, but our value is 5.7 g/100 g of water. The

(21) Allen, F. H. *Acta Crystallogr.* **2002**, *B58*, 380−388. Nov. 2004 Release (CSD V5.26).

(22) The CSD record of *dl* norvaline (ZZZODU) gives a different space group (*C*2/c) and slightly different lattice constants from the original reference (*I*2/*a*; $a = 9.93$, $b = 4.78$, $c = 30.04$; $\alpha = 90$, $\beta = 100$, $\gamma = 90$; see Dawson, B.; McL. Mathieson, A. *Acta Crystallogr.* **1951**, *4*, 475−477). The 3D structure was not determined.

(23) The *l* norvaline sample used was characterized by major PXRD peaks at $2\theta = 6.23$ (max), 12.47, 18.76, 19.47, 25.11, and 31.525, and the *dl* norvaline sample used was characterized by major PXRD peaks at $2\theta = 5.86$ (max), 11.72, 17.62, 18.27, 21.09, 21.99, 23.58, and 29.59.

Table 3. DSC Data of Eutectic Melting of Amino Acids[a]

	alanine		valine		norvaline		leucine		isoleucine		norleucine	
	l	*dl*	*l*	*dl*	*l*	*dl*	*l*	*dl*	*l*	*dl*	*l*	*dl*
						Additive = Dulcitol						
x_e	0.17	0.22	0.057	0.114	0.041	0.065	0.028	0.029	0.050	0.080	0.028	
T_e, °C	183.4	181.9	186.11	184.49	186.49	185.81	186.88	186.82	186.27	185.39	186.86	
ΔH_{me}, kJ/mol	55.2	49.4	67.07	61.33	61.20	63.46	67.00	68.70	62.71	63.15	60.18	
						Additive = D-Mannitol						
x_e	0.14	0.19	0.042	0.076	0.032	0.048	0.020	0.019	0.034	0.052	0.018	
T_e, °C	162.4	161.2	164.93	163.85	165.17	164.69	165.55	165.58	165.14	164.55	165.61	
ΔH_{me}, kJ/mol	48.2	46.6	54.82	52.18	51.56	54.71	55.35	58.09	53.71	52.97	53.44	
						Additive = I-Erythritol						
x_e	0.08	0.09	0.021	0.038	0.018	0.025	0.010	0.008	0.016	0.024	0.010	
T_e, °C	117.2	116.6	118.02	117.50	118.09	117.88	118.36	118.42	118.17	117.91	118.37	
ΔH_{me}, kJ/mol	38.0	38.1	40.53	40.97	39.62	41.51	41.88	42.56	40.48	40.84	40.40	
						Additive = Xylitol						
x_e	0.11	0.11	0.016	0.027	0.014	0.018	0.008	0.006	0.010	0.015	0.006	0.004
T_e, °C	90.7	90.4	91.95	91.63	92.03	91.90	92.20	92.27	92.14	92.01	92.25	92.31
ΔH_{me}, kJ/mol	33.1	32.9	35.52	35.90	36.65	36.85	37.99	40.69	37.31	36.96	36.07	37.80
						Additive = Ice						
x_e	0.024	0.023	0.010	0.013	0.017	0.015	0.003	0.002	0.007	0.006	0.002	0.001
T_e, °C	−2.79	−2.75	−0.98	−1.33	−1.71	−1.53	−0.35	−0.15	−0.67	−0.60	−0.25	−0.13
ΔH_{me},[b] kJ/mol	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0

[a] x_e, T_e, and ΔH_{me} are eutectic composition, eutectic melting point, and heat of eutectic melting, respectively. T_m (°C) and ΔH_m (kJ/mol) of pure alditols, respectively: dulcitol, 187.7, 66.8; D-mannitol, 166.4, 54.9; I-erythritol, 118.9, 41.7; xylitol, 93.2, 37.4. [b] Heat of melting of pure ice.

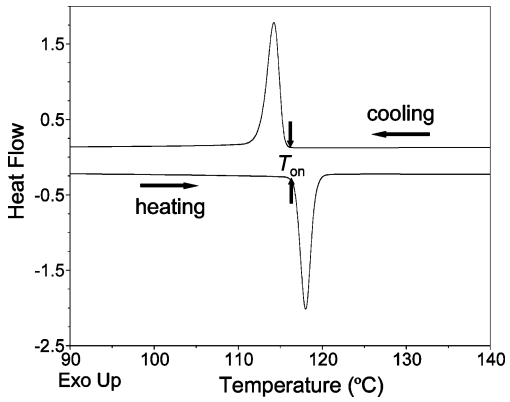

Figure 1. DSC data of the reversible solid-state transformation of *dl* norleucine at 117 °C. The mechanism of this transformation is still unclear.

Table 4. Aqueous Solubility (g/100 g of Water) of Amino Acids

amino acid	T = 4 °C	T = 21 °C
l alanine	13.24	15.81
dl alanine	15.25	15.73
l valine	5.69	5.67
dl valine	6.89	7.06
l leucine	2.06	2.11
dl leucine	0.81	0.93
l isoleucine	3.43	3.40
dl isoleucine	3.72	3.82

solubilities of *l* amino acids of Rousseau and co-workers[24] also differ from the CRC values but agree better with ours.

Figure 2a shows the free-energy difference between the conglomerate and the racemate of each amino acid studied over a temperature range of ca. 180 °C calculated from the eutectic-melting and solubility data. Although relying on different principles and operating at different temperatures, the two methods yielded consistent results. The eutectic-melting method yielded data points below and above the temperatures of solubility measurement. Figure 2a shows that, for most of the amino acids studied, the racemate has lower free energy than

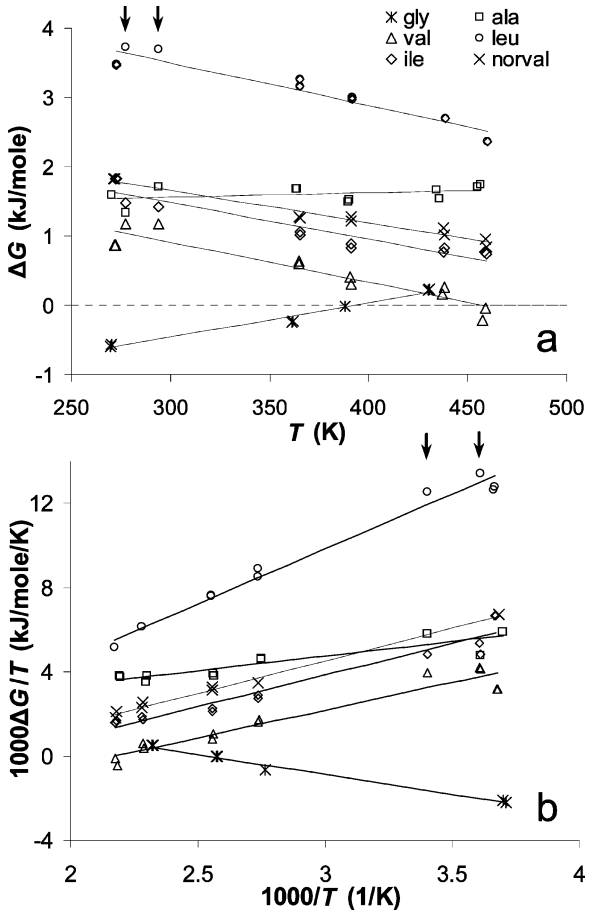

Figure 2. $\Delta G - T$ and $\Delta G/T - 1/T$ plots ($\Delta G = G_C - G_R$) for the amino acids studied. Data points at 277 and 294 K (arrows) are from solubility, and others, from eutectic melting.

(24) (a) Givand, J.; Chang, B. K.; Teja, A. S.; Rousseau, R. W. *Ind. Eng. Chem. Res.* **2002**, *41*, 1873−1876. (b) Teja, A. S.; Givand, J.; Rousseau, R. W. *AIChE J.* **2002**, *48*, 2629−2634. (c) Givand, J.; Teja, A. S.; Rousseau, R. W. *AIChE J.* **2001**, *47*, 2705−2712.

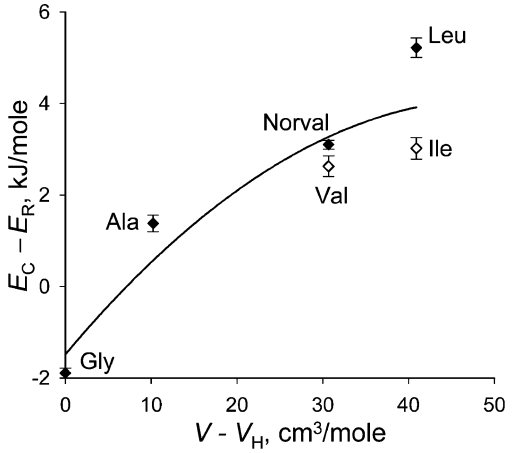

Figure 3. Crystal energy difference between conglomerate and racemate of amino acids vs the size of the R group. Valine and isoleucine are labeled separately (open symbols) because they have significantly different molecular conformations in different crystal forms (see text). Trend line is fit to all data points.

the corresponding conglomerate: $G_R < G_C$. Glycine is an exception: its "conglomerate" (γ polymorph) is more stable than its "racemate" (α polymorph) below 396 K. Valine may be another exception: its racemate may become less stable than its conglomerate above 450 K. This trend agrees with data on other systems,[2,4,5] confirming that when experimentally compared, the racemate tends to have lower free energy (higher stability) than the conglomerate. But as pointed out by Brock et al.,[3] because of a sampling bias, this trend does not prove that the racemate is intrinsically more stable than the conglomerate.

Following the approach of a homologous series, we examined whether ($G_C - G_R$) increases with the degree of chirality (size of the R group; Table 1). This requires specifying the temperature of comparison because ($G_C - G_R$) varies with temperature. At 300 K, on going from glycine to higher amino acids, the racemate changes from being less stable than the conglomerate to more stable (Figure 2a). Among the higher amino acids, however, no simple relation between ($G_C - G_R$) and the degree of chirality can be discerned at 300 K or other temperatures of study. We next inquired whether a relation exists between ($H_C - H_R$), the enthalpy difference between C and R, and the degree of chirality. This is of interest because the free energy at finite temperatures has enthalpy and entropy contributions ($G = H - TS$) and ($H_C - H_R$) may have a simpler relation with the degree of chirality. ($H_C - H_R$) determines the relative stability of C and R at low temperature and, at 1 atm, is effectively ($E_C - E_R$), the energy difference between C and R.[25] ($H_C - H_R$) was obtained from the slope of the $\Delta G/T - 1/T$ plot (Figure 2b). Figure 3 plots ($E_C - E_R$) against ($V - V_H$), the van der Waals volume of the R group minus that of *H*. Figure 3 shows that, for this series of molecules, the excess energy of the conglomerate over the racemate and hence the relative stability of the racemate *at low temperature* increases with the degree of chirality. At elevated temperatures (e.g., the room temperature), the relative stability of C and R, measured by ($G_C - G_R$), has no simple relation to the degree of chirality because of the entropy effect on crystal stability.

Table 5. Torsional Angles (deg) of Amino Acids $^+H_3NCHRCO_2^-$ [a]

molecule	τ_1	τ_2	τ_3	τ_4
l Val A	81.83	−153.61	−42.24	82.33
l Val B	179.19	−59.29	59.24	−179.25
dl Val	82.76	−152.39	−39.24	85.61
l Ile A	79.33	−155.52	−42.83	82.32
l Ile B	176.71	−60.06	56.88	−179.89
dl Ile	81.48	−153.14	−41.24	84.14
l Leu A	−175.44	67.11	−174.60	64.84
l Leu B	−169.47	71.08	−169.07	68.17
dl Leu	−168.98	71.29	−161.86	75.88

[a] Val: R = $C^3H(C^4H_3)(C^5H_3)$ (superscripts are atom numbers). τ_1 = [N−C^2−C^3−C^5]; τ_2 = [N−C^2−C^3−C^4]; τ_3 = [C^1−C^2−C^3−C^5]; τ_4 = [C^1−C^2−C^3−C^4]. Ile: R = $C^3H(C^4H_2C^5H_3)(C^6H_3)$. τ_1 = [N−C^2−C^3−C^6]; τ_2 = [N−C^2−C^3−C^4]; τ_3 = [C^1−C^2−C^3−C^6]; τ_4 = [C^1−C^2−C^3−C^4]. Leu: R = $C^3H_2C^4H(C^5H_3)(C^6H_3)$. τ_1 = [N−C^2−C^3−C^4]; τ_2 = [C^1−C^2−C^3−C^4]; τ_3 = [C^2−C^3−C^4−C^6]; τ_4 = [C^2−C^3−C^4−C^5]. A and B are independent molecules.

Crystallographic data reveal conformational differences between C and R of several amino acids studied (Table 5).[21] These differences may affect the apparent relation between ($E_C - E_R$) and ($V - V_H$). The energy of a molecular crystal consists of intermolecular (or lattice) energy and intramolecular (or conformational) energy: $E = E_{lat} + E_{conf}$. Because the greater stability of the racemate over the conglomerate, if true, should arise from intermolecular interactions, it should be the lattice-energy difference between the conglomerate and the racemate, ($E_{lat\_C} - E_{lat\_R}$), that correlates with ($V - V_H$). Thus we expect a better correlation between ($E_C - E_R$) (total energy difference between C and R) and ($V - V_H$) if conformational changes are minimal between C and R, such that ($E_C - E_R$) ≈ ($E_{lat\_C} - E_{lat\_R}$). For this analysis, changes in the torsional angle O−C^1−C^2−N are assumed negligible compared to those within the R group (e.g., trans to gauche).[9] Molecules capable of conformational changes involving the R group are norvaline, valine, isoleucine, and leucine. Although the molecular coordinates are unknown in the crystals of norvaline, we assume its aliphatic chain is in the extended zigzag conformation in both *l* and *dl* norvaline crystals, as in the crystals of norleucine and fatty acids.[21] For the remainder, Table 5 shows the relevant torsional angles of the molecules in *l* and *dl* crystals. Of the two molecules in *l* valine, one (A) has the same conformation as that in *dl* valine but the other (B) does not.[26] The same holds for isoleucine.[27] With leucine, the two independent molecules in the *l* crystal and the molecule in the *dl* crystal have approximately the same conformation.[28] On the basis of this analysis, we separate the molecules in Figure 3 into two groups: (*i*) glycine, alanine, norvaline, and leucine (amino acids that undergo no significant conformational changes between the *l* and *dl* crystals); and (*ii*) valine and isoleucine (amino acids that undergo significant conformational changes between the *l* and *dl* crystals). Figure 3 shows a consistent trend for the first group. It is possible that the difference between the two groups

(25) At 1 atm, the difference between ΔH and ΔE, the enthalpy and energy differences between C and R, is negligible. This is seen from $\Delta H = \Delta E + P\Delta V$, where $P = 1$ atm and ΔV is the difference in molar volumes between C and R. At room temperature, the $P\Delta V$ term for valine (amino acid studied with the largest density difference between C and R) is (1 atm)[1/(1.261 g/cm³) − 1/(1.323 g/cm³)](117.15 g/mol) = 0.44 J/mol, which is much smaller than the ΔH values (at least several hundred J per mol).

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and the fluctuation seen in Figure 3 may arise in part from the conformational changes between the *l* and *dl* crystals.

Our chirality measure $V - V_H$ is reasonable for the series of amino acids studied and perhaps for other molecular series similarly constructed. This function, however, is not general; for example, it fails when the R group becomes so large that it is no longer appropriate to treat the molecule as a substituted amino acid. The generalization of our approach will require careful selection and evaluation of chirality measures.[8] The kind of correlation as reported here between the chirality measure and physical stability of a well-defined series of molecules may prove helpful in evaluating and standardizing the functions for quantifying chirality.

Conclusions

Through eutectic-melting and solubility data, we obtained the relative free energies and energies of the racemates and the conglomerates of a series of α-amino acids with nonpolar R groups. The energy difference (and thus relative stability at low temperature) between the conglomerate and the racemate, ($E_C - E_R$), was found to increase with the molecule's degree of chirality measured by the size of the R group. If the same trend holds for other systems, the greater stability of the racemate than the conglomerate can be demonstrated as a general property of chiral molecules. It would be worthwhile to study this relation with other homologous series and by computational methods. Computational studies are attractive because they can compare structures that do or do not exist in reality, thus eliminating the bias of experimental sampling. At elevated temperatures (e.g., room temperature), the free-energy difference between the conglomerate and the racemate, ($G_C - G_R$), has no simple relation with the degree of chirality owing to the entropy effect on crystal stability.

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