Characterization of Racemic Species of Chiral Drugs Using Thermal Analysis, Thermodynamic Calculation, and Structural Studies

Z. JANE LI,[†,‡] MARK T. ZELL,[§] ERIC J. MUNSON,[§] AND DAVID J. W. GRANT*[,†]

Contribution from *Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Weaver-Densford Hall, 308 Harvard Street SE, Minneapolis, Minnesota 55455-0343, and the Department of Chemistry, University of Minnesota, Smith Hall, Minneapolis, Minnesota 55455.*

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Abstract □ The identification of the racemic species, as a racemic compound, a racemic conglomerate, or a racemic solid solution (pseudoracemate), is crucial for rationalizing the potential for resolution of racemates by crystallization. The melting points and enthalpies of fusion of a number of chiral drugs and their salts were measured by differential scanning calorimetry. Based on a thermodynamic cycle involving the solid and liquid phases of the enantiomers and racemic species, the enthalpy, entropy and Gibbs free energy of the racemic species were derived from the thermal data. The Gibbs free energy of formation, $\Delta G^{\circ}_{T_f}$, is always negative for a racemic compound, if it can exist, and the contribution from the entropy of mixing in the liquid state to the free energy of formation is the driving force for the process. For a racemic conglomerate, the entropy of mixing in the liquid state is close to the ideal value of R ln 2 (1.38 cal·mol^{-1}·K^{-1}). Pseudoracemates behave differently from the other two types of racemic species. When the melting points of the racemic species is about 30 K below that of the homochiral species, $\Delta G^{\circ}_{T_f}$ is approximately zero, indicating that the racemic compound and racemic conglomerate possess similar relative stabilities. The powder X-ray diffraction patterns and ^{13}C solid-state nuclear magnetic resonance spectra are valuable for revealing structural differences between a racemic compound and a racemic conglomerate. Thermodynamic prediction, thermal analysis, and structural study are in excellent agreement for identifying the nature of the racemic species.

Introduction

Chiral drugs comprise more than one-half of drugs approved worldwide.[1,2] In recent years, enantioselective production of chiral drugs has continued to grow at a rapid pace. Although catalytic asymmetric syntheses and biocatalytic resolutions have advanced steadily, resolution of racemates by crystallization (enantioselective crystallization) remains an important and the most economic process for the industrial-scale production and purification of single enantiomers.

A racemic species (also termed a racemate) can exist as a racemic compound, a racemic conglomerate, or a pseudoracemate (racemic solid solution), through different arrangements of equal numbers of moles of the opposite enantiomers in the crystalline state.[3] Characterization of the racemic species is a prerequisite for the design of industrial-scale resolution processes. Depending on the nature of the racemic species, different resolution techniques may be employed for the separation of the opposite enantiomers. Formation of a racemic conglomerate, consisting of homochiral crystals (same chirality),[4] facilitates resolution by crystallization. The outcome of a crystallization process, homochiral or heterochiral (differing chiralities), is governed by the nature of the solid−liquid-phase equilibrium that occurs in mixtures of enantiomers.[5] The formation of these different types of crystals is a result of difference in the structure and energetics between the homochiral and heterochiral crystals, which is the origin of chiral discrimination in the solid state.[6] For this reason, understanding the thermodynamic basis of the stereoselective interactions in these systems is essential for predicting and optimizing the course of resolution.

Construction of the binary phase diagram from simple measurements of the melting temperatures of the racemic species and of the corresponding enantiomers has traditionally been used for identifying the nature of the racemic species, usually a racemic compound (Figure 1a or 1b), or a racemic conglomerate (Figure 1c), or rarely a pseudoracemate (Figure 1d).[7,8] However, examination of melting temperatures alone may not be adequate in some cases, in particular when the racemic species exists either as a metastable racemic compound or as a metastable racemic conglomerate as in Figure 1c. The definitive identification of the structural differences between a racemic compound and the enantiomers usually comes from powder X-ray diffraction patterns, or from spectroscopic techniques, such as infrared and solid-state nuclear magnetic resonance (SSNMR) spectroscopy.

Questions arise as to the thermodynamic basis for the formation of different racemic species and as to the ability of the thermodynamic properties of chiral systems to serve as a reliable tool for the identification of racemic species. In view of the significant differences in the melting behavior of these racemic species (Figure 1), their thermodynamic properties must differ. These differences may be used to characterize the racemic species and may furthermore reveal the driving force for the formation of a racemic compound versus that of a racemic conglomerate or a pseudoracemate.

Although some studies on a number of chiral organic compounds have been carried out,[3,5] no investigation of this type has been reported for chiral pharmaceuticals. Therefore, the specific aims of this work are (1) to characterize various racemic species of chiral drugs using thermodynamic properties derived from calorimetric measurements, (2) to explore the thermodynamic factors determining the formation of homochiral and racemic crystals, (3) to identify the solid racemic phase by powder X-ray diffraction and by SSNMR, and to correlate the structural differences with the calculated thermodynamic quantities.

* Corresponding author. Tel (612) 624-3956. Fax (612) 625-0609. E-mail: grant001@maroon.tc.umn.edu.
† Department of Pharmaceutics.
‡ Present address: Process R & D, Pfizer Central Research, Groton, CT 06340.
§ Department of Chemistry.

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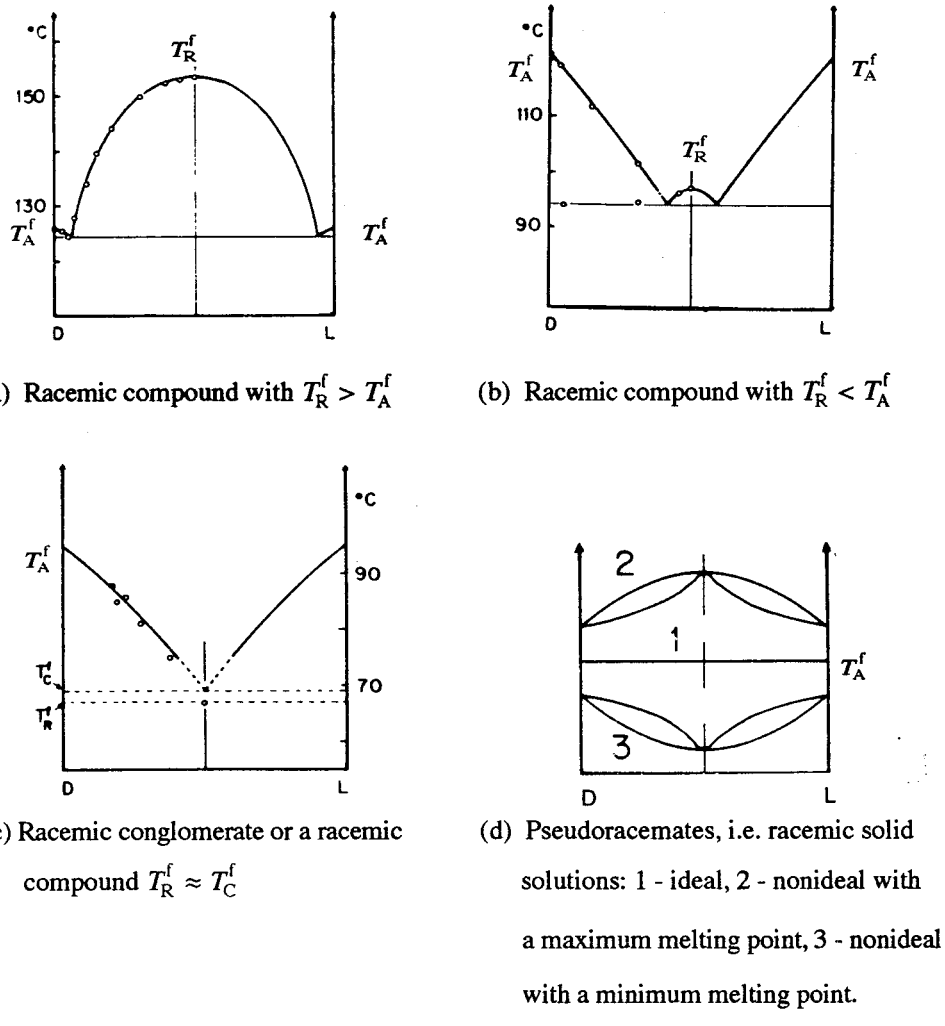

Figure 1—Typical phase diagrams of various racemic species[3] (reprinted with the permission of the copyright owner, Krieger Publishing Co.)

Twenty five chiral compounds of pharmaceutical interest were selected (see Table 1). Several compounds, specifically ephedrine and its derivatives and their salts, were prepared in this work, while others were collected from previously reported thermal analytical data of chiral drugs. These chiral compounds have various molecular structures and therapeutic applications, including several β-adrenergic antagonists, mucoregulating agents, and diagnostic agents. The overall goal of this work is to reveal unique thermodynamic properties of chiral solids of pharmaceutical interest.

Thermodynamics of Racemic Species—*Various Racemic Species.* Figure 1 shows three types of racemic species, sometimes termed racemates. However, because the term racemate has also been applied to racemic compounds only, use of the word racemate is avoided in this paper. A racemic conglomerate is an equimolar physical mixture of the individual homochiral crystals of the two opposite enantiomers. A racemic compound consists of crystals in which the two enantiomeric molecules of opposite chirality are paired up in the unit cell of the crystal lattice. A pseudoracemate consists of the two enantiomeric molecules of opposite chirality arranged more or less randomly in the same crystal lattice. All these three types are collectively termed racemic species in this work.

These structural differences in the solid state give rise to a difference in the energetics of the solid, which can be described by various thermodynamic properties that are either experimentally determined or derived quantities. To calculate the differences in the thermodynamic quantities between a racemic compound and its corresponding racemic conglomerate, Jacques et al.[3] developed a thermodynamic approach, using thermodynamic cycles. In the present work, the thermodynamic cycles of Jacques et al.[3] are modified and applied to the 25 racemic species studied. The thermodynamic cycle involving the two enantiomers, D and L, and their corresponding racemic species, R, is shown in Figure 2 for the enthalpy changes and in Figure 3 for the corresponding entropy changes.

Racemic Conglomerate—In a racemic conglomerate, if the enantiomers are perfectly immisible in the solid state, $\Delta H_s^m = 0$. Because of the structural similarity of the enantiomeric molecules, their liquid mixture is close to ideal, so that $\Delta H_l^m \approx 0$. The entropy of mixing of the enantiomers in the liquid state can be derived as described by Jacques et al.[3] and may be stated as follows:

$$\Delta S_l^m = \frac{\Delta H_R^f}{T_R^f} - \frac{\Delta H_A^f}{T_A^f} - \frac{\Delta H_R^f - \Delta H_A^f}{T_R^f - T_A^f} \ln\frac{T_R^f}{T_A^f} \qquad (1)$$

Equation 1 allows us to calculate the entropy of mixing of the liquid enantiomers from the enthalpies of fusion and

Table 1—List of the Chiral Compounds Used in This Study

compound[a]	acronym[a]	source[b]	thermal data	ref
(–)-norephedrine	(–)-NE	Sigma	this work	
(±)-norephedrine	(±)-NE	this work	this work	
(–)-norephedrine·HCl	(–)-NE·Cl	Sigma	this work	
(±)-norephedrine·HCl	(±)-NE·Cl	Sigma	this work	
(+)-norephedrine·HS	(+)-NE·S	this work	this work	
(±)-norephedrine·HS	(±)-NE·S	this work	this work	
(+)-pseudoephedrine	(+)-PE	Sigma	this work	
(±)-pseudoephedrine	(±)-PE	this work	this work	
(+)-pseudoephedrine·HCl	(+)-PE·Cl	Sigma	this work	
(±)-pseudoephedrine·HCl	(±)-PE·Cl	Sigma	this work	
(+)-pseudoephedrine·HS	(+)-PE·S		this work	10
(±)-pseudoephedrine·HS	(±)-PE·S		this work	10
(–)-ephedrine	(–)-E	Sigma	this work	
(±)-ephedrine	(±)-E	Sigma	this work	
(–)-ephedrine·HCl	(–)-E·Cl	Sigma	this work	
(±)-ephedrine·HCl	(±)-E·Cl	Sigma	this work	
(–)-ephedrine·napsylate	(–)-E·NS	this work	this work	11
(±)-ephedrine·napsylate	(±)-E·NS	this work	this work	11
(–)-methylephedrine	(–)-ME	Sigma	this work	
(±)-methylephedrine	(±)-ME	this work	this work	
(–)-ibuprofen	(–)-IB	Ethyl	this work	
(±)-ibuprofen	(±)-IB	Ethyl	this work	
(–)-mandelic acid	(–)-MA	Sigma	this work	
(±)-mandelic acid	(±)-MA	Sigma	this work	
(–)-propranolol·HCl	(–)-PN·Cl	Sigma	this work	
(±)-propranolol·HCl	(±)-PN·Cl	Sigma	this work	
(–)-propranolol	(–)-PN		this work	12
(±)-propranolol	(±)-PN		this work	12
(+)-atenolol	(+)-AN	Aldrich	this work	
(±)-atenolol	(±)-AN	Sigma	this work	
(+)-alprenolol	(+)-APN			12
(±)-alprenolol	(±)-APN			12
(–)-*trans*-sobrerol	(–)-t-SB			13
(±)-*trans*-sobrerol	(±)-t-SB			13
(–)-*cis*-sobrerol	(–)-c-SB			13
(±)-*cis*-sobrerol	(±)-c-SB			13
(–)-bevantolol	(–)-BT			8
(±)-bevantolol	(±)-BT			8
(–)-bevantolol·HCl	(–)-BT·Cl			8
(±)-bevantolol·HCl	(±)-BT·Cl			8
(–)-pindolol	(–)-PD			8
(±)-pindolol	(±)-PD			8
(–)-iopanoic acid	(–)-IA			14
(±)-iopanoic acid	(±)-IA			14
(–)-dropropizine	(–)-DPP			15
(±)-dropropizine	(±)-DPP			15
(–)-sulpiride	(–)-SP			16
(±)-sulpiride	(±)-SP			16
(–)-dexrazoxane	(–)-DZ			17
(±)-dexrazoxane	(±)-DZ			17
(–)-4-hydroxy-2-pyrrolidone	(–)-HPL			18
(±)-4-hydroxy-2-pyrrolidone	(±)-HPL			18

[a] Cl and S represent the chloride and salicylate anions, respectively. [b] Sigma Chemical Co. (St. Louis, MO); Ethyl Corporation (Baton Rouge, LA); Aldrich Chemical Co. (Milwaukee, WI).

melting points, as measured by differential scanning calorimetry (DSC). If the enantiomeric molecules are randomly mixed in the liquid state, the entropy of mixing is ideal and its value is given by:

$$\Delta S_l^{\mathrm{m}} = R \ln 2 = 1.38 \text{ cal·mol}^{-1}\text{·K}^{-1} \qquad (2)$$

For a number of racemic conglomerates, the average entropy of mixing of the enantiomers in the liquid state was found to be 1.33 ± 0.14 cal·mol^{-1}·K^{-1}, indicating that mixing of the enantiomers is nearly ideal in the liquid state.[3] The small deviation from the ideal value may be attributed to the possibility that the corresponding enthalpy of mixing, ΔH_l^{m}, may not be exactly zero.

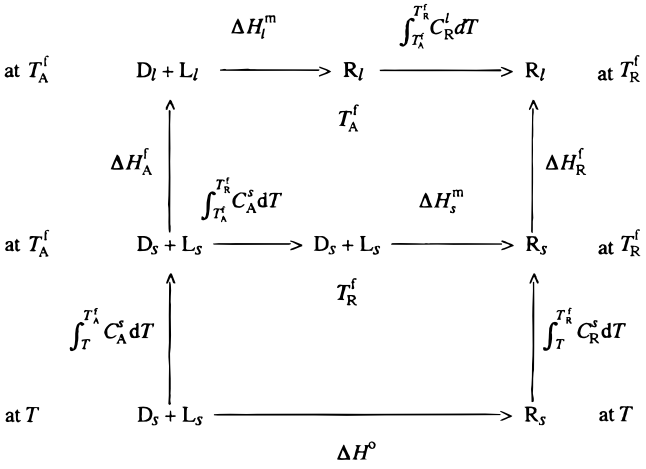

Figure 2—The enthalpy changes during various stages of a thermodynamic cycle involving the enantiomers, D and L, and the racemic species, R, where ΔH^{f}, C^{l}, C^{s} and T^{f} represent the enthalpy of fusion, heat capacity of the liquid and solid, and melting temperature, respectively. The subscript A denotes the enantiomer and R the racemic species; and the subscripts *l* and *s* denote the liquid and solid state, respectively. ΔH^{m} and ΔH° represent the enthalpy of mixing and the enthalpy of formation, respectively.

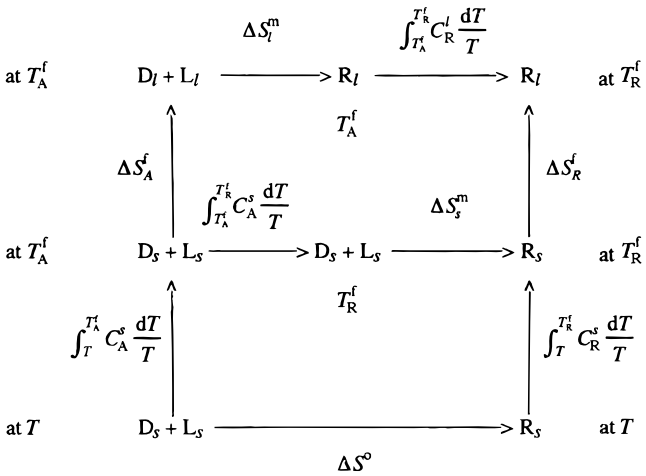

Figure 3—The entropy changes during various stages of a thermodynamic cycle involving the enantiomers, D and L, and the racemic species, R, where ΔS^{f}, C^{l}, C^{s}, and T^{f} represent the entropy of fusion, heat capacity of the liquid and solid, and melting temperature, respectively. The subscript A denotes the enantiomer and R the racemic species; the subscript *l* and *s* denote the liquid and solid state, respectively. ΔS^{m} and ΔS° represent the entropy of mixing and the entropy of formation, respectively.

Racemic Compound—The stability of a racemic compound can be defined by the Gibbs free energy change, $\Delta G°$, of solid-state transformation, corresponding to the "reaction" between the crystals of the two enantiomers, D and L, in the racemic conglomerate to yield crystals of the racemic compound, R:

$$\mathrm{D_s} + \mathrm{L_s} \rightarrow \mathrm{R_s}$$

where the left-hand side refers to the racemic conglomerate, which consists of an equimolar mixture of crystals of D and L, and the subscript, s, refers to the solid, i.e., the crystalline state. For a stable racemic compound, *this free energy change must be negative*. For this purpose, $\Delta G°$ is the Gibbs free energy of formation of the racemic compound from the two opposite enantiomers. $\Delta G°$ may be also expressed as a function of the corresponding enthalpy of formation, $\Delta H°$, and entropy of formation, $\Delta S°$:

$$\Delta G° = \Delta H° - T\Delta S° \qquad (3)$$

The thermodynamic quantities in eq 3 are not directly measurable, but can be determined from calorimetry data using eqs 4a−7b, as discussed below.

Assuming that the above "reaction" occurs at the melting point of that species (racemic species or enantiomer) which has the lower melting point, eqs 4a−7b may be derived to calculate the thermodynamic properties for the formation of a racemic compound. The enthalpies of fusion, ΔH^f, and the melting temperature, T^f, of both the racemic compound, R, and its enantiomer, A (in subscript), are determined experimentally. As shown in Figure 1a and 1b, the two situations, $T^f_A < T^f_R$ and $T^f_A > T^f_R$, are presented separately.

Enthalpy of formation:

$$\Delta H^\circ_{T^f_A} = \Delta H^f_A - \Delta H^f_R + (C^l - C^s_R)(T^f_R - T^f_A), \quad \text{when } T^f_A < T^f_R \quad (4a)$$

$$\Delta H^\circ_{T^f_R} = \Delta H^f_A - \Delta H^f_R + (C^l - C^s_A)(T^f_R - T^f_A), \quad \text{when } T^f_A > T^f_R \quad (4b)$$

Entropy of formation

$$\Delta S^\circ_{T^f_A} = \Delta S^f_A - \Delta S^f_R + R \ln 2 + (C^l - C^s_R)\ln \frac{T^f_R}{T^f_A}, \quad \text{when } T^f_A < T^f_R \quad (5a)$$

$$\Delta S^\circ_{T^f_R} = \Delta S^f_A - \Delta S^f_R + R \ln 2 + (C^l - C^s_A)\ln \frac{T^f_R}{T^f_A}, \quad \text{when } T^f_A > T^f_R \quad (5b)$$

Substituting the enthalpy of formation and the entropy of formation into eq 3 affords the free energy of formation, $\Delta G°$. The contribution from the terms containing the heat capacities in eqs 4 and 5 is always small and is effectively negligible.[3] Taking the difference in the melting points, $\Delta T = T^f_R - T^f_A$, and neglecting the small difference in the heat capacities, the free energy of formation is given by:

$$\Delta G^\circ_{T^f_A} \cong -\Delta S^f_R \Delta T - T^f_A R \ln 2, \text{ when } T^f_A < T^f_R, \text{ i.e., } \Delta T > 0 \quad (6a)$$

$$\Delta G^\circ_{T^f_R} \cong -\Delta S^f_A \Delta T - T^f_R R \ln 2, \text{ when } T^f_A > T^f_R, \text{ i.e., } \Delta T < 0 \quad (6b)$$

When, as in Figure 1a, the racemic compound melts at a higher temperature than its enantiomers, represented by eq 6a, $\Delta G° < 0$, suggesting that the formation of the racemic compound is always thermodynamically favorable in this situation. Figure 1b and eq 6b, however, present a more complicated situation. When $\Delta T < 0$, eq 6b is applicable and the first term on the right becomes positive. As ΔT becomes increasingly negative, $\Delta G°$ becomes less negative, eventually approaching zero (as ΔT approaches −30 K, to be considered later following eqs 7a and 7b). When $\Delta G°$ is zero or positive, there is no driving force for the formation of a racemic compound, and the racemic species remain as a racemic conglomerate as shown in Figure 1c. In other words, no "reaction" occurs between the enantiomers, when the racemic species is a racemic conglomerate.

Equations 4a−6b are valid only at the melting temperature of the enantiomers (or of the racemic species). In the pharmaceutical sciences, however, we are more interested in the thermodynamic values, especially $\Delta G°$, below the melting temperatures, e.g., at 25 °C or 37 °C. Extrapolation of the thermodynamic quantities from the melting temperature to another temperature, T, requires knowledge of the heat capacity terms. Accordingly, $\Delta G°$ at any temperature T, ΔG°_T, can be derived from the thermodynamic cycles in Figures 2 and 3:

$$\Delta G^\circ_T = \Delta G^\circ_{T^f_A} + \Delta\Delta S(T^f_A - T) + (C^l - C^s_R)\left[T^f_R - T^f_A - T \ln \frac{T^f_R}{T^f_A}\right] + (C^s_A - C^s_R)\left[T^f_A - T - T \ln \frac{T^f_A}{T}\right]$$

where

$$\Delta\Delta S = \Delta S^f_A - \Delta S^f_R + R \ln 2, \text{ when } T^f_A < T^f_R \quad (7a)$$

$$\Delta G^\circ_T = \Delta G^\circ_{T^f_R} + \Delta\Delta S(T^f_R - T) + (C^l - C^s_A)\left[T^f_R - T^f_A - T \ln \frac{T^f_R}{T^f_A}\right] + (C^s_A - C^s_R)\left[T^f_R - T - T \ln \frac{T^f_R}{T}\right]$$

where

$$\Delta\Delta S = \Delta S^f_A - \Delta S^f_R + R \ln 2, \text{ when } T^f_A > T^f_R \quad (7b)$$

The magnitude of the last three terms is relatively small. In the case of eq 7a, ΔG°_T is likely to remain negative over a wide temperature range below the melting point. However, when the free energy of formation at T^f_R in eq 7b has a small negative value close to zero (see examples in Tables 3), the sign of ΔG°_T may become positive depending on the sign of the sum, i.e., the relative magnitudes, of the last three terms. This possibility, arising from eq 7b, provides a thermodynamic basis for the melting point phase diagrams, shown in Figure 1c, and for the solubility diagrams of chiral systems that display a transformation from a racemic compound to a racemic conglomerate at certain temperatures.[3,9]

Materials and Methods

Materials—The names, acronyms, and sources of the chiral compounds used in this study are listed in Table 1. Some of these compounds were prepared by the methods described in the next paragraph. Others were purchased from chemical suppliers, with reported purity exceeding 99%, and were used as received.

Crystallization—(+)-Norephedrinium salicylate, (+)-NE·S, was obtained by dissolving equimolar quantities of (+)-norephedrine and salicylic acid in anhydrous ether followed by complete drying to yield a solid mass. The purity of (+)-NE·S was verified by a single sharp exotherm in the DSC curve and also by a single thermal event in the derivative of heat flow versus temperature. (+)-Pseudoephedrinium salicylate, (+)-PE·S, was prepared by crystallization.[10,11]

The racemic species of NE, E, PE, NE·S, PE·S, and ME, listed in Table 1, were prepared by dissolving equimolar quantities of the two enantiomers in methanol or ethanol and allowing the solvent to evaporate completely at room temperature (22.5 °C).

Differential Scanning Calorimetry (DSC)—Measurement of melting point and enthalpy of fusion of the crystalline chiral compounds was performed using a Du Pont 910 differential scanning calorimeter equipped with a data station (Thermal

Table 2—Physical Properties of Homochiral and Racemic Species

no.[a]	code name[a]	T^f(R)[b] (°C)	T^f(A)[b] (°C)	ΔT^f (°C)	ΔH^f(R)[b] (kcal/mol)	ΔH^f(A)[b] (kcal/mol)	$\Delta\Delta H^f$ (kcal/mol)	$\Delta\Delta S^{fc}$ (cal/mol·K)
1	NE	101.1	51.2	49.8	6.241	3.792	2.449	4.99
2	NE·Cl	195.9	172.8	23.1	6.924	4.839	2.085	3.91
3	NE·S	117.3	101.4	15.9	7.120	5.559	1.561	3.39
4	PE	117.9	119.2	–1.3	8.149	7.636	0.513	1.38
5	PE·Cl	166.0	182.9	–16.9	6.738	6.680	0.058	0.70
6	PE·S	108.2	131.2	–23.0	7.769	8.752	–0.983	–1.27
7	E	77.5	39.7	37.8	6.953	4.141	2.812	6.59
8	E·Cl	190.8	219.1	–28.3	8.348	7.577	0.771	2.60
9	E·NS	170.4	170.6	–0.2	9.203	7.878	1.325	3.00
10	ME	62.8	88.01	–25.2	6.358	7.304	–0.946	–1.30
11	IB	77.7	54.0	23.7	6.142	4.278	1.864	4.43
12	MA	120.6	131.5	–10.9	6.398	6.147	0.251	1.06
13	PN·Cl	163.4	194.6	–31.2	9.322	8.605	0.717	2.96
14	PN	92.3	71.5	20.8	10.385	8.665	1.720	3.28
15	AN	150.2	147.2	–3.0	8.523	8.789	–0.266	–0.48
16	APN	58.0	25.3	32.7	8.512	5.684	2.828	6.66
17	t-SB	131.7	150.4	–18.7	8.22	8.29	–0.07	0.73
18	c-SB	105.7	109.7	–4.0	6.18	5.54	0.64	1.84
19	BT	87.4	75.1	12.3	10.97	10.33	0.64	0.76
20	BT·Cl	134.5	154.8	–20.3	9.68	11.03	–1.35	–2.03
21	PD	169.7	92.5	77.2	13.84	6.14	7.70	14.46
22	IA	153.8	165.6	–11.8	6.62	6.21	0.41	1.35
23	SP	177.8	186.3	–8.5	11.03	10.04	0.98	2.59
24	DZ	234.2	194.4	39.8	10.75	9.04	1.71	1.85
25	HPL	121.6	156.6	–35.0	6.39	6.81	–0.42	0.34

[a] Numbers are given to identify the entries; code names are the acronyms explained in Table 1. [b] R and A denote the racemic species and its enantiomers, respectively. For entries 1–10, thermal analysis was carried out in this work, the standard deviation being less than 2.5%. [c] Entropy of fusion was obtained as $\Delta H^f/T^f$ of the corresponding homochiral or racemic species, but only the differences, $\Delta\Delta S^f$, are given.

Analyst 2000, TA instruments, New Castle, DE). The temperature axis and the cell constant were calibrated with indium (~3 mg, 99.99%, peak maximum at 156.6 °C and heat of fusion 28.4 J/g). Samples of 3.5 ± 0.5 mg in crimped aluminum pans were heated at a rate of 10 °C/min, and the peak melting temperature was recorded. All samples were measured in triplicate, and the standard deviations were less than ± 2.5%. Any small variations in the enthalpy of fusion as a result of differences in crystallinity of the homochiral and racemic species were expected to be negligible. The errors in determining the enthalpy of fusion when followed by possible decomposition were practically canceled out in the calculations, because small deviations in the baseline after melting occurred in the melt state for both the pure enantiomers and the racemic species.

Powder X-ray Diffraction (PXD) Pattern—Experimental PXD patterns of the compounds, both racemic and homochiral crystals, were determined at room temperature using a powder diffractometer (Model D-500, Siemens, Germany) with Cu Kα radiation at 30 mA, 45 kV. The sample was packed into an aluminum holder and scanned with the diffraction angle 2θ increasing from 2 to 30°, with a step size of 0.02°/min and counting time of 1 s per step.

^{13}C Solid-State Nuclear Magnetic Resonance (SSNMR) Spectroscopy—^{13}C SSNMR spectra were acquired at 75.743 MHz using a Chemagnetics CMX-300 spectrometer (Fort Collins, CO) and a Chemagnetics Pencil probe equipped with a 7.5 mm magic-angle spinning system using zirconia rotors. All spectra were acquired with cross polarization, magic-angle spinning, and high power ^{1}H decoupling. Spinning speeds were typically 5−6 kHz. Between 1024 and 2048 transients were acquired with a repetition delay of 3 s, contact time of 5 ms, and pulse width of 4 ms. No apodization was applied to the free induction decay prior to the Fourier transform.

Results and Discussion

Thermal Properties and Thermodynamic Calculations—To compare the thermodynamic properties of the enantiomers and their racemic species, the melting temperatures and enthalpy of fusion of the 25 chiral compounds are compiled in Table 2. The difference in melting temperature, ΔT^f, enthalpy of fusion, $\Delta\Delta H^f$, and entropy of fusion, $\Delta\Delta S^f$, of the two species are also given in Table 2 and are illustrated in Figure 4. Entry numbers, instead of compound names, are used for unbiased analysis and

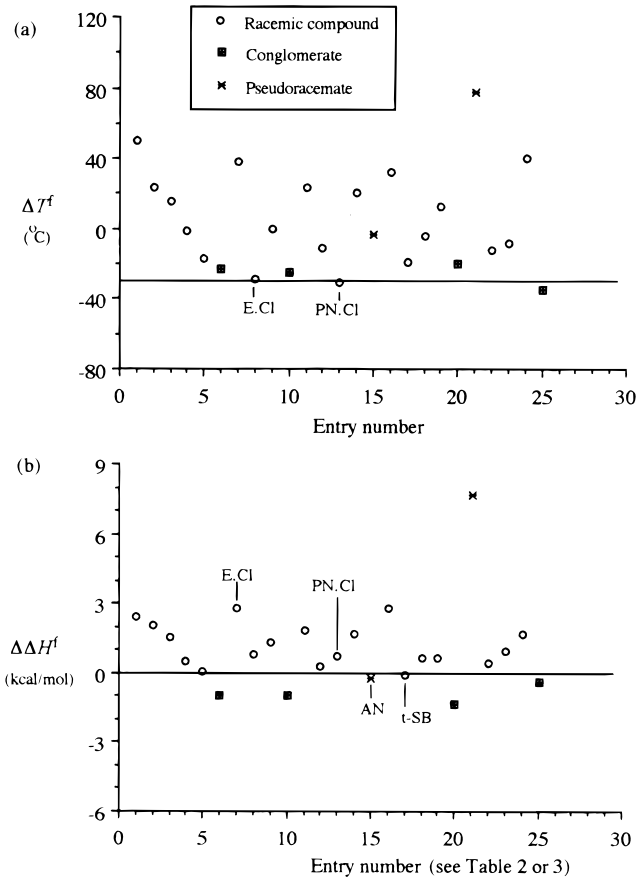

Figure 4—Differences between homochiral and racemic species in (a) the melting points, ΔT^f, and (b) the enthalpies of fusion, $\Delta\Delta H^f$.

Table 3—Comparison of the Experimental Thermal Properties and the Calculated Thermodynamic Properties of Racemic Species

		thermal properties			thermodynamic properties			
no.[a]	code name[a]	ΔT^f (°C)	$\Delta\Delta H^f$ (kcal/mol)	$\Delta\Delta S^f$ (cal/mol·K)	$\Delta H^{\circ b}$ (kcal/mol)	$\Delta S^{\circ b}$ (cal/mol·K)	$\Delta G^{\circ c}$ (kcal/mol)	ΔS^{md} (cal/mol·K)
1	NE	49.8	2.449	4.99	–1.453	–3.61	–1.278	–2.039
2	NE·Cl	23.1	2.085	3.91	–1.623	–2.53	–0.955	–0.648
3	NE·S	15.9	1.561	3.39	–1.244	–2.02	–0.805	–0.688
4	PE	–1.3	0.513	1.38	–0.539	0.00	–0.513	0.067
5	PE·Cl	–16.9	0.058	0.70	–0.396	0.68	–0.357	0.566
6	PE·S	–23.0	–0.983	–1.27	0.523	2.65	***–0.027***	***1.231***
7	E	37.8	2.812	6.59	–2.057	–5.22	–1.180	–1.895
8	E·Cl	–28.3	0.771	2.60	–1.336	–1.22	–0.204	0.986
9	E·NS	–0.2	1.325	3.00	–1.329	–1.62	–0.607	0.008
10	ME	–25.2	–0.946	–1.30	0.442	2.68	***0.048***	***1.418***
11	IB	23.7	1.864	4.43	–1.390	–3.05	–0.865	–1.074
12	MA	–10.9	0.251	1.06	–0.469	0.32	–0.376	0.429
13	PN·Cl	–31.2	0.717	2.96	–1.341	–1.58	***–0.027***	***1.370***
14	PN	20.8	1.720	3.28	–1.304	–1.90	–1.066	–1.572
15	AN	–3.0	–0.266	–0.48	0.206	1.86	–0.516	0.146
16	APN	32.7	2.828	6.66	–2.174	–5.28	–1.252	–2.337
17	t-SB	–18.7	–0.07	0.73	–0.304	0.65	–0.191	0.900
18	c-SB	–4.0	0.64	1.84	–0.720	–0.46	–0.464	0.161
19	BT	12.3	0.64	0.76	–0.394	0.61	–0.854	–1.044
20	BT·Cl	–20.3	–1.35	–2.03	0.944	3.41	***–0.038***	***1.205***
21	PD	77.2	7.70	14.46	–6.156	–13.08	–2.917	–4.653
22	IA	–11.8	0.41	1.35	–0.646	0.030	–0.421	0.404
23	SP	–8.5	0.98	2.59	–1.152	–1.21	–0.435	0.432
24	DZ	39.8	1.71	1.85	–0.913	–0.47	–1.487	–1.657
25	HPL	–35.0	–0.42	0.34	–0.281	1.03	***0.011***	***1.361***

[a] Numbers are given to identify the entries; code names are the acronyms explained in Table 1. [b] Enthalpy and entropy of formation were calculated according to eqs 4 and 5, respectively. [c] ΔG° was calculated by eq 6; those values that are approximately zero are shown in bold italics. [d] Entropy of mixing in the liquid state was calculated by eq 1, those values that are close to the ideal value are shown in bold italics.

convenience. The errors in the values of ΔH^f and T^f from literature references in Table 1 are less than 5%, if reported.

If ΔT^f approaches −30 K, the racemic species is likely to be a racemic conglomerate, such as PE·S, ME, BT·Cl and HPL, identified as the filled squares in Figure 4a. This generalization is not conclusive for (±)-PN·Cl and (±)-E·Cl, which are racemic compounds. The nature of these racemic species was determined by a comparison of the experimental PXD pattern with the PXD pattern calculated from the crystal structures, as derived from single-crystal X-ray analysis.[19a] Positive values of $\Delta\Delta H^f$, i.e., $\Delta H^f_R > \Delta H^f_A$, are found for all the racemic compounds, including (±)-PN·Cl and (±)-E·Cl, reflecting their preferential formation (Figure 4b). The racemic compound of t-SB is an exception to this trend; the very small negative value of $\Delta\Delta H^f$ (−0.07 kcal·mol^{-1}) may lie within experimental error.[13] For those racemic species that are identified as racemic conglomerates, e.g. PE·S, ME, BT·Cl, and HPL, their $\Delta\Delta H^f$ values are negative.

Two chiral compounds in this study do not belong to the above series. Pindolol, (PD entry 21) forms a pseudoracemate with a maximum melting point (Figure 1d(2)), and shows exceptionally large values of ΔT^f = 77.2 K and of $\Delta\Delta H^f$ = 7.7 kcal·mol^{-1}.[8] Atenolol (AN entry 15), whose racemic species was not identified, has a negative value of $\Delta\Delta H^f$, similar to those of racemic conglomerates, but has a small value of $-\Delta T^f$ (3.0 K), too small for a stable racemic conglomerate.[12] The formation of a pseudoracemate is suggested for (±)-AN.

Large differences in the melting points (ΔT^f approaching −30 K) between the homochiral and racemic species have been observed for all the racemic conglomerates examined and for a few of the racemic compounds. Therefore, the melting point phase diagram is not an adequate single criterion for identifying the nature of the racemic species. A positive value of $\Delta\Delta H^f$ may be a more reliable indicator of the formation of a racemic compound, which evidently is the enthalpically favorable species. This finding is consistent with the conclusion from lattice energy calculations that the racemic compound has a greater stabilization energy than the individual enantiomers.[19a,b]

Thermodynamic Properties of Racemic Species—The thermodynamic quantities for the formation of the racemic compound and the entropy of mixing of the enantiomers in the liquid state for racemic conglomerates were derived from the equations shown previously. Assuming that the nature of the racemic species is unknown, the thermodynamic calculations were carried out for all 25 chiral compounds in Table 3 to reveal any trends in the calculated values for different racemic species.

Table 3 presents the calculated thermodynamic values, ΔH°, ΔS°, ΔG°, and ΔS^m_l. The ΔH° and ΔS° values were calculated using eqs 4 and 5 assuming an average heat capacity difference of 20 cal·mol^{-1}·K^{-1} for ($C^l - C^s$) in each case.[20] The ΔG° values were obtained using eq 6, in which the heat capacity terms are neglected because they practically cancel in the free energy of formation as explained in the preceding section. The entropy of mixing in the liquid state, ΔS^m_l, was calculated by eq 1.

Comparison of the data in Table 3 reveals that ΔG° and ΔS^m_l show interesting trends between different racemic species, but the trends in the enthalpy of formation and the entropy of formation between racemic species are difficult to interpret.

Free Energy Formation, ΔG°—The calculated ΔG° values are shown in Figure 5. The free energy of formation for racemic compounds, ΔG°, is negative for 23 of the 25 entries, because, as expected, the majority of the racemic species are racemic compounds. However, not every negative ΔG° indicates a racemic compound.

In Figure 5, the five ΔG° values within the range of −0.05 to 0.05 kcal·mol^{-1} correspond to the four compounds (entries 6, 11, 20,[21] 25 in Table 3) which are identified as racemic conglomerates; the fifth is the racemic compound

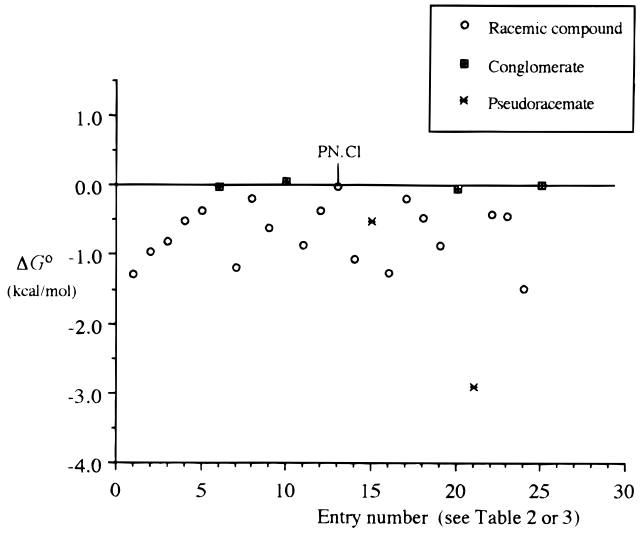

Figure 5—The free energy of formation, $\Delta G°$, of the racemic compound.

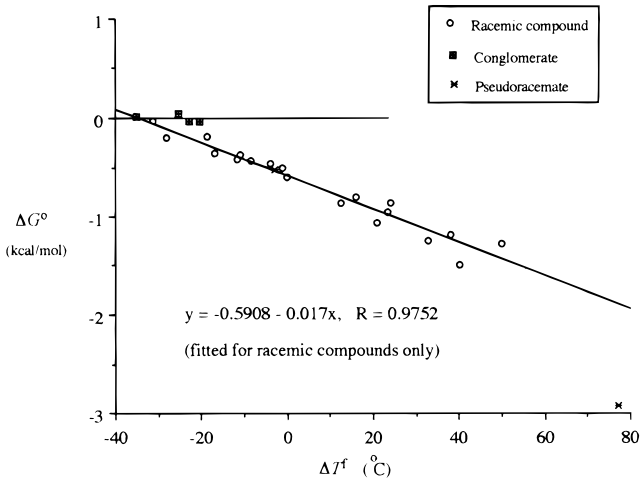

Figure 6—A plot of free energy of formation of racemic compounds, $\Delta G°$, as a function of the difference in melting temperatures, ΔT^f.

of PN·Cl (entry 13 in Table 3). Although PN·Cl forms a racemic compound, its thermodynamic properties are similar to those of racemic conglomerates. The fact that its $\Delta G°$ value is close to zero (-0.027 kcal·mol^{-1}) indicates lack of driving force for the formation of the racemic compound, (±)-PN·Cl. Such a small value may be within experimental error. In such a case, it is proposed that the formation of the racemic compound may be reversed under controlled conditions. Thus, to achieve resolution of this type of racemate by crystallization, the kinetic factors may be very important to offset the possible formation of the racemic compound.

Combining eqs 6a and 6b, a general expression for $\Delta G°$ as a function of the difference in melting points, ΔT^f, can be derived:

$$\Delta G°_{T^f} = -\Delta S^f \Delta T^f - T^f R \ln 2, \text{ where } \Delta T = T^f_R - T^f_A \quad (8)$$

ΔS^f and T^f are the mean entropy of fusion and the mean melting temperature, respectively, of the racemic compounds in the series studied. Figure 6 demonstrates a significant linear correlation for the 19 racemic compounds used in this study. In Figure 6, the negative free energy of formation (reflecting the stability) of a racemic compound is proportional to the difference in the melting temperatures between the racemic compound and its enantiomers.

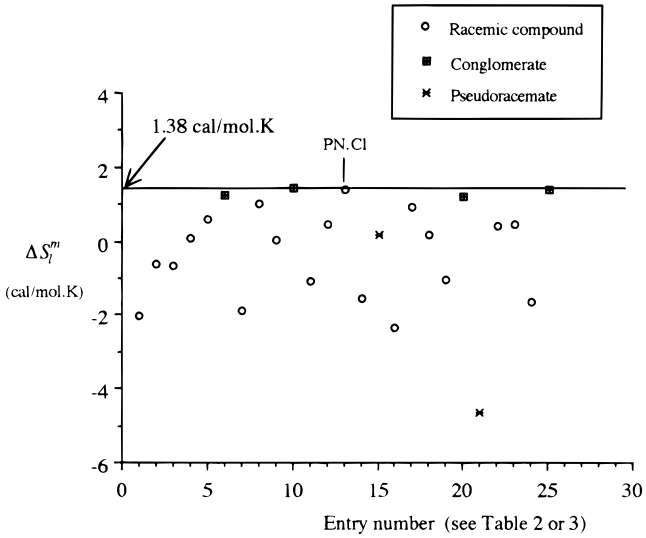

Figure 7—The entropy of mixing in the liquid state, ΔS^m_l.

This apparent linearity was observed previously for a number of organic racemic compounds.[3,5,22] According to eq 8, the slope of the regression line can be identified as the mean entropy of fusion, $\langle \Delta S^f \rangle = 17.04$ cal·mol^{-1}·K^{-1}. Similarly, the intercept represents the contribution of the ideal entropy of mixing, $\Delta S^m_l = 1.38$ cal·mol^{-1}·K^{-1}, at the average melting temperature of $\langle T^f \rangle = 427$ K (154 °C).

In eq 8, as ΔT^f approaches -30 K, the $\Delta G°$ values become close to zero. The entropy of mixing term, the second term on the right, is always negative and contributes to stabilize the racemic compound over its enantiomers. When the pure enantiomer and the racemic compound have the same melting temperature, $\Delta T^f = 0$, the racemic compound is stabilized by a $\Delta G°$ value of -0.59 kcal·mol^{-1}. This result suggests that the entropy of ideal mixing in the liquid state is the driving force for the formation of racemic compounds.

The calculated $\Delta G°$ values for all the racemic conglomerates (PE·S, ME, BT·Cl, and HPL) are approximately zero, which may serve as an indicator for identifying racemic conglomerates. However, the $\Delta G°$ value may be close to zero for racemic compounds, such as (±)-PN·Cl. To identify the nature of the racemic species which show $\Delta T^f \sim -30$ K, further characterization by X-ray diffraction and/or spectroscopic methods is necessary.

Entropy of Mixing in the Liquid State, ΔS^m_l—Values of the entropy of mixing in the liquid state, calculated by eq 1 are given in Table 3 and are shown in Figure 7. The average value of ΔS^m_l for the racemic conglomerates (PE·S, ME, BT·Cl, and HPL) is 1.30 ± 0.10 cal·mol^{-1}·K^{-1}, close to the ideal entropy of mixing of liquid enantiomers ($R \ln 2 = 1.38$ cal·mol^{-1}·K^{-1}). The small deviations of the entropy of mixing of the liquid enantiomers from the ideal value for racemic conglomerates may be related to deviation of these systems from the assumption that the corresponding enthalpy of mixing has the ideal value of zero. For racemic species which are not racemic conglomerates, with the exception of (±)-PN·Cl, their ΔS^m_l values (<1.0 cal·mol^{-1}·K^{-1}) deviate significantly from, and are smaller than, the ideal value. In other words, the assumptions made for racemic conglomerates are invalid for racemic compounds.

Pseudoracemates, i.e., Racemic Solid Solutions—A single, macroscopically homogeneous, crystalline phase may occasionally be formed by mixtures of the two enantiomers in any proportion, i.e., a racemic solid solution, termed a pseudoracemate. This miscibility in the solid state may be demonstrated by the melting point phase diagrams

shown in Figure 1d. Three types of solid solution are observed: (1) ideal, (2) nonideal with a maximum melting, and (3) nonideal with a minimum melting temperature. The few available crystallographic data show that the lattice parameters of a solid solution are very similar to that of the enantiomers, though not identical. In addition, each type of solid solution may be related to a given structural type, namely disordered for type 1, short range ordered for type 3, and nonstatistical inverse symmetry for type 2.[3]

The melting point phase diagram with no eutectic melting shows that the chiral compound pindolol, PD (entry 21 in Tables 2 and 3), forms a type 2 solid solution.[8] The calculated thermodynamic quantities of this pseudoracemate have unusually large negative values in comparison with the other compounds in this study. These unusual values are indicative of the unique properties of the racemic species. In the structure of this type of solid solution, one enantiomer can substitute for the other at one site only, forming a real (nonstatistical) inverse symmetry element.[3] The structure of this pseudoracemate may be similar to that of the racemic compound. The maximum difference in melting temperature of the pseudoracemate of PD, $\Delta T^f = 77.2$ K in Table 1, suggests more favorable interactions between the paired enantiomers in the racemic solid than in the single enantiomers.

The racemic species of atenolol, AN (entry 15 in Tables 2 and 3), was found to be a quasi-ideal solid solution ($\Delta T^f = -3$ K, not zero). Its negative $\Delta\Delta H^f$ (-0.266 kcal·mol^{-1}) seems to follow the trend of racemic conglomerates, but ΔT^f is small and $\Delta G°$ is negative, suggesting a nonconglomerate phase. The DSC trace of mixtures containing unequal amounts of the two enantiomers of AN showed no eutectic melting, which supports the predication from thermodynamic calculations that the racemic species of AN is a racemic solid solution. Unlike PD, AN with small ΔT^f corresponds to a quasi-ideal solid solution of type 1. The structure of a type 1 solid solution is almost identical to that of the pure enantiomer with the two enantiomers randomly occupying the lattice sites. Such a structural feature implies negligible differences in the intermolecular interactions between molecules with the same or opposite handedness in the solid state, i.e., lack of chiral recognition in the solid state.

Characterization of Racemic Species by Powder X-ray Diffractometry and ^{13}C Solid-State Nuclear Magnetic Resonance Spectroscopy—Powder X-ray diffractometry (PXD) and ^{13}C solid-state nuclear magnetic resonance (SSNMR) spectroscopy are two complementary techniques for the structural characterization of powder samples.[23,24] PXD patterns reveal differences of long range order in the packing of the crystal lattice. SSNMR spectra, on the other hand, can probe the short range order of the molecular environments in the solid and can effectively differentiate dynamic or static disorders.[25] The information from ^{13}C chemical shifts can be particularly useful for identifying conformational changes and structural differences, especially when they are difficult to recognize from the PXD patterns.

A number of racemic species in this study were investigated using both PXD patterns and ^{13}C SSNMR spectra. The PXD patterns of the enantiomers and of their racemic species for all the available compounds were first determined and compared. The two opposite enantiomers have identical PXD patterns because their crystal structures are identical, apart from their handedness which confers mirror symmetry. On the other hand, a racemic compound has a PXD pattern different from that of the two enantiomers. A close match of the 2θ values of the peaks in the PXD patterns of the enantiomers and of their racemic species indicates the same crystal structure, suggesting that the racemic species is a racemic conglomerate. Differences in in relative intensity of the PXD patterns may arise from differences in crystallinity and/or preferred orientation. A pseudoracemate displays a PXD pattern closely resembling that of the enantiomers but with some peak broadening. In this work, the findings from the PXD patterns were further confirmed by the ^{13}C SSNMR spectra.

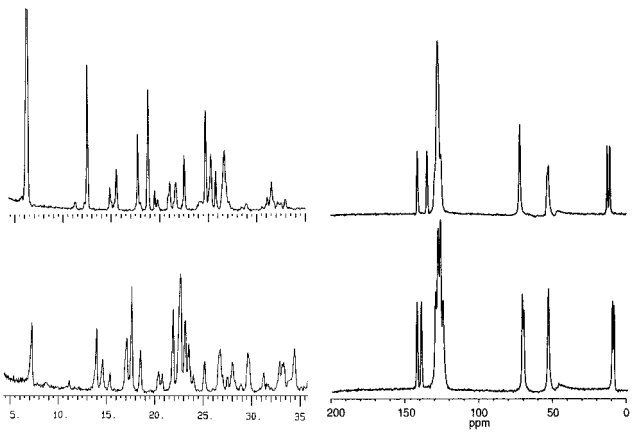

Figure 8—Powder X-ray diffraction patterns (left) and ^{13}C solid-state nuclear magnetic resonance spectra (right) of the racemic compound (upper traces) and of the (–)-enantiomer (lower traces) of norephedrine hydrochloride (NE·Cl).

The PXD patterns and SSNMR spectra of the enantiomers and of their racemic species, for the three possible racemic species: racemic compound, racemic conglomerate, and pseudoracemate, are illustrated in Figures 8, 9, and 10, respectively.

Figure 8 refers to a racemic compound, norephedrine hydrochloride, (±)-NE·Cl (entry 2 in Tables 2 and 3). The PXD pattern of the enantiomer is significantly different from that of the racemic compound. Likewise, the ^{13}C chemical shifts for the enantiomer and the racemic compound are markedly different. For both the homochiral and racemic crystals, the asymmetric unit contains two molecules with different conformations[19a] which are crystallographically nonequivalent.[26] Each carbon in the molecule should theoretically have two chemical shifts, one for each conformation. However, the chemical shifts for two conformations may or may not differ substantially to give distinct peaks. In this case the two peaks are distinguishable for both the aliphatic carbons and the substituted aromatic carbons.

An example of a racemic conglomerate, methylephedrine (ME entry 10), is given in Figure 9. Most of the peak positions in the PXD patterns show a good match between (−)-ME and (±)-ME. Difference in peak intensity may be ascribed to preferred orientation of the thin plates (−)-ME. The ^{13}C chemical shifts in the SSNMR spectra of the homochiral and racemic species agree well, except for the two *N*-methyl carbons. Crystallographically, the two *N*-methyl carbons are nonequivalent in the unit cell, so two peaks are expected. The two *N*-methyl carbons of the racemic species show two peaks. In (−)-ME, the two *N*-methyl carbon signals coalesce into one broad peak. The relatively broad peaks of the *N*-methyl carbons indicate mobility of the methyl groups. In conjunction with X-ray data, NMR results suggest that (±)-ME is a racemic conglomerate, although the nature of the small difference for the *N*-methyl carbons is unclear.

The PXD pattern of atenolol (AN entry 15) in Figure 10 also demonstrates no substantial differences between the enantiomers and the racemic species; only minor differ-

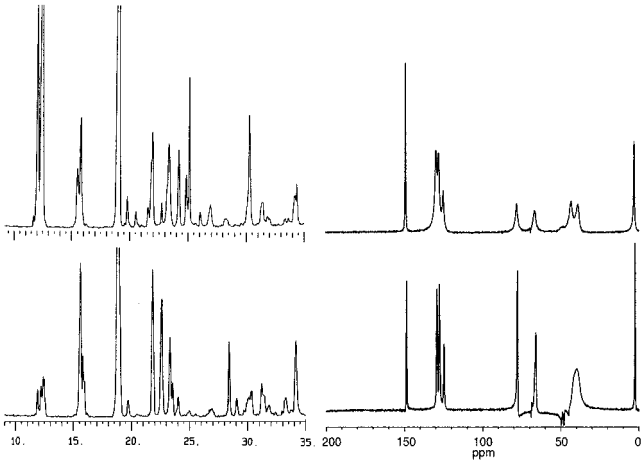

Figure 9—Powder X-ray diffraction patterns (left) and ^{13}C solid-state nuclear magnetic resonance spectra (right) of the racemic conglomerate (upper traces) and of the (–)-enantiomer (lower traces) of methylephedrine (ME).

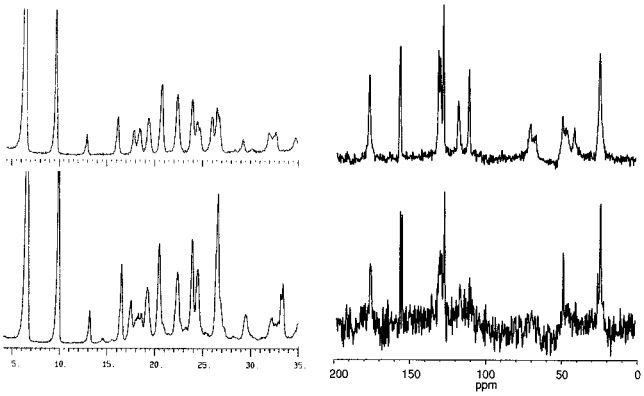

Figure 10—Powder X-ray diffraction patterns (left) and ^{13}C solid-state nuclear magnetic resonance spectra (right) of the pseudoracemate (upper traces) and of the (–)-enantiomer (lower traces) of atenolol (AN).

ences are noted at 17.5° and 33.3° 2θ. Most of the ^{13}C chemical shifts of the enantiomer and racemic species match well, but a few peaks in (−)-AN are difficult to detect above the noise in the spectrum. The reasonably good agreement between the two PXD patterns and between the two SSNMR spectra for racemic and enantiomeric AN suggests that these two forms have very similar crystal structures. The minor differences observed are attributed to decreased crystallinity of the single enantiomer, (−)-AN. Moreover, both the DSC analyses and the thermodynamic calculations indicate that the racemic species of AN is a pseudoracemate, confirming the deduction made above.

In summary, the structural identification of the chiral compounds studied has, in all cases, confirmed the nature of the racemic species suggested by the thermodynamic calculations. However, for differentiation between a racemic conglomerate and a pseudoracemate, PXD and SSNMR may not be adequate. Identification of the pseudoracemate is then shown by the absence of eutectic melting in DSC.

Phase Diagrams and Thermodynamic Aspects—Among the 25 chiral pharmaceutical compounds included in this study as a subset of chiral compounds, 19 racemic species are racemic compounds, corresponding to a 76% frequency. The lower frequency of racemic compounds among these 25 chiral drugs, as compared with 90% among chiral organic compounds in general, is partly explained by the sample collection, of which seven are salts. Nevertheless, this lower frequency of racemic compounds may reflect their occurrence among chiral pharmaceuticals because many drugs are formulated as salt forms.

Several compilations of racemic and enantiomeric pairs of organic chiral compounds have been published.[3,5,22,27] In many respects, the results of the thermodynamic calculations in this study with 25 chiral pharmaceutical compounds are in general agreement with those reported previously for a much larger set of other organic compounds.[3]

The free energy calculations show that the entropy of mixing is the driving force for the formation of racemic compounds. This interpretation can be given from a different point of view in terms of phase separation. Considering crystallization of a racemic conglomerate from a racemic liquid, separation of the two enantiomers as homochiral crystals is not entropically favorable. In some cases, this entropic cost for the phase separation may be merely compensated by the slightly lower enthalpy of the pure crystalline enantiomer as compared with the racemic compound, resulting in an approximately zero value of $\Delta G°$, indicating approximately equal stability of the racemic compound and racemic conglomerate. Hence, crystallization of conglomerates is unlikely to be thermodynamically favored in most cases, but may be controlled by the kinetics of the solid−liquid interface as well as by nucleation and crystal growth.

Emphasis has been placed on those systems whose racemic species are ambiguous in nature, particularly racemic conglomerates or racemic compounds for which $\Delta T^f \approx -30$ K. The reason for this emphasis is that this type of system is particularly important in the resolution of racemates by crystallization. In theory, such systems exist as a thermodynamic equilibrium between the racemic conglomerate and the racemic compound. It may be possible to vary the temperature and kinetic factors to steer the crystallization in the desired direction, so as to facilitate the separation of enantiomers by crystallization. For example, the small difference in the stability of the racemic compound and enantiomeric crystals in the racemic conglomerate may give rise to a significant difference in their solubilities at certain temperatures, which may be utilized for preferential crystallization.[3,9]

It is known that conversion of a free acid or base into a salt increases the likelihood of a racemic conglomerate.[3] In the present study, all the hydrochloride salts in Table 2 show substantially smaller values of ΔT^f values than their free bases or acids. The thermodynamic calculations show that the negative free energy change, $\Delta G°$, approaches zero as $T_R^f - T_A^f$ approaches −30 K. This result provides the thermodynamic basis for the greater frequency of racemic conglomerates among the salts than among the free acids or bases, corresponding to a significant reduction of the difference in melting point between the racemic and homochiral species.

The use of salts to facilitate the resolution of racemates has been attempted.[9] Conglomerates, resolvable by preferential crystallization, were sought by Coquerel and coworkers[28] among various salts of fenfluramine, whose *R* enantiomer is an anorectic agent, and among norfenfluramine, its precursor. Numerous salts of these bases with achiral acids were tested, and several were found to form conglomerates, resolvable by preferential crystallization. Another proposed method for increasing the occurrence of racemic conglomerates is the use of a pressure-induced transition of a racemic compound to a conglomerate.[5] Both methods rely on a significant reduction of the difference in melting point between the racemic compound and its enantiomers. Therefore, a rational procedure for the resolution of racemates by crystallization requires, first, the conversion of the chiral drug into a suitable salt with $T_R^f - T_A^f$ approaching −30 K, and second, a search for the optimal crystallization conditions to facilitate separation

of the two enantiomers by thermodynamic and kinetic factors, such as solubility differences at various temperatures or nucleation, which may be probed by seeding with homochiral crystals.

Conclusions

The free energy of formation of a racemic compound from its pure enantiomers is always negative, indicating that the racemic compound, if it exists, is the thermodynamically favored racemic species. For a racemic conglomerate the entropy of mixing of the two enantiomers in the liquid state is close to the ideal value of R ln 2 (1.38 cal·mol^{-1}·K^{-1}). In comparison to racemic compounds and racemic conglomerates, unusual thermodynamic behavior was observed for racemic solid solutions. Furthermore, thermodynamic calculations reveal that the contribution of the nonideal entropy of mixing to the free energy of formation is the driving force for the formation of racemic compounds. The results show that the combination of thermal analysis with thermodynamic calculations provides a powerful tool to identify the three racemic species: racemic compound, racemic conglomerate, and racemic solid solution. A dynamic equilibrium exists between the racemic compound and the racemic conglomerate when the difference in the melting points between the racemic and homochiral species, ΔT^{f}, approaches −30 K and ΔG°_{Tf} becomes approximately zero. Structural studies using powder X-ray diffraction patterns and solid-state NMR are valuable for distinguishing between a racemic compound and either a racemic conglomerate or a pseudoracemate. Thermal analysis can be used to differentiate between a pseudoracemate and the other two types of racemic species. A preliminary report of this work has been presented as a poster at the 1996 Annual Meeting of the American Association of Pharmaceutical Scientists.[29]

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4. A homochiral crystal is composed of a single enantiomer, whereas a heterochiral crystal contains both opposite enantiomers in the crystal lattice. A racemic conglomerate is an equimolar physical mixture of homochiral crystals of both enantiomers, while a racemic compound and a pseudoracemate are heterochiral crystals. In a racemic compound, the two opposite enantiomers are paired up in the unit cell of the crystal lattice, whereas in a pseudoracemate the opposite enantiomers are arranged more or less randomly as a solid solution.
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