fluxed for 3 h.[46] The dark solution was washed with saturated bicarbonate and water, the organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure to leave a dark oil. This oil was chromatographed on silica gel with a mixture of chloroform and hexane. The fractions that showed spots with rf between 0.2 and 0.5 in 100% chloroform on analytical TLC (silica) were combined, the solvent was removed, and the resulting solid was purified by preparatory TLC (silica gel) in $CHCl_3$. A faint blue band at about rf 0.35 was collected and found to be the product. ^1H NMR ($CDCl_3$) δ 7.78 (d, 4 H), 7.59 (m and s, 10 H), 7.43 (m, 12 H), 7.32 (s, 6 H), 7.10 (m, 20 H), 6.93 (t, 8 H) (aromatic hydrogens), 5.77 (s, 6 H, H(10)), 2.05 (s, 6 H, CH_3 in the achiral isomer), 2.01 (s, 12 H, CH_3 in the DL isomer), 1.55 (s, 6 H, CH_3 in the achiral isomer), 1.34 (s, 12 H, CH_3 in the DL isomer). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ 162.63, 160.91 (cyclopropenone carbons), 144.66, 142.35, 142.15, 141.85, 141.79, 138.84, 138.60, 133.37, 132.69, 132.31, 125.58, 125.00, 124.76, 124.67, 124.56, 123.36, 122.48, 122.36, 122.30 (C_{ar}), 58.36 (C(9)), 53.12 (C(10)), 18.79, 18.32, 18.18 (CH_3); mass spectrum (high resolution), m/z 614.2616 (614.2610 calcd for $C_{47}H_{34}O$).

X-ray Crystallography. Crystals of **1** were grown from 1-butanol/ethyl acetate by slow evaporation. A truncated trigonal prism of approximately 0.30 × 0.38 × 0.33 mm was chosen for X-ray measurements. The crystals are trigonal, space group $R3c$ (No. 161), with $a = b = 13.090$ (3) Å, $c = 43.577$ (13) Å, $V = 6466$ (3) Å^3, and $d_{calcd} = 1.34$ g cm^{-1} for $Z = 6$ ($C_{60}H_{39}GeCl$, $M = 868.0$). Intensity data were measured at 237 K on a Nicolet R3m diffractometer with $3° < 2\theta < 50°$ ($-h + k + l = 3n$; $k, l \geq 0$) with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Of 2584 unique reflections 2027 were considered to be observed [$|F_o| > 3\sigma(F_o)$] after applying Lorentz and polarization corrections. The structure was solved in $R3c$ with SHELXTL software. The germanium and chlorine atoms were located in a Patterson map, and the carbon atoms were subsequently located in electron density difference maps. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were located at standard positions (C–H = 0.96 Å; C–C–H = 120° or 109.5°) and refined isotropically with a riding model. Refinement with 186 least-squares parameters converged at $R = 0.037$ and $R_w = 0.032$.

Crystals of **2** perchlorate were obtained from an acetonitrile solution by slow evaporation. A hexagonal prism of approximately 0.30 × 0.20 × 0.25 mm was chosen for the X-ray measurements. The crystals are hexagonal, space group $P6_3/m$ (No. 176), with $a = b = 15.145$ (5) Å, $c = 13.617$ (4) Å, $V = 2704$ (1) Å^3, and $d_{calcd} = 1.10$ g cm^{-1} for $Z = 2$ ($C_{36}H_{39}ClO_4$, $M = 895.5$). Intensity data were measured at room temperature on a Nicolet R3m diffractometer with $3° < 2\theta < 114°$ with graphite monochromated Cu Kα radiation ($\lambda = 1.54178$ Å). Of 1281 unique reflections, 1148 were considered to be observed [$|F_o| > 3\sigma(F_o)$] after applying Lorentz and polarization corrections. Three additional reflections (001, 020, and 040) were omitted because $F_o \ll F_{calcd}$ for these reflections, presumably due to extinction. The structure was solved in $P6_3$ with the SHELXTL direct methods software and was refined in $P6_3/m$. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included at standard positions (C–H = 0.96 Å; C–C–H = 120° or 109.5°) and refined isotropically with use of a riding model. Refinement with 130 least-squares parameters converged at $R = 0.057$ and $R_w = 0.065$. The unit cell contains one independent molecule with crystallographic C_{3h} site symmetry. The perchlorate anion is disordered and no satisfactory scheme was found to model this disorder by a superposition of tetrahedral perchlorate anions with standard bond lengths and angles. This disorder would also mask the molecule of water that is indicated by the elemental analysis.

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Registry No. 1, 119480-90-9; **1** (isomer 1), 125829-99-4; **1** (isomer 2), 125830-00-4; **2**, 119503-08-1; **2**·H_2O, 125830-04-8; **3** (achiral isomer), 125830-03-7; **3** (DL isomer), 125876-02-0; **4** (achiral isomer), 125829-97-2; **4** (DL isomer), 125876-00-8; $GeCl_4$, 10038-98-9; Tp_3SnBr, 125829-98-3; 9-bromotriptycene, 15364-55-3; bis(9-triptycyl)cyclopropenone, 119480-91-0; bis(9-anthryl)cyclopropenone, 78594-10-2; propylene oxide, 75-56-9; 9-bromo-2,3-dimethyltriptycene, 125830-01-5; 4,5-dimethylanthranilic acid, 15089-51-7; 4,5-dimethylbenzenediazonium-2-carboxylate hydrochloride, 39654-49-4; 9-bromoanthracene, 1564-64-3; benzenediazonium-2-carboxylate hydrochloride, 4661-46-5.

Supplementary Material Available: Tables of bond lengths and bond angles with standard deviations, anisotropic thermal parameters, and hydrogen atom coordinates with isotropic thermal parameters for **1** and **2** perchlorate (5 pages); tables of observed and calculated structure factors for **1** and **2** perchlorate (14 pages). Ordering information is given on any current masthead page.

Chiral Molecular Recognition in the Thermodynamics of Spreading and Transition for Racemic and Enantiomeric Stearoyltyrosine Films

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Abstract: Equilibrium spreading thermodynamics, surface pressure vs area isotherms, and surface shear viscosities were measured for ionized monolayer films of the title compounds on an aqueous buffer subphase at pH 6.86. When allowed to equilibrate with their bulk crystalline phases (equilibrium spreading pressures), the racemic and enantiomeric films spread to significantly different surface pressures and displayed clearly defined transitions in their equilibrium spreading pressure vs temperature-phase diagrams at 30.3 and 26.3 °C, respectively. A thermodynamic analysis of the results demonstrates large differences between the racemic and enantiomeric films in terms of their changes in entropy and internal energy as they undergo the transition. In sharp contrast, racemic and enantiomeric films, spread from solution in the absence of the bulk phase, demonstrate only scant differences in their packing arrangements as reflected by surface pressure vs area isotherms taken in the same temperature range. Surface shear viscosities indicate that both spread films may be characterized as fluid. Taken together with previous results, these data indicate that short-range forces govern enantiomeric discrimination in fluid monolayer films and that the mechanism of detectable chiral molecular recognition between enantiomers lies in the transition to a tightly packed, crystalline surface state.

It is well-known that stereoselective interactions between enantiomeric pairs form a special subset of molecular recognition that is based entirely on molecular symmetry properties.[1] There is apparently no general pattern governing the preference of a given molecule for heterochiral (R,S) or homochiral (R,R or S,S) interactions. Extremely short-range forces (r^{-6}–r^{-12}) differentiate the interactions between enantiomers, so that one might reasonably expect the greatest degree of stereorecognition to occur in very tightly packed, condensed states. This implies that any difference

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in the properties of their mixtures should be highly dependent on the phase (i.e., solid, liquid, or gaseous) of the mixed system.

Enantiomers are considered to be perfect physical and chemical models for each other since all of their properties are identical except those that involve their interaction with other chiral systems. Therefore, mirror images which obey the laws of the physical world are said to conserve parity.[2] However, this parity is ultimately a result of intermolecular interactions based on symmetry relationships. So-called weak interactions (such as β-decay) have been shown to violate parity.[3] Using ab initio calculations, Tranter has shown that the naturally occurring L-α-amino acids can have an enantiomeric excess of 10^6 molecules per mole for a "racemic" mixture in thermodynamic equilibrium.[3c] This uneven distribution of enantiomers is based on parity-violating energy differences and has been offered as a possible explanation for the predominance of the L-α-amino acid in biological systems where the interactions between chiral species (e.g., substrates and receptors) are responsible for communication of biological information.

Differences in the intermolecular interactions of like and unlike pairs are well-known in the solid state and are reflected, for example, by the differences in their densities, melting points, heats of fusion,[4] heats of sublimation,[5] and heats of solution and are the mechanism for some of the classical techniques for resolving racemic mixtures.[6] The differences between the physical properties of solid, pure enantiomers and those of their mixtures at clearly defined conditions of temperature, pressure, and enantiomeric excess are evidenced perhaps most clearly in their phase diagrams.[1,4]

In the liquid phase the forces of discrimination *between* homochiral and heterochiral interactions are much weaker than in the solid phase by as much as a factor of 1000.[7] Nevertheless, there have been reports suggesting that barely measurable differences between like and unlike pairs may exist *in solution*.[8] For example, the excess molar volumes obtained upon the mixing of both enantiomers of liquid limonene, fenchone, and α-methylbenzylamine suggest that heterochiral packing is more favorable in mixtures of enantiomers than the homochiral packing of the pure antipodes.[9] On the other hand, the excess molar enthalpies of mixing obtained for fenchone and for α-methylbenzylamine indicate that heterochiral associations are stronger for the former whereas homochiral associations are stronger for the latter.[10] We have demonstrated strong stereodifferentiation of solutions of chiral hydrogen-bonded ion pairs in nonpolar solvents.[11]

The above differences in liquid-state packing between like and unlike pairs may be small or even undetectable by current methods, but the necessity from the rules of symmetry that such differences must exist implies that stereochemistry is relevant to the study of association in systems which are looser than solids. The ultimate proof of this assertion is the high degree of stereoselectivity in the attack of enzymes on chiral substrates. It also follows that wherever chiral discrimination is due to the pairwise packing of adjacent chiral centers, stronger selectivity should be expected in highly oriented systems. Monolayers of amphiphilic surfactants

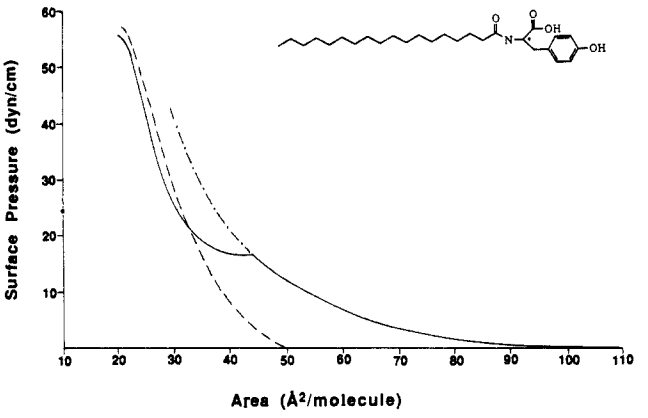

Figure 1. Surface pressure vs area isotherms for the compression cycle of D,L-stearoyltyrosine (---) and L-stearoyltyrosine (—) on a 0.01 N HCl subphase at 22 °C and D,L-Stearoyltyrosine on distilled water (-·-·-).

that are confined to a surface where intermolecular separation, and hence aggregation, may be controlled directly constitute such a system.[12]

Previous studies have indicated that stereochemically dependent phase transformations in monolayer systems rest not only on system variables such as temperature and surface pressure but may be enhanced by the possibility of specific molecular interactions such as hydrogen bonding, π–π interactions,[13] and Coulombic attractions[14] in much the same manner as regular three-dimensional systems. However, the differences in the surface behavior of spread films of the enantiomers and their mixtures must ultimately depend solely on their asymmetry.[1]

We have demonstrated repeatedly that chiral molecular recognition is detected readily in monolayers cast from pure enantiomers and their mixtures and in combinations of diastereomeric surfactants and that such recognition is dependent upon the phase of the monolayer system.[15] Although we have shown that recognition between the *diastereomers* of a series of two-chain keto dicarboxylic acids may be evidenced clearly in their excess free energies of mixing in fluid monolayer phases,[16] we have not been able to detect significant chiral molecular recognition between *enantiomers* and their mixtures in any fluid, monolayer phase. Indeed, stereorecognition between enantiomeric amphiphiles and their racemic mixtures at the air–water interface as reported by ourselves and others[17] for several systems occurs predominantly under conditions of high surface pressure and/or low temperature where tightly packed, condensed film systems are favored.

It appears that in all the above studies, the force–area isotherms and other film properties of the pure enantiomers and their mixtures start to differ at surface pressures exceeding their equilibrium spreading pressures (ESPs), i.e., the surface pressure of the film in equilibrium with its crystals.[18] Thus, the ESP is

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a thermodynamic limit above which monolayers must sooner or later revert to a crystalline state as the lowest energy bulk phase.[19] It is therefore reasonable to suggest that the differences observed between the surface properties of films cast from like and unlike pairs are due to the differences in the energetics of transition to tightly packed, quasicrystalline surface states. Indeed, recent theoretical treatments have suggested that detectable chiral molecular recognition between enantiomers in solution, as well as in monolayers, is most likely to occur in the transition from solvated species to highly ordered crystalline phases.[20] It is therefore reasonable to assume that molecular recognition between enantiomers in monolayers will most likely be observed in the energies of transition from one loosely aggregated surface phase to one of higher order.

Despite the implications of the surface phase dependent nature of enantiomeric discrimination in monolayers spread from homogeneous solutions, there has never been a systematic attempt to quantify the difference in the energetics of the spreading process from a bulk crystalline state to the more loosely aggregated monolayer state for highly purified enantiomers and their racemates. Accordingly, we report here a series of experiments performed with (*R*)- and (*S*)-*N*-stearoyltyrosine, which demonstrates surface-phase dependent stereorecognition in its thin film properties. *N*-Stearoyltyrosine was chosen for this analysis because it has demonstrated considerable chiral recognition as evidenced by differences in the shapes of surface pressure vs area isotherms of racemic and optically active films when spread from homogeneous solution onto acidic subphases (Figure 1)[17a] and also because it forms stable spread monolayers over a wide range of temperatures under proper conditions of subphase pH in which the stereochemical dependence of the film properties is lost.

The degree of detectable chiral recognition between the antipodes of *N*-stearoyltyrosine in its bulk crystalline and fluid monolayer states on an aqueous subphase will be approached here by comparison of (1) the surface pressure vs area isotherms and surface shear viscosities of monolayers as spread from homogeneous solution in the 15–35 °C temperature range, (2) the ESP vs temperature phase diagram in the same temperature range, and (3) differential scanning calorimetry of the dry and hydrated crystals of both enantiomers and the racemate. The goal of these experiments is to clarify further the necessary packing conditions, and hence phase dependence, of enantiomeric discrimination in monolayer films, and to demonstrate the onset of chiral molecular recognition during the transition from a fluid-like, disordered state to a more highly ordered surface bulk phase. These experiments also demonstrate, as have previously established data,[17a] the dependence of enantiomeric discrimination on the degree of chiral headgroup ionization in the film.

Experimental Section

All instruments and subphase water used in these experiments were purified and cleaned by the proven methods described in previous reports.[15b]

Surfactant Preparation and Purification. The enantiomeric *N*-stearoyltyrosine methyl esters were synthesized by the coupling of the tyrosine methyl ester and stearoyl chloride as described previously for *N*-stearoylserine methyl ester.[15d] The *N*-stearoyltyrosines were prepared by hydrolyzing *N*-stearoyltyrosine methyl esters[21] with sodium hydroxide in aqueous dioxane. The racemate, recrystallized several times from a distilled acetone/methanol mixture, melted at 127–128.5 °C (uncorrected). The optically active material was purified through slow recrystallizations from acetone and gave a melting point of 138–139.8 °C. Structures of the *N*-stearoyltyrosines were confirmed by ^{13}C and ^{1}H NMR and IR spectroscopy.

Differential Scanning Calorimetry. The thermal-phase transition temperatures and enthalpies were determined with a Du Pont Instruments 1090 thermal analyzer by testing 5–7-mg samples sealed in copper/aluminum DSC pans. These were equilibrated thermally against an air blank at a scan rate of 10 °C/min. Thermograms were obtained in the 18–150 °C range at least four times for both the pure antipode and the racemic mixture.

Preparation of Buffered Subphase Solution. The water used to prepare the subphase solution was purified extensively as described previously.[15b] A potassium phosphate/disodium phosphate buffer (Fisher, certified) was recrystallized from 3:1 ethanol/acetone, dissolved in the highly purified water, cooled to 15 °C, and filtered through fluted paper (Whatman #1) before use. Identical results were obtained with the buffer salt which had been filtered but not recrystallized.

Preparation of Spreading Solution. Spreading solutions for the monolayers of *N*-stearoyltyrosine were prepared by weighing out the racemic and enantiomeric crystals on a Cahn RG electrobalance and dissolving into a 9:1 benzene/methanol solution. Benzene (Mallinckrodt, thiophene-free reagent grade) was distilled twice from P_2O_5 after refluxing for 12 h. Methanol (Mallinckrodt, HPLC grade) was distilled once from $Mg(OCH_3)_2$. The resulting *N*-stearoyltyrosine solution was diluted to 25 mL in hand-calibrated flasks and stored in a benzene atmosphere at 25 °C.

The suitability of the benzene/methanol mixture as a spreading solvent was determined by aliquoting a drop of the solvent (surfactant-free) on the surface of the buffered subphase and measuring the decrease in surface pressure as a function of time with Langmuir film balances equipped with Wilhelmy plate and torsion head detector systems at 25 °C. The surface pressure generated immediately after deposition of the solvent decayed rapidly and then exponentially for 3–4 min. After 8 min, the surface pressure had returned to its original value of zero. The surface area to which the benzene/methanol solution had been deposited was reduced by sweeping the surface with the moving barrier of the film balance, and no surface pressure was produced.

The compression/expansion Π/A isotherm experiments entailed delivering enough spreading solution to the subphase surface to deposit 4×10^{16} molecules to a surface area of 1×10^{19} Å^2. The spreading solvent was allowed to dissipate for 15–30 min at each temperature in the 15–35 °C range. The spreading of the monolayers for surface shear viscosity measurements was performed in the same manner.

Langmuir Film Balance and Surface Shear Viscometer Techniques. The technical specifications, cleaning, and calibration of our Langmuir film balance and surface shear viscometer have been described elsewhere.[15b]

The rate of compression and expansion for all *N*-stearoyltyrosine monolayers was varied from 7.7 to 19.2 Å^2 molecule^{-1} min^{-1} during initial runs at 16 °C. The Π/A isotherms from each compression/expansion rate were identical within ±2.0 Å^2/molecule. Little or no compression/expansion hysteresis was observed for the films in this rate regime (see for example Figure 1). All isotherms reported here were compressed at 19.2 Å^2 molecule^{-1} min^{-1}.

The stability of the spread films was checked at each temperature by the stepwise compression technique. The film was judged stable if the surface pressure decayed no more than 0.1 dyn cm^{-1} min^{-1}. The integrity of the film balance calibration was confirmed after experiments at each temperature with the standard stearic acid isotherm.[22]

The surface shear viscosities of racemic and enantiomeric *N*-stearoyltyrosine were determined at surface pressures of 2.5 and 5.0 dyn/cm at viscometer slit widths of 1.4 and 2 mm in order to determine if their flow was Newtonian (shear viscosity independent of rate of shear). Each reported viscosity run consisted of 5–10 repetitions at each surface pressure and temperature. The duration of each flow determination was 5–10 min. The surface temperature was kept constant to within ±1 °C by means of a serpentine glass circulating coil (placed in the aqueous subphase) connected to a circulating bath. The entire viscometer setup is housed in a temperature-controlled cabinet as described previously.[23]

Equilibrium Spreading Pressures (ESPs). The ESPs of the racemic and enantiomeric forms of *N*-stearoyltyrosine were determined by the Du Noüy and Wilhelmy plate methods. A constant temperature circular T-cup (surface area = 50 cm^2) connected to a constant-temperature circulating bath capable of maintaining temperatures to within ±0.3 °C in the 18–40 °C range was used in the Du Noüy platinum ring (Cenco,

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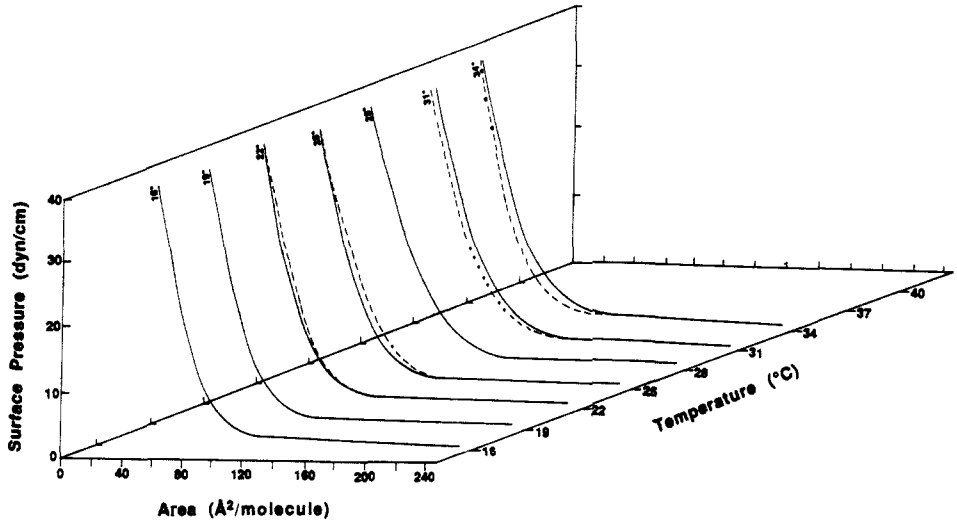

Figure 2. Surface pressure vs area isotherms for the compression cycles of stearoyltyrosine on a buffered pH 6.86 subphase carried out at a compression rate of 19.24 Å^2 molecule^{-1} min^{-1} at 16, 19, 22, 25, 28, 31, and 34 °C.

6.005-cm diameter) experiments. The temperature of the subphase was measured before and after each surface tension measurement with an NBS thermometer. After the surface tension of the film-free buffered subphase had been determined, crystals of the surfactant were deposited carefully on the surface of the buffered subphase, the system was allowed to come to equilibrium for 12–24 h, and the surface tension of the system was determined. Identical experiments were performed after 48 and 72 h of equilibration time in order to insure that equilibrium spreading had been attained. In general, both the racemic and optically active systems reached their ESPs within 24–36 h.

The Wilhelmy plate method entailed the use of a 1-cm-wide plate (Whatman filter paper #1) for monitoring the generation of surface pressure over time. The detector plate was hung from an electrobalance and immersed in the aqueous phase and was allowed to saturate for 1 h before depositing a surfactant crystal on the subphase surface. A Cahn RG electrobalance connected to a Linseis LY-1800 X-Y recorder operating in the "time" mode was used to detect changes in surface pressure. The system was judged to be in equilibrium when the surface pressure changed no more than 0.1 dyn cm^{-1} h^{-1}. In general, the results from both techniques agreed within ±0.3 dyn/cm. The temperature of the surface system was kept to within ±0.2 °C by placing the entire apparatus in a Rheem Puffer-Hubbard temperature control cabinet, and the surface temperature was measured throughout the experiment by means of a thermistor situated at the air/water interface.

As a check on the reversibility of the spreading process, the surface area of the film system was reduced, and the crystals and film were allowed to equilibrate for up to 48 h, or until a constant value of surface pressure was obtained.

For both the Du Noüy ring and Wilhelmy plate methods, surface thermistor measurements indicated that, in the studied temperature range, the temperature difference between the surface and the subphase was well within the experimental error of $d\Pi_e/dT$.

Results

Π/A Isotherms of Spread Monolayers. The compression/expansion Π/A isotherms of racemic and optically active *N*-stearoyltyrosine monolayers in the 16–34 °C temperature range on pH 6.86 buffered subphase are given in Figure 2. As demonstrated by these isotherms, there is apparently very little or no stereoselectivity in the packing order of these films as they are compressed and reexpanded. At temperatures of 22 and 25 °C the racemic films appear to be slightly more expanded than their optically active counterparts, while at 31 and 34 °C the films cast from pure enantiomers are slightly more expanded. It should be noted that the differences in the isotherms at a given surface pressure in either case are no more than 10 Å^2/molecule at the greatest.

At every surface temperature, both the racemic and enantiomeric systems are very highly expanded at low surface pressures, having lift-off areas greater than 300 Å^2/molecule ($\Pi \cong 0.5$ dyn/cm at 240 Å^2/molecule). Compression of these films results in a gradual rise in surface pressure until they reach an average molecular area of less than 120 Å^2/molecule, at which point the isothermal compressibility of these films is significantly lower. The monolayer stability limits as determined by stepwise compression (Table I) indicate that both films are stable to considerable surface pressures, with the racemic films being stable to higher surface pressures than the optically active systems at temperatures greater than 22 °C.

Table I. Monolayer Stability Limits for Spread Films of *N*-Stearoyltyrosine on pH 6.86 Aqueous Buffered Subphase[a] in the 16–34 °C Temperature Range

	stability limit (dyn/cm)	
T (°C)	(*R*,S)-(±)	(*R*)-(+)
16	~8	~10
19	~9	~10
22	~10	~12
25	~15	~13
28	~15	~10
31	~15	~10
34	~15	~10

[a] Subphase buffered with potassium phosphate/disodium phosphate.

Table II. Surface Shear Viscosities of Racemic and Enantiomeric Films of *N*-Stearoyltyrosine on pH 6.86 Buffered Aqueous Subphase at Π = 2.5 and 5.0 dyn/cm Surface Pressure in Millsurface Poise

	η (Π = 2.5 dyn/cm)		η (Π = 5.0 dyn/cm)	
T (°C)	(*R*,*S*)-(±)	(*R*)-(+)	(*R*,*S*)-(±)	(*R*)-(+)
20	0.63 ± 0.05	0.61 ± 0.06	0.71 ± 0.09	0.68 ± 0.04
25	0.66 ± 0.06	0.64 ± 0.04	0.62 ± 0.04	0.61 ± 0.05
35	0.59 ± 0.06	0.53 ± 0.03	0.66 ± 0.06	0.58 ± 0.04

Surface Shear Viscosity. Surface shear viscosities of racemic and optically active *N*-stearoyltyrosine films on pH 6.86 subphase at 20, 25, and 35 °C are given in Table II. At the studied surface pressures of 2.5 and 5.0 dyn/cm, both racemic and enantiomeric films flow as Newtonian liquids, independent of stereochemistry. Within this 15 °C temperature range, the surface shear viscosities are nearly constant (within experimental error). On pure water subphases at 25 °C and pH 5.55, neither the racemic nor enantiomeric films spread from solution are fluid. Indeed, both films flow only as condensed solids, with $\eta > 20$ millisurface poise and experimental error exceeding 50%.

Equilibrium Spreading Pressures. The ESPs of (*R*,*S*)-(±) and optically active *N*-stearoyltyrosine were first approached at 25 °C on purified H_2O (pH ~ 5.20). No surface pressure could be detected even with equilibration times extending to 72 h. Reduction of the surface area after these long equilibration times gave no increase in surface pressure. Thus, the ESPs on pure water at 25 °C are too low to be detected by our methods or require excessively long equilibration times.

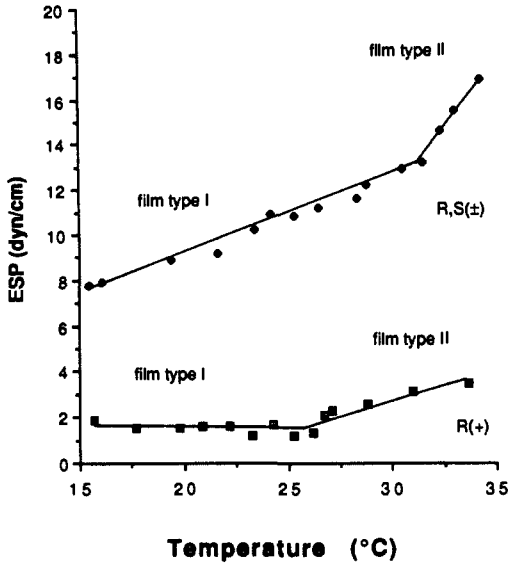

Figure 3. Equilibrium spreading pressures of (*R,S*)-(±)- and (*R*)-(+)-stearoyltyrosine on an aqueous subphase of pH = 6.86 (potassium phosphate/disodium phosphate buffer) as a function of temperature. Film type II is the film at temperatures above the transition and film type I is the film at temperatures below the transition.

The ESPs of racemic and enantiomeric *N*-stearoyltyrosine in the 15–35 °C temperature range at pH 6.86 are given graphically in Figure 3. At each temperature the racemic system spreads to higher surface pressures than the optically active system. The Wilhelmy plate experiments indicated that spreading from the homochiral crystals was a gradual process, leading up to a final ESP. The racemic system began spreading within 1–5 min after contact with the subphase, and large surface pressures were obtained within an hour at every temperature. However, this high pressure decreased gradually with time until the surface pressure remained constant within our defined stability limits (±0.1 dyn/cm).

When placed in contact with the buffered subphase at temperatures below 27 °C, the enantiomeric crystals underwent immediate swelling and, in some instances, sank completely into the aqueous subphase. Additional crystals of the corresponding enantiomer were placed at the interface when this occurred. At temperatures above 27 °C, the enantiomeric crystals underwent swelling and remained at the interface during the entire equilibration. In contrast, the racemate crystals underwent significant swelling only at temperatures above 28 °C.

Small reductions of the surface area of the Wilhelmy plate trough (about 1/6 of the total film-covered area) after the crystal/film systems had reached equilibrium resulted in an immediate increase in surface pressure. Over the course of 3–10 h, however, the surface pressure gradually decayed (at every temperature) to within ~1 dyn/cm of the originally obtained ESP. At higher temperatures (above about 25 °C), both racemic and enantiomeric systems reequilibrated within 24 h.

The difference in temperature dependence between the racemate and enantiomers and the change in the slopes of $d\Pi_e/dT$ in both $\Pi_e - T$ curves were analyzed by the least-squares method. The intersection of the two lines for each isomer gives the temperature and pressure of transition (Table III), which differ by about 4 °C and 11 dyn/cm, respectively. However, the ESP is determined by the properties of both the lipid bulk phase and the surface monolayer phase so that a change in $d\Pi_e/dT$ might just as well be the result of a transition in the bulk crystal, a transition in the monolayer, or from a combination of the two. An independent method is needed to distinguish between these possibilities.

Differential Scanning Calorimetry. In order to establish whether the bulk phase undergoes a transition in the above temperature range, DSC measurements were performed with crystals which had been exposed to buffer solutions under conditions identical to those for the ESP measurements, and with dry crystals (Table IV). No bulk phase transitions were detected at the temperatures where the discontinuities in $d\Pi_e/dT$ were observed, and no difference in the heats of transition were noticed between crystals that had been exposed to subphase and those that had not.

Table III. Equilibrium Spreading Pressures $\Pi_e(T_t)$ at the Transition Temperatures, Average Molecular Areas at $\Pi_e(T_t)$ for Film Types I and II, and the Temperature Coefficient of the Equilibrium Spreading Pressure for Film Types I and II for Monolayers of *N*-Stearoyltyrosine in Equilibrium with their Crystals on an Aqueous Subphase of pH = 6.86

	T_t (°C)	$\Pi_e(T_t)$		A_e	$d\Pi_e/dT$ (dyn K^{-1} cm^{-1})
(*R*)-(+), (*S*)-(−)	30.3 ± 1.0	13.1 ± 0.3	$T < T_t$	74.0 ± 2.5	0.360
			$T > T_t$	79.5 ± 2.5	1.104
(*R*)-(+)	26.3 ± 1.0	1.5 ± 0.4	$T < T_t$	105.0 ± 5.0	−0.044
			$T > T_t$	112.0 ± 7.0	0.246

Table IV. Enthalpy, Entropy, and Temperature of Fusion for Racemic and Enantiomeric *N*-Stearoyltyrosine

	T_f (°C)	ΔH_f (kcal/mol)	ΔS_f (cal K^{-1} mol^{-1})
(*R*)-(+),(*S*)-(−)	66.8, 126.0	3.4 ± 0.1, 9.7 ± 0.2	10.0 ± 0.3, 24.3 ± 0.5
(*R*)-(+) or (*S*)-(−)	136.8	19.6 ± 0.2	47.8 ± 0.5

Discussion

Comparison of Spread Film Isotherms and Surface Shear Viscosities. The shapes of the Π/A curves of the racemic and optically active forms of *N*-stearoyltyrosine on pH 6.86 subphase as shown in Figure 2 differ dramatically from those obtained by Zeelen (Figure 1) on 0.01 N HCl subphase (pH = 2).[17a] At the lower pH, it is clearly evident that the films cast from single enantiomers are more highly expanded than those of their racemic mixture. When the racemic film was spread on pure distilled water (pH ~5.2), the monolayer became more expanded, especially at higher surface pressures. This result suggests that the expression of stereoselective packing in the spread films as exhibited by differences in the degree of film expansion is dependent on subphase pH.

If one considers the ionizable nature of the headgroup, it is not surprising that films of *N*-stearoyltyrosine should be more highly expanded as the basicity of the subphase is increased. Such effects have been well documented for simple fatty acids.[24] It is significant that the expression of chiral recognition is severely decreased or even lost once the tyrosine headgroups are ionized (Figure 2). The high degree of expansion of both the racemic and enantiomeric ionized films at low surface pressures most likely reflects Coulombic repulsions between headgroups of like charge. As the films are compressed, chain–chain interactions are presumably enhanced[25] and the chiral centers of the headgroups are forced closer together. However, even under conditions of low film compressibility (Π > 10 dyn/cm) there is very little difference between the Π/A isotherms of the racemic and optically active films.

We have demonstrated recently that temperature dependent hydrogen-bonding forces between the headgroups of *N*-stearoylserine methyl ester may serve as a driving force for stereoselective interactions in monolayers,[15d] especially under conditions of high surface pressure and short intermolecular distance. In the case of the nonionized films of *N*-stearoyltyrosine, it is plausible that such hydrogen-bonding effects are present and may enhance the close approach and stereoselective packing of chiral centers. Upon ionization, however, the close approach and subsequent stereochemically dependent aggregation of ionized species

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Table V. Helmholtz Free Energy, Entropy, and Internal Energy of Spreading and of Transition for *N*-Stearoyltyrosine on an Aqueous Subphase of pH = 6.86 at the Transition Temperature for Each Film

	ΔF (kcal/mol)		ΔS (cal K^{-1} mol^{-1})		ΔU (kcal/mol)	
	(*R*)-(+),(*S*)-(−)	(*R*)-(+)	(*R*)-(+),(*S*)-(−)	(*R*)-(+)	(*R*)-(+),(*S*)-(−)	(*R*)-(+)
bulk → film I[a]	−1.40 ± 0.07	−0.22 ± 0.04	38 ± 6	0	10.10 ± 1.80	−0.23 ± 0.04
bulk → film II[b]	−1.50 ± 0.07	−0.24 ± 0.05	126 ± 7	40 ± 6	36.71 ± 2.20	11.93 ± 1.80
film I → film II	0.10 ± 0.09	0.02 ± 0.01	88 ± 9	40 ± 6	26.62 ± 2.80	12.10 ± 1.80

[a] Film I: $T < T_t$. [b] Film II: $T > T_t$.

is greatly diminished due to increased charge repulsions and/or steric repulsions due to counterion binding effects.[26]

The above proposal is supported indirectly by our observation that ionized *N*-stearoyltyrosine monolayers flow as Newtonian liquids, while their nonionized films are apparently solid-like and flow in a non-Newtonian manner (Table II). The pH dependence of film flow properties is an indication that ionized films of *N*-stearoyltyrosine are in a state of greater disorder (e.g., packed more loosely) than those of the free acid. In addition, it should be noted that both the Π/A isotherms and surface shear viscosities (Table II) of the ionized films are nearly independent of temperature in the somewhat narrow 15 °C range, and that the monolayers are stable to ~10–15 dyn/cm. This result is indicative of the absence of the strong, temperature-dependent, intermolecular hydrogen-bonding forces present in films of *N*-stearoylserine methyl ester.[15d] However, as in this case, the stereoselective interaction between tyrosine headgroups, as reflected in spread film properties, is reduced nearly below our limit of detection when the monolayers are in a stable, clearly fluid phase.

Equilibrium Spreading Thermodynamics. The above spread film experiments demonstrate that fluid monolayers of ionized *N*-stearoyltyrosine have surface properties which are nearly independent of stereochemistry. However, the degree of stereorecognition exhibited in surface thermodynamic properties increases dramatically if the monolayer phase is allowed to come to equilibrium with its bulk solid phase. This point is demonstrated clearly in the Π_e vs temperature phase diagram of Figure 3. A comparison of the thermodynamics of spreading *from the bulk phase* of films composed of racemic pairs or homochiral species with the properties of their films spread from homogeneous solution *in the absence of the bulk phase* allows for a simple determination of whether detectable chiral molecular recognition occurs within the film itself, or arises as the result of a transition to a more closely packed, crystalline surface phase. Accordingly, we shall describe a thermodynamic analysis of the data shown in Figure 3 according to the treatment given by Eriksson.[27]

At equilibrium with an excess of the bulk crystalline phase, the standard Helmholtz free energy (F), entropy (S), and internal energy (U) of spreading of lipid film from the bulk phase to a given surface concentration are determined by a difference between the thermodynamic properties of the crystal and those of the film in equilibrium with the crystal (eq 1–3).[28] (Superscripts S and C refer to the surface and crystalline states and subscript e to the equilibrium spreading measurement.)

$$(F_e^{oS} - F^{oC}) = -\Pi_e A_e \quad (1)$$

$$(S_e^{oS} - S^{oC}) = A_e(d\Pi_e/dT) \quad (2)$$

$$(U_e^{oS} - U^{oC}) = -A_e(\Pi_e - T\, d\Pi_e/dT) \quad (3)$$

Evaluation of the thermodynamics requires a knowledge of the surface concentration of the film at equilibrium, i.e., the molecular area A_e. Traditionally, the molecular areas of films at a pressure corresponding to the ESP are read from Π/A isotherms of the film spread from solution. The legitimacy of this approach was questioned by Gershfeld, who demonstrated with radiotracers that the surface concentration of palmitic acid at pH = 2 as obtained from Π/A isotherms was higher than that obtained through spreading from the crystal.[29] From this it follows that for surfactant monolayers having a high activation barrier for dissolution, the surface concentration of spread films will be different from those films which are in ultimate thermodynamic equilibrium with their bulk phases (if indeed such has ever been observed).

The goal of the experiments presented here is to determine the differences in the energetics of spreading from two different crystalline states which differ only in their chirality. The optically active and racemic forms of the tyrosine surfactant have ESPs which differ by several dyn/cm at every temperature. Even if the error in A_e were on the order of that obtained by Gershfeld for palmitic acid (~10 Å²/molecule), the resulting differences between racemic and enantiomeric systems in terms of their free energies, entropies, and enthalpies of spreading would still be outside of the error inherent to the assumption.

Spreading from the Crystal. The free energies, entropies, and internal energies of film spreading for film types I and II at transition temperatures T_t are given in Table V. At temperatures above and below T_t it is clearly evident that both the racemic film types I and II form more spontaneously than their optically active counterparts by about 1.2 kcal/mol.

Comparison of the entropies of spreading indicates a net gain in entropy as the racemic film is spread, while the change in entropy upon spreading of the enantiomeric material is zero (within experimental error) for film type I. This is a direct consequence of the slightly negative slope of $d\Pi_e/dT$ for the optically active material in the 15–26 °C temperature range. This low slope may be a reflection of the hydration observed for the enantiomeric crystals. The hydration of crystals on the surface has been established in the equilibrium-pressure measurements of several long-chain alcohols and acids.[30] The hydration of monooctadecyl phosphate actually resulted in a negative entropy change upon spreading, suggesting that the loss of entropy by the system due to hydration of the molecules in the spread monolayer more than compensates for the normal entropy gain as molecules spread from the crystal.[31] Usually, the entropy of spreading from the bulk phase is positive.[32] Upon spreading to film types II, the racemic system again spread with a greater increase in entropy.

The internal energies (or enthalpies) of spreading for films of type I indicate that the spreading of the racemic system is endothermic, while that of the enantiomeric system is slightly exothermic at the transition temperatures T_t. This suggests that, at temperatures below T_t, spreading of the racemic film is driven entropically, while spreading of the optically active film is driven enthalpically. At temperatures above T_t, the spontaneous spreading of film types II is driven by a net gain in entropy, indicating that both the racemic and enantiomeric films are more disordered than their crystals.

The equilibrium free energies, entropies, and enthalpies of spreading calculated at the transition temperature T_t (or any other temperature) suggest that, when in equilibrium with the bulk phase, enantiomers of *N*-stearoyltyrosine in ionized films are capable of displaying detectable stereodifferentiation *at the point*

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of transition to the bulk phase. The ESP experiment may be likened to a surface sublimation which occurs at a critical temperature and pressure; when the proper conditions are met such as adequate hydration of the headgroup, the more disordered gaseous (monolayer) state undergoes an equilibrium transition to the more highly ordered, tightly packed solid state where short range forces predominate over molecular interactions and molecular symmetry can dictate the physical properties of the solid continuum. Similar analogies may be made with more common phase transition data such as melting points and heats of fusion of racemic and enantiomeric crystals (Table IV).

The above model of the reversible spreading process may have significant limitations in the case of ionized films in equilibrium with their nonionized crystals.[24c,33] It is conceivable that ionization of the headgroup by the subphase produces a driving force for film expansion from the solid phase which is opposed directly by the aggregation forces (such as hydrogen bonding, van der Waals interactions, etc.) between neutral tyrosine surfactant molecules. Indeed, the resolution of the antipodes of *N*-(α-methylbenzyl)-stearamide from their ionized racemic films by equilibration with nonionized crystals of the highly purified enantiomers on acidic subphases indicates that the principle of microscopic reversibility may apply in such cases.[15c] The reversibility of the spreading process as demonstrated by reattainment of the ESP after a reduction in the surface area of the crystal/film-covered interface in the case of the ionized stearamide films,[15b] as well as in the case of the present tyrosine surfactant, lends credence to the spreading model.

Although the surfactant must be equilibrated totally throughout both the surface phase and aqueous subphases, the ESP represents the surface state in which the molecules in the monolayer are in equilibrium with the bulk crystalline phase and may thus describe the intermolecular associations in the film as it undergoes transition to the bulk phase. If the equilibrium spreading pressures of the *N*-stearoyltyrosine ionized films represent the transition between film and bulk states, one might then reasonably assume that compression of monolayers spread from solution past the ESP would result in spontaneous collapse of the film back to the lower energy solid bulk phase. As has been discussed by Andelman,[20] the phase transition between these states could be described in terms of the surfactant chirality. This is clearly not the case with ionized monolayers of *N*-stearoyltyrosine. Inspection of Figure 2 shows that the Π/A isotherms are continuous throughout the compression/expansion regime and give no indication of a stereochemically dependent phase change. However, as has long been recognized,[34] films spread from solution may be metastable with respect to their bulk phases to surface pressures significantly above their ESPs. We have shown this to be the case with monolayers of other chiral surfactants[15] whose overcompression eventually leads to a divergence in the monolayer properties of the enantiomers and their racemate.

Equilibrium Transitions between Film Types I and II. An obvious point of interest in this work is the change in the slope of $d\Pi_e/dT$ at clearly defined temperatures and equilibrium spreading pressures for the racemic and optically active systems (Figure 3). Comparison of the transition temperatures obtained in the ESP experiment with those obtained for the crystals by DSC (Table IV) implies that *the surface-phase transition occurs within the film itself and is not a result of a change in crystalline phase.* Furthermore, the fact that both the hydrated and dry crystals gave the same calorimetry results indicates that the difference between dry and hydrated crystals in terms of their internal structure is small.

Under the major assumption of thermodynamic reversibility, these discontinuities indicate a first-order transition between two types of film which are in equilibrium with the crystals. At the transition temperature, T_t, the surface phase rule of Defay and Crisp[35] dictates that a three-way equilibrium must exist at the surface between film types I and II and the bulk crystal. The heats of transition from film I to film II may therefore be obtained by solving $U_{II}^s - U_I^s$ simultaneously, thus eliminating the internal energy of the solid in water at T_t:

$$U_{II}^s - U_I^s = \Pi_e(A_e^I - A_e^{II}) + T_t[A_e^{II}(d\Pi_e/dT)_{II} - A_e^I(d\Pi_e/dT)_I] \quad (4)$$

Similar transformations may be performed for entropy and free energy terms (Table V).

Comparison of the Helmholtz free energies of transition between film types indicates that, within the large expermental error, there is no net difference in the energy required for transition that can be attributed to stereochemistry. The small values of transition free energies for films spread from the crystal are complementary to our observation that the shapes and degrees of expansion of the spread monolayer isotherms are barely affected by changes in temperature (Figure 2). Although slight, reproducible differences between the isotherms of the fluid racemic and enantiomeric films are detected in the temperature range between the transition temperatures obtained in the ESP experiments, the differences in their Gibbs free energies of monolayer compression are less than 50 cal/mol. Furthermore, the isotherms are clearly free of discontinuities which would indicate a first-order phase transition within the monolayer or a collapse to a three-dimensional bulk state. The metastabilities of these monolayer films spread from solution, as reflected in the monolayer stability limits of Table I, may, therefore, be a result of high activation barriers for reversible collapse of the films.

In contrast, the equilibrium entropies and enthalpies of film transition are differentiated stereochemically, with the racemic system having the higher heat and entropy of transition. This of course is a direct result of the differences in the slopes $d\Pi_e/dT$ for film types I and II in equilibrium with their crystals. Although treatment of these data by equations such as 4 allows one to discount contributions of the bulk phase to the energetics of film transition, and hence may reflect indirectly stereoselective interactions in the monolayer phase, it must be remembered that the crystalline phases from which the films are spread have completely different internal energies that are differentiated by molecular asymmetry.[1] Any consideration of the derived entropies and enthalpies of film transition as proof of chiral recognition in the monolayer phase *must*, therefore, take into account the equilibrium between the films and the clearly different racemic and enantiomeric solids from which they were spread. The ESP may only be regarded as a description of the stereochemically dependent interactions within the monolayer between enantiomers in a reversible equilibrium which leads to the formation of the solid bulk phase.

Unfortunately, the thermodynamic analysis presented here does not allow for a description of the differences in film types I and II, either in terms of specific stereochemical interactions within the films as they undergo transition between film types, or of their physical properties when in equilibrium with their crystals. The thermodynamic properties of a monolayer are the result of van der Waals attractive forces between hydrocarbon chains, attractive or repulsive forces between polar groups, and interaction of the headgroup with the subphase. Not only do the equilibrium spreading pressure measurements fail to differentiate these forces, they do not even determine the surface energy itself. Since the ESPs are composite values reflecting both the properties of the films and the crystals, they cannot form a basis for speculation on monolayer behavior alone. Nevertheless, the thermodynamic properties of spreading for racemic and enantiomeric systems must reflect, totally or in part, the important differences in the internal energies of the crystals from which the films were spread, and hence define the conditions necessary for detectable stereoselective

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interaction between antipodes in the monolayer under conditions of equilibrium with the bulk phase.

Summary

This study highlights the importance of a tightly packed crystalline surface phase for the onset of detectable chiral molecular recognition between enantiomers in monolayer films. The Π/A isotherms and surface shear viscosities indicate that there are only scant differences between the ionized films *cast* from *solutions* of enantiomeric and racemic stearoyltyrosine. By comparison with previously established data of Zeelen,[17a] we interpret this as a reflection of repulsive coulombic interactions between ionized tyrosine headgroups which tend to fluidize the monolayer system. In direct contrast, the thermodynamic treatment of films in equilibrium with their *crystals* over a temperature range indicate that the presence of the bulk solid phase in the surface system allows for expression of enantiomeric discrimination at a transition point between the ionized monolayer and the bulk crystalline phase. Enantiomeric discrimination is also reflected in the thermodynamics of transition between film types which are in equilibrium with each other and the bulk phase. These experiments constitute, to our knowledge, the first *quantitative* description of the dependence of chiral molecular recognition on the surface phase of the surface film system of a chiral amphiphile as an ionized monolayer.

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Methyl Transfers. 14. Nucleophilic Catalysis of Nucleophilic Substitution

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Abstract: Nucleophiles X^- can catalyze the substitution $Nu^- + RY \rightarrow NuR + Y^-$ by adding the faster pathway $X^- + RY \rightarrow XR + Y^-$ followed by $Nu^- + XR \rightarrow RNu + X^-$. New examples include catalysis by I^- of the exchange of methyl between two dialkyl sulfides and the transfer of methyl from an arsonium salt to a phosphine. The individual reactions are separately studied, and some equilibrium information is presented. Iodide is ineffective in the transfer of methyl between two phosphines, which is not detected with or without iodide. The Marcus equation treatment of this catalysis is shown to require that the identity transfer of R between two X^- groups be far faster than that for transfer of R between two Nu^- groups. Nucleophiles other than I^- are discussed. The possibility that some "supernucleophiles" may have fast identity rates is discussed, and literature evidence that this is indeed the case is presented. Stereochemical studies using chiral methyl derivatives have shown that vitamin B_{12} does provide a nucleophilic catalysis to methyl transfer in living systems. Thus, the apparently superfluous participation of B_{12} in some biological methyl transfers is explained.

The S_N2 mechanism for reaction 1 is not always a fast process. The catalysis by electrophiles which make Y^- a better leaving group is well-established, and many protic nucleophiles can be rendered far more nucleophilic by loss of a proton to a base. In this paper the catalysis by X^- through the mechanism of (2) followed by (3) is discussed, and the reasons for the apparent rarity are presented.

$$Nu^- + RY \rightarrow NuR + Y^- \quad (1)$$

$$X^- + RY \rightarrow XR + Y^- \quad (2)$$

$$XR + Nu^- \rightarrow X^- + RNu \quad (3)$$

Implied by the notation is the fact that since each step occurs with inversion of configuration, the catalytic sequence must involve a net retention of configuration. This successive displacement mechanism is described by Hammett,[1] who notes that it constitutes an example of the failure of a rate–equilibrium correlation. Hammett's two examples are the hydrolysis of methyl bromide catalyzed by iodide ion and the ethanolysis of active α-phenylethyl toluenesulfonate, which has predominent retention of configuration only in the presence of high concentrations of chloride ion. Curiously, the first example is not catalytic because (contrary to Hammett's statement) the hydrolysis of iodomethane, which is indeed formed, is somewhat slower than that of bromomethane.[2] In the second, catalysis is not demonstrated, although we shall see that this stereochemical criterion is nevertheless valuable.

However, authentic examples do exist. The transfer of methyl between tertiary amines has been shown to be catalyzed by iodide ion, as has the attack of enolate ions on alkyl bromides.[3] The Finkelstein reactions of alkyl halides with halide ions in acetone give rate constants, corrected for degree of dissociation of the lithium salts,[4] as shown for reactions 4–6. Thus the path through

$$Cl^- + MeBr \rightarrow ClMe + Br^- \quad k_4 = 0.595 \quad (4)$$

$$I^- + MeBr \rightarrow IMe + Br^- \quad k_5 = 0.70 \quad (5)$$

$$IMe + Cl^- \rightarrow I^- + MeCl \quad k_6 = 4.70 \quad (6)$$

IMe is somewhat faster than the direct path of eq 4. I^- is thus a catalyst, and because iodides are more dissociated than chlorides, the practical effects are larger. In the present work we add to these examples and show, in terms of the Marcus equation treatment of these reactions,[5] the criteria for the existence of catalysis, and we point out directions to find new examples.

Results

Reaction 7 with R = octyl and R′ = decyl is slow at 120 °C, when the counterion is trifluoromethanesulfonate (OTf^-) or the

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