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Chiral Aggregation Phenomena. 1. Acid Dependent Chiral Recognition in a Monolayer

Sir:

We present here a preliminary report of surface tension measurements and force-area curves which demonstrate a clear acid dependence between molecular packing in enantiomeric and racemic *N*- α -methylbenzylstearamide (I) monolayers. The observation may be of importance to the study of biomembranes. To the best of our knowledge it is also unprecedented and is probably quite general.

Figure 1 shows that films of I spread on aqueous sulfuric acid solutions are surface active (by du Noüy tensiometer), commencing at ~ 1 N acid for racemic amide and 4.5 N acid for pure (*S*)-(-) or (*R*)-(+) enantiomers. Figure 2 shows the same type of acid-dependent discrimination as manifested through force-area curves at different acidities.^{1,2}

It is significant that chiral discrimination commences at rather large molecular areas ($85\text{--}90 \text{ \AA}^2/\text{molecule}$) where intermolecular packing is still quite loose. Figure 2 shows clearly that enantiomer-racemate discrimination becomes increasingly pronounced as the molecular area is reduced even though both films are monolayers and no sharp phase changes have occurred. The force required to pack racemic molecules is consistently higher, at a given molecular area, than is that for pure enantiomers. In harmony with this observation, Figure 1 shows that, at $60 \text{ \AA}^2/\text{molecule}$, the racemic monolayer is more easily expanded as a function of increasing acid than are the enantiomeric monolayers.

Biomembranes are very thin multilayers composed largely of chiral amphiphilic molecules. The significance of our observation to membrane study comprises the following. (a) Chiral recognition probably can occur in multilayers even at molecular separations which are considerably larger than those encountered in lipid crystals. (b) Chiral recognition for oriented biological systems such as membranes may be quite pH dependent. (c) Monolayer studies of racemic lipids as models for optically active natural material are necessarily inconclusive. (d) Chiral discrimination between pure enantiomeric and racemic mixtures has previously been reported for several long-chain alcohols,³⁻⁵ their esters,⁵ and a polyamide.⁶ Similar behavior of the amide reported here, despite its drastically different shape, implies that such discrimination is not a very subtle effect and is probably quite general.

In view of the small ($30 \mu\text{g}$) quantities of material used to establish the monolayer, and also the notorious sensitivity of monolayer studies to impurities, we stress the significance of the *absolute method* used here to confirm that the observed differences between films spread from enantiomers and those cast from the racemate are truly due to differences in intermolecular packing rather than to artifacts.⁷ Enantiomers are perfect models for each other since all of their physical properties are identical except for their interactions with polarized light or with other chiral materials. Thus, the purity of enan-

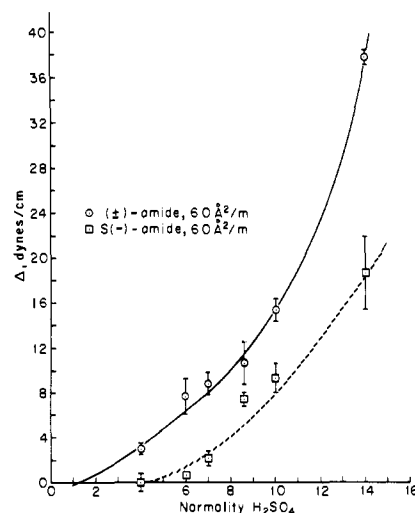


Figure 1. Surface tension lowering ($\Delta\gamma$) by racemic and (*S*)-(-)-*N*- α -methylbenzylstearamide films at 25°C and molecular area of $60 \text{ \AA}^2/\text{molecule}$ as a function of subphase acidity.

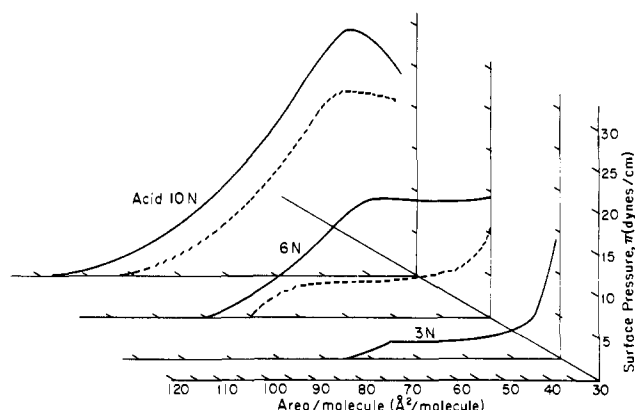


Figure 2. Force-area curves for compression of monolayers of racemic (-) and pure enantiomeric (*R* and *S*) (- - -) *N*- α -methylbenzylstearamide at 25°C spread from hexane on 3, 6, and 10 N H_2SO_4 .

tiomeric monolayers is demonstrated when all physical properties, including their surface behavior, are the same within experimental error. When this criterion is met, their (enantiomeric) behavior with each other or their (diastereomeric) behavior with other chiral surfactants can be assigned rigorously to stereospecific intermolecular packing within the monolayer.

The stearamides were prepared by aminolysis of highly purified methyl stearate with (*R*)-(+)- and (*S*)-(-)- α -methylbenzylamine. The resulting enantiomeric amides were purified to identical physical properties and were spread on aqueous solutions prepared from triply distilled water and distilled sulfuric acid using purified hexane as a spreading solvent. Racemic monolayers were produced both from racemic amide and by spreading a 1:1 solution of the pure (*R*)-(+)- and (*S*)-(-) enantiomers. Results were identical. Correspondingly, all measurements with pure enantiomer were checked with both antipodes.

The film balance (designed by B.K.) was operated at $25 \pm 0.2^\circ\text{C}$ at a normal compression rate of $20 \text{ \AA}^2 \text{ molecule}^{-1} \text{ min}^{-1}$. Surface pressures could be measured to $\pm 1.4\%$. Features of the force-area curves were reproducible to $\pm 2\%$ for the enantiomers and to $\pm 5\%$ for the racemate molecules as determined from the standard deviations of 22 points derived from 14 replica curves for the enantiomers and 10 curves for the racemate. Curves shown in Figure 1 are the composite averages for such samples. Surface tensions were measured with a Cenco du Noüy type tensiometer calibrated against

water at 25 °C before each series of measurements. Further details of the experiments will be presented in a full paper.^{8,9}

Acknowledgments. We are glad to acknowledge support of this work by NIH Grant GM-20386 and assistance in the laboratory by Jerry Magone and Eric Arnett.

References and Notes

- (1) On pure water and dilute acid solutions the amide appeared to be aggregated as microcrystals rather than to spread as a monolayer.
- (2) See G. L. Gaines, Jr., "Insoluble Monolayers at Liquid-Gas Interfaces", Interscience, New York, N.Y., 1966, p 228 ff, for an example of film expansion as a result of protonation of an amino head group. Amides are weak Brønsted bases and so require strongly acid media for protonation. See M. Liller, *Adv. Phys. Org. Chem.*, 11, 267 (1975), for discussion of this matter.
- (3) S. Stållberg-Stenhagen and E. Stenhagen, *Ark. Kemi, Mineral. Geol.*, 18A, 2 (1945).
- (4) T. Tachibana and K. Hori, *J. Colloid Interface Sci.*, 61, 398 (1977).
- (5) M. Lundquist has reported very careful studies of enantiomeric-racemic interactions: (a) *n*-eicosanol-2 and *n*-tricosanol-2 and their acetates, *Ark. Kemi*, 17, 183 (1961); (b) 2-methylhexacosanoic acid, *ibid.*, 21, 395 (1965); (c) quasi-racemic monolayers of methyl 2-methylhexacosanoate and 2-acetoxytetracosane. Lundquist examined the monolayer behavior of these systems as a function of temperature and composition and found that their two-dimensional phase changes were sharply dependent on both.
- (6) T. Isemura and K. Hamaguchi, *Bull. Chem. Soc. Jpn.*, 27, 125 (1954), noted different force-area curves for poly(γ -benzyl L-glutamate) and the racemic polypeptides.
- (7) The original example of chiral monolayer behavior of *d*-eicosanol-2 vs. the synthetic material reported by the Stenhagens⁹ could have been subject to error from this source since it was shown subsequently that the original racemic sample was impure (see K. Serck-Hanssen, S. Stållberg-Stenhagen, and E. Stenhagen, *Ark. Kemi*, 5, 203 (1953)).
- (8) The following publications provide authoritative background to the study of monolayers at the air-water interface: (a) G. L. Gaines, Jr., in ref 2; (b) E. D. Goddard, Ed., *Adv. Chem. Ser.*, No. 144 (1975); (c) A. W. Adamson, "Physical Chemistry of Surfaces", 3rd ed, Wiley, New York, N.Y., 1976; (d) J. T. Davies and E. K. Rideal, "Interfacial Phenomena", Academic Press, New York, N.Y., 1963; (e) N. K. Adam, "The Physics and Chemistry of Surfaces", 3rd ed, Oxford University Press, London, 1941.
- (9) Evidence that the amide was behaving as a monolayer is taken from (a) the close correspondence between the film behavior portrayed in Figures 1 and 2; (b) the fact that force-area curves were reproducible and reversible; (c) the fact that film pressures held constant during stepwise compression up to intermediate pressures; (d) similarity of behavior of our films to those of Lundquist's. Film balance performance was checked from time to time against monolayers of pure stearic acid.

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Noncoulomb Variation of Ion Pairing in Polar Solvents

Sir:

For the primitive model (rigid charged spheres of diameter a in a continuum), it is easy to show¹ that the association constant K for contact pairs is given by

$$K = (4\pi N a^3 / 3000) \exp(e^2 / a D k T) \quad (1)$$

(N = Avogadro's number, e = unit charge, D = dielectric constant, k = Boltzmann's constant, and T = absolute temperature). Constants for systems in which the ions are large compared with solvent molecules (e.g., tetraalkylammonium tetraphenylborides in acetonitrile-carbon tetrachloride mixtures²) conform to eq 1, but, for systems in which the ions are smaller than or comparable in size with solvent molecules, eq 1 fails completely to describe the change of K on changing the solvent.³ Figure 1 displays the pairing constants for potassium iodide⁴ in various mixtures of water, ethylene carbonate (EC), tetramethylene sulfone (TMSu), dimethyl sulfoxide (Me₂SO), and tetrahydrofuran (THF). A 75:25 wt % mixture of EC and TMSu is isodielectric with water: addition of this mixture to water initially decreases and subsequently increases K . Ad-

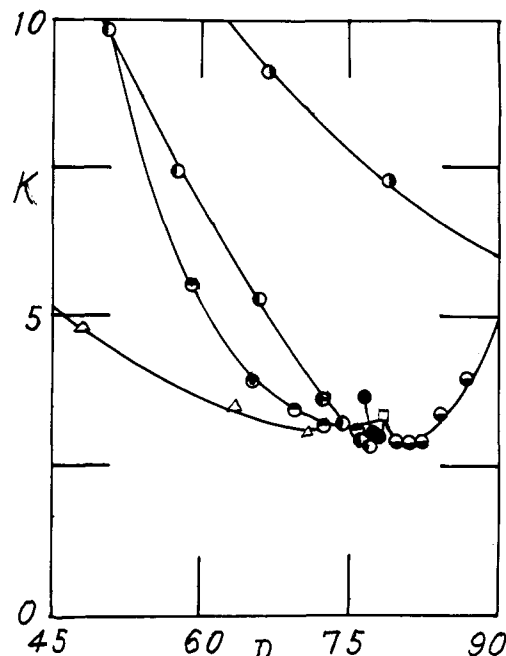
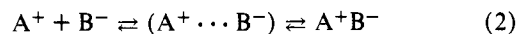


Figure 1. Pairing constants for potassium iodide in different solvents: \square , H₂O; \bullet , H₂O-EC; \circ , H₂O-TMSu; \bullet , H₂O-EC-TMSu (see text); \circ , EC-TMSu; \circ , H₂O-Me₂SO; Δ , H₂O-THF.

dition of TMSu to water decreases both K and D , while addition of EC to water decreases K but increases D . Different K 's are seen in Figure 1 at the same values of D , while equal values of K are observed for different values of D . A smooth curve can be drawn through the points for a given solvent pair, but obviously no function $K = F_0(aD)$ exists which describes the systems shown in Figure 1.

The qualitative explanation of the situation is simple: any theory based on the primitive model (which assumes only Coulomb interaction between ions) ignores completely all short range ion-ion and ion-solvent interactions. The latter are system specific and control the final steps in the formation of contact pairs in real solutions. Therefore the primitive model must be replaced by one which will permit inclusion of short-range effects in addition to those due to the long-range Coulomb force.

Consider the coupled equilibria



where the symbol $(A^+ \cdots B^-)$ represents a solvent separated pair, and $A^+ B^-$ a contact pair. Unpaired ions (concentration $c\gamma$) are ions which find no other ion in a sphere of diameter R centered on those ions; R is the diameter of the Gurney cosphere. Paired ions are ions which find one ion of opposite charge in the range $a \leq r \leq R$ where r is the center-to-center distance of the pair. Contact pairs are ions which find one ion of opposite charge in the shell of nearest neighbors; all other nearest and next-nearest neighbors are solvent molecules; if α is the fraction of paired ions which are in contact, the concentration of contact pairs is $\alpha c(1 - \gamma)$. The first step of (1) is diffusion controlled; it can be shown⁵ that

$$K_R = (1 - \alpha)(1 - \gamma) / c\gamma^2 f^2 \\ = (4\pi N R^3 / 3000) \exp(\beta / R) \quad (3)$$

where $\beta = e^2 / D k T$. For $r > R$, continuum theory may be used because by definition the solvent has bulk properties outside the cospheres. Consider a cation which finds an anion at the distance R : the anion may diffuse to distances $r > R$ (become unpaired) or, by site interchanges with solvent molecules, eventually form a contact pair. The constant for the second step of (1) is