Pearce, R. *J. Am. Chem. Soc.* **1977**, *99*, 6645, and references therein.
(14) Data of J. Myatt cited in ref 5.
(15) The ESR spectra of $Cp_2TiX_2(PR_3)^-$ systems display $a(^{31}P) \sim 20$ G: El Murr, N., personal communication.
(16) (a) For **8**, light brown crystalline solid (THF–petroleum ether): mp 186–194 °C dec; IR (THF) 1930 (vs), 2050 (m) cm^{-1}; NMR (benzene-d_6) δ 1.92 (d, $J = 11$ Hz), 5.82 (s), 7.1–7.95 (m) ppm. (b) For **9**, light orange-brown solid (petroleum ether, −40 °C); IR (THF) 1919 (vs), 1959 (s), 2045 (s) cm^{-1}; NMR (benzene-d_6) δ 2.21 (d, $J = 17$ Hz), 6.05 (s), 6.95–8.1 (m) ppm.
(17) (a) M = Cr: Grim, S. O.; Wheatland, D. A.; McFarlane, W. *J. Am. Chem. Soc.* **1967**, *89*, 5573. NMR (benzene-d_6): δ 1.45 (d, $J = 7$ Hz) ppm. (b) M = Fe: Treichel, P. M.; Douglas, W. M.; Dean, W. K. *Inorg. Chem.* **1972**, *11*, 1615. NMR (benzene-d_6): δ 1.70 (d, $J = 9.5$ Hz) ppm.
(18) $Cr(CO)_5THF$ was prepared via photolysis in an evacuated vessel of a degassed $Cr(CO)_6$ solution in dry THF. Evolved CO was periodically removed by freezing the photolysis solution and re-evacuating the vessel. Commercial $Fe_2(CO)_9$ was repurified to remove Fe^{+n}, H_2O, and CH_3CO_2H contaminants. All preparations were carried out under an atmosphere of prepurified N_2 (Vacuum Atmospheres Dri-Lab) using solvents distilled from sodium benzophenone ketyl or dianion.

Neil E. Schore,* Håkon Hope
Department of Chemistry, University of California, Davis
Davis, California 95616

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Stable Single-Compartment Vesicles with Zwitterionic Amphiphile Involving an Amino Acid Residue

Sir:

Phospholipids play an important role as an integral part of biological membranes and their dispersions in aqueous media form various types of bilayer aggregates.[1,2] Although the structures of phospholipid bilayers have been extensively investigated in connection with their biological functions,[3] their complexities and chemical instabilities have necessitated to develop more stable membrane-forming amphiphiles. Although such efforts have been exerted in these years,[4] stable single-compartment vesicles have not been obtained with single species of amphiphiles.

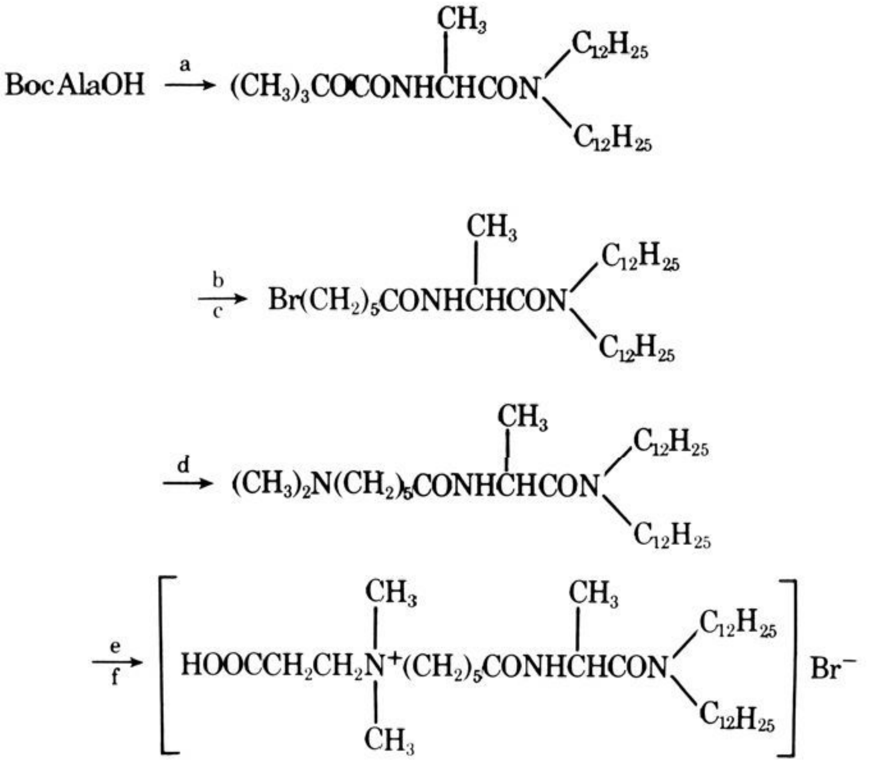
The phospholipids are known to have a tripartite structure:[5] a hydrophobic aliphatic double chain, a hydrophilic head group of phosphate ester, and the region where these two moieties are linked. Brockerhoff named the interface between hydrophobic and polar layers "hydrogen belt".[5] We intend to improve the stability of bilayer assemblies by modifying the hydrogen belt, in reference to our results that an amino acid residue placed in the hydrophobic region acts to tighten the micellar structures.[6] In this communication, we report the synthesis of *N*,*N*-didodecyl-N^{α}-[6-(dimethyl-2-carboxylatoethyl)ammoniohexanoyl]alaninamide (**1**) and its aggregation behaviors in aqueous media. Amphiphile **1**, which involves an amino acid residue as the hydrogen belt, has all the tripartite components in one molecule. In addition, **1** is expected to be chemically more stable than the phospholipids since it does not involve a labile carboxyl ester group.

Amphiphile **1** was prepared according to Scheme I. Amphiphile **1**:[7] liquid crystal with final mp 98 °C; $[\alpha]^{20}_D$ −18.7° (*c* 1.23, EtOH); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.88 (6 H, t, $-(CH_2)_{11}CH_3$), 1.25 (40 H, s, $-CH_2(CH_2)_{10}CH_3$), 1.36 (3 H, s, $-CH(CH_3)-$), ~2.00 (6 H, m, $-NCH_2(CH_2)_3CH_2-$), 2.21 (4 H, br t, $-N(CH_2)_4CH_2CO-$ and $HOOCCH_2CH_2N-$), 2.89 (6 H, s, $-N(CH_3)_2(CH_2)_5-$), 2.75–3.71 (8 H, m, $HOOCCH_2CH_2NCH_2-$ and $-N[CH_2(CH_2)_{10}CH_3]_2$), 6.74 (1 H, d, NH), 8.18 (1 H, br s, $-COOH$). Anal. Calcd for $C_{38}H_{76}N_3O_4Br$ (**1** HBr): C, 63.48; H, 10.65; N, 5.84. Found: C, 64.07; H, 11.07; N, 6.15.

An aqueous dispersion of **1** (turbid solution) was negatively stained, applied on a carbon grid, and dried in a vacuum desiccator. The sample was examined by electron microscopy (JEOL JEM-100CX) as shown in Figures 1A and 1B. Bangham-type multilayered vesicles[1] are mainly observed (Figure 1A) and diameters of the vesicles are widely distributed from 1000 Å to 1 μ. Well-developed lamella structures are also partly observed[8] (Figure 1B). These aggregate structures bear a close resemblance to those formed with the phospholipids. Figures 1C and 1D show electron micrographs for the ultrasonicated solutions of **1** (clear solution). In these micrographs, small particles (125–600 Å) observed are apparently single-layered vesicles.[2] The vesicles of relatively uniform size were obtained by sonicating the sample solution with a bath-type sonicator at a constant temperature. The thickness of each layer, regardless of multi- or single-layered vesicles, is ~40–60 Å, approximately twice the length of the hydrophobic segment of **1**. The sonicated solutions were maintained at clear state over a month without any additives, and their electron micrographs remain unchanged indicating that the single-layered vesicles are stable for such a prolonged period of time in aqueous media.

The transition between crystalline and liquid crystalline states for these vesicles was examined by ESR technique[9]

Scheme I[a]



1 HBr

[a] Reagents: a, $(C_{12}H_{25})_2NH$ and DCC; b, CF_3COOH; c, $Br(CH_2)_5COCl$; d, $(CH_3)_2NH$; e, $BrCH_2CH_2COOH$ and NaOH; f, HBr.

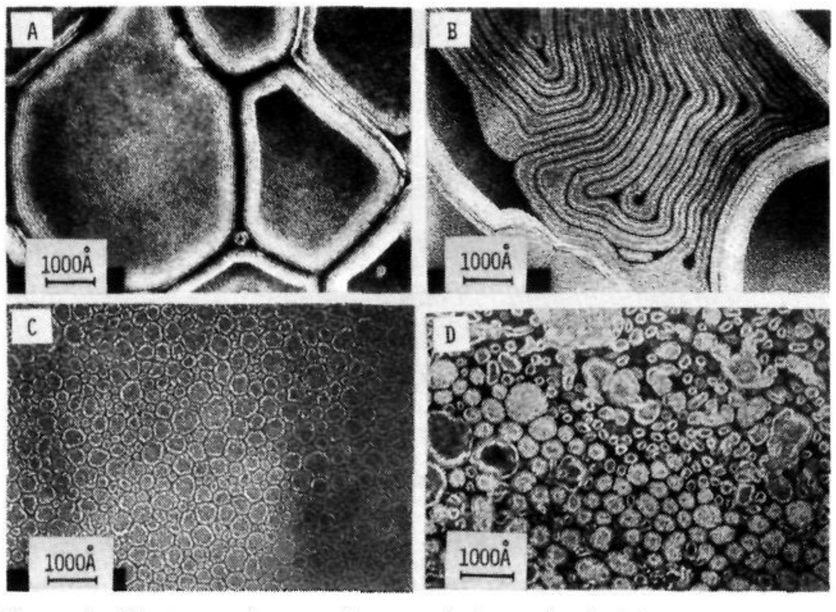


Figure 1. Electron micrographs negatively stained with uranyl acetate: A and B, 5 mM aqueous dispersion of **1** (magnification, × 49 000); C, 5 mM aqueous solution of **1** sonicated at 50 °C for 30 min with a bath-type sonicator (Bransonic 12, Yamato Scientific Co.) (magnification, × 49 000); D, 5 mM aqueous solution of **1** sonicated for 1 min with a probe-type sonicator at 30-W power (W-220F, Heat Systems-Ultrasonics) and allowed to stand for 30 min at 5 °C (magnification, × 53 000).

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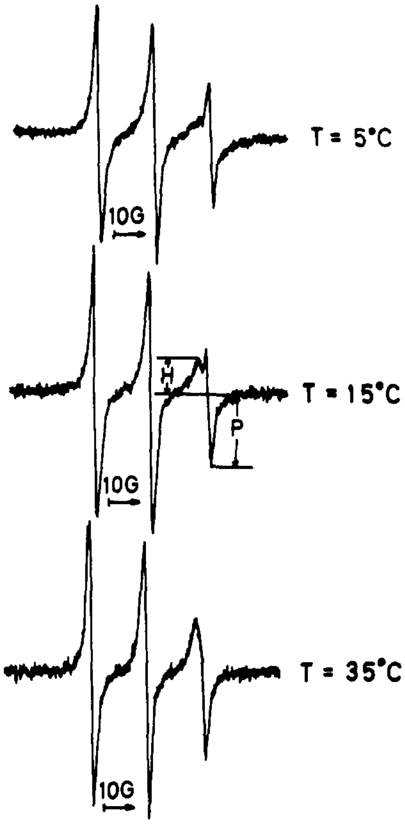

Figure 2. ESR spectra of **2** (2.72×10^{-4} M) in the sonicated aqueous solution of **1** (5.39×10^{-3} M).

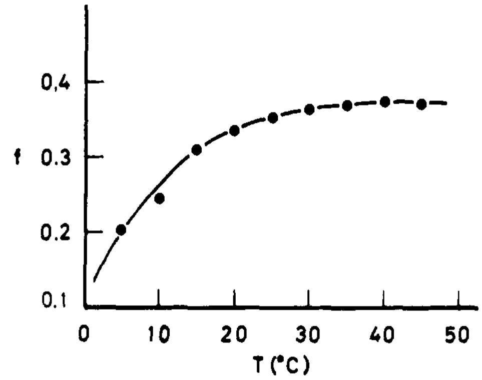

Figure 3. Correlation of spectral parameter *f* for **2** with temperature; measured in the sonicated aqueous solution of **1**.

(JEOL JES-ME-3, X-band); 4-(cyclohexylacetoxyl-2,2,6,6-tetramethylpiperidine-1-oxyl (**2**)[10] was used as a spin probe. The ESR spectral change with temperature is shown in Figure 2; signal P arises from **2** dissolved in the aqueous region and signal H is due to **2** placed in the hydrophobic interior of bilayer membrane. The spectral parameter, *f*, equal to $H/(H + P)$, approximately shows the fraction of the spin-labeled probe distributed to the membrane interior. Such a phenomenon was observed for the phospholipid bilayer system by using 2,2,6,6-tetramethylpiperidine-1-oxyl.[9] In Figure 3 is plotted *f* value against temperature; the *f* value tends to decrease below 20 °C, and hence the phase transition for the vesicular assembly of **1** must occur below 20 °C.

Our present amphiphile, as a modification of the phospholipids, may form the bilayer aggregates similar to those observed for the naturally occurring lipids. Single-compartment vesicles are quite stable in aqueous media at room temperature (above 20 °C) owing to the hydrogen belt effect provided by an amino acid residue. Since the present vesicles involve asymmetric centers in the hydrophobic region, they may provide an asymmetric recognition site for various guest molecules.

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References and Notes

(1) Bangham, A. D.; Standish, M. M.; Watkins, J. C. *J. Mol. Biol.* **1965,** *13,* 238-252.
(2) Huang, C. *Biochemistry* **1969,** *8,* 344-351.
(3) For example: Bangham, A. D. In "Liposomes in Biological Systems", Gregoriadis, G., Allison, A. C., Eds.; Wiley: New York, 1978.
(4) Kunitake, T.; Okahata, Y. *J. Am. Chem. Soc.* **1980,** *102,* 549-553, and references therein.
(5) Brockerhoff, H. "Bioorganic Chemistry", van Tamelen, E. E., Ed.; Academic Press: New York, 1977; Vol. 3, Chapter 1.
(6) Murakami, Y.; Nakano, A.; Iwamoto, K.; Yoshimatsu, A. *Chem. Lett.* **1979,** 951-954.
(7) The critical micelle concentration of **1** was determined by the surface tension method based on the Wilhelmy principle: 2.1×10^{-5} M in water. The weight-average molecular weight was determined for single-layered vesicles by using a low angle laser light scattering photometer LS-8 (Toyo Soda Manufacturing Co., Ltd.) with a sample of poly(ethylene oxide) (Toyo Soda SE-30, mol wt 2.8×10^5) as reference. Sample solutions for the measurements were prepared by sonicating aqueous dispersion of **1** (2.0×10^{-4} to 1.0×10^{-3} M range): aggregate weight determined, 4.8×10^6.
(8) Lucy, J. A.; Glauert, A. M. *J. Mol. Biol.* **1964,** *8,* 727-748.
(9) Shimshick, E. J.; McConnell, H. M. *Biochemistry* **1973,** *12,* 2351-2360.
(10) Murakami, Y.; Nakano, A.; Miyata, R.; Matsuda, Y. *J. Chem. Soc., Perkin Trans. 1* **1979,** 1669-1676.

Yukito Murakami,* Akio Nakano, Kiyoshi Fukuya
Department of Organic Synthesis, Faculty of Engineering
Kyushu University, Fukuoka 812, Japan
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Raman Phonon Spectroscopy of Solid-State Reactions: Thermal Rearrangement of Methyl *p*-Dimethylaminobenzenesulfonate in Solid State

Sir:

In this communication we propose a new approach utilizing laser Raman phonon spectroscopy that can be used to understand details of reaction dynamics in solids. The use of Raman spectroscopy itself in investigating solid-state reactions is not new. The novel feature of the present approach is the use of phonon spectra to derive the reaction mechanism. It is also shown that the new approach leads to a concept of phonon assisted reactions in solids. Such information is not readily available from X-ray diffraction techniques used widely in the past[1-9] to study organic solid-state reactions. We apply the method to investigate the thermal rearrangement reaction of methyl *p*-dimethylaminobenzenesulfonate (MSE) into *p*-trimethylammonium benzenesulfonate zwitterion (ZWT).

Phonons are low-frequency intermolecular vibrations of a crystal. The phonon spectral pattern contains both structural and the dynamical information. First, from the structural point of view, the Raman phonon spectra can be used to derive the mechanism of the reaction: (i) homogeneous where a solid solution of the reactant and the product forms; (ii) heterogeneous, in which the product forms its own lattice and no solid solution results. Our previous study of phonon spectra in organic solid solutions reveals that the phonon bands exhibit an amalgamation behavior.[10,11] The amalgamation behavior implies that the phonon frequencies change monotonically as the concentration of solid solution is changed. In the case where no solid solution forms, the unchanged phonon bands of the two compounds superimpose. Furthermore, the short-range character of the interactions that determine the phonon motions in molecular solids make these bands ideal for distinguishing between a truly random solid solution and segregated