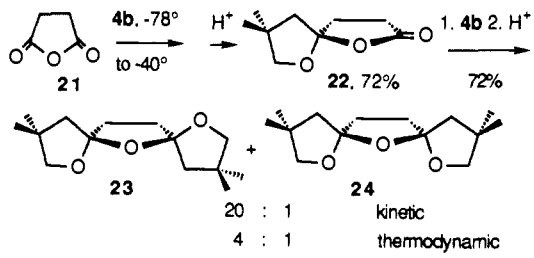
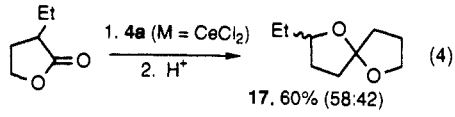
Scheme IV



Equation 4 presents one of the shortest and most convenient syntheses of racemic 2-ethyl-1,6-dioxaspiro[4.4]nonane (**17**) (chalcogran), a major pheromone component of the Norway spruce pest.[19] The latter was obtained in only 15% yield when the dilithio version of **4a** was employed.



(4)

Oxaspiroannulation of six-membered rings to lactones is also successful (Scheme III). The requisite lithium 4-lithiobutoxide can be generated by deprotonation of 4-(phenylthio)butanol by *n*-butyllithium followed by reductive lithiation[20] with LDBB in THF at -78 °C. Transmetalation with $CeCl_3$ provides the valuable organocerium species **18**, which reacts with lactones as shown. 1,7-Dioxaspiro[5.5]undecane (**19**) is a major component of the olive fruit fly pheromone,[14,21] and the reaction product (**20**) of **18** and ϵ-caprolactone is a ring system that is also found in nature.[22]

Finally, monoaddition of cerium 3-cerio propoxide **4b** to cyclic anhydrides occurs in variable yields to provide, after acidic workup, oxaspirolactones, a rare type of compound.[23] The best yield was obtained with succinic anhydride (**21**, Scheme IV).[24] When the dilithio analogue of **4b** was used instead, only 13% of **22** could be obtained. Preliminary experiments indicate that both maleic and phthalic anhydrides also provide oxaspirolactones but in the reduced yields of 40 and 25%, respectively. Lactone **22** can be induced to undergo another addition of organocerium **4b** leading to a diastereoisomeric mixture of the 1,6,8-trioxadispiro-[4.1.4.2]tridecane system, **23** and **24**.[25,26]

Acknowledgment. We thank the National Science Foundation for financial support.

Supplementary Material Available: Sample procedures for additions of organocerium reagents to lactones and cyclic anhydrides and the spectral data for the products (3 pages). Ordering information is given on any current masthead page.

(18) Although the reaction of *n*-butyllithium and δ-valerolactone has been reported to give " an extremely complex mixture of products",[1] in our hands, 50% of monoaddition was observed.

(19) Isolation and characterization: Francke, W.; Heeman, V.; Gerken, B.; Renwick, J. A. A.; Vité, J. P. Naturwissenschaften **1977**, *64*, 590. Recent syntheses: Högberg, H.-E.; Hedenström, E.; Isaksson, R.; Wassgren, A.-B. *Acta Chem. Scand.* **1987**, *B41*, 694 and citations therein.

(20) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.

(21) Baker, R.; Herbert, R.; Howse, P. E.; Jones, O. T. *J. Chem. Soc., Chem. Commun.* **1980**, 52. DeShong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901.

(22) Kitching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R.; Moore, C. J.; Schurig, V.; Kõnig, W. A.; Francke, W. *J. Org. Chem.* **1989**, *54*, 3893.

(23) See, for example: Fukuda, H.; Takeda, M.; Sato, Y.; Mitsunobu, O. *Synthesis* **1979**, 368. Yamamoto, M.; Yoshitake, M.; Yamada, K. *J. Chem. Soc., Chem. Commun.* **1983**, 991. Ousset, J. B.; Mioskowski, C.; Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 5903.

(24) A solution of **4b** at -78 °C in THF is cannulated into a solution of the anhydride at -78 °C.

(25) Related systems are known: Ponomarev, A. A.; Markushina, I. A. *Zh. Obshch. Khim.* **1963**, *33*, 3955. Baker, R.; Brimble, M. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 125.

(26) The relative stereochemistry was surmised from the higher dielectric constant of **24**.

Relation of Surfactant Monomer Structure to Flip-Flop Dynamics in Surface-Differentiated Synthetic Bilayer Membranes†

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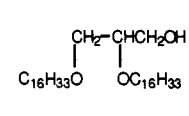
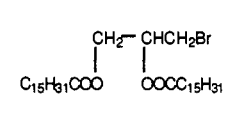
The transverse or "flip-flop" migration of a lipid molecule from one leaflet of a hydrated bilayer membrane to the other is an activated process that requires disruption of the membrane packing, as well as energetically costly transient interactions of the polar lipid head group with the bilayer's hydrocarbon interior, and of the lipid's hydrocarbon chains with water.[1,2] There is intense current interest in the dynamics of lipid flip-flop in biological membranes or liposomes created from naturally occurring lipids.[3] Recently, we showed that bilayer vesicles created from simple tetraalkylammonium ion surfactants could be chemically differentiated at their exovesicular and endovesicular surfaces, enabling us to visualize the dynamics of subsequent endovesicular/exovesicular exchanges.[4] Here we demonstrate that bilayer vesicles constructed of structurally diverse synthetic surfactants can be similarly studied, and that monomer structure can be readily related to flip-flop dynamics within the membrane.

The functional (**F**) and corresponding nonfunctional (**NF**) surfactants appear in Chart I. Surfactants **1-F** and **1-NF** were known.[4] For **2** or **3**, *N*-methyl-*N*,*N*-diethanolamine was either etherified or esterified to afford the precursor tertiary amines, which were then quaternized with GCH_2Br[4a] (**F** surfactants) or MeBr (**NF** surfactants).

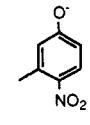
Surfactant **4-F** was prepared by quaternization with GCH_2Br of the tertiary amine obtained from the reaction of (2,2-diheptadecyl-1,3-dioxolan-4-yl)methyl bromide[5] with dimethylamine, whereas **4-NF** resulted directly from quaternization of the same bromide with Me_3N. In the **5** system, racemic glycerol dipalmityl ether (**7**)[6] was converted to the analogous bromide with CBr_4/Ph_3P; the bromide was then reacted with dimethylamine; and the resulting tertiary amine was quaternized with GCH_2Br or MeBr to afford **5-F** or **5-NF**. Surfactants **6** were derived from racemic bromide **8**,[7] which either was directly quaternized to **6-NF** with Me_3N or reacted with dimethylamine to give a tertiary amine that was converted to **6-F** by quaternization with GCH_2Br. All surfactants were crystalline solids that were purified by chromatography and recrystallization and characterized by NMR spectroscopy and elemental analysis.[8]



7



8



9 (G')

† Dedicated to Professor Clifford A. Bunton on the occasion of his "retirement".

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(8) Details of synthetic procedures and spectroscopic and analytical characterization are available upon request.

0002-7863/90/1512-6391$02.50/0

Chart I

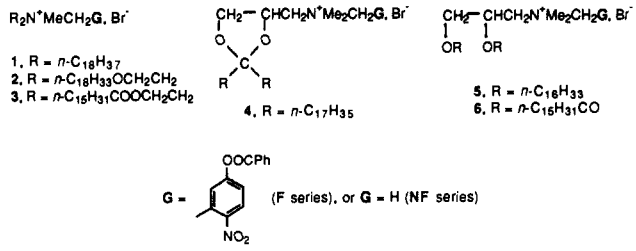

Table I. Dynamics of Covesicular Systems

covesicle[a]	d,[b] nm	T_c, °C	k_f,[c] s^{-1}	k_s,[c] s^{-1}	$t_{1/2}$ flip
1[d]	48	39	0.17	0.0018	>1 h/25 °C; 2 min/38-40 °C
2	27	37	0.32[e]	0.055	4 min/25 °C; 1 min/30 °C
3	29	40	0.42[e]	0.0039	20 min/30 °C; 1-2 min/35 °C
4	44	31	0.067	0.0018	3 min/35 °C; 1 min/40 °C
5	48	37	0.075	0.0010	5 min/40 °C; 1 min/45 °C
6	41	44	0.053	0.000062	5 min/55 °C; 1 min/65 °C

[a] See text for structures and compositions.[9] [b] Diameters from dynamic light scattering at pH 4, 0.01 M KCl. [c] k_f and k_s were determined at 25 °C. [d] See refs 4a and 4b. [e] By stopped-flow spectroscopy.

Covesicles of surfactants **1-F/1-NF** to **6-F/6-NF** were created by sonication of $CHCl_3$-cast films of surfactant mixtures in pH 3.9 aqueous HCl, containing 0.01 M KCl.[9] The gel to liquid crystal phase transition temperatures (T_c) of the covesicles were determined from temperature-dependent discontinuities in the fluorescence polarization of covesicalized 1,6-diphenyl-1,3,5-hexatriene;[4,10] cf. Table I.

For flip-flop studies, the covesicles were first surface-differentiated by exposure to 1×10^{-4} M glutathione in 0.01 M pH 8 Tris buffer (0.01 M in KCl) at 25 °C. These reactions rapidly (k_f) converted the covalently bound, *exovesicular* *p*-nitrophenyl benzoate moieties (**G**) of **1-F** to **6-F** to *p*-nitrophenolates (**G'** or **9**), as monitored spectroscopically at 400 nm. If the reactions were allowed to continue, slower, H^+/OH^- *permeation-limited*,[4] *endovesicular* cleavages of **G** to **G'** were observed with rate constants k_s.[4] Values of k_f and k_s appear in Table I.[11] To assess flip-flop, the external pH was reduced to 3.9 (HCl) immediately after completion of the exovesicular reaction, quenching further benzoate cleavage.

The surface-differentiated covesicles were warmed to a selected "incubation" temperature, for a specific time to induce flip-flop; cooled back to 25 °C; and then readjusted to pH 7.9 (NaOH). The *new, fast* (k_f) appearance of *p*-nitrophenolate, initiated by the pH change, represented the cleavage of those surfactant **G** moieties that had "flipped" from endo- to exovesicular loci during the incubation procedure.[12] The subsequent, residual k_s reaction was due to the cleavage of still-intact, endovesicular **G** groups. In all cases, the absorptions of **G'** released in the initial k_f and postincubation k_f and k_s reactions summed to the stoichiometric value. The extent of flip-flop equilibration induced by incubation was revealed by the **G'** absorptions attending the postincubation k_f and k_s reactions. By exploring different incubation times and temperatures, we obtained approximate half-times for the flip-flop equilibrations of the surface-differentiated covesicles; cf. Table I.

The $t_{1/2}$ data demonstrate correlations between surfactant molecular structure and monomer stability toward transverse redistribution within the bilayer. The bilayer stabilities of simple double long chain ammonium ion surfactants increase with chain length and diminish abruptly at T_c, where bilayer rigidity relaxes.[4b,13] An ether oxygen near the head group (**2**) enhances the ease of flip-flop, relative to **1** of similar chain length, whereas bilayers of the related ester (**3**) are considerably more stable than those of **2** and similar to **1**. Ether oxygen may reduce the hydrophobic bonding contributions of neighboring CH_2 groups, reducing both the lipid's effective chain length and bilayer stability,[14,15] whereas acyl moieties may stabilize bilayers via carbonyl-water H-bonding networks.[14,15] Bilayers of **2** and **3** display rapid flip-flop at $T \lesssim T_c$.

Ketal surfactant **4** is a structural bridge between "geminal" double long chain surfactants **1-3** and "vicinal", glycerol-derived surfactants **5** and **6**. Bilayers of **4** display modest stability *above* T_c and are thermally more resistant to flip-flop than those of ether surfactant **2**. "Opening" the cyclic ketal structurally transposes **4** to **5**, affording bilayers of still greater resistance to flip-flop. Bilayers of **5** manifest stability above T_c, while the enhanced stability of ester vs ether lipid bilayers is again apparent in the **6** vs **5** comparison. Bilayers of **6** are quite stable at T_c and require elevated temperatures to induce rapid flip-flop, as is the case with vesicles of egg lecithin or dipalmitoylphosphatidylcholine.[2]

The sensitivity of monomer dynamics within the membrane to molecular structure, in bilayers constructed of lipids **1-6**, is noteworthy and suggests that related methodology could be used to effectively model the behavior of biologically relevant artificial membranes.

Acknowledgment. We are grateful to Professor D. A. Jaeger for a gift of the ketal bromide precursor of **4** and to the U.S. Army Research Office for financial support.

(9) The general procedure is described in ref 4a. The **F/NF** molar ratios were 1:10 for **1** and 1:7 in all other cases. The total [surfactant] was 4×10^{-4} M. The sonication methods employed here apparently produce unilamellar vesicles.[4a] Observed mean diameters of the covesicles (Table I) are compatible with this idea.

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(11) The distributions of exovesicular and endovesicular reactions were (ca.) 50/50 (**1**), 65/35 (**3**, **4**), and 70/30 (**2**, **5**, **6**).

(12) The methodology, as applied to **1-F/1-NF** covesicles, is described in detail in ref 4a. Note that some exovesicular (**G'**) surfactant molecules must "flop" to endovesicular loci during incubation.[4a]

(13) To obtain $t_{1/2}$ values of 1-12 min requires temperatures ($\sim T_c$) of 25, 39, and 50 °C, respectively, for **1**, R = $C_{16}H_{33}$, $C_{18}H_{37}$, or $C_{20}H_{41}$.[4b]

(14) Tirri, L. J.; Schmidt, P. C.; Pullarkat, R. K.; Brockerhoff, H. *Lipids* **1977**, *12*, 863. The enhanced permeabilities of vesicular **2** or **5** (vs **3** or **6**, respectively) are related, expected consequences of their ether (vs ester) lipid structures.

(15) See also: Wong, P. T. T.; Mantsch, H. H. *Chem. Phys. Lipids* **1988**, *46*, 213. Ruocco, M. J.; Siminovitch, D. J.; Griffen, R. G. *Biochemistry* **1985**, *24*, 2406.

Titanium-Mediated Carbonyl Olefinations. 1. Methylenations of Carbonyl Compounds with Dimethyltitanocene

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The methylenation of aldehydes and ketones is a useful synthetic transformation, performed with Wittig-type reagents,[1] with geminal dimetallic derivatives ($L_nM^1CH_2M^2L_m$) or with nucleophilic metallocarbenes ($L_nM{=}CH_2$).[2] Similar conversions of esters or lactones to enol ethers are normally not possible with most of these reagents.[3] An exception is the titanocene methy-

(1) (a) Cadogan, J. I. G., Ed. *Organophosphorous Reagents in Organic Synthesis*; Academic Press: London, 1979. (b) Bestman, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 65. See also: (c) Johnson, C. R.; Shanklin, J. R.; Kirchhoff, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 6462. (d) Welch, S. C.; Log, J.-P. *J. Org. Chem.* **1981**, *46*, 4072. (e) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.

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