surprising since the reaction is a close model of water addition to a protonated ester $RC^+(OH)OEt$, the tetrahedral intermediate-forming step in H^+-catalyzed ester hydrolysis. As in the present study, an explanation can be advanced invoking steric effects on solvation.[27]

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Supplementary Material Available: Table of first-order rate constants for product formation in 2-methoxy-2-alkyl-1,3-dioxolanes (4 pages). Ordering information is given on any current masthead page.

Reactivity Control by Microencapsulation in Simple Ammonium Ion Vesicles

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Abstract: The quantitative oxidation of Ellman's anion (**2**) to Ellman's reagent (**3**) by *o*-iodosobenzoate (**4**) can be kinetically controlled by microencapsulation in vesicles of dioctadecyldimethylammonium chloride (DODAC (**1b**)). Reactions at pH 8 between **2** and excess **4** occur rapidly on the surface of DODAC vesicles ($k \sim 0.16$–$0.24\ s^{-1}$). When either **2** or **4** is encapsulated within the DODAC vesicles, rapid reaction with the other *exovesicular* reagent does not occur; instead, a slow ($k \sim (2$–$7) \times 10^{-3}\ s^{-1}$) permeation-limited oxidation is observed, in which **4** is probably the key permeant. Individually encapsulated **2** and **4** react with each other only to the extent of ~5–10% over 20 h, a rate retardation >18 000 relative to the unmodulated exovesicular reaction. Similarly, the cleavage of Ellman's reagent (**3**) to Ellman's anion (**2**) by dithionite can be controlled by DODAC vesicles. The rapid, exovesicular cleavage ($k \sim 33$–$35\ s^{-1}$) disappears when endovesicular **3** is challenged by exovesicular dithionite and is replaced by the slow ($k \sim (5$–$7) \times 10^{-4}\ s^{-1}$) hydrolysis of **3**. In contrast to the observed facile vesicular DODAC control of these anion–anion reactions, the cleavage of neutral *p*-nitrophenyl diphenyl phosphate by **4** is not strongly affected by encapsulation of either substrate or **4**.

A decade has elapsed since Kunitake[1] and Fendler[2] introduced dialkyldimethylammonium ion surfactant vesicles as simple membrane models. It was quickly demonstrated that the rates of (e.g.) esterolysis[3] or electron-transfer[4] reactions occurring between reagents *separated* by these surfactant bilayers could be modulated by them.[5] Additionally, intravesicular bimolecular reactions between nucleophiles and reactive esters or phosphates were strongly accelerated due to reactant concentration on the membrane.[3,5]

Control of reagent and substrate permeation across bilayers is crucial to the rational use of synthetic vesicles as "microreactors".[1c,2,6,7] Additionally, liposomes or vesicles have long been used as drug delivery vehicles; the vesicle both protects the encapsulated drug from the external environment and controls its release via permeation.[2d] One widely studied method of enhancing control over permeation is by polymerizing the surfactant monomers that comprise the vesicle to impart greater structure and impermeability to the bilayers.[8] Variations of this approach include polymer-encased liposomes[9] and surfactant-coated polymer capsules.[10]

In our laboratory, we have focused on the applicability of *nonpolymerized*, simple dialkyldimethylammonium ion vesicles **1** (16_2 or 18_2) as agents of reactivity control. In a previous

$$R_2\overset{+}{N}Me_2,X^-$$

1a, R = *n*-$C_{16}H_{33}$ (16_2); **1b**, R = *n*-$C_{18}H_{37}$ (18_2)

X = Cl or Br

communication, we reported that the oxidation of 16_2-vesicle-entrapped Ellman's anion (**2**) to Ellman's reagent (**3**) by exo-

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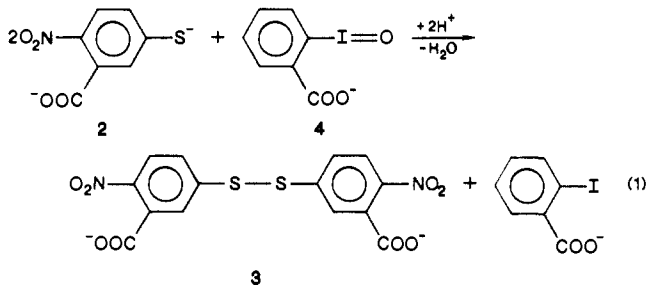
vesicular *o*-iodosobenzoate (**4**) (eq 1) was permeation limited and



slowed by a factor of >400 relative to the same reaction occurring between these reagents on the exovesicular membrane surface.[11] However, the sonicated 16_2 vesicles that we used had a very low endovesicular capacity for the reagent to be protected. Moreover, subsequent studies revealed the porousness of 16_2 vesicles toward various spectroscopic probes,[12] a problem that carried over to the reactivity of functionalized dihexadecylmethylammonium surfactant vesicles.[13,14]

In the present full paper, we describe the remarkably superior reactivity control available with dioctadecyldimethylammonium chloride (**1b**, 18_2, or DODAC) vesicles. For example, Ellman's anion (**2**) and *o*-iodosobenzoate (**4**) can be separately entrapped in DODAC vesicles and maintained in the same aqueous solution for many hours with minimal reaction, even though they react within 10 s when free. Additionally, DODAC-encapsulated Ellman's reagent (**3**) does not react with exovesicular dithionite ion, although, in 16_2 vesicles, very rapid endovesicular/exovesicular equilibration of **3** leads to quantitative reaction within 10 s.[15] We will also describe how solutions of (separately) DODAC-encapsulated **2** and **4** can be used as monitors for chemically or physically induced vesicle "damage".

Results and Discussion

Methodology. Small DODAC vesicles were created by sonication (70 W, 15 min) of **1b** (X = Cl) in N_2-purged, pH 8 Tris buffer, μ = 0.01 (KCl) at 50–55 °C. These "small" vesicles had diameters of 700–800 Å by dynamic light scattering. In several experiments, "large" vesicles, with d = 2900 ± 500 Å, were generated by slow injection (1 mL/h) of $CHCl_3$ solutions of **1b** into N_2-sparged Tris buffer at 70 °C.

Generation of the vesicles in the presence of a dissolved reagent (e.g., **2**, **3**, or **4**) afforded encapsulated (endovesicular) or surface-bound (exovesicular) reagent. When desired, the exovesicular reagent was removed by chromatography on a Sephadex G-75 column that had been preequilibrated with buffer and (empty) DODAC vesicle solutions. Details of the sonication and chromatography protocols appear in the Experimental Section.

Oxidation of Ellman's Anion. The reaction between Ellman's anion (**2**) and *o*-iodosobenzoate (**4**), with the 2:1 stoichiometry shown in eq 1,[16] occurred quantitatively when a 2×10^{-4} M solution of **2** reacted with 1×10^{-4} M aqueous **4**. Decay of the UV absorption of **2** (λ_{max} 412 nm, ϵ = 13 600 M^{-1} cm^{-1} in pH 8 Tris buffer) was complete after 2 min and was replaced by the absorption of its disulfide oxidative dimer, Ellman's reagent (**3**) at 332 nm (ϵ = 19 860 M^{-1} cm^{-1}). When more than a 2:1 ratio of **2** to **4** was employed, UV spectroscopy revealed that a mixture of **3** and unreacted **2** was present.

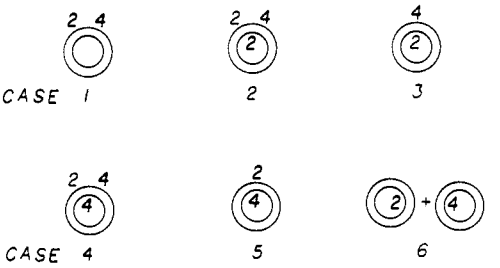


Figure 1. Reaction configurations for the oxidative dimerization of Ellman's anion (**2**) by *o*-iodosobenzoate (**4**) in the presence of DODAC (**1b**) vesicles. The examples (cases 1–6) are described in the text, and kinetic results appear in Table I.

Further substantiation of the clean course of eq 1 was provided by TLC examination of the product mixture on precoated, silica gel, polyester plates. The HCl-acidified (pH 3) reaction product mixture, eluted with 5:1 EtOAc/hexane containing a drop of HOAc, afforded only two UV-active spots, with R_f 0.28 and 0.75, corresponding to **3** and *o*-iodobenzoic acid, respectively. Finally, although peroxide formation would not accord with the observed 2:1 stoichiometry of the reaction, a starch/iodide test of the product solution demonstrated the absence of peroxide, so that the initial iodoso oxygen of **4** ends up as water and not hydroperoxide.

The kinetics of the oxidation of **2** by excess **4** were studied under a variety of vesicular and micellar conditions at 25 °C. The progress of reaction was followed spectrophotometrically by decay of the absorption of **2** at 412 nm (in pH 8 Tris buffer) or at 450 nm (when surfactant was present). The absorbance of **2** in vesicular solutions was corrected for background scatter by zeroing against identical solutions of "empty" vesicles. Fast reactions were followed with a Durrum Model D-130 stopped-flow spectrometer. Pseudo-first-order rate constants were obtained by standard computational treatments and with generally good (±3%) reproducibility in duplicate runs on the same vesicle preparations. However, greater variance (up to 20%) was observed in comparisons between different vesicle preparations.

Kinetic results are collected in Table I. Runs 1 and 2 show that the rapid oxidation (k_ψ = 0.143 s^{-1}) in pH 8 aqueous buffer is significantly catalyzed by cationic CTAB (cetyltrimethylammonium bromide) micelles (k_ψ = 3.28 s^{-1}, a kinetic enhancement of ~23). This acceleration of a reaction between two anions on a cationic micellar aggregate is expected and reflects strong electrostatic binding of the reactants, coupled with their concentration into the small reaction volume of the micellar Stern layer.[17]

Runs 3–8 comprise six basic reaction "configurations" or "cases" modulated by DODAC vesicles and schematically described in Figure 1. In case 1 (run 3), anion **2** and excess oxidant **4** were added sequentially to preformed, "empty" DODAC vesicles. Reaction ensued with a single, rapid, quantitative exponential decay of the absorbance of **2**. For reasons that will become apparent as we proceed, this reaction is assigned to the exovesicular surface of the DODAC vesicles. The reduction of k_ψ (vs micellar run 2) is similar to that observed with vesicles of **1a**[7] and may reflect tight binding of **2** and **4** to the aggregates' $^+NMe_3$ head groups coupled with the greater structuring and slower mutual monomer motion of vesicles as opposed to micelles.

In case 2, the DODAC vesicles are created in the presence of substrate **2**, which now assumes both exo- and endovesicular binding sites. Subsequent addition of **4** initiates *two* distinct reactions: a rapid exovesicular process (k_ψ = 0.177 s^{-1}) similar to that of case 1 and a much slower reaction (k_ψ = 0.002 s^{-1}) that accounts for ~45% of the total absorbance of **2**. We believe that

(11) See ref 7 and: Moss, R. A.; Bizzigotti, G. O.; Ihara, Y. In *Studies in Organic Chemistry*; Yoshida, Z.-I., Ise, N., Eds.; Elsevier: New York, 1983; Vol. 13, pp 189–205, especially p 199ff.

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(14) See, however, the comparative impermeability of functionalized 1,2-diacylglyceryl surfactants: Moss, R. A.; Swarup, S. *J. Am. Chem. Soc.* **1986**, *108*, 5341. Moss, R. A.; Bhattacharya, S.; Scrimin, P.; Swarup, S. *Ibid.* **1987**, *109*, 5740.

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(16) Although it is written in its iodoso form **4** (eq 1), it is well-known that *o*-iodosobenzoate preferentially exists as its valence tautomeric 1-oxido-1,2-benziodoxolin-3-one isomer. See: Moss, R. A.; Alwis, K. W.; Bizzigotti, G. O. *J. Am. Chem. Soc.* **1983**, *105*, 681 and references therein.

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Table I. Oxidation of Ellman's Anion by *o*-Iodosobenzoate[a]

run	conditions	reagent sequence[b]	case[b]	k_ψ,[f,c] s^{-1}	$10^2 k_\psi$,[s,d] s^{-1}
1	Tris buffer	**2** + **4**		0.143	none
2	CTAB micelles	**2** + **4**		3.28	none
3	DODAC vesicles	18_2 + **2** + **4**	1	0.161	none
4	DODAC vesicles	(18_2 + **2**)[e] + **4**	2	0.177	0.20 (45%)[f]
5	DODAC vesicles	(18_2 + **2**) + S + **4**[g]	3	none	0.35
6	DODAC vesicles	(18_2 + **4**) + **2**	4	0.235	0.66 (25%)
7	DODAC vesicles	(18_2 + **4**) + S + **2**[h]	5	none	0.55
8	DODAC vesicles	(18_2 + **2**) + S + (18_2 + **4**) + S	6	none	v.v. slow[i]
9	DODAC vesicles	run 8 + 28 wt % EtOH	6	0.012	none
10	DODAC vesicles	run 8, then 38 °C	6	0.14	none
11	DODAC + CTAB[j]	(18_2 + CTAB + **2**) + **4**		0.234	1.8 (38%)
12	DODAC + CTAB[j]	(18_2 + CTAB + **2**) + S + **4**		none	2.1
13	DODAC + CTAB[k]	(18_2 + CTAB + **2**) + **4**		0.263	none

[a] All reactions were carried out in 0.01 M Tris buffer at pH 8, μ = 0.01 (KCl) at 25 ± 1 °C (unless otherwise noted). Surfactant concentrations were 1 × 10^{-3} M, [**2**] = 2.5 × 10^{-4} M, and [**4**] = 5 × 10^{-4} M (excess). Where Sephadex chromatography was employed, the appropriate reagent concentration was lower. "Vesicles" refers to small, sonicated vesicles; see text. [b] See text and Figure 1. [c] Pseudo-first-order rate constant of "fast" reaction. [d] Pseudo-first-order rate constant of "slow" reaction. [e] Parentheses indicate *cosonication*. [f] Percent of slow reaction as measured from the absorbance change. The balance is the fast reaction. [g] "S" indicates that Sephadex chromatography was carried out after cosonication. [h] 5 × 10^{-5} M **2** was added. [i] Only 5–10% loss of absorbance of **2** was detected over 20 h. [j] [18_2] = 1 × 10^{-3} M; [CTAB] = 5 × 10^{-4} M. [k] [18_2] = [CTAB] = 1 × 10^{-3} M. Dynamic light scattering demonstrates the presence of vesicles with d = 825 Å.

the latter reaction is rate limited by the permeation of **4** to endovesicular **2**.[18] The alternative permeation-limited process, endovesicular **2** moving to exovesicular **4**, is less likely; see below.

In case 3, the cosonicated (DODAC + **2**) vesicles were first chromatographed over a 1 × 27 cm column of Sephadex G-75 to remove exovesicular **2**. The resulting solution of endovesicular **2** eluted immediately after the 8-mL column void volume, whereas adsorbed **2** (or **4** in cases 5 and 6) emerged after 22–30-mL elution volumes. Addition of excess **4** then gave only a slow, permeation-limited oxidation, similar in rate to the slow reaction component of case 2; there was no fast oxidation.[19] Even after storage of a solution of endovesicular **2** for *3 days* at 25 °C, no rapid (exovesicular) reaction was evident upon the addition of **4**; the observed reaction (k_ψ = 7 × 10^{-4} s^{-1}) was extremely slow.[20]

The storage experiment not only demonstrates the lack of leakage of endovesicular **2** but also *excludes* the possibility that the slow reaction between **4** and **2** measures the rate-limiting "flip-flop" of a surfactant/**2** ion pair from an endovesicular to an exovesicular site, followed by rapid reaction with exovesicular **4**. If the observed slow reaction (k_ψ = 7 × 10^{-4} s^{-1}, $\tau_{1/2}$ ~ 16 min) did represent rate-limiting flip-flop, then it is obvious that 3 days of storage would have moved many ions of **2** into exovesicular sites, where they would rapidly (k_ψ > 0.1 s^{-1}) react with added **4**. The absence of rapid reaction after the extended storage of endovesicular **2** therefore excludes significant flip-flop.

In case 4 (run 6), cosonication of DODAC and *o*-iodosobenzoate (**4**) afforded 18_2 vesicles with **4** at both exo- and endovesicular sites. Subsequent addition of substrate **2** gave *both* fast exovesicular (k_ψ = 0.235 s^{-1}) and slow, permeation-limited (k_ψ = 0.0066 s^{-1}) reactions.

In case 5, exovesicular **4** was removed by Sephadex chromatography before addition of anion **2**. Subsequent addition of **2** then afforded only a slow, permeation-limited reaction (k_ψ = 0.0055 s^{-1}) similar to the slow reaction component of case 4. We suggest that both of these slow reactions represent limiting endo → exovesicular permeations of **4**, followed by rapid reactions with exovesicular **2**. Storage of the chromatographed solutions of endovesicular **4** (case 5) for 20 h, followed by the addition of **2**, gave a reaction with k_ψ = 0.07 s^{-1}, considerably faster than the slow reaction observed with freshly chromatographed (DODAC + **4**) vesicles but slower than the exovesicular **2** + **4** reaction. This result is difficult to interpret precisely but is most likely related to the slow leakage of encapsulated **4**. Note the marked contrast to the parallel experiments with encapsulated **2**, where leakage does not occur over 3 days (cf. the discussion of case 3). This is suggestive evidence that the permeation-limited reactions of **4** and **2** across DODAC membranes involve the migration of **4**, and not **2**. This is in keeping with expectations, because **2** is doubly charged and would be less prone to cross the cationic membrane than the singly charged **4**. Morever, at pH 8, **4** with pK_a ~ 7.2[16] is in equilibrium with its protonated, neutral, presumably more permeable form. In contrast, the carboxylate residue of **2** will remain anionic at pH 8.

In case 6 (run 8), chromatographed solutions of encapsulated **2** *and* encapsulated **4** were *separately* prepared and then combined. *Neither* fast nor slow reactions ensued; only a 5–10% loss of the absorbance of **2** was detected over 20 h. The *double* vesicle barriers of case 6 are therefore very successful in controlling the oxidation reaction. For comparison, note that even the slow reaction of case 2, limited by permeation of exovesicular **4** to endovesicular **2** is 50% complete in ~6 min, whereas the endovesicular **2**/endovesicular **4** reaction of case 6 requires at least 20 h for ~10% of reaction. This represents a rate retardation of >18 000 relative to the exovesicular reaction of **2** and **4** (case 1), where the half-life is ~4 s.

Runs 9 and 10 illustrate two ways in which the "protection" operative in run 8 can be overcome. Addition of pure ethanol to 28 wt % in run 9 initiates a relatively slow, single-exponential, quantitative oxidation of **2** with k_ψ = 0.012 s^{-1}, $\tau_{1/2}$ ~ 1 min.[21] This process is accompanied by an increase in aggregate size to ~3000 Å (dynamic light scattering), suggestive either of vesicle fusion or of an osmotic response[6] to the ethanol dilution. Either event could lead to "damage" of the vesicular compartmentalization, mixing of the encapsulated reagents, and the oxidation of **2** by **4**. Alternatively, in run 10, heating of the (18_2 + **4**)/(18_2 + **2**) vesicle solution to 38 °C, above the gel–liquid crystal phase transition temperture (T_c = 36 °C[2b]) of the DODAC vesicles, leads to a rapid, quantitative oxidation. Obviously, the permeability of the vesicles to **4** increases sharply above T_c.[22]

(18) When 16_2 (**1a**) vesicles were used in the experimental configuration of case 2, only 5% of the slow, endovesicular reaction was observed,[7] presumably because of the low endovesicular capacity of these vesicles. Note that we use "endovesicular" to refer *both* to substrate that is nonconvalently but tightly bound to the vesicles' interior head groups and to substrate that is "dissolved" in the internal water pools but not tightly bound. We cannot differentiate these situations with the current experiments, where they may be functionally identical.

(19) (a) Assuming a bilayer thickness of 36 Å for the DODAC vesicles[2b] and interpreting the reaction as a rate-limiting permeation of exovesicular **4** to endovesicular **2**, followed by a rapid oxidation, we calculate[19b] P ~ 10^{-8} cm/s for the permeation constant of **4** toward sonicated DODAC vesicles at pH ~8. For comparison, P ~ 2 × 10^{-10} cm/s was reported for the permeation of [^{3}H]glucose across 1000-Å DODAB (B = bromide) sonicated vesicles.[19b] (b) Dorn, K.; Klingbiel, R. T.; Specht, D. P.; Tyminiski, P. N.; Ringsdorf, H.; O'Brien, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 1627.

(20) During storage, precautions were taken to prevent the air oxidation of **2** by maintaining nitrogen coverage of the vesicle solutions. In the presence of air, we observed decay of the absorbance of **2** at about 5%/day.

(21) Control experiments demonstrated that 28 wt % ethanol had no effect on the absorbance of DODAC·vesicle-encapsulated **2** in the absence of encapsulated **4**.

Table II. Cleavage of PNPDPP[a] by *o*-Iodosobenzoate[b]

run	conditions	reagent sequence[c]	10^2k_ψ, s^{-1}
1	Tris buffer	PNPDPP + **4**	0.0039
2	CTAB	PNPDPP + **4**	4.7
3	DODAC vesicles	PNPDPP + **4**	3.8
4	DODAC vesicles	(18_2 + **4**) + S + PNPDPP	0.91
5	DODAC vesicles	(18_2 + PNPDPP)[d] + **4**	2.2
6	DODAC vesicles	(18_2 + PNPDPP)[e] + **4**	1.8

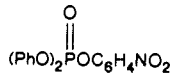
[a] *p*-Nitrophenyl diphenyl phosphate. [b] Reactions were carried out in 0.01 M Tris buffer at pH 8, μ = 0.01 (KCl), 25 ± 1 °C. [Surfactant] = 1×10^{-3} M; [PNPDPP] = 2.5×10^{-5} M; [**4**] = 2.5×10^{-4} M. In runs 4–6, the concentrations of PNPDPP and **4** were halved. [c] Parentheses indicate cosonication; S indicates chromatography on Sephadex G-75 after sonication. [d] Cosonication at pH 5.5; ~35% of PNPDPP was cleaved during sonication. [e] Large vesicles were prepared at pH 5.5 by $CHCl_3$ injection; ~30% of the substrate was cleaved during this process.

Runs 11–13 indicate that DODAC vesicles persist when they are doped with the single-chain surfactant CTAB, even though they become "leaky" as the ratio of the two surfactants approaches 1:1. With DODAC/CTAB = 2:1, the vesicles of runs 11 and 12 behave similarly to the pure DODAC vesicles of runs 4 and 5, respectively. Although the successive fast and slow oxidations of **2** by added **4** are somewhat faster in the covesicles, the separation into distinct exovesicular and endovesicular reactions remains, and exovesicular **4** can be removed by chromatography (run 12). With 1:1 DODAC/CTAB (run 13), however, the vesicles (see note *k* in Table I) have become so leaky that only a single-exponential, very fast oxidation can be observed. All kinetic distinction between exo- and endovesicular events is lost.

Several experiments were also carried out with large ($d \sim 2900 \pm 500$ Å) DODAC vesicles. In an experiment parallel to case 2 (run 4) of Table I, 1×10^{-3} M DODAC was converted to large vesicles by slow injection in the presence of 1.25×10^{-4} M **2**. Subsequent addition of 2.5×10^{-4} M **4** initiated consecutive reactions with k_ψ^f = 0.13 s^{-1} (70%) and k_ψ^s = 0.0025 s^{-1} (30%). These results closely resemble those previously observed with the smaller, 800-Å DODAC vesicles.

A preliminary vesicle fusion experiment was performed with large DODAC vesicle-encapsulated **2** and **4**, parallel to case 6, run 8 of Table I. Control experiments with *emtpy* vesicles showed that the addition of 0.01 M dipicolinic acid (2,6-pyridinedicarboxylate) anions (DPA)[23] at 25 °C initiated an apparent growth in hydrodynamic diameter from 2890 to 5600 Å over ~40 min. The attendant increase in turbidity or adsorption at 400 nm was <0.2. Repetition of this experiment with separately vesicle-encapsulated **2** and **4** led to a very slow reaction with $k_\psi \sim 2 \times 10^{-4}$ s^{-1} (corrected for the absorption increase due to fusion). The reaction ceased after only ~20% decay of the absorbance of **2**. Although some fusion did occur, it was incomplete and inefficient. Related observations have been reported for the fusion of didodecyldimethylammonium bromide vesicles with DPA *below* their phase transition temperature.[23]

Cleavage of PNPDPP. In contrast to the reaction control conferred by DODAC vesicle microencapsulation on the oxidation of Ellman's anion by *o*-iodosobenzoate, little control was evident during the *o*-iodosobenzoate[16] cleavages of *p*-nitrophenyl diphenyl phosphate (PNPDPP (**5**)). The kinetics of these reactions were



5 (PNPDPP)

followed by monitoring the release of *p*-nitrophenoxide ion at 400 nm, and results appear in Table II. Runs 1 and 2 demonstrate the well-known catalysis of phosphate cleavage by cationic micelles.[16,24] Run 3, in comparison to run 2, shows that both vesicular DODAC and micellar CTAB aggregates have similar rate-enhancing effects on the phosphate cleavage of the strongly bound, hydrophobic PNPDPP substrate by the anionic catalyst **4**.

However, in contrast to anion **2** or **4**, which cannot readily permeate DODAC vesicles, *neutral* PNPDPP apparently transits DODAC membranes more rapidly. Thus, the cleavage reaction is slowed only ~4 times when the iodosobenzoate is first encapsulated in DODAC vesicles and subsequently challenged with PNPDPP (compare runs 4 and 3). Moreover, attempts to encapsulate the PNPDPP (runs 5 and 6) failed; reactions with **4** gave monoexponential, quantitative cleavages with rate constants that were similar to those observed in run 3.

Reaction control by microencapsulation in cationic vesicles is more efficient when the reactants are both anionic as with **2** and **4** (or **3** and dithionite; see below). This suggests that the protection afforded by DODAC microencapsulation depends on the ability of the cationic vesicles to inhibit transvesicular migration of the ionic reactants, a process that requires *concurrent* migration of their Na^+ or K^+ counterions in order to maintain electrical neutrality. It is passage of the cations across the DODAC bilayers that is strongly inhibited.[25] However, the neutral substrate, PNPDPP, can permeate relatively freely and subsequently react.

Cleavage of Ellman's Reagent. We reexamined the dithionite ($S_2O_4^{2-}$) ion cleavage of Ellman's reagent (**3**) to Ellman's anion (**2**) in DODAC vesicles, a reaction that we previously studied in vesicular 16_2 (**1a**), where a rapidly established, mobile equilibrium between **3** bound at exovesicular and endovesicular sites led to complex reaction dynamics and biphasic kinetics.[15]

Small DODAC vesicles were prepared by sonication methods (see above and the Experimental Section). In the initial experiments "empty" vesicles were rapidly mixed with substrate **3** and aged, and then the mixture was rapidly combined with $S_2O_4^{2-}$ or another cleavage reagent such as sulfite or thiophenoxide ion. This *normal* reagent addition sequence was sometimes replaced by the *inverse* sequence, where the cleavage reagent was added *before* substrate **3**.

The experiments employed a Dionex Model D-132 three-syringe multimix module, retrofitted to our Durrum Model D-130 stopped-flow spectrometer. Fast reactions were followed on this instrument by monitoring the formation of **2** at 450 nm. Reactions with slow kinetic components were also followed on a Gilford

Table III. Rate Constants for the Cleavage of Ellman's Reagent (**3**)[a]

run	reagent sequence[b]	$k_\psi^{f,c}$ s^{-1}	$10^4k_\psi^{s,d}$ s^{-1}
1	(18_2 + **3**)[e]	none	3.6
2	18_2 + **3**,[f] then $S_2O_4^{2-}$	33.5	none
3	18_2 + $S_2O_4^{2-}$,[g] then **3**	35.0	none
4	18_2 + **3**,[g] then $S_2O_4^{2-}$	48.6[h]	none
5	18_2 + $S_2O_4^{2-}$,[b] then **3**	41.2[h]	none
6	(18_2 + **3**),[g] then $S_2O_4^{2-}$	34.0	5.09 (48%)[i]
7	(18_2 + **3**) + S,[j] then $S_2O_4^{2-}$	none	7.2 (45%)
8	(18_2 + **3**),[g] then SO_3^{2-}	38.0	5.6 (45%)
9	(18_2 + **3**),[g] then PhS^-	64.2	none

[a] Conditions: 0.01 M Tris Buffer, pH 7.8–8.0, μ = 0.01 (KCl), N_2 purge. Final concentrations after mixing: [DODAC] = 5×10^{-4} M; [**3**] = 5×10^{-5} M, [$S_2O_4^{2-}$] = 5×10^{-4} M. [b] See text. [c] Fast pseudo-first-order rate constant obtained on stopped-flow spectrometer. [d] Slow pseudo-first-order rate constant obtained on Gilford spectrometer. [e] Parentheses indicate consonication (Model 1510 immersion probe, 55 °C, 80 W, 15 min). [f] Aged either 10 s or 30 min. [g] Aged 10 s. [h] At 42 °C. [i] Percent of absorbance change due to slow reaction; the balance is fast reaction. The total is the theoretically expected change. [j] S indicates chromatography over Sephadex G-75.

(22) The permeation of **2** into vesicles of 16_2 is accompanied by a time-dependent bathochromic shift of its absorption maximum from ~438 nm (surface binding of **2** to micellar CTABr) to ~450 nm when **2** is equilibrated in the vesicles.[12b] This behavior is *absent* with 18_2 vesicles; at both 25 and 40 °C, the absorbance at 450 nm is time independent. This suggests again that **2** does not permeate into (or out of) DODAC vesicles, so that the reactant with the more readily effected permeation rate must be **4**.

(23) Rupert, L. A. M.; Engberts, J. B. F. N.; Hoekstra, D. *J. Am. Chem. Soc.* **1986**, *108*, 3920.

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Model 250 spectrophotometer to permit more precise determination of their rate constants.

In some cases, the substrate and DODAC were first *cosonicated* at pH 5.5 in 5×10^{-3} M aqueous KCl solution, and the reactions were then initiated by combination with buffer, $S_2O_4^{2-}$, SO_3^{2-}, or PhS^- solution. Most reactions, after reagent combination, occurred at pH 7.8–8.0 in 0.01 M Tris buffer, $\mu = 0.01$ (KCl), and at 25 ± 1 °C. Results are collected in Table III.

In the absence of a specific cleavage reagent, only a slow, buffer (OH^-) cleavage of **3** is observed with $k_\psi = 3.6 \times 10^{-4}$ s^{-1} (run 1), similar to $k_\psi = 7.8 \times 10^{-4}$ s^{-1}, previously reported for the hydroxide ion cleavage of Ellman's reagent bound to DODAC vesicles.[26] This reaction is quantitative and monoexponential, prompting us to suggest that OH^- permeation is not rate limiting here and that the endo- and exovesicular OH^- cleavages of cosonicated **3**/DODAC proceed at similar rates.[27]

Reactions between **3** and $S_2O_4^{2-}$ on the surface of empty DODAC vesicles give simple, quantitative, monophasic kinetics with either the normal or inverse order of reagent addition (Table III, runs 2 or 3) either below (25 °C) or above (42 °C) the T_c of the DODAC vesicles (runs 4 and 5). The behavior of the DODAC vesicles contrasts strinkingly with that of 16_2 vesicles, where biphasic kinetics are observed in normal order reagent addition.[15]

Treatment of cosonicated **3**/DODAC with $S_2O_4^{2-}$ (run 6) or SO_3^{2-} (run 8) leads to rapid exovesicular cleavage of **3**, followed by very slow endovesicular cleavage. The latter reaction is most likely mediated by OH^- (cf. run 1), because neither $S_2O_4^{2-}$ nor SO_3^{2-} is likely to permeate the DODAC vesicles.[28,29] The exovesicular origin of k_ψ^f in run 6 is particularly evident in comparison to run 7. When cosonicated **3**/DODAC is chromatographed over Sephadex before reaction with $S_2O_4^{2-}$, the fast reaction component disappears; only the slow (OH^-) endovesicular reaction remains. In contrast to dithionite and sulfite ions, which do not rapidly permeate the DODAC vesicles, thiophenoxide (which can permeate at pH 8 in its neutral, thiophenol form[15]) cleaves both exovesicular and endovesicular **3** in a rapid, quantitative, monoexponential reaction (run 9).

An experiment was also carried out to show that the DODAC vesicles could be "damaged", negating their ability to prevent reaction between endovesicular **3** and $S_2O_4^{2-}$. Addition of 1×10^{-3} M CTAB to 5×10^{-4} DODAC (cosonicated with **3**), followed by the addition of $S_2O_4^{2-}$, gave only quantitative, monoexponential reaction with $k_\psi = 38$ s^{-1} (compare with runs 2 and 6, Table III). The slow reaction, attributable to endovesicular **3** disappeared, although dynamic light scattering revealed that small vesicles ($d \sim 850$ Å) persisted in the presence of CTAB.

Finally, large DODAC vesicles ($d \sim 3100 \pm 500$ Å) behaved similarly to their small relatives. In an experiment parallel to run 6 of Table III (but using 3 times more **3**), both fast ($k_\psi = 31.2$ s^{-1}) and slow ($k_\psi = 1.9 \times 10^{-3}$ s^{-1}) reactions were observed. Here, however, the fast, exovesicular $S_2O_4^{2-}$ cleavage of **3** accounted for only 17% of reaction. Most of the substrate was encapsulated in the large vesicles and cleaved slowly, presumably as the permeation of buffer hydroxide ions raised the internal pH from 5.5 (the pH during vesicle formation) to 7.9.

Conclusions. The utility of DODAC vesicles as agents of reactivity control is manifest in the results presented here. Pairs of reagents that would ordinarily react within seconds in aqueous solution can coexist for many hours with minimal reaction when encapsulated in DODAC vesicles. The example of Ellman's anion and *o*-iodosobenzoate (Table I and Figure 1) is particularly striking. Case 6, where both reagents are individually encapsulated, dramatically illustrates the effectiveness of the method. Nevertheless, despite the strong control over reactivity in this situation, reaction can be quickly initiated by the addition of a reagent (e.g., ethanol) or by a physical change, such as warming to 38 °C.

Although the encapsulated iodosobenzoate is unavailable to an anionic substrate such as **2**, a neutral substrate such as PNPDPP (**5**) can react with very little hindrance (Table II). The protection from ionic reactants afforded to iodosobenzoate by DODAC encapsulation does not hinder its reactivity toward covalent phosphates, a finding of potential significance in connection with the use of iodosobenzoate as a decontaminant for toxic phosphates.[16,24]

The results with dithionite and Ellman's reagent (**3**) are particularly interesting. Whereas 16_2 vesicles seem quite permeable to **3**,[15] this is not the case with DODAC vesicles, which afford long-lived protection to encapsulated **3** from exovesicular $S_2O_4^{2-}$ or SO_3^{2-} (Table III). We do not believe that this difference between 16_2 and DODAC vesicles is simply a reflection of the lower T_c of the 16_2 vesicles (~25 °C for 16_2Br[12a]) because the porousness of the latter toward **3** persists at 20 °C.[15] Further evidence for the lower permeability of the sonicated DODAC vesicles comes from their resistance to the permeation of **2** either above (40 °C) or below (25 °C) their T_c,[22] whereas $\tau_{1/2}$ for such permeation with sonicated 16_2Br vesicles is ~0.4 s at 25 °C.[12b] Additionally, $\tau_{1/2}$ for the permeation of ammonium 1-anilinonaphthalenesulfonate into sonicated 16_2 vesicles is only 0.7 s at 12 °C (below the T_c) of 0.2 s near the T_c at 25 °C, whereas $\tau_{1/2}$ is 19 s for DODAC vesicles below their T_c at 25 °C (decreasing to 0.4 s at 40 °C, above T_c).

It has been suggested that better "interdigitation" of the longer, opposing hydrocarbon chains within the bilayers of the dioctadecylammonium ion vesicles, and consequent better packing, may be responsible for their lower permeability relative to their lower hexadecyl homologues.[30] Whatever the exact reason(s), it is clear that these simple di-C_{18} vesicles[2] provide remarkable opportunities for reactivity control with a minimum of structural complexity. It is quite possible that *functionalized* dioctadecylammonium surfactant vesicles may also display permeability control and thus support surface-specific vesicular reactions,[14] a property not yet available with their lower hexadecyl homologues.[13] Appropriate experiments to test these possibilities are in progress.

Experimental Section

Materials. Dioctadecyldimethylammonium bromide (Sigma) was converted to its chloride salt (**1b**, DODAC) by ion exchange over 25–50 mesh Dowex 1-X8 resin (J. T. Baker) in its chloride form. DODAC was recrystallized twice from 70% aqueous ethanol; mp 75 °C, decomposition at 85 °C.[31] Elemental analysis and titration indicated 94 ± 3% chloride ion content in the product.

Dihexadecyldimethylammonium bromide (**1a**),[15] Ellman's anion (2-nitro-5-thiolatobenzoate (**2**)),[12b] and PNPDPP (**5**)[24] were prepared as previously described. Ellman's reagent [5,5'-dithiobis(2-nitrobenzoic acid) (**3**)] and *o*-iodosobenzoic acid (**4**) were obtained from Aldrich Chemical Co. and used as received. Buffers were prepared with "steam-distilled" water (distilled, U.S.P., Electrified Water Co., Newark, NJ).

Vesicle Preparation. Vesicle dispersions were normally generated in 0.01 M Tris buffer at pH 8, $\mu = 0.01$ (KCl). Buffer solutions were degassed previously by 30 min of N_2 sparging. Small vesicles were created by sonication with the 108 mm × 3 mm (diameter) immersion probe of a Braunsonic Model 1510 sonicator set at 70 W. Sonication was carried out for 15 min at 50–55 °C. Vesicle solutions were allowed to

(26) Fendler, J. H.; Hinze, W. L. *J. Am. Chem. Soc.* **1981**, *103*, 5439.

(27) At an externally adjusted pH of 11.5, however, exovesicular **3** cleaves with $k_\psi = 0.63$ s^{-1} (50–55%) [Fendler and Hinze[26] report $k_\psi \sim 0.8$ s^{-1} at pH 11.1], whereas endovesicular **3**, initially at pH 8, cleaves with $k_\psi = 9.2 \times 10^{-4}$ s^{-1} (45–50% of reaction). This latter process appears to be OH^- permeation limited.

(28) Baumgartner, E.; Fuhrhop, J. H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 550.

(29) However, at 42 °C (above the T_c of the DODAC vesicles), the reaction of cosonicated **3**/DODAC with $S_2O_4^{2-}$ proceeds rapidly and *quantitatively* with $k_\psi = 48$ s^{-1}. The slow, endovesicular reaction of run 6 has disappeared, indicating that the vesicles are now permeable to **3** or $S_2O_4^{2-}$, or both.

(30) Private communication from Professor H. Chaimovich, University of Sao Paulo.

(31) This is very similar to the melting behavior of the initial bromide salt (mp 75 °C with decomposition at 85 °C). We were unable to locate a literature melting point for DODAC.

(32) Titration was carried out with excess $AgNO_3$, followed by back-titration with aqueous NaBr to an end point indicated electrochemically by a bromide-specific electrode.

cool slowly to 25 °C and were then filtered through 0.8-μM Millipore filters before use. The vesicle size was 700–800 Å by light scattering measurements.

Large vesicles (3000 ± 500 Å) were created by 1 mL/h slow injection (Sage Instruments Model 341A syringe pump) of a 1-mL, 1×10^{-3} M $CHCl_3$ solution of surfactant into 25 mL of buffer at 70 °C. Nitrogen was bubbled through the buffer solution during the injection to facilitate removal of the $CHCl_3$.

Chromatography. If required (see above), vesicle suspensions were passed through a column containing Sephadex G-75. Sephadex G-75 powder (2.5 g, Pharmacia, Inc.) was allowed to swell overnight in ~12 mL of 5×10^{-3} M aqueous KCl or 0.01 M Tris buffer at pH 8. The resulting slurry was degassed by gentle swirling under aspirator vacuum until bubbling ceased. This process required ~1.5 h. The slurry was then diluted to 200 mL with KCl or buffer solution, swirled several times, and set aside until the Sephadex particles had settled. The supernatant, which contained fine particles, was then decanted away. The residual slurry was suspended in a 1 cm × 27 cm glass chromatography column, care being taken to avoid trapped air bubbles. Sephadex particles were allowed to settle by gravity for ~15 min. The column was then *conditioned* by successive passage of 20 mL of buffer, 20 mL of an "empty" vesicle solution, and, finally, 20 mL of buffer.

Solutions of substrate-loaded vesicles were put onto the column in 2-mL volumes, permitted to absorb, and then eluted with buffer. Vesicles with entrapped substrate were obtained from the initial 8–12 mL of eluent, as visualized by light scattering. Free substrate (i.e., exovesicular or nonentrapped) was held up by the Sephadex and eluted after 22–30 mL of eluent, depending on the nature of the substrate.

Light Scattering. Light scattering data were collected at 25 °C and a 90° scattering angle with a Nicomp Model TC-100 computing autocorrelator, an argon laser light source (488 nm), and a Hazeltine microcomputer that used the cumulant program. The channel width was adjusted to produce a decay of 1.5-2.0 s. Vesicles were generated as described above.

Kinetic Studies. Faster reactions were followed on a Durrum/Dionex Model D-130 stopped-flow spectrophotometer coupled either to a Tektronix Model 5103N storage oscilloscope or, via a custom-built interface, to a Commodore Model 8032 computer. Slower reactions were monitored on a Gilford Model 250 spectrophotometer coupled to a Gilford Model 6051 recorder. Rate constants were obtained from computer-generated correlations of log $(A_\infty - A_t)$ with time. Temperature (±1 °C) was controlled by a circulating-water bath. All solutions of **2** were flushed under nitrogen and stored under a nitrogen atmosphere to prevent air oxidation.

The buildup or bleaching of anion **2** was followed at 412 nm (in buffer) or at 450 nm in vesicle solutions. Static UV spectra were recorded on an HP Model 8451A diode array spectrophotometer. Vesicle-containing solutions for either static or kinetic spectroscopy were corrected for background scatter by referencing against "empty" vesicle solutions under identical conditions of concentration and solvent. Kinetic results appear in Tables I–III. Further experimental details are given in the Results and in the table notes.

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Regio- and Stereospecific Construction of Anthracyclinones: Total Syntheses of (±)-γ-Citromycinone and of (±)-Dimethyl-6-deoxydaunomycinone and (±)-Dimethyl-6-deoxyadriamycinone

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Abstract: Total syntheses of (±)-γ-citromycinone (**1**) and of the dimethyl ether derivatives of (±)-6-deoxydaunomycinone (**2a**) and (±)-6-deoxyadriamycinone (**2b**) are described. Key elements of these preparations were regiospecific construction of the anthraquinone **15** through condensation of the (phenylsulfonyl)isobenzofuranone **12** with the cyclohexenone **13**, ene cyclization of the anthraquinone aldehyde **17c** to the naphthacenone **18**, and use of the 7-hydroxyl group in **18** as a neighboring group to effect stereospecific cis epoxidation of the 9,13-olefinic moiety. Opening of the epoxide in **19** with phenyl selenide anion, followed by selenoxide elimination, furnished the allyic alcohol **20a**, which was selectively transformed to A-ring functionalization patterns present in (±)-γ-cytromycinone (**1**), (±)-6-deoxydaunomycinone (**2a**), and (±)-6-deoxyadriamycinone (**2b**).

A feature common to some of the most useful anthracyclines is an A ring with *cis*-7,9-dihydroxylation and a 9-acetyl- or 9-hydroxyacetyl functionality.[2] Stereospecific construction of this substitution pattern has been a continuing synthetic problem.[3] Typically, this fragment has been prepared by introducing the 7-hydroxyl group through bromination–solvolysis of a 9-hydroxyl-containing intermediate;[4-6] however, this approach has not been entirely satisfactory. Only moderate stereoselectivity has been achieved, and preparative scale has been limited by the low solubility of anthracyclinones in media that are compatible with the bromination step.[7] Also, attempted introduction of 7-hydroxyl groups in anthracyclines devoid of a 6-oxygen func-

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