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Chemical Reaction between Colliding Vesicles**

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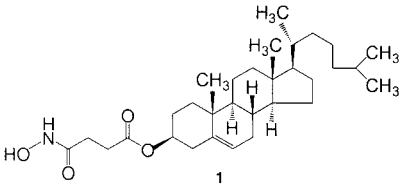
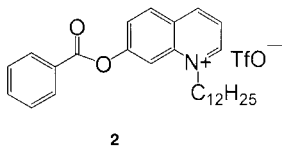
It is difficult to say exactly when the reaction kinetics of water-soluble agents with colloidal assemblies, now a venerable sector of chemistry, first came into prominence. Perhaps it occurred in the l960s when scientists worldwide began studying the reactions of hydroxide and hydronium ions with micelle-adsorbed substrates.[1] Modest rate increases or rate inhibitions (depending upon the electrostatics of the situation) were the general rule. For example, hydroxide-catalyzed ester hydrolysis is accelerated by cationic micelles and inhibited by anionic micelles.[2] A quantitative understanding of such rate effects is now in hand.[3] Later on, attention turned to bimolecular reactions between species in solution and vesicular reactants. For example, rates of reduction between external dithionite and vesicle-bound dye were established.[4] Owing in part to the hundreds of publications on the kinetics of reagent/colloid reactions, we now have an appreciation of colloids' interfacial polarity,[5] concentration of bound counterions,[6] molecular dynamics of assembly components,[7] and various size, shape, and phase properties.[8]

The next higher level of complexity, namely the reaction kinetics between two discrete molecular assemblies, has never received much attention. This is surprising considering the biological relevance of inter-assembly reactivity. One merely has to consider a sperm penetrating an ovum, or a virus penetrating a cell, to recognize the importance of membrane/membrane reactivity.[9] It is for this reason that we began examining vesicle/vesicle reactions. The idea was to place a nucleophilic lipid in one phospholipid vesicle, and an electrophilic lipid in another, and to monitor the ensuing reaction efficiency as the two vesicles collided. In preliminary experiments, we found that vesicle/vesicle reactivity is indeed an observable phenomenon, and that its rates depend upon the exposure of the membrane-bound functionalities to the external water.[10] Encouraged by these results, we continued our investigation and now report a reaction whose molecular features—including vesicle-to-vesicle transfer processes during collision—were revealed by the kinetics.

The reaction in question involves two amphiphilic compounds: a steroidal nucleophile **1** and a long-chain quinolium ester **2**. Nucleophile **1** is a known hydroxamic acid[10] (pK_a = ca. 9.4)[11] which, under the basic conditions of our experiments (pH 9.0), partially transforms into a powerful esterolytic species: hydroxymate.[12] The cholesterol moiety of **1**, with its known affinity for bilayer membranes,[13] serves to "anchor" the molecule in the vesicles. Substrate **2** is a labile ester whose cleavage leads to a marked increase in absorbance and fluorescence. Membrane affinity, in this case, derives from a hydrophobic dodecyl chain.





Reactant **2** possesses a useful trait that, to our knowledge, is rare or nonexistent among reactive fluorescent probes. Hydrolysis of **2** produces a fluorescent hydroxyquinolinium ion that retains its hydrophobic chain. Consequently, this ion tends to remain within the membrane where it is initially formed. This facilitates direct visualization of membrane reactions (as by fluorescence microscopy) compared to systems in which the reactive probes eject their incipient

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fluorescent moiety into the outlying solution. Compound **2** can be obtained by preparing 7-benzoxyquinoline according to the method of Cavallito and Haskel.[14] The quinoline (0.10 g, 0.40 mmol) and dodecyl triflate[15] (0.40 mmol) in dichloromethane under N_2 is then refluxed overnight. Solvent is removed to give a solid which, upon trituration with diethyl ether, yields a pure white solid (m.p. 80.5–82 °C) with the correct ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, FAB-HRMS, and C, H, N, and S elemental analyses.

Two sets of vesicles were prepared (one with **1** and the other with **2**) in the following manner: Solvent from a solution of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (2.2 mg) in chloroform plus either 10 mol % **1** or 2 mol % **2** was removed under reduced pressure in a 5 mL round-bottom flask to form a thin film. The phospholipid film was hydrated for 5 min with 0.05 M carbonate buffer (1.0 mL; pH 9.0) under stirring, whereupon the resulting suspension was passed back and forth (19 times) through a polycarbonate membrane (100 nm pore diameter) using a LiposoFast vesicle extruder. The vesicles had mean hydrodynamic diameters of 110–130 nm (measured routinely with a Coulter N4 particle-sizer and found to remain constant before and after the kinetic runs).

As seen in Table 1, seven different reaction modes, including our controls, were carried out. All runs were initiated by bringing ester **2** to a concentration of 2×10^{-5} M in a cuvette containing buffer or buffered nucleophile. This was accomplished by either a) adding a 30 μL aliquot of 2.0 mM **2** in acetonitrile to a 3.0 mL solution in a cuvette or b) adding a 1.0 mL suspension of vesicular **2** to a 2.0 mL solution in a cuvette. Nucleophile, already in the cuvette when the above additions occurred, consisted of 0.1 or 1.0 mM aqueous acetohydroxamic acid (in our control runs) or 0.1 mM vesicular **1** (in the vesicle/vesicle run). For convenience, experimental conditions are also specified in the table for each of the reaction modes. Note that all runs were carried out at 25.0 °C (a full 28 °C above the transition temperature of the carrier lipid).[16] Thus, our results reflect exclusively the behavior of a fluid, liquid-crystalline membrane phase.

Table 1. Rates of a bimolecular reaction in vesicular systems.

Entry	Type of reaction	Schematic[a]	$t_{1/2}$ [min]
1	solution background	E in buffer	38
2	solution – solution	E 1 mM AH	0.21
3	vesicle background	E in buffer	1700
4	vesicle – solution	E 1 mM AH	34
5	vesicle – solution	E 0.1 mM AH	180
6	vesicle – solution	E; Nu 0.1 mM Nu	0.75
7	vesicle – vesicle	E; Nu 0.1 mM Nu	4.2

[a] Carbonate buffer (0.05 M, pH 9.0) and 25 °C in all runs. Concentration of electrophile (*N*-dodecyl-7-benzoxy quinolinium triflate) = 2×10^{-5} M. AH = acetohydroxamic acid. Concentration of structural lipid (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine) = 2.2 mg mL^{-1}. The Nu-bearing compound represents **1**, and the E-bearing compound represents **2**.

Reactions were monitored spectrophotometrically (427 nm; Varian DMS 300) and spectrofluorometically ($\lambda_{ex} = 418$ nm, $\lambda_{em} = 521$ nm; Shimadzu RF-5000). The two methods gave rate constants that agreed, for example, to within 2 % for the vesicle/vesicle reactions. All pseudo-first-order plots (processed with the aid of Microsoft Excel) were linear to greater than two half-lives. Half-lives listed in the Table l are averages from two to six runs in good agreement with each other. Since the infinity absorbances of the spectrophotometric runs were always within 10 % of the absorbance expected from *total* hydrolysis of vesicular **2**, "flip-flop" of **2** from the inner leaflet to the outer leaflet of the bilayer (where exposure to the nucleophile occurred) must be fast on the time scale of our experiments.

Entry 1 of Table 1 shows that ester **2** in a pH 9.0 buffer at 25.0 °C hydrolyzes with a half-life $t_{1/2}$ of 38 min. Addition of l.0 mM nucleophilic acetohydroxamate diminishes $t_{1/2}$ to 0.21 min (Table 1, entry 2). (Ester **2** is undoubtedly monomeric in the reactions given in entry 1 and entry 2 because its concentration of 2×10^{-5} M lies far below the critical micelle concentration for a 12-carbon surfactant).[17] When the ester is incorporated into a phospholipid vesicle (Table 1, entry 3), the spontaneous hydrolysis rate becomes very slow ($t_{1/2}$ = 1700 min). Presumably, the ester **2** head group resides at the membrane/water interface (owing to its cationic charge) where it is protected from attack by hydroxide. Several factors could contribute to this protection: electrostatic repulsion of hydroxide by the lipid's phosphate groups; a reduced dielectric constant at the bilayer surface; and steric inhibition at the adsorption site. The comparison between $t_{1/2} = 1700$ min (Table 1, entry 3) and $t_{1/2} = 38$ min (Table 1, entry 1) proves that a *minimum* of 98 % **2** partitions into the vesicles. If, as is likely, vesicular **2** has an inherent reactivity, then the partitioning must be even greater than the minimum value.

A vesicular rate retardation was also found in the acetohydroxamate-induced hydrolyses. Thus, binding the ester to the vesicles inhibits the acetohyroxamate reaction by 162-fold (compare entry 4 and entry 2 in Table 1). Lowering the acetohydroxamate concentration from l.0 mM to 0.10 mM (Table 1, entries 4 and 5) slows the reaction from a $t_{1/2}$ of 34 min to a $t_{1/2}$ of 180 min, respectively.

The fastest hydrolysis in our vesicle series occurred when monomeric **2** was added externally to 0.1 mM vesicular **1** (Table 1, entry 6). A half-life of only 0.75 min was observed. The most plausible explanation involves the incorporation of ester **2** into the nucleophile-bearing vesicles where a fast *intra*-vesicular hydrolysis then takes place. Electrostatic effects (i.e.

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attraction between cationic ester **2** and vesicles rendered anionic by the presence of **1**) likely augment hydrophobic association. Adjusted for the concentration differences, the intra-vesicular reaction rate is equivalent to that of the intermolecular reaction between monomeric species (Table 1, entry 2). An entropically favorable confinement of the reactants within the bilayer assembly must evidently compensate for any inhibitory rate effects inherent to the membrane environment.

With all the control runs suitably investigated, we were able to examine the vesicle/vesicle reaction (Table 1, entry 7). Its $t_{1/2}$ of 4.2 min indicates a much faster reaction than vesicular **2** plus *monomeric* acetohydroxamate (Table 1, entry 4, $t_{1/2}=$ 180 min). This fact, plus the highly efficient intra-vesicular reaction evident in entry 6, suggests a reasonable mechanism for the vesicle/vesicle reaction: Collisions between vesicles containing **l** and vesicles containing **2** lead to a transfer of **2** from one vesicle population to the other.[18] (Potent steroidal anchoring of **1** has been shown previously to prevent a corresponding migration of the nucleophile within our timescale).[10] A fast intra-vesicular catalyzed hydrolysis, depicted schematically in Figure 1, ensues.

A possible variation of the above vesicle-transfer mechanism was considered. Perhaps ester **2** departs from its vesicles, enters the water, and re-adsorbs into the vesicles containing nucleophile **1**. To test this idea, we studied the vesicle/vesicle reaction with an ester in which the dodecyl chain had been replaced by an octadecyl group. Adding six more carbon atoms should seriously impede any partitioning of the ester from the membrane into the free solution. Yet the vesicle/vesicle rates with the octadecyl analogue are only fourfold smaller than with the dodecyl ester **2.** This result is fully consistent with a collision-induced vesicle-to-vesicle transfer that is mildly retarded by the longer chain length.

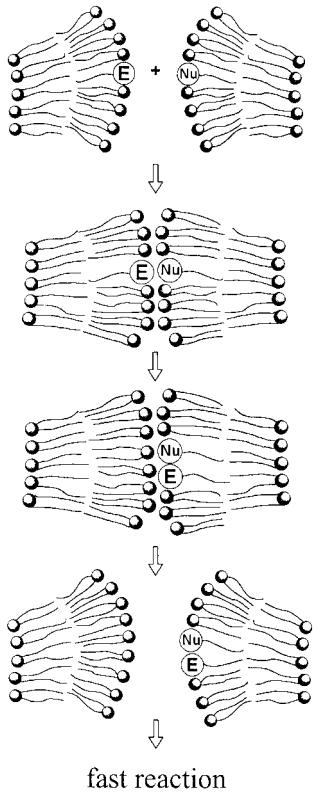

Figure 1. Proposed mechanism for a vesicle/vesicle reaction in which the vesicles collide, the electrophile gets transferred, and a fast intra-vesicular process ensues.

At the moment, organic reactivity among various colloidal particles is a scientific nursling. Further experimentation in the area, as colloid chemistry simulates and ultimately subsumes biology, is an easy call.

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Photochemical Activation of the N≡N Bond in a Dimolybdenum–Dinitrogen Complex: Formation of a Molybdenum Nitride**

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Herein we describe a novel contribution to the developing field of N≡N bond cleavage reactions,[1–3] in which we have for the first time cleaved the N≡N bond by using light and transition metal complexes. Only two groups[1, 2] have so far given detailed information on the pathways leading to the six-electron reduction of dinitrogen. Such a reduction is a stepwise metal-assisted transformation consisting, usually, of a four-electron reduction of N_2, leading to a dimetallahydrazone, $L_nM{=}N{-}N{=}ML_n$, followed by a final, thermally induced reductive cleavage of the residual N–N bond. The present report focuses on the generation of the d^3-$[Mo(Mes)_3]$ frag-

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