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Destructible Vesicles of a Functionalized Surfactant

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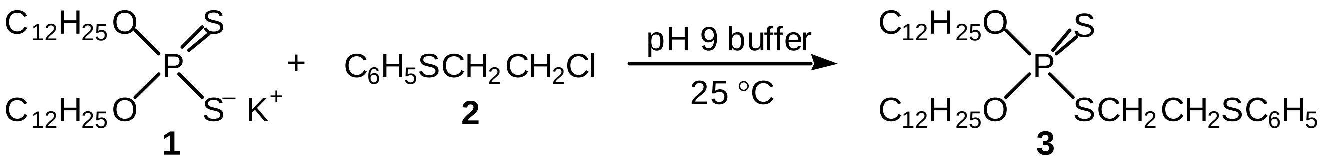
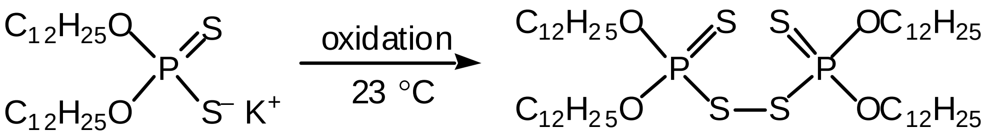
Vesicle Chemistry

- Numerous studies of vesicle chemistry have been reported. Most of these have involved submicroscopic vesicles (diameter ca. 20-200 nm) and several studies have involved giant vesicles (GVs, diameter ca. 10-200 μm).
- A notable feature available to GV, but not to submicroscopic, vesicle chemistry is the ability to observe the effects of chemical processes on the vesicles themselves in real time by optical microscopy.
- On the other hand, the course of submicroscopic vesicle but not that of GV processes can often be followed by spectroscopic methods.
- Among the studies of GV chemistry, some have involved processes that resulted in GV destruction/damage.
- In a study of simultaneous decontamination and signaling of chemical agents, we reported reactions of surfactant **1**'s GVs and small unilamellar vesicles (SUVs) with mustard simulant **2** to give **3**, which necessarily destroys the vesicles, since neutral **3** cannot support vesicle formation.



Jaeger, Schilling, Zelenin, Li, Kubicz-Loring *Langmuir* **1999**, *15*, 7180

- We have now studied the oxidation **1**’s GVs and SUVs to disulfide-linked dimer **4**, which results in vesicle destruction, and in particular, observable GV destruction during periods as short as ca. 16 sec.



1 **4**

- This reaction necessarily destroys **1**’s vesicles, because neutral **4** cannot support vesicle formation.

Jaeger, Zeng *Langmuir* **2003**, *19,* 8721

- Vesicles of **1** were prepared in both H_2O and a pH 8.0 phosphate buffer:

✓ SUVs by sonication, and multilamellar GVs by hydration of a thin smear of solid **1**.

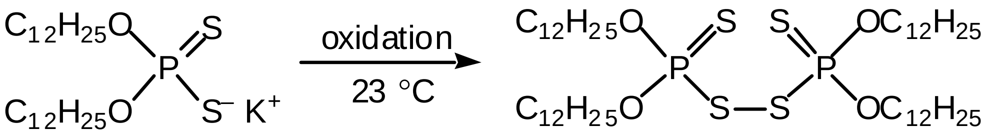
✓ GVs have diameters of ca. 25-100 *μ*m in both solvents and are stable for ≥5 days at 23 °C.

✓ SUVs in H_2O have hydrodynamic diameters of ca. 70 nm and are stable for ≥2 days; the phase transition temperature of **1** vortexed in H_2O is 16.3 °C.

- **1**'s SUVs and GVs were oxidized to **4** in the buffer or H_2O at 23 °C with sodium hypochlorite (bleach), ceric ammonium nitrate (CAN), hydrogen peroxide, and sodium hydrogenperoxymonocarbonate ($HOOCO_2Na$), prepared from hydrogen peroxide and sodium bicarbonate.

$$HOCO_2^- + H_2O_2 \rightleftharpoons HOOCO_2^- + H_2O$$

- In each reaction, the ratio of equivalent amounts of oxidizing agent and surfactant **1** was 2:1, respectively.

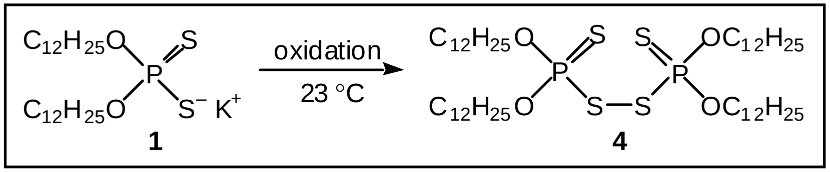


1 **4**

Oxidations of 1's SUVs to 4 at 23 °C

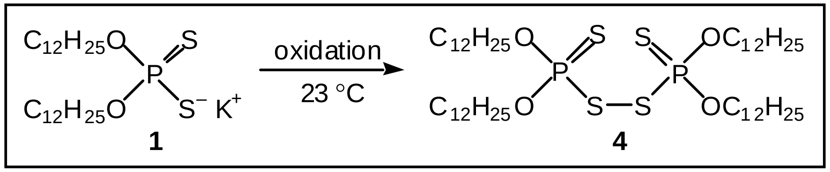
		small (NMR) scale		preparative scale	
oxidizing agent	**solvent**	**reaction time**	**% conversion of 1**	**reaction time**	**% yield of 4**
NaOCl	**pH 8.0 buffer**	**5 min**	**100**	**10 min**	**98 ± 3**
$(NH_4)_2Ce(NO_3)_6$	**water**	**5 min**	**100**	**10 min**	**88 ± 1**
H_2O_2	**pH 8.0 buffer**	**3 h**	**ca. 90**	**4 h**	**82 ± 2**
$HOOCO_2Na$	**pH 8.0 buffer**	**24 h**	**ca. 85**	**24 h**	**82 ± 4**

- In the small (NMR) scale reactions, the conversion of **1** into **4** was monitored by ^{31}P NMR. The signal for **1** (δ 111.7) decreased as that for **4** (δ 85.3) increased, and no other signals were detected (other than signal at δ 3.5 for phosphate buffer).
- The conversion of **1** to **4** was almost certainly 100% complete at much shorter reaction times than 5 min with NaOCl and CAN, based on the results with GVs.
- **4** was isolated by column chromatography in the preparative reactions and characterized combustion analyses and high resolution FAB MS, in addition to NMR.

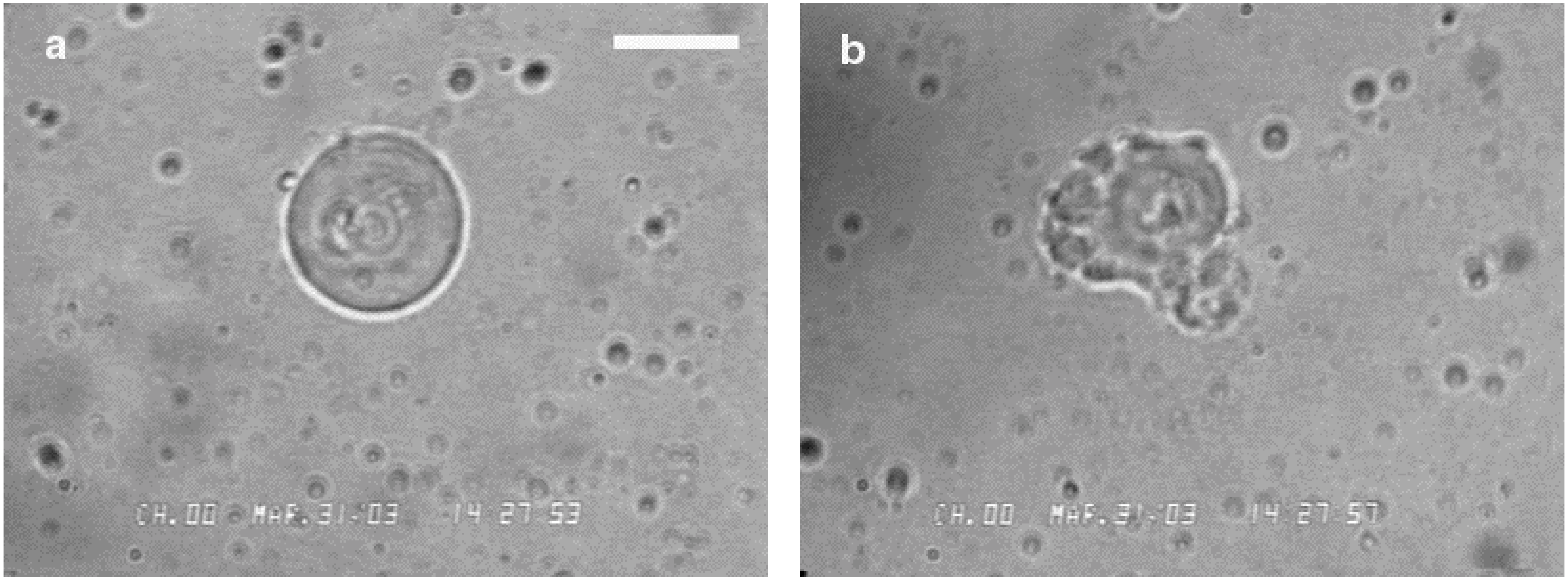


- GVs of **1** were oxidized to **4** at 23 °C with the same oxidizing agents, ratio of equivalent amounts, and solvents as used in the SUV oxidations.
- After the addition of oxidizing agent, each reaction mixture was observed in real time by phase-contrast optical microscopy.
- Approximate reaction times required for (complete) destruction of the GVs:
  - 16 sec with NaOCl (bleach)
  - 50 sec with CAN
  - 260 min with H_2O_2
  - 9 h with $HOOCO_2Na$

Phase-contrast photomicrographs of a GV of surfactant **1** undergoing oxidation to **4** with NaOCl at 23 °C (scale bar = 50 *μ*m)

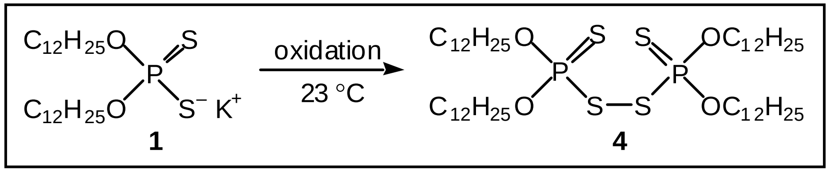


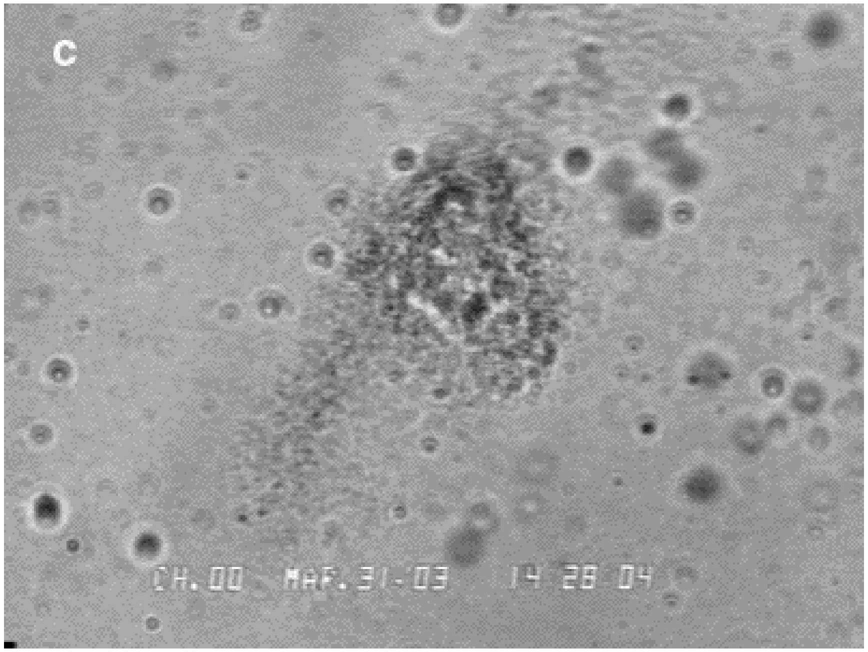
1 **4**



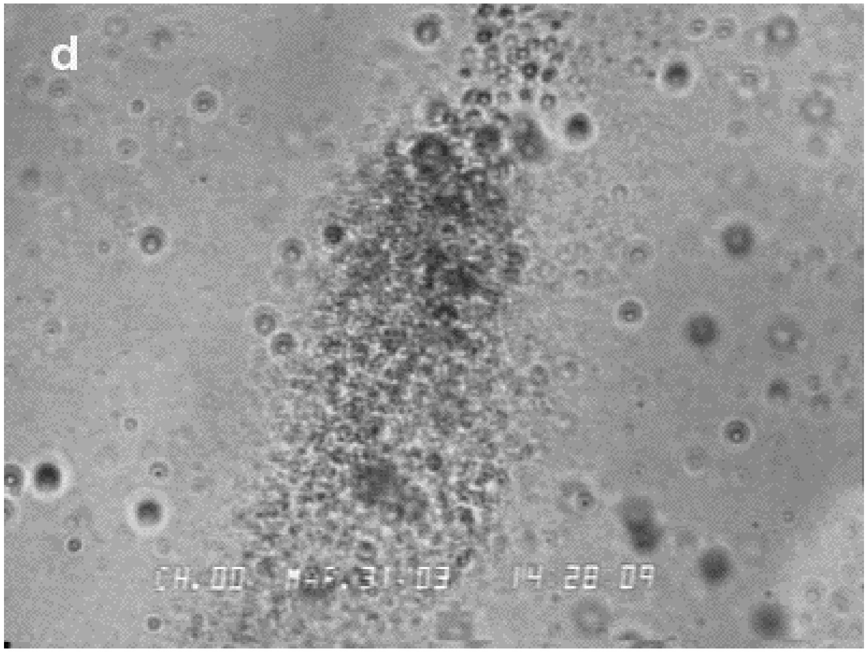
before addition of bleach

4 sec after addition



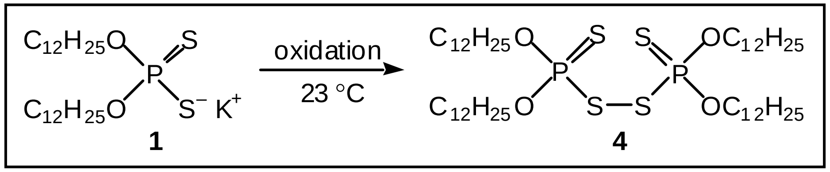


11 sec after addition of NaOCl

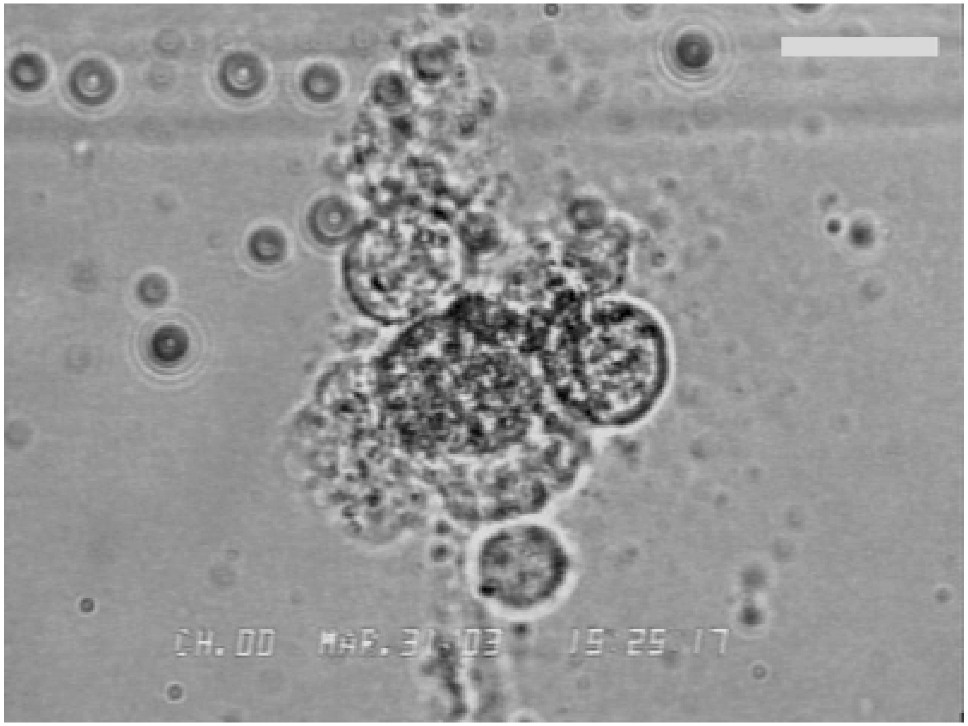


16 sec after addition

- The same oxidation of **1**'s GVs with NaOCl was performed in the pH 8.0 buffer prepared in D_2O at 23 °C.
- After 5 min, the reaction mixture was transferred to an NMR tube from microscope slide assembly used for observation by optical microscopy.
- ^{31}P NMR spectrum of the reaction mixture contained only one singlet at δ 86.0, which corresponds to **4,** in addition to the phosphate buffer signal.
- Thus GV destruction results from the conversion of surfactant **1** into disulfide-linked dimer **4**, which cannot support vesicle formation.
- The oxidative destruction of **1**'s GVs with CAN, as observed by phase-contrast optical microscopy, was comparable to that with bleach, occurring within ca. 50 sec.



- The destruction of **1**’s GVs was slower with H_2O_2 and $HOOCO_2Na$ than with NaOCl and CAN.
- Phase-contrast photomicrograph of GVs undergoing oxidation, recorded at 42 min after the addition of H_2O_2 (scale bar = 50 μm).
- Even though (complete) destruction of GVs required about ca. 260 min with H_2O_2, it is evident that observable damage to the GVs begins at shorter reaction times.
- Analogous observations were made in GV oxidations with $HOOCO_2Na$.

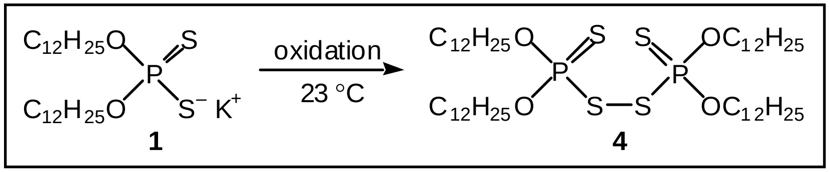


Nature of Actual Oxidizing Agents

- In the oxidation of vesicular **1** to **4** by $(NH_4)_2Ce(NO_3)_6$ (CAN) in water, the actual oxidizing agent is almost certainly Ce^{4+}.
- But the identities of the actual oxidizing agents in the pH 8 buffer with NaOCl, H_2O_2, and $HOOCO_2Na$ cannot be stated with certainty.
- The possible oxidizing agents with NaOCl include ^{-}OCl itself and HOCl, Cl_2, Cl_3^{-}, and Cl_2O.
- With H_2O_2, the possibilities are H_2O_2 itself and perhaps ^{-}OOH.
- With $HOOCO_2Na$, the possible oxidizing agents include $HOOCO_2^{-}$ itself and perhaps $HOOCO_2H$, as well as H_2O_2 and ^{-}OOH, since $HOOCO_2^{-}$ is in equilibrium with H_2O_2.

$$\boxed{HOCO_2^{-} + H_2O_2 \overset{K}{\rightleftharpoons} HOOCO_2^{-} + H_2O \qquad K = 0.32\ M^{-1}}$$

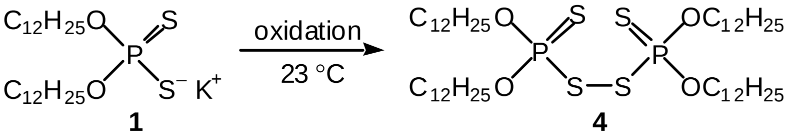
- Oxidation by an anionic species (*e.g.*, ^{-}OCl, Cl_3^-, ^{-}OOH, and $HOOCO_2^-$) should be impeded by its electrostatic repulsion from vesicular **1**'s negatively charged interfaces.
- But oxidation by Ce^{4+} should be facilitated by its electrostatic attraction to the interfaces.
- Oxidations of vesicular **1** to **4** with $HOOCO_2Na$ are slower than those with H_2O_2, in contrast to the greater reactivity of $HOOCO_2Na$ in the oxidations of aryl sulfides to sulfoxides, which proceed by nucleophilic attack of the sulfide at the electrophilic oxygen of $HOOCO_2^-$.
- Given the repulsion of $HOOCO_2^-$ from the interfaces of vesicular **1**, H_2O_2 is likely the major oxidizing agent in reactions with $HOOCO_2Na$.



- Note that all but one of the oxidations were performed in a pH 8 phosphate buffer.
- Given the formation of $HOOCO_2^-$ from $HOCO_2^-$ and H_2O_2, it is appropriate to address the formation of peroxyphosphate species $H_2PO_5^-$ and HPO_5^{2-} in the phosphate buffer.
- Since it is known that H_2O_2 does not convert $H_2PO_4^-$ or HPO_4^{2-} into the corresponding peroxy anions, the possibility of these species as oxidizing agents can be discounted.
- Also, $H_2PO_5^-$ and HPO_5^{2-} are not formed in reaction mixtures containing NaOCl either, since it is known that $H_2PO_5^-$ oxidizes Cl^- to Cl_2.
- Peroxymonophosphoric acid (H_3PO_5) can be formed by the reaction of H_2O_2 and P_2O_5.

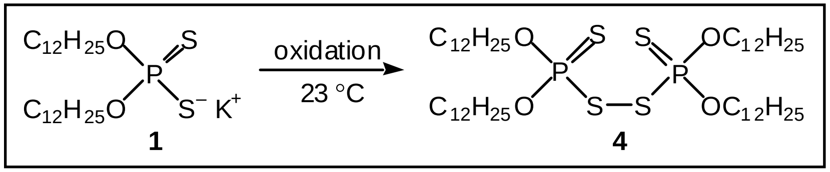
Possible Mechanisms for Oxidation of 1 to 4

- It is known that the mechanism of thiol (RSH) to disulfide (RSSR) oxidation varies with the oxidizing agent.
- Possible mechanisms for RSH to RSSR include sequences such as:
  - (a) Oxidation of RSH/RS$^-$ to RS·, followed by radical coupling to give RSSR.
  - (b) Nucleophilic displacement by sulfur at the active oxygen of a peroxy species to give sulfenic acid (RSOH), followed by its reaction with RSH to afford RSSR.



Summary

- The results suggest that surfactant **1**’s vesicles have potential as storage and release devices.
- Water-soluble compounds could be entrapped within their aqueous compartments and then released upon demand as **1** is oxidized to **4**.
- Note that in its oxidation to disulfide-linked dimer **4**, surfactant **1** functions as a chemodegradable surfactant, since it is converted into a nonsurfactant product by a chemical reaction.



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