Direct Observation of Exovesicular and Endovesicular Diazo Coupling Reactions

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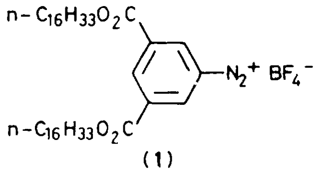
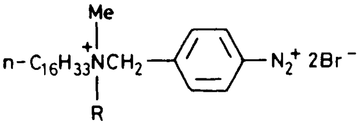
Azo coupling reactions between β-naphthol substrates and vesicular arenediazonium ion surfactants take place at both external and internal vesicular surfaces with distributions that are sensitive to the presence of anionic substituents on the substrates.

Fuhrhop recently reported that vesicles prepared by sonication of the arenediazonium ion (**1**) underwent diazo coupling to 7-amino-1-hydroxynaphthalene-3-sulphonic acid only at the external (exovesicular) surface.[1] The evidence for exovesicular reaction, however, was indirect, being based on differential u.v. spectra of the completely reacted compounds in organic solvents and of the (partially) reacted compounds in vesicular aqueous solution.[1] Our interest in surfactant arenediazonium ions[2] and vesicle-localized reactions[3] has now led to a comparative study of the diazo coupling reactions of micellar (**2**) and vesicular (**3**). The results show that both exovesicular and endovesicular reactions are clearly manifested by (**3**), but that the endovesicular process can be suppressed with appropriate substrates.

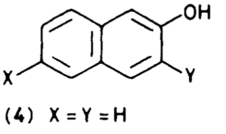
The dihexadecyl surfactant (**3**) was prepared by a reaction sequence which closely paralleled that employed in the synthesis of its monohexadecyl analogue (**2**).[2a]† The anilinium ion precursor of (**3**) ($-NH_3^+$ instead of $-N_2^+$) was sonicated (Braun-sonic model 1510 sonifier, 60—65 °C, 200 W, 30 min) in aqueous HBr (pH 2) to form vesicles of *ca.* 900 Å diameter.‡ The vesicular anilinium ions were then diazotized with equimolar $NaNO_2$ (15 °C, 20 min, pH 2) yielding vesicular (**3**), *d ca.* 660 Å‡ at pH 5. The small decrease in vesicle diameter between the anilinium and diazonium ion vesicles could be due to the decrease in the diameter of the head group functionality. Solutions of vesicular (**3**) could be stored briefly at pH 5 and 0 °C, where they were moderately stable, but they were generally used immediately in coupling reactions.



(1)



(2) R = Me
(3) R = n-$C_{16}H_{33}$



(4) X = Y = H
(5) X = $SO_3^-Na^+$, Y = H
(6) X = Y = SO_3^- Na^+

Coupling of micellar (**2**) to β-naphthol (**4**) and to the sulphonate (**5**) has been reported;[2a] azo coupling at the α-aromatic position occurs very rapidly at pH *ca.* 7, with micellar catalytic advantages of 122 and 244, respectively. Azo coupling of (**4**) to vesicular (**3**) was similarly examined on a stopped-flow spectrophotometer, following the formation of azo product at 485 nm.§ The vesicular process was kinetically *biphasic*, consisting of a rapid, pseudo-first-order reaction, $k_\psi = 0.600 \pm 0.005$ s^{-1} (*ca.* 85% of reaction), followed by an approximately first-order, slower reaction, where k_ψ ranged from 0.005 to 0.015 s^{-1} (*ca.* 15% of reaction) over several experiments. In contrast, the analogous micellar reaction of (**2**) with (**4**) was rigorously *monophasic*, with $k_\psi = 0.107 \pm 0.002$ s^{-1}.

In analogy to the kinetically biphasic esterolysis of *p*-nitrophenyl acetate by fully functionalized thiol vesicles,[3a] we assign the rapid coupling reaction of (**3**) to *exovesicular* diazonium ion moieties, and the slower coupling reaction to *endovesicular* diazonium groups. Micellar (**2**), with only one (time averaged) reactive surface, gives a kinetically monophasic coupling reaction. Because the micellar and exovesicular surfaces of (**2**) and (**3**) are similar, they afford k_ψ values of similar magnitude, although the vesicular reaction is somewhat faster at [surfactant] = 5 × 10^{-4} M, presumably owing to a greater binding constant of vesicular (**3**) towards (**4**). Again in parallel, both (**2**) and (**3**) (exovesicular reaction) exhibit increasing k_ψ with increasing surfactant concentrations at constant [(**4**)]. The forms of these relations are typical of micellar[2a] or vesicular[3a] saturation kinetics.[4]

Most significantly, when the coupling reactions of vesicular (**3**) are extended to the sulphonates (**5**) and (**6**), the slow, endovesicular reaction is suppressed. Analogous micellar reactions of (**2**) with (**5**) or (**6**) remain uniphasic. Table 1 collects observed pseudo-first-order rate constants for the diazo coupling reactions of (**2**) or (**3**) to β-naphthols (**4**)—(**6**). Rapid exovesicular reactions of (**3**) are observed with each substrate, and with increasing kinetic advantage relative to the comparable micellar process, as the number of substrate sulphonate residues increases.¶ However, the slow, endovesicular reactions of (**3**) are concomitantly suppressed,

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† *N,N*-Dihexadecyl-*N*-methylamine was quaternized with *p*-acetamidobenzyl bromide in $MeNO_2$, affording the crystalline (m.p. 102—103 °C) acetamido precursor of (**3**), which was characterized by n.m.r. and elemental analysis. Deprotection (5% HBr–MeOH, 60 °C, 2 days) gave the corresponding aniline derivative (liquid cryst. 85—150 °C, decomp.), which was characterized by n.m.r., but was unstable and required storage at −70 °C.

‡ Light scattering measurements employed an Ar laser (488 nm) and a Nicomp model TC-100 computing autocorrelator.

§ Conditions: 0.01 M Tris buffer, pH 7.1, μ = 0.01 M (KCl), 15 °C, [surfactant] = 5 × 10^{-4} M, [substrate] = 5 × 10^{-6} M.

¶ This trend reflects the generally greater binding capacity of (cationic) vesicles relative to micelles; the advantage increases with each additional anionic residue substituted on the substrate. The trends exhibited by the individual rate constants are more complicated and cannot be readily explained with the available information.

Table 1. Pseudo-first-order rate constants (s^{-1}) for azo coupling reactions.[a]

		Substrate		
Reagent	Phase	(4)	(5)	(6)
(2)	Micellar	$0.107 \pm 0.002_3$	$0.096 \pm 0.001_3$	$0.0086 \pm 0.0001_2$
(3)	Vesicular	$0.600 \pm 0.005_3$	$1.58 \pm 0.04_3$	$0.51 \pm 0.02_3$
k_3/k_2		5.6	16	59

[a] Conditions are described in the notes.§ Errors in rate constants are average deviations of *n* (subscript) runs.

decreasing from 14—15% of the total vesicular reaction with (**4**), to 2—3% (k_ψ *ca.* 5×10^{-4} s^{-1}) with the naphthol sulphonate (**5**), and to 0% with the naphthol disulphonate (**6**).

We suggest that (**4**), in its neutral (naphthol) form, permeates vesicular (**3**) at a rate comparable to the exovesicular azo coupling rate; consequently both exovesicular and endovesicular reactions are observable. However, the permeation rate of the anionic sulphonate (**5**), relative to exovesicular azo coupling, is not as favourable as is that of (**4**), so that endovesicular reaction of (**5**) is largely suppressed. Continuation of this trend with dianionic (**6**) leads to elimination of the endovesicular reaction in favour of the exclusive exovesicular reaction.

The reaction of (**3**) with (**5**) corresponds to the system studied by Fuhrhop,[1] but the present, *direct* kinetic study of exo- and endo-vesicular reactions is surely more sensitive than a differential u.v. study of the reaction products formed under vesicular or nonvesicular conditions. Our work therefore provides direct evidence for the kind of 'unsymmetrical' (exovesicular) reaction reported by Fuhrhop.[1]

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