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LETTERS

Regioselectivity Control in a Diels-Alder Reaction of a Surfactant 1,3-Diene with a Surfactant Dienophile

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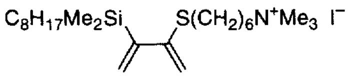
Abstract: The Diels-Alder reaction of surfactant 1,3-diene **1** and surfactant dienophile **2** within aqueous mixed micelles at 25 °C gave a 6.6:1 ratio of cycloadducts **11** and **12**, and that of nonsurfactant analogues **10** and **13** in C_6H_5Me at 75(85) °C gave a 1:1 ratio of cycloadducts **14** and **15**. The regioselectivity of the reaction of **1** and **2** was controlled by their alignment at the mixed micelle-H_2O interface.

Keywords: Diels-Alder reactions; Micellar systems; Regiocontrol; Surfactants

Diels-Alder reactions performed in H_2O and aqueous surfactant-based media generally benefit from increased rates and stereoselectivities relative to reactions in conventional organic solvents.[1] The ability of surfactant-based media to control the regioselectivity of Diels-Alder reactions has received only limited attention.[2,3]

Previously, we reported two studies of Diels-Alder reactions in aqueous surfactant aggregates: one of a cationic surfactant 1,3-diene with a neutral nonsurfactant dienophile,[2] and another of a different cationic surfactant 1,3-diene with cationic surfactant dienophiles.[3] In the first study, orientational effects within the aggregates were not strong enough to overcome the intrinsically preferred regiochemistry of the reaction. In the second, only modest regioselectivity was obtained, in part due to the fact that the Diels-Alder reactions were performed at 100 °C, where the organizational abilities of aqueous aggregates are almost certainly less than at lower temperatures.

Herein we report the results of a study of regioselectivity control in Diels-Alder reactions of surfactant 1,3-diene **1** with surfactant dienophile **2** resulting from interfacial orientational effects within aqueous mixed micelles at 25 °C. This Diels-Alder system should display no regiochemical preference in the absence of such effects, since the substituents at carbons 2 and 3 within **1** and those at carbons 1 and 2 within **2** are close to being both electronically and sterically equivalent with respect to the diene and dienophile reaction centers, respectively.



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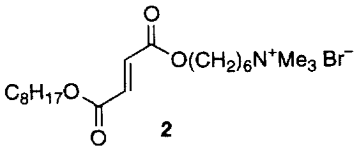

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Diene **1** was synthesized as summarized below;[4] dienophile **2** has been reported[3] previously. Quaternary hydrazinium chloride **3**, obtained from the reaction of 6-chloro-1-hexanol (Aldrich) with *N,N*-dimethylhydrazine, was converted[5] into amino alcohol **4**.[6] The reaction[7] of this material with hydrobromic acid and thiourea gave, with the intermediacy of the corresponding bromo amine, isothiuronium salt **5**, which without isolation was hydrolyzed[7] to yield amino thiol **6**. Then **6** was converted[8] into disulfide **7**. 1,3-Diene **8**[9] was transformed[9]

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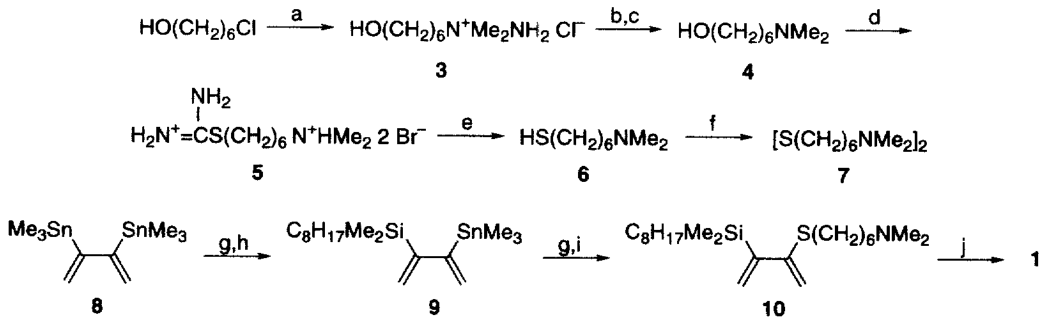
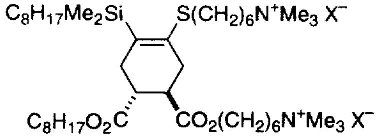
into 1,3-diene **10** in a one-pot sequence of reactions. The reaction of **8** with MeLi was followed by that of the resultant carbanion with *n*-octyldimethylchlorosilane (United Chemical Technologies) to give 1,3-diene **9**. Then the reaction of **9** with MeLi was followed by that of the resultant carbanion with disulfide **7** to give **10**. Quaternization of **10** with MeI gave **1**. By surface tensiometry (du Noüy ring) the critical micelle concentrations (cmcs) of **1** and **2** in H_2O at 25 °C are 1.0×10^{-4} and 4.4×10^{-3} M,[3] respectively.



(a) Me_2NNH_2, 50 °C; (b) $NaNO_2$, 4 M HCl, 0 °C; (c) 3 M NaOH; (d) 48% HBr, H_2NCSNH_2, reflux; (e) NaOH pellets, reflux; (f) $NaClO_2$, MeOH-H_2O, 0 °C; (g) MeLi, THF, -78 °C; (h) $C_8H_{17}SiMe_2Cl$; (i) $[S(CH_2)_6NMe_2]_2$ (**7**) (j) MeI, THF.

Diels-Alder reactions of **1** and **2** in H_2O at 25 °C, with added 4-*tert*-butylcatechol, gave cycloadducts **11** and **12**. The molar ratio of **2** to **1** was 4:1. Each reaction mixture was diluted with MeCN and rotary evaporated to dryness at ca. 45 °C. The resultant residue was analyzed by ^1H NMR ($CDCl_3$) and analytical reversed-phase (C8) HPLC[10a] to give the **11**/**12** ratio and the yield of **11** + **12**.[11] Preparative reversed-phase (C8) HPLC[10b] afforded separated **11** and **12**. The results are summarized in runs 1-6 of Table I.



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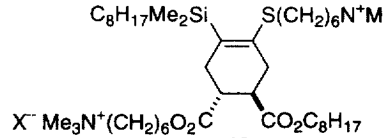

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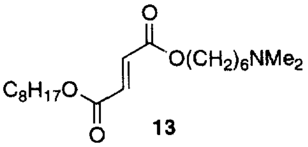
Table I. Diels-Alder Reactions

run	1,3-diene nature	1,3-diene concn, M	dienophile nature	dienophile concn, M	medium[a]	reaction temp, °C	reaction time, h	% yield[b]	regioisomer ratio[c,d]
1	**1**	0.021	**2**	0.082	H_2O	25	21	85	6.7:1
2	**1**	0.020	**2**	0.074	H_2O	25	52	95	6.6:1
3	**1**	0.024	**2**	0.098	H_2O	25	45		6.6:1
4	**1**	0.030	**2**	0.12	H_2O	25	22	85	6.4:1
5	**1**	0.031	**2**	0.12	H_2O	25	26	86	6.6:1
6	**1**	0.038	**2**	0.15	H_2O	25	45		6.7:1
7	**10**	0.076	**13**	0.17	C_6H_5Me	75	24	71	1:1
8	**10**	0.12	**13**	0.28	C_6H_5Me	85	24	71	1:1

[a] Reaction mixtures contained 4-*tert*-butylcatechol (10 mol % with respect to 1,3-diene). [b] Determined by ^1H NMR analysis of crude mixtures of products and unreacted starting materials: **11** + **12** in runs 1-6; **14** + **15** in runs 7 and 8. [c] In runs 1-6, **11**/**12** ratios determined by ^1H NMR analysis of crude mixtures of products and unreacted starting materials. [d] In runs 7 and 8, **14**/**15** ratios obtained from masses of isolated **14** and **15** and by HPLC analysis of crude mixtures of products and unreacted starting materials.

The ^1H and ^{13}C NMR spectra of **11** and **12** did not allow their differentiation. The assignments illustrated are based on their HPLC behavior and analogy to a closely related system[3] and are therefore tentative. Definitive assignments based on chemical conversions and/or an X-ray diffraction study were precluded by the small amounts of **11** and **12** available and their amorphous natures, respectively.

Diels-Alder reactions of **10** and **13**[12] to give regioisomers **14** and **15** were performed in C_6H_5Me at 75(85) °C, with added 4-*tert*-butylcatechol, to establish the regioselectivity that would likely result from the reaction of **1** and **2** in the absence of interfacial orientational effects. The reaction mixtures were rotary evaporated at ca. 70 °C, and the resultant residues were analyzed by analytical reversed-phase (C8) HPLC.[10c] Cycloadducts **14** and **15** were separated by medium pressure liquid chromatography (Baeckström Separo) on silica gel (Merck 9385) with gradient elution (100% hexane to 60:20:20 hexane-EtOAc-Et_3N). The ^1H and ^{13}C NMR spectra of **14** and **15** did not allow their differentiation. The results are summarized in runs 7 and 8 of Table I. Note that **14** and **15** were obtained in equal amounts. Thus, without micellar orientational effects, the Diels-Alder reaction of **1** and **2** should have no regiochemical preference. Separately, **14** and **15** were converted into **11** and **12** (X^- = I^-), respectively, by quaternization with MeI in MeCN.



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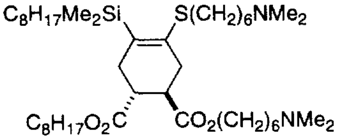

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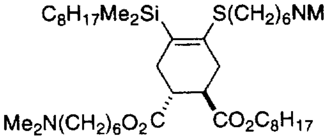

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As noted above, the cmcs of **1** and **2** in H_2O at 25 °C are 1.0×10^{-4} and 4.4×10^{-3} M, respectively. Thus runs 1-6 were performed well above their cmcs. An excess of cycloadduct **11** over **12** was obtained in runs 1-6. The former is the expected regioisomer if **1** and **2** react in their preferred aligned orientations within a mixed micelle, with the quaternary ammonium head groups at the aggregate-H_2O interface and the remainder of each surfactant extended into the mixed micelle interior. It is possible that a fraction of the reaction occurs outside of micelles between **1** and **2** in monomeric and/or premicellar forms,[13] wherein orientational effects are expected to be absent or less.

The **11**/**12** ratio of 6.6:1 obtained in this study at 25 °C is more than twice the maximum regioisomer ratio (3.0:1) obtained under aqueous micellar conditions at 100 °C in a related study[3] involving a surfactant 1,3-diene and surfactant dienophiles (among them **2**). The greater regioselectivity in the present study is attributed at least in part to the expected greater organizational abilities of micelles at low compared to high temperatures. Also, **1** does not contain aromatic groups, unlike the surfactant 1,3-diene in the related study.[3] It is known that aromatic groups can associate with quaternary ammonium head groups.[14] In the related study it was proposed that looping of aromatic groups to the mixed micelle-H_2O interface, where they can associate with quaternary ammonium groups, resulted in misalignment of the 1,3 diene and dienophile surfactants, with subsequent formation of the minor regioisomer.

Overall, we have shown that interfacial and related orientational effects associated with surfactant aggregation can impart substantial regioselectivity to a thermal cycloaddition reaction.

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(10) HPLC was performed with evaporative light scattering detection (Sedex 55) on 8-μm C8 columns: analytical, 25 cm × 4.6 mm (i.d.) (Rainin R0086300C8); preparative, 25 cm × 21.4 mm (i.d.) (Rainin R0080320C8). (a) Eluant = 0.020 M ammonium trifluroacetate in 90:10 (v/v) MeCN-H_2O; flow rate = 1.0 mL/min; retention times = 8.4 min for **11** and 6.2 min for **12**. (b) Eluant = same as for (a); flow rate = 20.0 mL/min; retention times = 8.8 min for **11** and 7.8 min for **12**. (c) Eluant = 0.020 M ammonium trifluroacetate in MeCN; flow rate = 1.0 mL/min; retention times = 7.7 min for **14** and 6.0 min for **15**.

(11) Controls demonstrated that any Diels-Alder reaction of **1** and **2** during workup did not affect the **11**/**12** ratios and the yields of **11** + **12**.

(12) Amino diester **13** was prepared as follows. The reaction of maleic anhydride with **4** in C_6H_5Me at reflux gave 6-(dimethylamino)hexyl hydrogen fumarate, which was converted into **13** by reaction with 1-octanol, dicyclohexylcarbodiimide, and 4-(dimethylamino)pyridine in CH_2Cl_2.

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