Pergamon

Tetrahedron Letters 40 (1999) 7871–7874

TETRAHEDRON
LETTERS

High regioselectivity in the Diels–Alder reaction of a surfactant 1,3-diene with a surfactant dienophile resulting from a short tether between their functional groups and head groups

Dan Su and David A. Jaeger *

Department of Chemistry, University of Wyoming, Laramie, Wyoming 82071, USA

Received 12 July 1999; accepted 3 August 1999

Abstract

The Diels–Alder reaction of surfactant 1,3-diene **5** and surfactant dienophile **6** within their aqueous mixed micelles at 25(35)°C gave a 30:1 ratio of cycloadducts **14** and **15**, respectively. The high regioselectivity was ascribed to a combination of alignment of **5** and **6** at the mixed micelle–H_2O interface and the short tether between their functional groups and head groups. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Diels–Alder reactions; micellar systems; regiocontrol; surfactants.

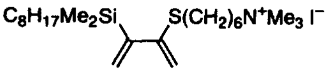
Water is becoming an ever-more useful solvent for organic reactions.[1] In particular, Diels–Alder reactions performed in H_2O and aqueous surfactant-based media generally exhibit increased rates and stereoselectivities relative to reactions in conventional organic solvents.[2] But the ability of surfactant-based media to control the regioselectivity of Diels–Alder reactions has received only modest attention.[3]

In several studies,[3a–c] we have utilized orientational effects within aqueous micelles to control the regioselectivity of Diels–Alder reactions between surfactant 1,3-dienes and surfactant dienophiles. The reaction of **1** with **2** in H_2O at 25°C gave a 6.6:1 ratio of cycloadducts **3** and **4**, respectively.[3a] 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. This Diels–Alder system should display no regiochemical preference in the absence of such orientational effects, since the substituents at carbons 1 and 2 within **2** are close to being both electronically and sterically equivalent with respect to the dienophile reaction center.

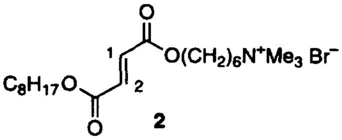
---

* Corresponding author.

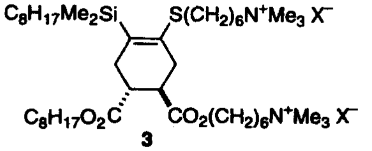
PII: S0040-4039(99)01637-8



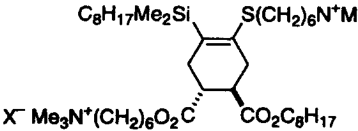
1



2

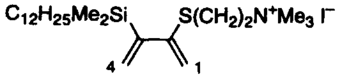


3

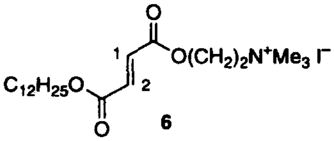


4

In surfactants **1** and **2**, the substituted 1,3-diene and dienophile groups are separated from the quaternary ammonium head groups by a tether of six methylene units. Herein, with surfactants **5** and **6**, we report the effect on Diels–Alder regioselectivity of decreasing the length of the tether from six to two methylene units, while maintaining at 14 the total number of carbon atoms in the tether and terminal alkyl chain.

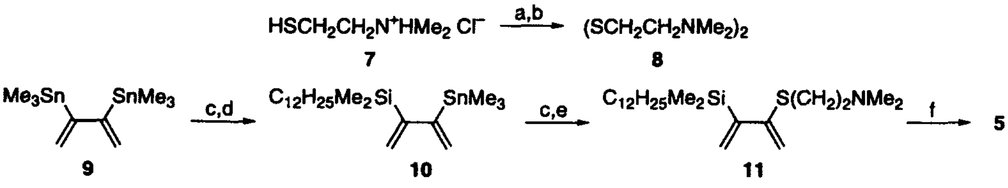


5



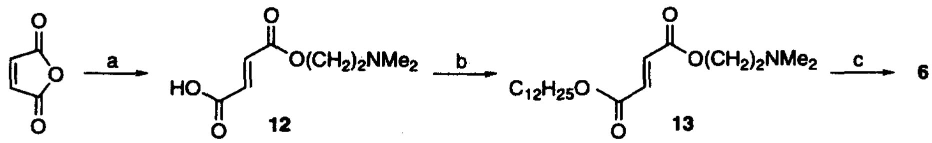
6

The synthesis of surfactant 1,3-diene **5** is summarized below.[4] Amino thiol hydrochloride **7** (Aldrich) was converted[5] into disulfide **8** (Scheme 1). 1,3-Diene **9**[6] was transformed[6] into 1,3-diene **11** in a one-pot sequence of reactions. The reaction of **9** with MeLi was followed by that of the resultant carbanion with *n*-dodecyldimethylchlorosilane (Aldrich) to give 1,3-diene **10**. Then the reaction of **10** with MeLi was followed by that of the resultant carbanion with disulfide **8** to give **11**. Quaternization of **11** with MeI gave **5**. By surface tensiometry (du Noüy ring) the critical micelle concentration (cmc) of **5** in H_2O at 25°C is 7.5×10^{-5} M.



Scheme 1. (a) $NaClO_2$, MeOH–H_2O, 0°C; (b) NaOH; (c) MeLi, THF, −78°C; (d) $C_{12}H_{25}SiMe_2Cl$; (e) $(SCH_2CH_2NMe_2)_2$ (**8**); (f) MeI, THF, 25°C

The synthesis of surfactant dienophile **6** is summarized below. The reaction of maleic anhydride with 2-(*N*,*N*-dimethylamino)ethanol gave half ester **12** (Scheme 2). This material was converted into diester **13**, which on quaternization with MeI gave **6**. The cmc of **6** in H_2O at 25°C is 3.0×10^{-4} M.



Scheme 2. (a) $HOCH_2CH_2NMe_2$, C_6H_5Me, reflux; (b) $C_{12}H_{25}OH$, DCC, DMAP, CH_2Cl_2, 25°C; (c) MeI, MeCN, 25°C

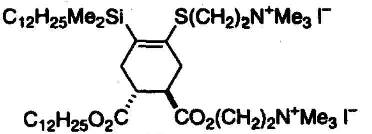
Diels–Alder reactions of **5** with excess **6** in H_2O at 25°C, with added 4-*tert*-butylcatechol, gave cycloadducts **14** and **15**. Each reaction mixture was diluted with MeCN and rotary evaporated to dryness at ca. 45°C. The resultant residue was analyzed by ^1H NMR ($CDCl_3$) and analytical reversed-phase (C8) HPLC[7] to give the **14**/**15** ratio and the yield of **14**+**15**. The results are summarized in runs 1–4 in Table 1.

Table 1
Diels–Alder reactions

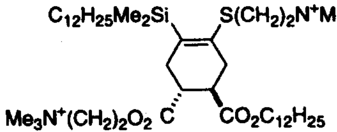
run	1,3-diene nature	1,3-diene concn, M	dienophile nature	dienophile concn, M	medium[a]	reaction temp, °C	reaction time, h	% yield[b]	regioisomer ratio[c,d]
1	**5**	0.0078	**6**	0.013	H_2O	25	40	79	[e]
2	**5**	0.0081	**6**	0.013	H_2O	25	25	83	26:1
3	**5**	0.0086	**6**	0.014	H_2O	25	48	70	36:1
4	**5**	0.019	**6**	0.027	H_2O	35	48	98	28:1
5	**11**	0.066	**13**	0.14	C_6H_5Me	75	36	74	1:1.6
6	**11**	0.066	**13**	0.15	C_6H_5Me	80	48	84	1:1.3

[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: **14**+**15** in runs 1-4; **16**+**17** in runs 5 and 6. [c] In runs 2-4, **14/15** ratios were determined by HPLC analysis of crude mixtures of products and unreacted starting materials. [d] In runs 5 and 6, **16/17** ratios were determined from masses of isolated **16** and **17**. [e] No **15** was detected by ^1H NMR analysis of the crude mixture of products and unreacted starting materials.

The structural assignments illustrated for **14** and **15** are based on their HPLC behavior and analogy to closely related systems[3] and are therefore tentative.

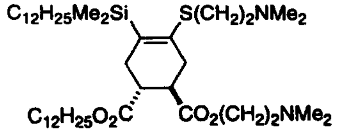


14

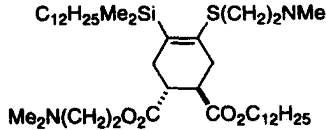


15

Diels–Alder reactions of amines **11** and **13** were performed in C_6H_5Me at 75(80)°C, with added 4-*tert*-butylcatechol, to give regioisomeric cycloadducts **16** and **17**. The reaction mixtures were rotary evaporated at ca. 70°C, and **16** and **17** were separated by medium pressure liquid chromatography (Baeckström Separo) on silica gel (Merck 9385) with gradient elution (100% hexane to 70:28:2 hexane:EtOAc:Et_3N). The results are summarized in runs 5 and 6 in Table 1. Separately, **16** and **17** were converted into **14** and **15**, respectively, by quaternization with MeI in MeCN.



16



17

As noted above, the cmcs of **5** and **6** in H_2O at 25°C are 7.5×10^{-5} and 3.0×10^{-4} M, respectively. Thus, runs 1–4 were performed well above their cmcs under mixed micellar conditions. The excess of **14** over **15** obtained from the cycloaddition of **5** and **6** is consistent with interfacial orientational effects analogous to those elaborated above for the Diels–Alder reaction of **1** and **2**. But unlike for dienophile **2**, the substituents at carbons 1 and 2 within dienophile **6** are not electronically and sterically equivalent, since the tether between the substituted dienophile unit and the quaternary ammonium head group is only two methylene units, as opposed to six in **2**. The proximity of the positively charged head group to the substituted dienophile unit renders the ester group at carbon 1 of **6** more electron withdrawing than the ester group at carbon 2. The Hammett σ_m and σ_p values for $-(CH_2)_nN^+Me_3$ are as follows: 0.88 and 0.82 for n=0; 0.40 and 0.44 for n=1; 0.16 and 0.13 for n=2; 0.06 and −0.01 for n=3, respectively.[8] These values indicate that the electron withdrawing inductive effect of $-(CH_2)_nN^+Me_3$ decreases substantially as n increases but is still finite for n=2. The Hammett σ_m and σ_p values for -Me and $-CO_2R$ are as follows: −0.07 and −0.17; 0.37 and 0.45, respectively.[8] A comparison of the values for -Me and $-(CH_2)_2N^+Me_3$ supports the above conclusion that the ester group at carbon 1 of **6** is more electron withdrawing than that at carbon 2.

For a 2,3-disubstituted 1,3-diene bearing thio and silyl groups, the former is expected to direct the regioselectivity of its Diels–Alder reactions.[9] The electron withdrawing inductive effect of -$(CH_2)_2N^+Me_3$ within **5** should not alter this expectation. Thus, the reaction of **5** and **6**, whose ester group at carbon 1 dominates that at carbon 2 in electron withdrawal as noted above, is predicted[9] to give an excess of cycloadduct **15** over **14** in the absence of interfacial orientational effects.

In runs 5 and 6 in Table 1, a 1:1.4 ratio of regioisomers **16** and **17** was obtained in the Diels–Alder reaction of unaggregated nonsurfactant analogues **11** and **13**. The modest excess of **17** over **16** is consistent with steric effects but inconsistent with electronic effects. The former involves an unfavorable interaction between the large dodecyl-containing substituents within the cycloaddition transition state leading to **16**, which is unmitigated by hydrophobic association as within mixed micellar **5** and **6**. The latter effects predict[9] an excess of **16** over **17** as the result of regiochemical direction by the thio group of 2,3-disubstituted 1,3-diene **11** and a greater inductive electron withdrawal by the dodecyl ester group of **13** relative to its 2-(*N*,*N*-dimethylamino)ethyl ester group. The Hammett σ_m and σ_p values for -NMe_2 are as follows: –0.16 and –0.83, respectively.[8]

The 30:1 ratio of **14** and **15** obtained in the cycloaddition of **5** and **6** within aqueous mixed micelles at 25(35)°C in this study is substantially greater than the 6.6:1 ratio of **3** and **4** obtained in that of **1** and **2** under comparable conditions.[3a] The greater regioselectivity with **5** and **6** is attributed to the shorter tether between their quaternary ammonium head groups and reactive 1,3-diene and dienophile groups. The shorter tether provides less opportunity for misalignment of the 1,3-diene and dienophile groups, which can lead to minor regioisomer **15**.

Acknowledgements

We thank the National Science Foundation (CHE-9526188) for support of this research and Dr. Abdullah Zafar for the final purification of **15**. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource.

References

1. Grieco, P. A., Ed. *Organic Synthesis in Water*; Blackie Academic and Professional: London, 1998.
2. For examples, see: (a) Engberts, J. B. F. N. *Pure Appl. Chem.* **1995**, *67*, 823. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (c) Otto, S.; Engberts, J. B. F. N.; Kwak, J. C. T. *J. Am. Chem. Soc.* **1998**, *120*, 9517. (d) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (e) Braun, R.; Schuster, F.; Sauer, J. *Tetrahedron Lett.* **1986**, *27*, 1285. (f) Diego-Castro, M. J.; Hailes, H. C. *J. Chem. Soc., Chem. Commun.* **1998**, 1549. (g) Garner, P. P. In Ref. 1, p. 1, and references cited therein.
3. (a) Jaeger, D. A.; Su, D. *Tetrahedron Lett.* **1999**, *40*, 257. (b) Jaeger, D. A.; Wang, J. *Tetrahedron Lett.* **1992**, *33*, 6515. (c) Jaeger, D. A.; Wang, J. *J. Org. Chem.* **1993**, *58*, 6745. (d) Jaeger, D. A.; Shinozaki, H.; Goodson, P. A. *J. Org. Chem.* **1991**, *56*, 2482. (e) Jaeger, D. A.; Wang, J.; Goodson, P. A. *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 955.
4. New compounds **5**, **6**, and **11**–**17** were characterized by ^1H and ^{13}C NMR spectroscopy and high resolution FAB mass spectrometry or carbon and hydrogen combustion analyses; synthetic intermediate **8** was characterized by ^1H and ^{13}C NMR.
5. Ramadas, K.; Srinivasan, N. *Synth. Commun.* **1995**, *25*, 227.
6. Reich, H. J.; Reich, I. E.; Yelm, K. E.; Holladay, J. E.; Gschneidner, D. *J. Am. Chem. Soc.* **1993**, *115*, 6625.
7. HPLC was performed with evaporative light scattering detection (Sedex 55) on a 25 cm×4.6 mm (i.d.) 8 μm C8 column (Rainin R0086300C8); eluant=0.020 M ammonium trifluroacetate in 85.5:9.5:5 (v/v/v) $MeCN:CH_2Cl_2:MeOH$; flow rate=1.0 mL/min; retention times=5.7 min for **14** and 4.2 min for **15**.
8. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
9. Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381.