Pergamon

Tetrahedron Letters 40 (1999) 4935–4938

TETRAHEDRON
LETTERS

Preparation of a new class of cleavable surfactants based on the silicon–carbon bond

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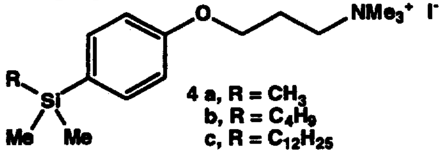
Received 2 April 1999; revised 23 April 1999; accepted 26 April 1999

Abstract

The ability of silicon to direct electrophiles to the *ipso*-position is used in developing a new class of cleavable amphiphiles containing an acid labile silicon–carbon (aromatic) bond. The synthesis of these amphiphiles is carried out in four steps to yield the positively charged surfactants 4, in 37–50% overall yield. The amphiphiles are soluble in a variety of solvents as disparate as benzene and water. They are indefinitely stable in the air, in all of the solvents used in this study, and in aqueous solution over a range of pH values from 3–14. Around a pH of 1, the surfactant molecules are cleaved in less than 5 min, resulting in aqueous and organic soluble moieties that are easily recovered. The cleavage is independent of the kind of acid used. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: amphiphiles; cleavable; destructible; surfactants.

Amphipathic molecules have numerous uses in chemistry and biology, ranging from solubilizing insoluble materials via regular[1] or reverse micelles,[2] enabling the recovery of membrane bound proteins,[3] providing a wide range of useful properties in soaps, paints, and other materials,[4] as well as participating and providing micellar effects both in catalytic and in non-catalytic chemistry, sometimes leading to unprecedented, yet beneficial results.[5] A general problem in the utilization of surfactants has been that recovery of materials is often problematic due to the formation of persistent emulsions. In order to alleviate this problem, one solution is the cleavable or destructible amphiphile,[6] wherein the molecule contains within itself a portion that may be cleaved by heat,[7] light,[8] or chemical means.[9] Efficient cleavage into pieces that have sufficiently different aggregation properties, would then enable ease of workup. Such amphiphiles would have tremendous potential utility in that they could provide a wide range of useful properties and could then be removed by targeted destruction. In this communication, we introduce a new class of cleavable amphiphile 4.



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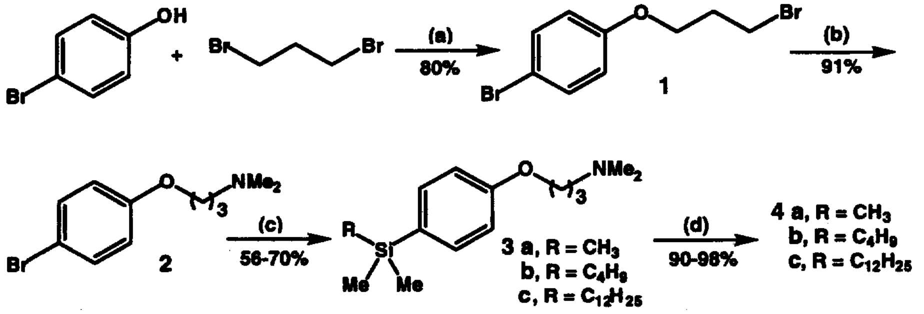
PII: S0040-4039(99)00863-1

The design makes use of a well-established idea, that is, silicon directs electrophiles to the *ipso*-position on an aromatic ring.[10] Destruction of the amphiphile 4 would then be a facile process since a variety of potential electrophiles, the simplest of which would be a proton, could be used to trigger the cleavage. In the case of using a proton source for cleavage of the amphiphile, the surfactant would essentially be destroyed using a 'pH switch'. The surfactants 4 are completely stable (Table 1) over a range of pH values, and are quite easily cleaved under acidic conditions (pH ~1).

The synthesis of the amphiphile 4 is quite simple and effected in 37–50% overall yield, as described in Scheme 1. Alkylation of 4-bromophenol with 1,3-dibromopropane was followed by displacement of the alkylbromide using dimethylamine. The appropriate silyl group was introduced after halogen–metal exchange using *n*-BuLi. Finally, quaternization of the nitrogen was accomplished using iodomethane to afford the surfactants 4.[11]

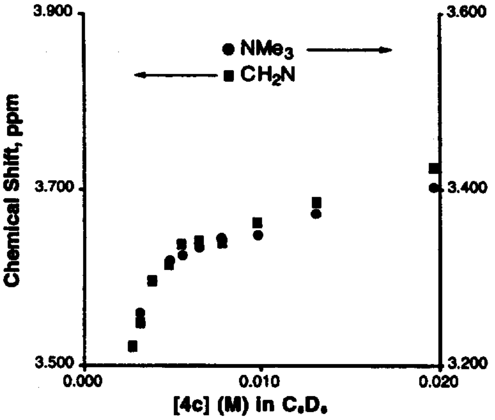


Scheme 1. (a) K_2CO_3, MeCN; (b) Me_2NH_2Cl, TEA, AgOTs, CH_2Cl_2; (c) (i) *n*-BuLi, THF, (ii) RMe_2SiCl; (d) MeI, MeOH

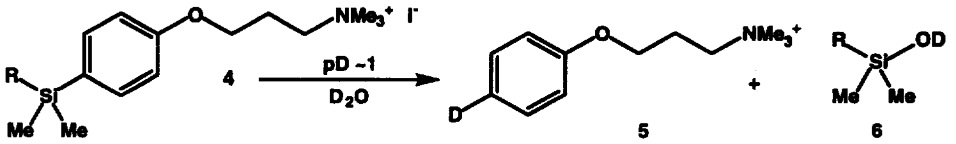
There are three distinct advantages to this kind of surfactant design. First, this particular synthesis sequence lends itself quite nicely to the formation of either charged or uncharged amphiphiles since the terminal alkyl bromide is easily replaced (step (b) in Scheme 1) and thus positively charged, negatively charged, or neutral (for example, carbohydrate-based) amphiphiles could be easily synthesized. Second, a number of commercial alkyldimethylsilyl chlorides are available and thus, the length of the hydrocarbon tail is easily varied (step (c) in Scheme 1). A third advantage would be to use a series of different anions, exploring differences in solubilities and aggregation properties, as required. In this particular study, iodides were used as the counter-ions.

The amphiphiles 4 are air stable, non-hygroscopic white solids. They are soluble in a variety of solvents including benzene, toluene, CH_2Cl_2, $CHCl_3$, ethyl acetate, acetone, MeCN, MeOH, EtOH, DMSO, DMF, CH_3NO_2, dioxane and water.[12] All the amphiphiles demonstrate characteristic foaming on shaking in solution, and show emulsification when partitioning is attempted between two insoluble phases.

The ^1H NMR chemical shifts of several groups within **4c** ($R=C_{12}H_{25}$) were monitored as a function of concentration in C_6D_6 at 20°C, and the results for Me_3N and CH_2N are plotted as shown below. The curves from surfactant **4c** suggest the formation of reverse micelles[13] with an apparent cmc of 5 mM. Downfield movement, as seen for these two residues in C_6D_6 is not unusual in going from an unaggregated to an aggregated (micellar) state. What is notable though, is that above ca. 10 mM, there appears to be another slight, yet perceptible downfield shifting in the positions of the two groups, perhaps indicating the formation of higher aggregates. In keeping with this result, **4b** and **4c** form lyotropic liquid crystalline phases and require ca. 40% (v/v) acetone or MeOH for aqueous solubility.[12]



The silicon–carbon bond is easily cleaved electrophilically. In this particular study, the only electrophiles used were H^+ or D^+ resulting in the substitution of an H, or a D in the position *ipso* to the silicon. In C_6D_6 solution, for example, **4b** or **4c** are cleaved in less than 5 min on using DBr (0.10 M) as the acid source.[14] Similar results are observed in water using **4a** (Scheme 2).



Scheme 2. Amphiphiles **4** are cleaved quantitatively in less than 5 min to give **5** and **6**, on making the solution acidic

In order to avoid complications arising from mixed solvent systems, and to simplify the NMR analysis, we carried out all of our detailed cleavage studies in D_2O using amphiphile **4a**. A systematic investigation of the stability of **4a** was carried out over a range of pH values. The data are collected in Table 1. The three major points to note are: first, the amphiphile is quite stable over a range of pH values starting at ca. 3 and going upwards. Second, at a pH of ca. 1, the cleavage is apparently really quick and usually completely effected before a ^1H NMR could be obtained (ca. 5 min). Third, the cleavage is completely independent of the kind of acid used. Extraction experiments using water and ethyl acetate, or water and CH_2Cl_2 gave problematic emulsions, as is to be expected, when the surfactants were intact, but on lowering the pH to ca. 1 using HCl (aq.), clean separations were possible almost as soon as the pH adjustment was made. Cleavage is effected just as well with fluoride sources (KF and Bu_4NF; for example, entry 8 in Table 1).[15] In a separate model study using uncharged Boc-protected primary amine analogs of **4b** and **4c**, we were able to cleave the C–Si bond selectively in the presence of the Boc group using 1–5% TFA in CD_2Cl_2 or $CDCl_3$ solvents.

In summary, we have prepared a new class of cleavable surfactant **4**, and in this letter we have described the synthesis and facile cleavage of these molecules. The versatility in the synthesis lends itself to the preparation of neutral, or ionic surfactants quite readily. The ability of silicon to stabilize a β positive charge,[16] resulting in *ipso*-electrophilic substitution is the basis for these amphiphiles to be destroyed. Thus, simply lowering the pH results in clean and quantitative cleavage. We are using these surfactants to enable solubilization of lipophilic substrates and thus we are performing C–C bond-forming chemistry in aqueous media. We will report shortly on this work, as well as on our complete studies on the aggregation phenomena of surfactants **4**, in the solution state, as well as in the solid state.

Table 1

No	Additive	~pD	Time	Comments
1.	0.10 M DBr	1	5 min	complete cleavage
2.	1.46 M D_3PO_4	1	5 min	complete cleavage
3.	0.01 M DBr	2	12 h	4% cleavage[a]
4.	1.75 M CD_3CO_2D	2.5	1 d	3% cleavage[a]
5.	none	6	10 d	stable
6.	0.1 M Na_2CO_3	10	10 d	stable
7.	0.10 M NaOD	13	10 d	stable
8.	1 mol equiv. KF	-	10 min	complete cleavage

All reactions were run at [**4a**] >20 mM at ca. 20°C. ^{1}H NMR (200 MHz) were referenced via external standard. Cleavage products were identified by comparing their ^{1}H NMR signals with authentic samples, and confirming by HRMS on isolated **5** and **6**.

[a] Determined from the integrals of the ^{1}H NMR signals.

Acknowledgements

The authors would like to thank the Center for Environmental Risk Reduction (CERR), an Engineering Lead Campus Program at UCLA for generous financial support of this work, and Professor Douglas Gin (UC, Berkeley) for helpful and stimulating discussions.

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11. All compounds were isolated and characterized completely by ^{1}H NMR, IR and HRMS.
12. The surfactant **4c**, (R=$C_{12}H_{25}$) shows liquid crystalline behavior-forming lamellar, lyotropic phases in the solid state (powder X-ray) and in aqueous solution (gel-phase) even at low concentrations. The complete physical characterization and behavior of these aggregates is beyond the scope of our initial report, and will be the topic of a separate paper.
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14. In principle, with slight modification, **5** and **6** could be used to remake surfactants **4**, since recovery of the pieces is quite efficient (>95%). Facile cleavage of this kind has been demonstrated in a solid phase system using HCl gas in CH_2Cl_2 solvent: Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006–6007. In this ref., the cleavage products were quantitatively isolated.
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