Novel application of chiral micellar media to the Diels–Alder reaction

Michael J. Diego-Castro and Helen C. Hailes*†

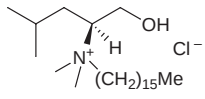
Department of Chemistry, University College London, London, UK WC1H 0AJ

A novel chiral surfactant has been used in the first reported aqueous chiral micellar catalysis of a Diels–Alder reaction and enantioselectivities have been observed.

The chemical industry is undergoing an important transition period in which they are reacting to ever increasing governmental and public pressure to reduce the use of volatile organic solvents. In the context of Diels–Alder reactions, there is also an urgent need to seek alternatives to Lewis acids, since they are typically dumped when spent.

There is good reason to believe that chiral micellar media offer a viable clean alternative to more traditional methods of accomplishing many organic reactions. In particular, aqueous micellar media have the potential to confer special properties on reactions due to their ability to, for example, solubilise substrates and concentrate and preorientate reactants within the micellar core.[1] Furthermore, they are recyclable; there is the potential for enantioselection; they can be prepared at low cost, particularly when using synthons from the chiral pool; they can be applied to a range of different reactions; they are more versatile than other chiral aqueous systems such as cyclodextrins due to the potential number of structural variations; and they are more robust than enzymes. Whilst this field exhibits considerable promise, it is at an early stage in its development. Consequently, there are relatively few currently reported applications of chiral micellar media[2] and, until now, none at all for their application to Diels–Alder reactions.

Here we outline our initial investigations into a methodology, which enabled us to perform a Diels–Alder reaction using chiral micellar media, with enantioselectivities comparable with the best obtained for cyclodextrin based aqueous Diels–Alder reactions.[3] The reaction in question was performed using a novel (*S*)-leucine-derived surfactant **1**[4] to catalyse the reaction between cyclopentadiene and nonyl acrylate, under a variety of conditions.



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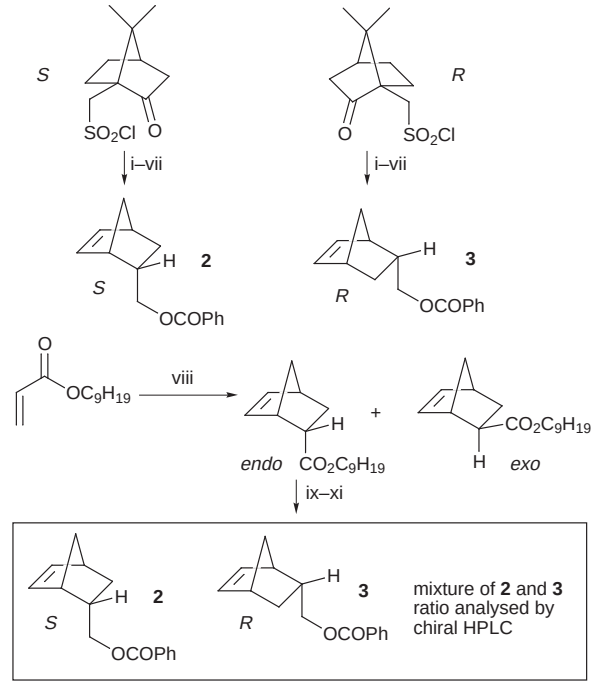
In a previous paper,[5] we demonstrated that a variety of factors influence the overall efficiency of the cycloaddition and the diastereoselective *endo* : *exo* (*N*/*X*) ratio. Amongst these are the chain length of the acrylate, the selection of the surfactant concentration and the pH of the solution. In view of the first of these factors, we chose to use nonyl acrylate as the test substrate to explore the feasability of the methodology, both because its long alkyl chain increases the pre-orientation effects within the micellar structure, and because the cycloadduct is stable to chiral HPLC analysis.

In order to ascertain the concentration at which micelles or micellar-like aggregates will be present and some enantioselective induction could be expected, we initially utilised a dye method which gave a value of *ca.* 0.011 g l^{-1} (0.027 mM).[6] Whilst it is well known that the critical micellar concentration (cmc) for a particular surfactant can vary depending on the method that is used,[7] and indeed, surface tension experiments indicated a higher value,[4,6] we felt that in our synthetic applications a dye method gave an appropriate starting point. This is because, in the micellar reaction system with nonyl acrylate present mixed micellar aggregates will be generated, as is also likely when the indicator dye is present.

Analysis of our initial experiments in the presence of the chiral surfactant **1** indicated some chiral induction in the *endo* adduct but negligible induction in the *exo* isomer. It was therefore necessary to assess whether the *R* or the *S endo* adduct was formed preferentially. To this end, we correlated our products using Oppolzer's sultam auxiliary methodology.[8] As outlined in Scheme 1, (*S*)-camphorsulfonyl chloride was treated with aq. NH_3, heated in the presence of Amberlyst-15, then reduced to a cyclic amine which was coupled with acryloyl chloride. The subsequent Diels–Alder cycloaddition reaction with cylopentadiene and the Lewis acid $TiCl_4$, followed by reduction and reaction with benzoyl chloride generated the *endo-S* isomer **2**. An analogous route using (*R*)-camphorsulfonyl chloride was used to synthesise the *R endo* ester **3**. The Diels–Alder *endo* cycloadducts generated in the reaction between nonyl acrylate and cyclopentadiene with **1** present were then isolated from the *endo–exo* mixture using chromatographic techniques. These were converted into a mixture of **2** and **3** *via* reduction and ester formation. Finally, HPLC analysis revealed that the *R* isomer was formed preferentially.‡



Scheme 1 *Reagents and conditions*: i, NH_4OH, THF, 83%; ii, Amberlyst-15, toluene, 110 °C, 18 h, 99%; iii, $LiAlH_4$, THF, 69%; iv, NaH, acryloyl chloride, 65%; v, $TiCl_4$, Et_2O, cyclopentadiene, −78 °C, 20 h, 55%; vi, $LiAlH_4$, Et_2O, 99%, vii, BzCl, CH_2Cl_2, 54%, viii, cyclopentadiene, 20 h, surfactant **1**, 55%; ix, only *endo* isomer was carried through subsequent steps (SiO_2, 4% Et_2O in hexane); x, $LiAlH_4$, Et_2O, 99%; xi, BzCl, CH_2Cl_2, 55%

Table 1 Addition of cyclopentadiene to nonyl acrylate in water containing surfactant **1**

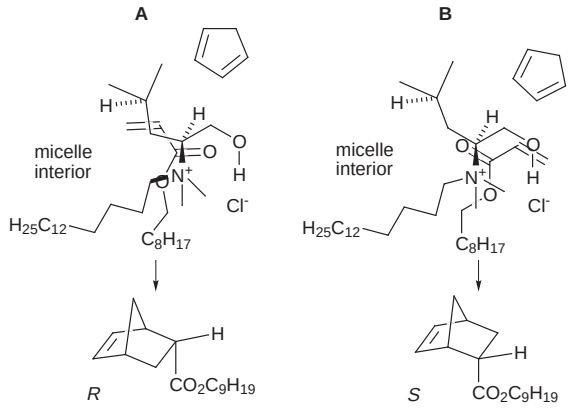
Entry	[Surfactant]/g l^{-1}	Yield[a] (%)	*N/X*	Ee[b] (%) (*R*)
1	0.011	55	2.1	10
2	0.022	72	2.1	12
3	0.006	43	2.0	7
4	0.011[c]	29	2.1	13
5	0.011[d]	75	2.2	15

[a] Isolated yields. [b] Determined by chiral HPLC. [c] pH 3. [d] pH 3 with LiCl.

In view of the initial uncertainty in the optimum surfactant concentration for use in such applications, the concentration of **1** was varied and the effects on enantioselectivities and yield were noted,§ see summarised results in Table 1. For comparison purposes, the reaction in water alone under identical conditions, gave a yield of 70% and an *N/X* selectivity of 1.7.

At the starting point, an ee of 10% was observed (entry 1), rising slightly (entry 2) as surfactant concentration was increased then falling as the concentration was decreased (entry 3) together with a lowering of the yield, which could be due to the presence of non-micellar aggregates. Previously, we had seen the greatest yields and *N/X* selectivities in acrylate systems in the absence of surfactant when operating at pH 3.[5] In this instance, we found that when the solution was at pH 3 the enantioselectivity increased, although the yield of cycloadduct that was isolated was poor (entry 4). In determining how to increase the yield in this system, we reasoned that a salting-out agent would tend to remove the reactants from the aqueous pseudo-phase, increasing the complexation of the substrates to the micelles. Further, it is known that an increased concentration of chloride counterions can cause a shrinkage in the Stern layer, leading to a concentration of reactants[1] which, in our system, could translate to greater pre-orientation and enhanced yield and ees. In view of these factors, we added lithium chloride (4.86 M) to the reaction at pH 3, thence obtaining both the highest yield (75%) and the greatest ee (15%). This result compares well with the results quoted for Diels–Alder reactions in cyclodextrins in which maximum enantioselectivities of 21% are reported.[3]

A number of conformations of the surfactant **1** could be considered (since surfactants are dynamic in nature) and a representative one, consistent with NOE difference experiments is shown below in Scheme 2, in an attempt to provide a tentative simplistic model which nevertheless helps to visualise the observed preferences. All possible conformations have the common feature of a more hindered top face of the molecule as drawn due to the chirality present. Alignment of nonyl acrylate with the underside of **1** results in the cyclopentadiene having to approach from below the acrylate. As shown in Scheme 2 (for the reaction under neutral conditions), the carbonyl moiety can complex to the nitrogen and hydrogen bond to the O–H group with the alkene beneath the isopropyl group in **A**, with subsequent approach of cyclopentadiene beneath the complex leading to the formation of the *R*-isomer. However, in **B**, reaction with the diene would generate the *S*-isomer. Since **A** is complexed more favourably (with possible hydrogen bonding and carbonyl complexation) as well as having the polar carbonyl moiety directed towards the Stern layer, the *R*-isomer would be expected to be more prevalent. Future work will shed more light on this model.



Scheme 2 Positioning of the acrylate with respect to the surfactant head group

In summary, we have performed the first Diels–Alder reaction in aqueous chiral micellar media, obtaining selectivities comparable with the best reported for other non-enzymic aqueous Diels–Alder reactions. We established that the *R* enantiomer in the *endo* isomer was formed preferentially in this system and have rationalised these results.

Subsidiary results include a further confirmation of the fact that the selection of the surfactant concentration is an important but elusive parameter in organic synthesis and that the pH is significant in chiral micellar catalysis. Finally, we have seen that lithium chloride may prove to be useful in such systems.

This work is part of a series of ongoing projects. We are aiming at further enhancing selectivity in Diels–Alder reactions by investigating a range of substrates with the aim of reducing the effects of the competing reaction in the water phase. We are also investigating the use of chiral surfactants in other classes of reaction as well as exploring the effect of more conformationally constrained surfactants.

We are grateful to University College London (Access Funds for M. J. D.-C.), Bush Boake Allen, Central Research Fund University of London, The Royal Society, and The Nuffield Foundation for funding. We thank Dr P. Sandor for running NOE experiments.

Notes and References

† E-mail: h.c.hailes@ucl.ac.uk

‡ Chiralcel OD column, 0.5% propan-2-ol–hexane, 1 ml min^{-1}. Retention times: **2** 7.0 min; **3** 4.8 min. Optical rotations were: **3** *via* $TiCl_4$ catalysis, $[\alpha]_D$ +8.1 (*c* 1.00, in CH_2Cl_2, 20 °C), **2** and **3** *via* micellar catalysis $[\alpha]_D$ +5.0 (*c* 1.03, in CH_2Cl_2, 20 °C).

§ Reactions were repeated a minimum of three times, giving enantioselectivities consistent to ± 0.5%. Cyclopentadiene (3.8 mmol) was reacted with nonyl acrylate (1.9 mmol) in water (25 ml) containing surfactant **1** for 20 h. Acidity adjusted with HCl. Chiralcel OD column, 0.1% propan-2-ol–hexane, 0.75 ml min^{-1}. Retention times: *exo*, 6.7 and 6.9 min; *endo*, 7.9 and 9.0 min.

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Received in Liverpool, UK, 15th April 1998; 8/02825G