

**Micellar Media
and Catalysis of the
Diels-Alder Reaction**

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Abstract

This thesis is divided into eight chapters. Initially the Diels-Alder reaction is described from its mechanism using Frontier Molecular Orbital theory to rate enhancements of the reaction using Lewis acid catalysis, together with the use of chiral auxiliaries and the selectivity rules for the Diels-Alder reaction. Finally some solvent effects on the Diels-Alder reaction are reviewed. Surfactant and micelle solutions are then discussed, describing their physical properties and known effects of micellar solutions on selected organic reactions, as well as the study of micellar systems using light scattering and surface tension experiments.

The first section of the results and discussion describes the study of Diels-Alder reactions of the acrylates and cyclopentadiene using solvents of varying polarity, highlighting the different yields and selectivities observed together with a rationalisation of the results. Rate acceleration was observed with the Diels-Alder reaction when performed in aqueous media, more so in the presence of surfactants at their critical micelle concentration (*cmc*). The rate acceleration was accompanied with higher *endo/exo* ratio when compared to organically mediated Diels-Alder reactions. Hydroquinone derivatives were shown to act as dienophiles, participating in the Diels-Alder reactions in an aqueous media but not in organic solvents.

The synthesis of surfactants derived from amino acids, together with measurements of some physical properties is given, including the determination of their *cmc* using methyl orange dye and surface tension experiments. Brief calculations are given to determine their aggregation number and micelle size of the phenylalanine-derived (**86**) (aggregation number: 23; micelle size: 43.6 Å²) and leucine-derived (**89**) surfactants (aggregation number: 19; micelle size: 54.6 Å²).

Finally, the use of chiral surfactant in water as a reaction medium for the Diels-Alder reaction is described, including analysis of results, enantioselectivity observed, and determination of the direction of selectivity. The phenylalanine-derived (**86**) surfactant gave an enantiomeric excess (*e.e.*) of 16-18% in the *exo*

isomer (**74b**), whilst the leucine-derived (**89**) surfactant gave a 15% *e.e.* with the *endo* isomer (**74a**) in the Diels-Alder reaction between nonyl acrylate and cyclopentadiene.

A conclusion, summarising the key results to date and future work is outlined. A detailed description of the experimental procedures and summary of spectroscopic data are given in the experimental chapter. This includes a brief description of the physical chemistry studies on the synthetic chiral surfactants and the results obtained.

Abbreviations

°C	Degrees centigrade
1°	Primary
2°	Secondary
2D	2 dimensional
Phenylalanine-derived (85) surfactant	(2 <i>S</i>)- <i>N</i> -Hexadecyl-(1-hydroxy-3-phenylpropyl)- <i>N</i> , <i>N</i> -dimethyl-2-ammonium bromide
Phenylalanine-derived (86) surfactant	(2 <i>S</i>)- <i>N</i> -Hexadecyl-(1-hydroxy-3-phenylpropyl)- <i>N</i> , <i>N</i> -dimethyl-2-ammonium chloride
Leucine-derived (89) surfactant	(2 <i>S</i>)- <i>N</i> -Hexadecyl-(1-hydroxy-4-methylpentyl)- <i>N</i> , <i>N</i> -dimethyl-2-ammonium chloride
Å	Angstrom, 10 ⁻¹⁰ m
A	Temperature dependent constant, 1.2095 cm ³ mol ⁻¹ at 25 °C
ABS	absorbance
AO	Acridine Orange
B	Second virial coefficient
br s	Broad singlet
CD	Cyclodextrin
<i>cmc</i>	Critical micelle concentration
<i>cmt</i>	Critical micelle temperature, Krafft point
CPB	Hexadecylpyridinium bromide
C _R	Alkyl chain
CTAB	Hexadecyltrimethylammonium bromide
D	Doublet
d ₆ -DMSO	Deuterated dimethyl sulfoxide
DCC	<i>N</i> , <i>N</i> -dicyclohexylcarbodiimide
Dd	Double doublet
DDAO	Dimethyldodecyl amine- <i>N</i> -oxide
<i>d.e.</i>	Diastereomeric excess
DMAP	4-dimethylaminopyridine
<i>e.e.</i>	Enantiomeric excess
E.I.	Electron impact
equiv.	Molar equivalent

ESR	Electron spin resonance
EtOAc	Ethyl acetate
FAB	Fast atom bombardment
fcc	Flash column chromatography
FMO	Frontier molecular orbital
g	Gram
h	Hours
HCl _(aq)	Hydrogen chloride solution
Hex	Hexane
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
Hz	Hertz
I ₀	Intensity of the incident light
IPA	Isopropanol
I _t	Intensity of the transmitted light beam
K ₁	An optical constant
k ₂	Rate velocity
l	Length of the sample
Leu	Leucine
Lit.	Literature
LUMO	Lowest unoccupied molecular orbital
M	Molar
M _w .	Molecular weight of the scattering unit
m	Multiplet
(m)	Medium (Infra red)
m.pt	Melting point
M ⁺	Molecular ion
MDEB	(-)- <i>N</i> -Dodecyl- <i>N</i> -methyl ephedrium bromide
mg	Milligram
MgSO ₄	Magnesium sulfate
MHz	Mega Hertz
min	Minute
ml	Millilitre

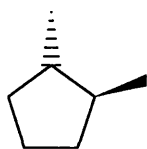
Abbreviations

mM	Millimolar
mmol	Millimoles
mN/m	Milli Newton per metre
MS	Mass spectrometry
mW	Milli Watts
<i>N</i>	Endo
nOe	Nuclear Overhauser enhancement
<i>N/X</i>	<i>Endo/exo</i> ratio
N_a	Avogadro constant – $6.0221367 \times 10^{23} \text{ mol}^{-1}$
NaOH _(aq)	Sodium hydroxide solution
NFR	Nitroxide-free radical
nm	Nanometre
NMR	Nuclear magnetic resonance
P.M.	Photo multiplier
Ph	Phenyl
PhH	Benzene
PNDS	4-Phenylazo-1-naphthol-2, 3'-disulfonate
ppm	Parts per million
Q	Quantum
q	Quartet
R^2	Correlation coefficient
R_{90}	Rayleigh ratio of sample relative to toluene
RI	Refractive Index
rt	Room temperature 25 °C
s	Singlet
(s)	Strong (Infra red)
S_{90}	The scattering of the surfactant sample and toluene at the 6 apertures were determined then the mean ratio of all the apertures calculated
SDS	Sodium dodecyl sulfate
ST	Surface tension
Surfactant	Surface active agent
t	Triplet
T	Temperature

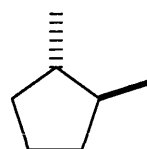
THF	Tetrahydrofuran
TILS	Total intensity light scattering
tlc	Thin layer chromatography
TS	Transition state
UV	Ultraviolet
(w)	Weak (Infra red)
<i>X</i>	<i>Exo</i>
Z_{45}	Ratio of scattered light from a sample at 45° to that of 135°
Γ	Surface excess
Ω	Log[<i>endo/exo</i>]

Stereochemical Notation

Throughout this thesis, the graphical representation of stereochemistry is in accordance with the convention proposed by Maehr*. The solid and broken wedges denote absolute configuration and the solid and broken lines denote racemates. For the former, greater narrowing of both solid and broken wedges indicates distance from the viewer.



Absolute



Relative

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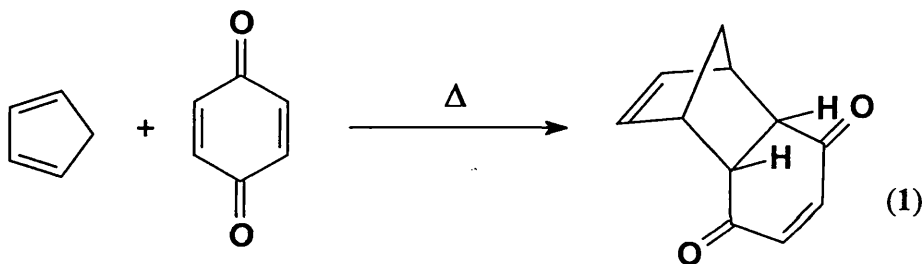
1 Introduction:

The Diels-Alder Reaction

1 The Diels-Alder Reaction

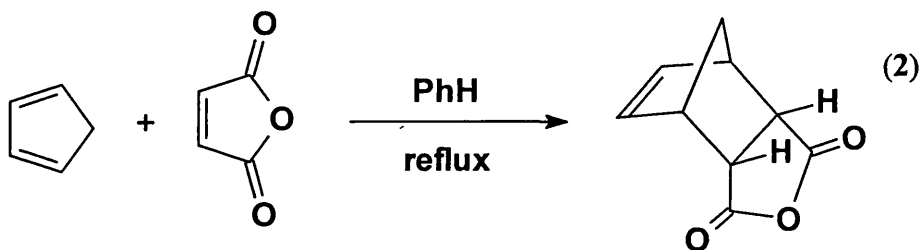
Molecules that possess a conjugated 4π electron diene system and a 2π electron system dienophile can undergo a cyclic addition known as the Diels-Alder reaction. This involves the formation of a six-membered ring with two new σ -bonds at the expense of two π -bonds.

Albrecht reported the first “Diels-Alder” cycloaddition between a diene and a dienophile.¹ He observed the thermal reaction between cyclopentadiene and *p*-benzoquinone to give a “dimeric complex” (1), which we now refer to as the $[4\pi+2\pi]$ cycloadduct (scheme 1.1).



Scheme 1.1: Albrecht's first 'Diels-Alder' reaction between cyclopentadiene and benzoquinone

It was not until twenty years later that Diels and Alder reported similar observations, together with several other reactions between different dienes and alkenes.² They characterised the products they obtained and found that for one specific reaction, between cyclopentadiene and maleic anhydride in benzene, the adduct (2) was isolated in quantitative yield (scheme 1.2).



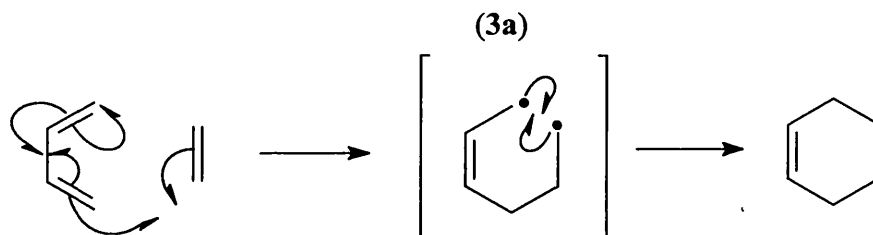
Scheme 1.2: A Diels and Alder reaction

From these initial reactions, countless different variations have been reported and it has become one of the most important methods for constructing cyclic molecules.^{3, 4, 5, 6}

1.1 The Diels-Alder Mechanism

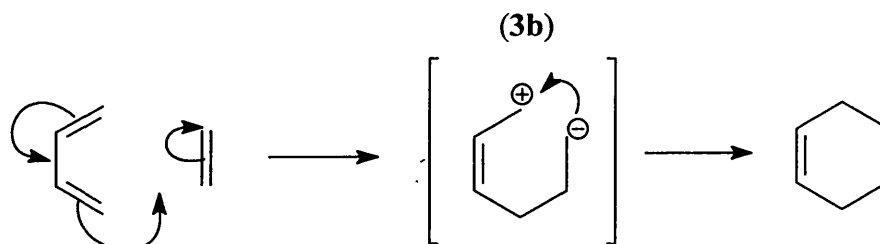
1.1.1 A concerted mechanism?

The issue of whether the Diels-Alder mechanism is concerted or stepwise has frequently been discussed,⁷ although the concerted argument has always been predominantly favoured. A transition model, first proposed by Wassermann, shows the reaction proceeding in a concerted fashion, with the formation of the two new σ bonds in a single transition state (TS).⁸ This mechanism has provoked many debates because it can also follow a step-wise mechanism leading to the formation of the σ bonds. A non-concerted mechanism could involve a diradical intermediate, (3a) (scheme 1.3).^{9, 10}



Scheme 1.3: Concerted Diels-Alder reaction

A further mechanism, involving a di-ion (3b) could also be proposed (scheme 1.4).

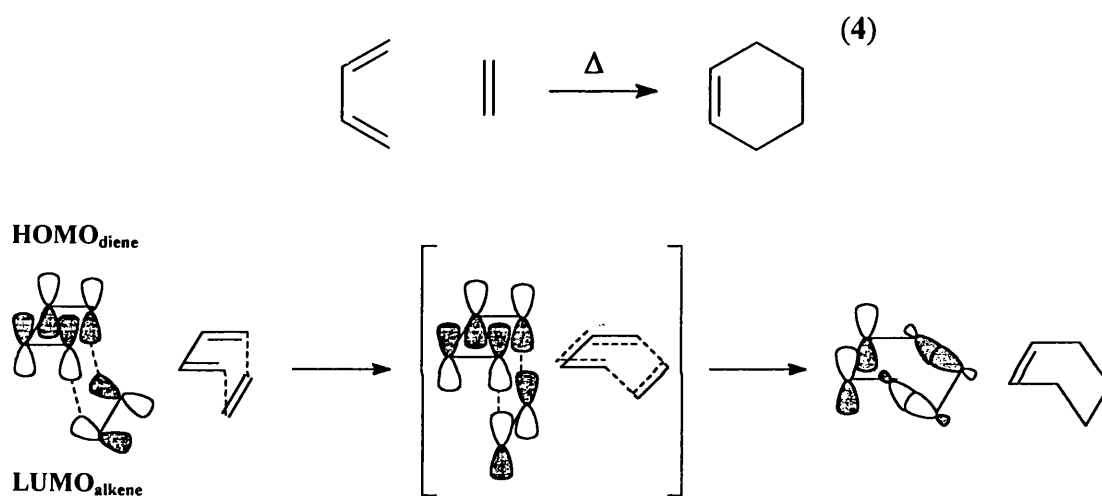


Scheme 1.4: Di-ion mechanism for the Diels-Alder reaction

The concerted, one step mechanism illustrated in scheme 1.5 is favoured as the Diels-Alder mechanism.

1.1.2 Frontier Molecular Orbital Theory (FMOT)

Woodward and Hoffmann proposed rules for the Diels-Alder reaction using Frontier Molecular Orbital Theory (scheme 1.5).⁷ As examples they considered the reaction between a 4π -electron system, butadiene and a 2π -electron system, ethene, where the electrons of the **Highest Occupied Molecular Orbital** or HOMO in the butadiene are donated to the **Lowest Unoccupied Molecular Orbital** or LUMO of the ethene during the thermal reaction. During the reaction the orbitals align to form two new σ bonds and a new π bond, to yield cycloadduct (4).



Scheme 1.5: HOMO and LUMO electron orbitals

The overlap of orbitals and the simultaneous creation of two new σ bonds constitute a movement of 6 electrons around the molecule. This concerted mechanism is now generally accepted as the mechanism for the Diels-Alder reaction.^{7,}

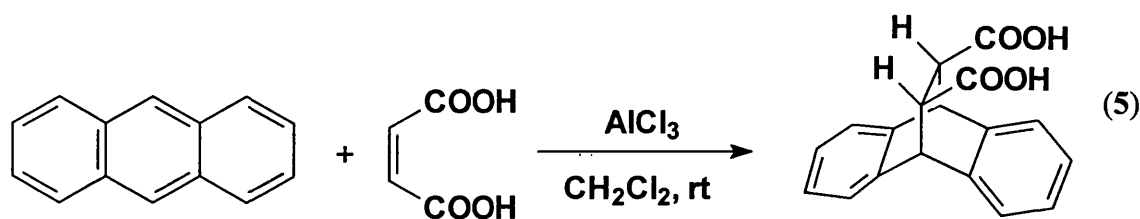
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1.2 Rate Enhancements in the Diels-Alder Reaction

1.2.1 Catalysis by Lewis acids

a) Aluminium chloride

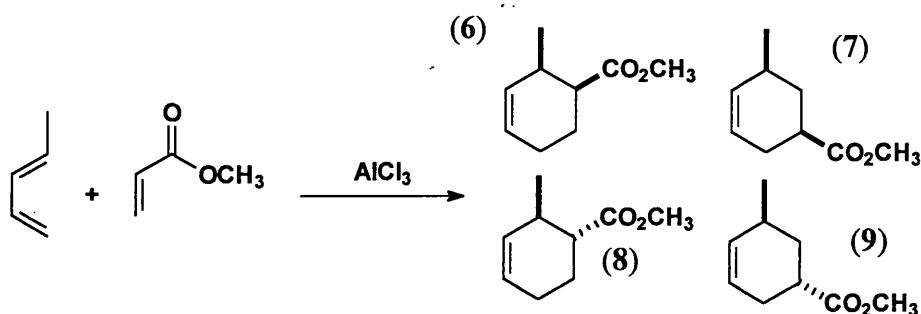
It has been well documented that Lewis acids can act as catalysts in Diels-Alder reactions.¹³⁻¹⁶ Wasserman first noted that the reaction between anthracene and maleic acid, to yield cycloadduct (5) was accelerated (scheme 1.6) in the presence of aluminium chloride: it was complete after 1.5 minutes.¹⁷



Scheme 1.6: Lewis acid catalysed Diels-Alder reaction with aluminium chloride

An extrapolation of the rate curve was used to determine the extent of the reaction under equivalent conditions (same temperature and concentration of reactants) in the absence of aluminium chloride. It was estimated that the reaction would be 95% complete after 4800 hours.

Aluminium chloride has been utilised extensively, but Inukai's work on the catalysis of the reaction between *trans*-piperylene and methyl acrylate highlights its effect.¹⁸ He found that with the catalyst present, the highly selective *cis*-ortho isomer (6) was formed in preference to the *trans*-meta isomer (9). (See scheme 1.7 & table 1.1)



Scheme 1.7: Inukai's reaction using aluminium chloride

Catalyst	Conditions	Concentration of reactants [A]:[B]	Results
<i>Reaction 1</i> AlCl ₃	10-20 °C 3 hours	1:1	6: 93.1%, 7: 4.9 % 8: 2%, 9: Neg*. Overall yield 50%.
<i>Reaction 2</i> None	25 °C 70 days	1.25:1	6: 51.3%, 7: 38.7% 8: 7.3%, 9: 2.7% Overall yield 39%.
<i>Reaction 3</i> None	120 °C 6 hours	1:1	6: 45.2%, 7: 38.6% 8: 10.6%, 9: 5.4% Overall yield 53%.

Neg*. Negligible products present.

Table 1.1

The Lewis acid catalyst facilitated the reaction even at low temperatures (10-20 °C). At 25 °C, the reaction needed 70 days to give a 39% yield and using similar conditions to the catalysed reaction but without AlCl₃, a 53% yield required higher temperatures (120 °C) and longer reaction times of 6 hours compared to 3 hours. It should be noted that even though the temperatures used in *reaction 1* and *3* are different, kinetic studies have shown that temperature does not affect the distribution of isomers in the products. Also, epimerisation is not possible even when the *cis*-ortho isomers were heated at 120 °C for 6 hours.

It is believed that the presence of aluminium chloride accelerates the reaction by forming a complex between the carbonyl moiety and the Lewis acid, thus lowering the net energy difference between the **HOMO** of the diene and the **LUMO** of the dienophile.^{18, 19} Woodward and Katz proposed a two-step mechanism describing how aluminium chloride could catalyse the Diels-Alder reaction between 1, 3-butadiene and an acrylate derivative (**10**, figure 1.1).^{7, 20}

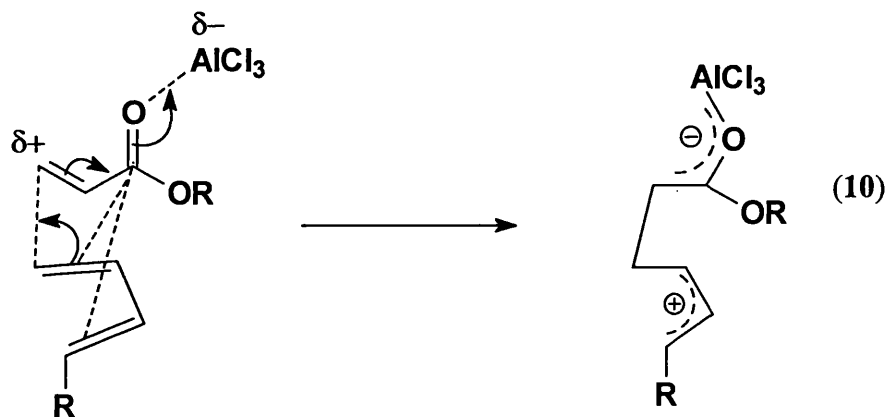
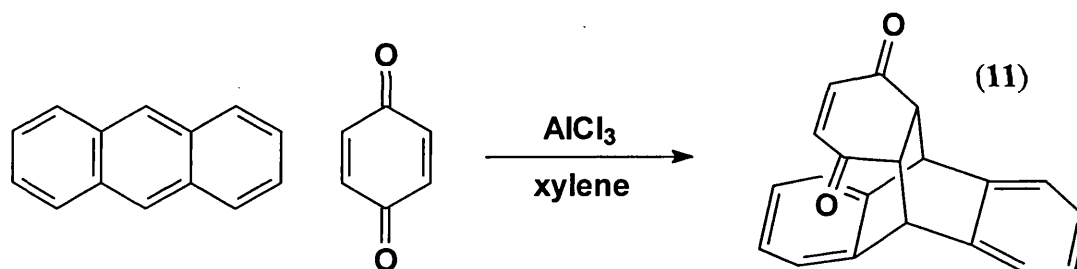


Figure 1.1: Lewis acid, aluminium chloride catalysis

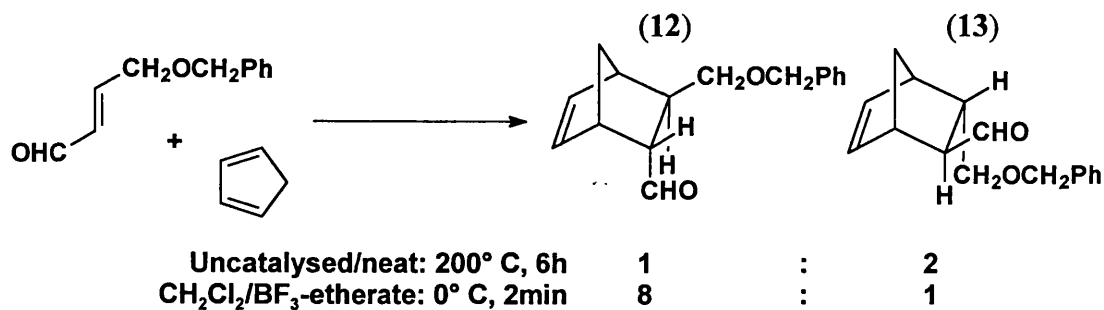
This two step and non-concerted mechanism is often used to describe the Lewis acid catalysed mechanism. Since this early work, aluminium chloride has been used in numerous Diels-Alder reactions as a catalyst and its utility is highlighted by Yates *et al.* as shown in scheme 1.8, where in the absence of aluminium chloride, the cycloadduct (11) does not form in xylene.^{21, 22}

Scheme 1.8: In the absence of the AlCl_3 the cycloadduct does not form in xylene

Other metal salts have also been employed as Lewis acids to catalyse Diels-Alder reaction in addition to aluminium chloride.

b) Boron trifluoride-etherate (BF_3 -etherate)

Lindsay-Smith observed that Diels-Alder reactions are also dramatically accelerated in the presence of the Lewis acid catalyst, boron trifluoride-etherate (scheme 1.9). This acceleration was accompanied by a reversal in the *endo/exo* (12/13) ratio in his system, from 1:2 to 8:1.²³

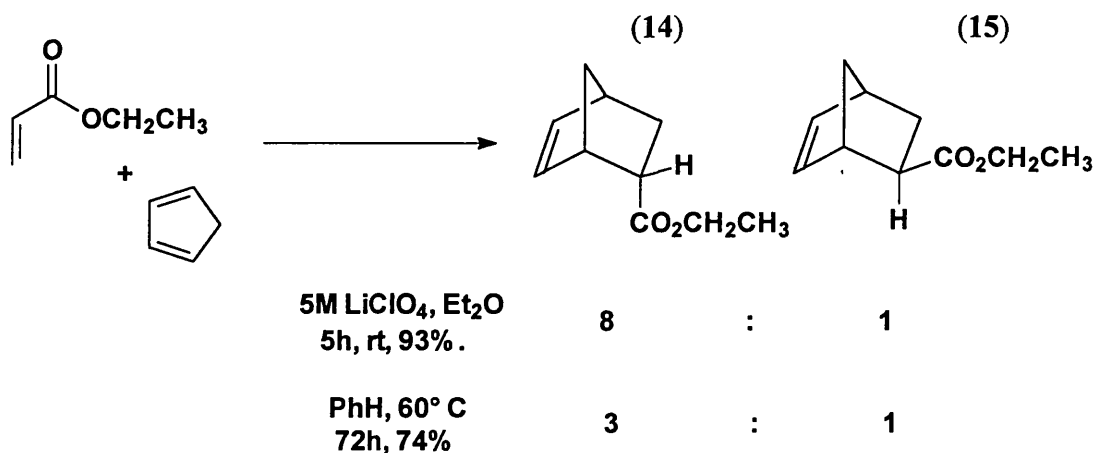


Scheme 1.9: Boron trifluoride-etherate catalysed Diels-Alder reaction

This catalyst is believed to act in a similar fashion to aluminium chloride, by forming a complex with the heteroatom of the dienophile, creating a partial positive charge across the double bond, thus making one carbon site more susceptible to attack by the diene, and accelerating the reaction.

c) Lithium perchlorate (LiClO₄)

Grieco reported that lithium perchlorate also accelerates Diels-Alder reactions. The reaction between cyclopentadiene and ethyl acrylate in the presence of lithium perchlorate in ether, at room temperature, gave an 8:1 *endo/exo* (14/15) ratio of cycloadducts (scheme 1.10).²⁴

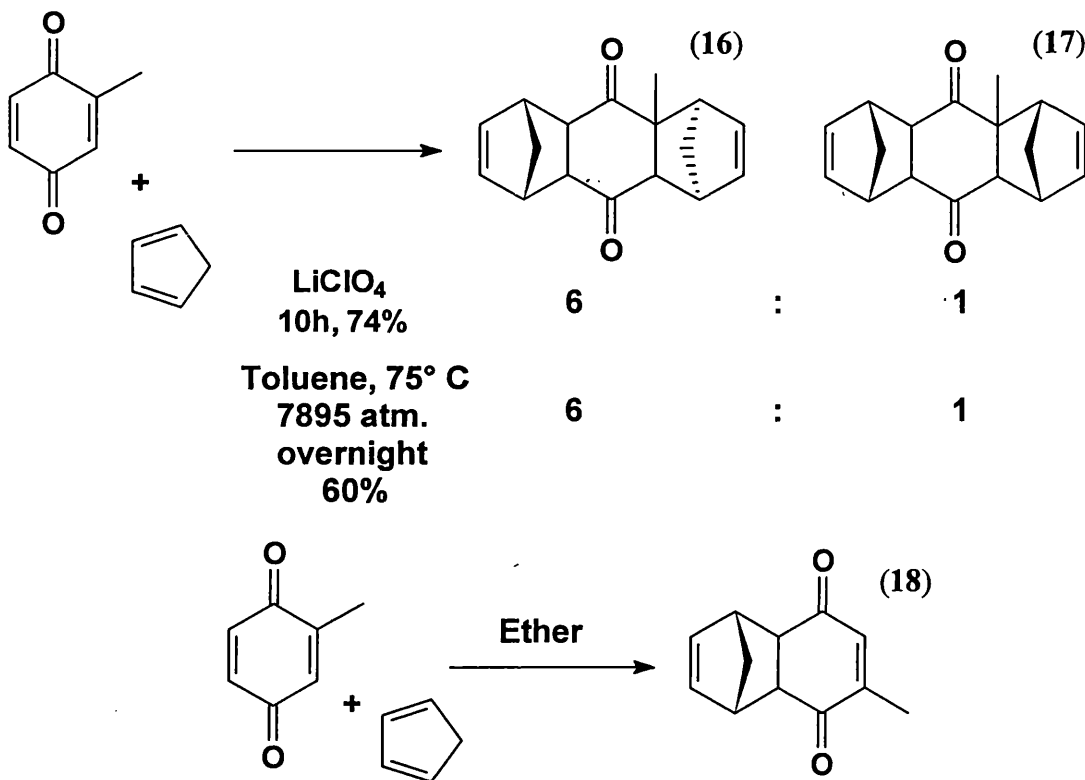


Scheme 1.10: Lithium perchlorate catalysed Diels-Alder reaction

Grieco postulated that the lithium cation could act in a Lewis acid fashion, complexing with the heteroatom of the acrylate. He also made a premise that lithium perchlorate salts can exert or induce compression within the solvent, increasing the inner pressure of the reactant and forcing the reacting species together, thus accelerating the reaction.²⁴

Lithium perchlorate was also compared to the use of water as a solvent, which was known to accelerate the Diels-Alder reaction (scheme 1.10) and afforded the product in 73% yield with a (14)/(15) ratio of 4:1. Similarly, lithium perchlorate has been used in the reaction between cyclopentadiene and methylbenzoquinone (scheme 1.11). Before the advent of the lithium perchlorate catalytic systems, high temperatures and pressures were needed to facilitate the reaction between cyclopentadiene (in excess to account for the diene polymerisation at high temperatures) and methylbenzoquinone.

The cycloadducts were isolated in a 6:1 ratio favouring the *endo-trans-endo* (16) isomer over the *endo-cis-endo* (17) product. However, when the reaction was repeated in the absence of lithium perchlorate the cycloadducts isolated did not contain any *bis*-adducts but rather the mono substituted product (18, scheme 1.11). They postulated that the lithium perchlorate was stabilising the polar TS of the Diels-Alder reaction, which enabled the cyclopentadiene molecule to add on to both sides of the dienophile.



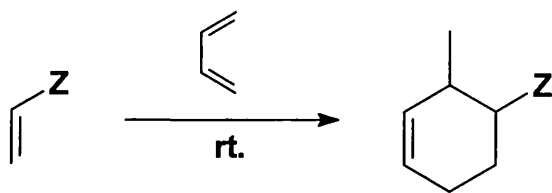
Scheme 1.11: Lithium perchlorate catalysis of the Diels-Alder reaction

In summary, cycloadditions using lithium perchlorate can lead to the use of ambient temperatures and shorter reaction times, leading to the preferential formation of the kinetically favoured *endo* isomer. Since the first reports of lithium perchlorate as a Lewis acid catalyst, it has been used in several key cycloadditions.^{25, 26}

1.3 Selectivity in the Diels-Alder Reaction

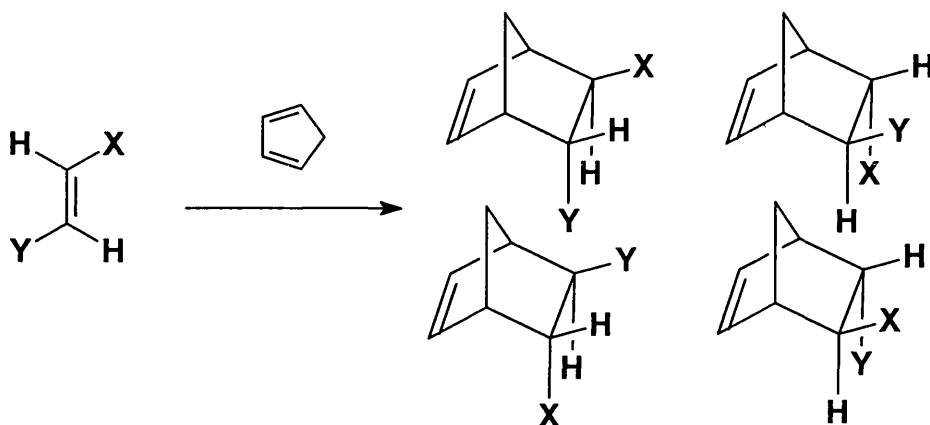
1.3.1 The Diels-Alder reaction rules

There are four general rules that have been surmised in the Diels-Alder reaction. Firstly, electron withdrawing substituents (**Z**) on the dienophile and electron releasing substituents on the diene increase the rate of reaction. The reverse group effects (inverse electron demand) likewise increase the rate (scheme 1.12).²⁷



Scheme 1.12: Z-Reverse electron demand in a Diels-Alder reaction

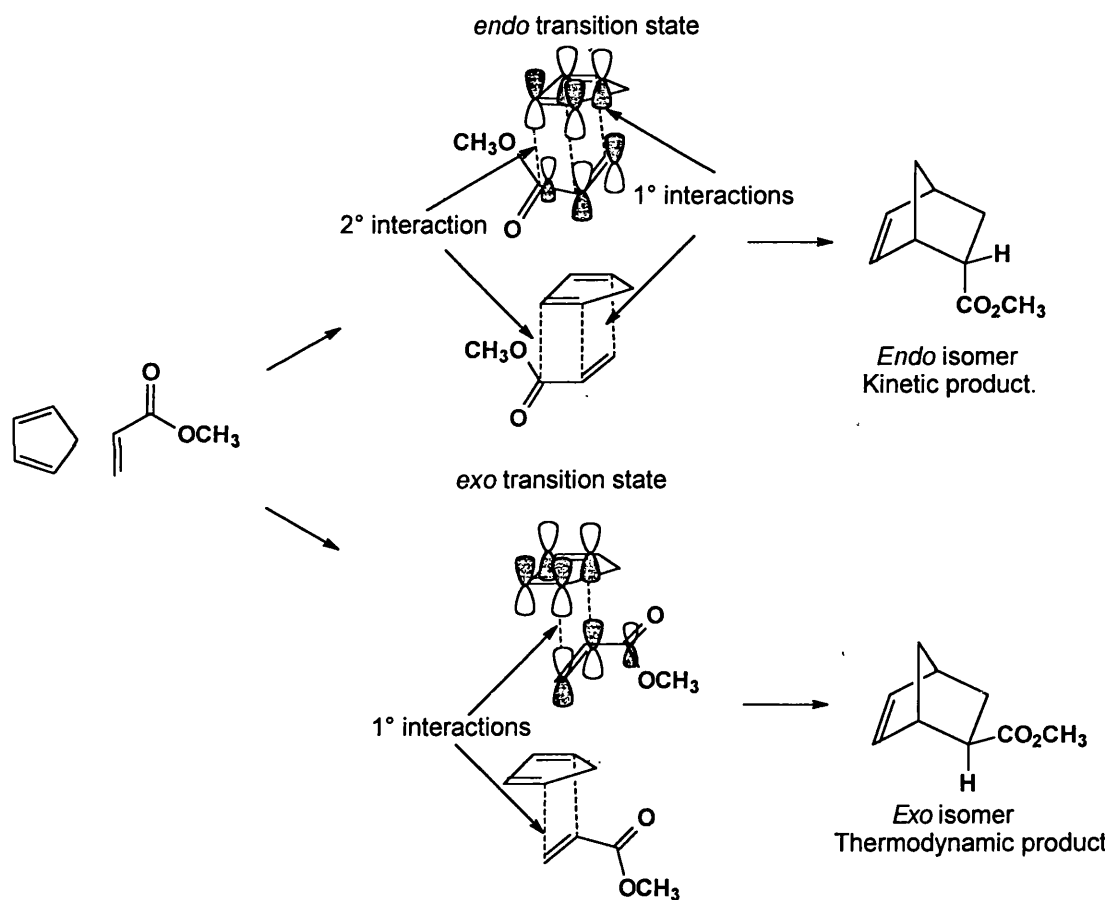
Secondly, the diene and dienophile configuration are retained in the cycloadduct, which is known as the *cis* principle. As outlined in scheme 1.13, the relative stereochemistry of the adducts is retained in the product.²⁷



Scheme 1.13: Example of *cis* principle in the Diels-Alder reaction

Thirdly, the *endo* rule, where the *endo* TS is favoured over the *exo* TS.²⁸ The *endo* rule can be best explained using FMOT. If the reaction between cyclopentadiene and methyl acrylate is considered, on comparing the *endo* TS with the *exo* TS it is apparent that the orbitals of the carbonyl are orientated to overlap with

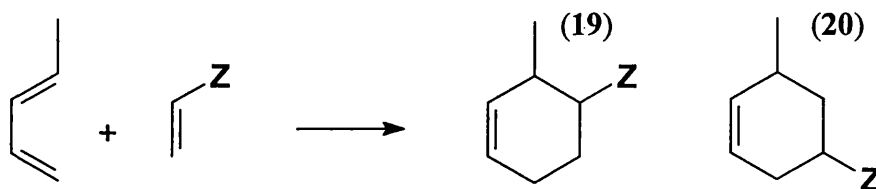
the orbitals of the diene in the *endo* TS (scheme 1.14).²⁹ Houk formulated a general approach for secondary orbital interactions and undertook investigations into these interactions.^{11,28,30} There are secondary interactions between the molecular orbitals of the double bonds in the diene and the molecular orbital of the carbonyl group in the dienophile. This secondary interaction stabilises the *endo* TS, lowering the energy, making the *endo* more favourable than the *exo* TS. These secondary interactions in the transition states can and often will determine the stereoselectivity of the products in Diels-Alder reactions.



Scheme 1.14: Orbital overlap of adducts giving *endo* and *exo* isomers

Finally, *Z*-substituted dienophiles react with 1-substituted butadienes (in normal electron demand Diels-Alder reactions, scheme 1.15) to give 3,4-disubstituted cyclohex-1-enes, independent of the nature of the diene substituents (the *ortho* effect).³¹ The partiality for the '*ortho*' or the '*meta*' selectivity of the Diels-Alder product was found to vary with the dienes electron releasing or withdrawing

substituents as well as the alkenes substituents (table 1.2), however the *ortho* isomer always predominates.



Scheme 1.15

Z	19	20
CHO	8	1
CN	10	1
CO ₂ CH ₃	6.8	1

Table 1.2: '*Meta*' versus '*Ortho*'

1.4 Chiral Diels-Alder Reactions

Stereochemical control of any organic reaction is of huge importance in chemical applications. The Diels-Alder reaction has proven to be versatile in this context, creating up to four chiral centres with the simultaneous formation of two σ bonds during the reaction.

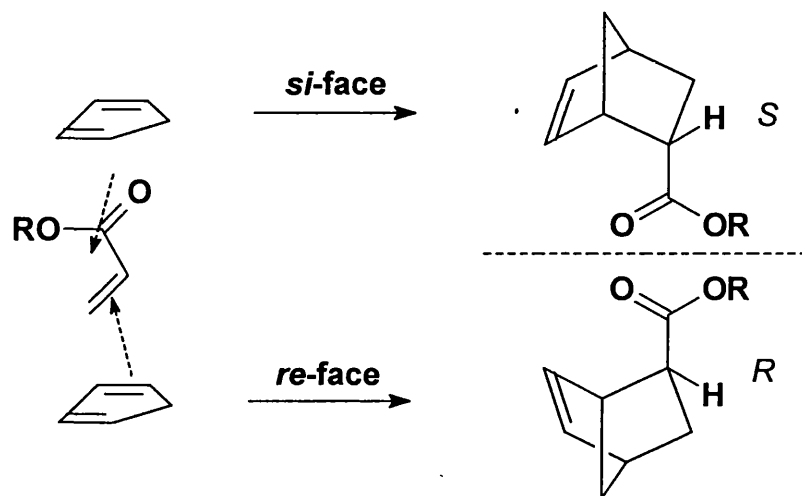


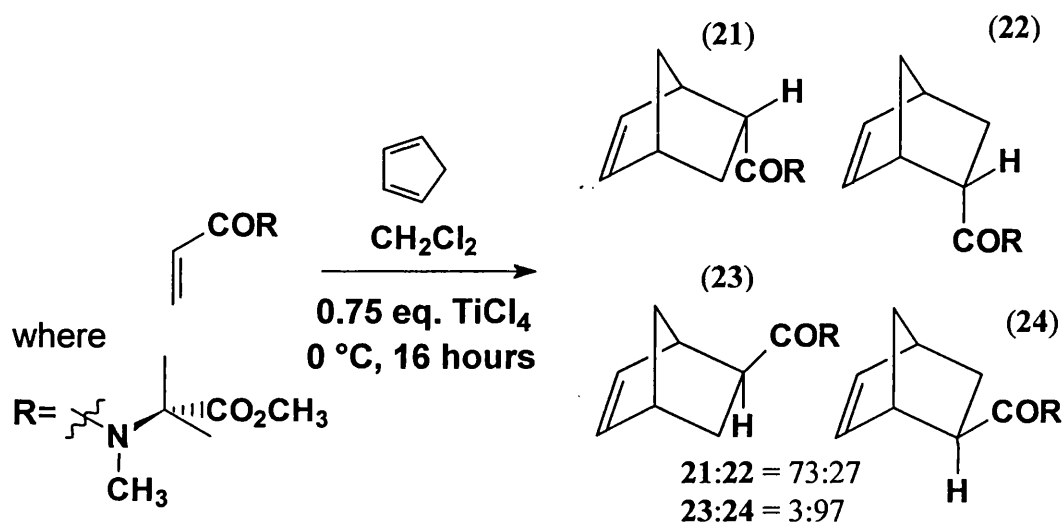
Figure 1.2: Enantiomeric Pairs

Asymmetric Diels-Alder reactions involve the manipulation of the Diels-Alder rules using a chiral auxiliary or a chiral environment that can block one 'face' in the TS, resulting in the formation of one enantiomerically pure cycloadduct. One way this has been tackled is with the use of chiral auxiliaries. An ideal chiral auxiliary must meet the following criteria:³²

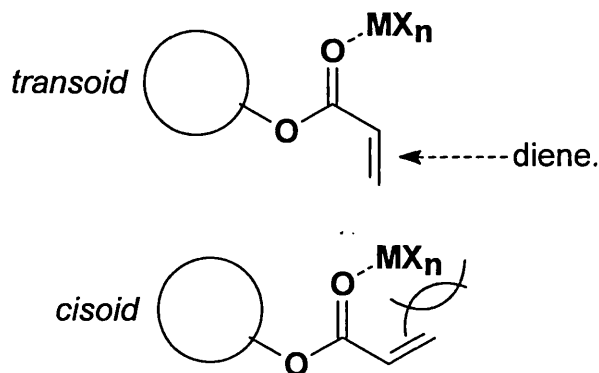
- The auxiliaries must ideally be applicable to a wide array of Diels-Alder substrates.
- Effective attachment and removal of the auxiliary must not compromise the desired configuration in the cycloadducts.

1.4.1 Chiral auxiliaries

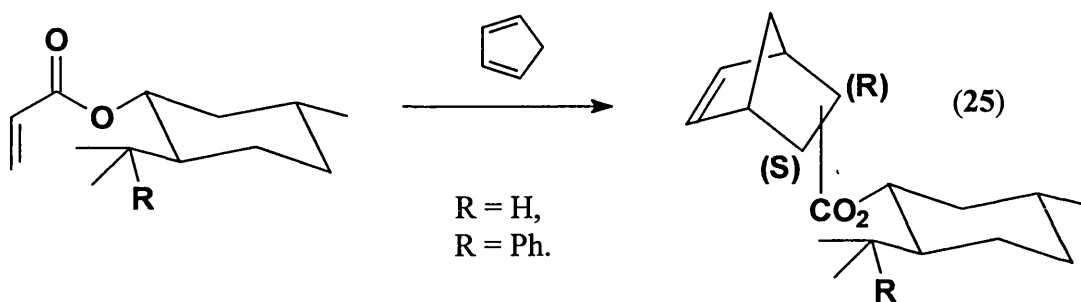
Chiral auxiliaries have been used extensively with conjugated carboxylic esters. These types of reaction systems have proven to be predictable, as addition can only come from one face enabling the prediction of the absolute stereochemistry of the product.³³ Introduction of a bulky chiral group on the ester can effectively block one face and preferential addition will be limited to the other. Cativiela best illustrates this, where he used α -amino acids as chiral auxiliaries (scheme 1.16).³⁴

Scheme 1.16: α -Amino acids as a chiral auxiliary

Many chiral auxiliaries are used in conjunction with Lewis acids, which facilitate the reaction.^{13, 35} The acrylate can adopt a *transoid* or *cisoid* conformation (figure 1.3), however the latter is prohibited due to the unfavourable spatial interaction between the double bond and the co-ordinated Lewis acid. Taking advantage of the Lewis acid co-ordinating to the heteroatom, the dienophile is then held in one conformation allowing the diene to preferentially add on one face only.

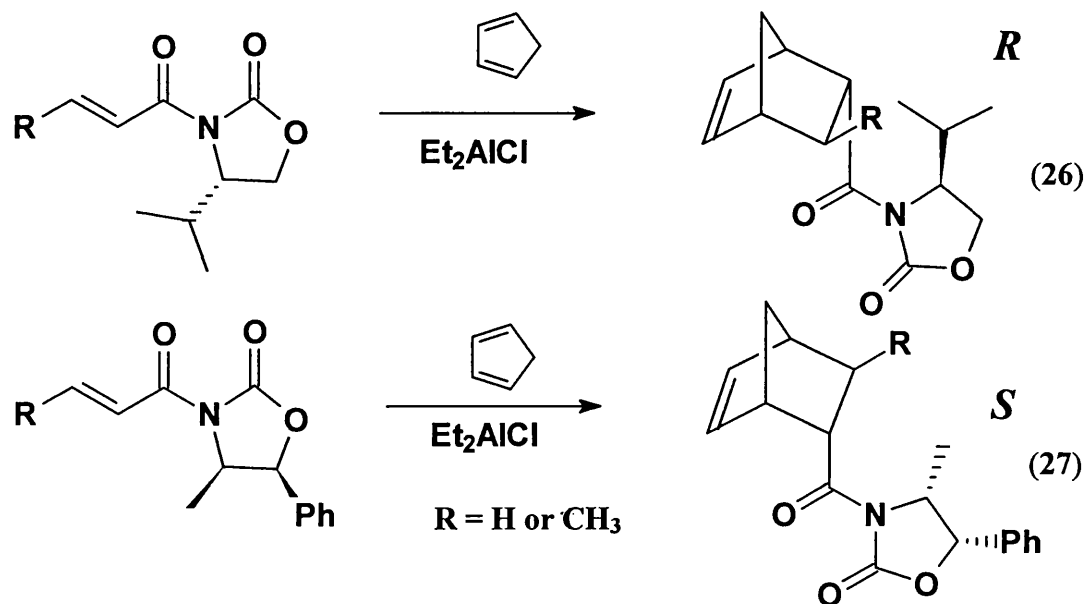
Figure 1.3: *Cisoid* and *transoid* conformation

Examples of chiral dienophiles include menthyl and oxazolidinones groups as shown below (schemes 1.17 and 1.18). The use of the menthyl group has led to high enantioselectivities in Diels-Alder reactions. When tin chloride was used as a Lewis acid with the menthyl acrylates, the reaction yielded an enantiomeric excess (*e.e.*) of 91% of the (*R*)-enantiomer (**25**) and an 8:1 *N/X* ratio. Removal of the auxiliary was achieved *via* a reduction step with lithium aluminium hydride and the auxiliary was recovered and re-used again in subsequent reactions.³⁶



Scheme 1.17: The use of the menthyl group

When using oxazolidinones (scheme 1.18), the auxiliary can be selected to generate either the *R* (**26**) or *S* (**27**) in the cycloadducts. Not only were high percentages of diastereomeric excesses [*d.e.*, >98%] observed but also a high *endo/exo* ratio was observed due to the secondary interactions of the carbonyl group with the double bond in the diene.^{33, 37, 38}



Scheme 1.18: The use of oxazolidinone auxiliaries

Oppolzer has also reported the use of camphor sultam auxiliaries, where in the presence of the Lewis acid, titanium (IV) chloride, high diastereomeric excesses (scheme 1.19) were observed. This was explained by a π -face selectivity where the Lewis acid can chelate to the heteroatom and the sulfur group which 'locks' the conformation, thus preventing the addition of the diene to the *si*-face and only exposing the *re*-face during the TS (figure 1.4).³³

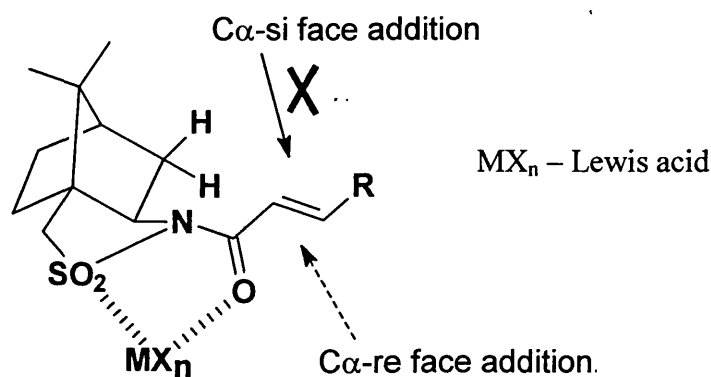
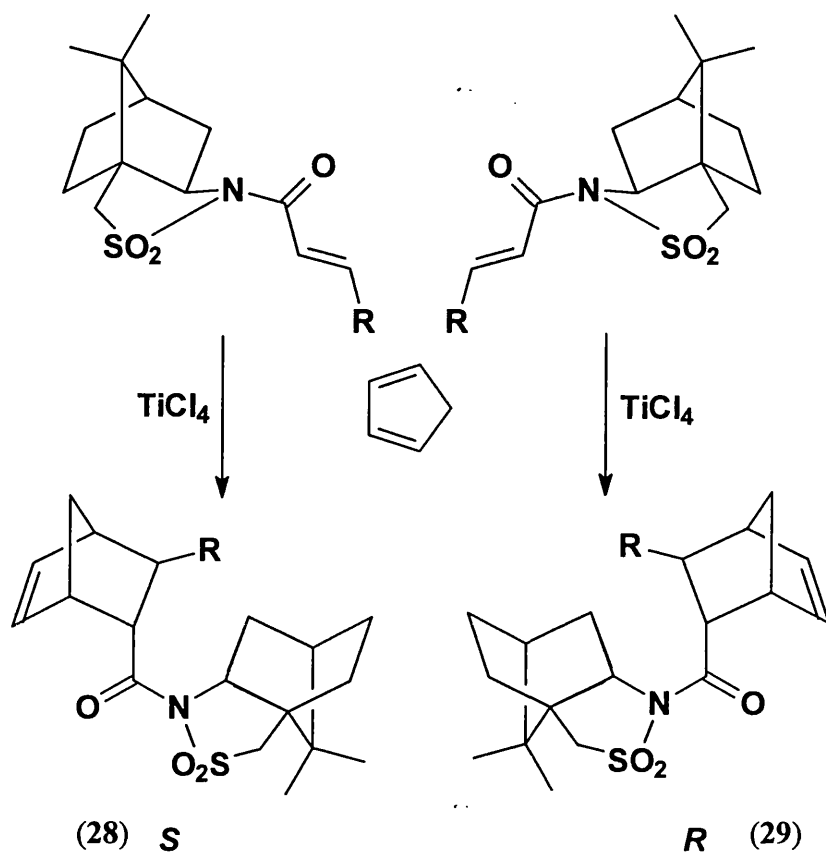


Figure 1.4: One face blocked by camphor sultam moiety

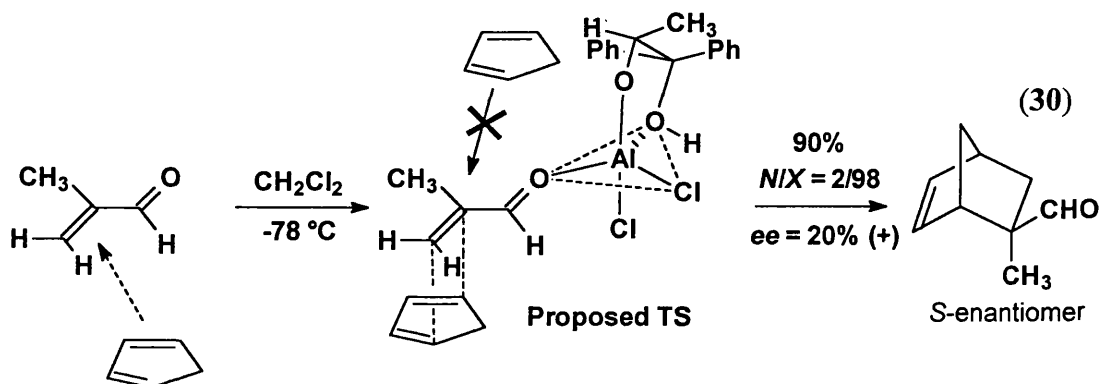


Scheme 1.19: Camphor sultam auxiliaries

Thus, chiral auxiliaries and Lewis acids have been used to give high selectivities in Diels-Alder reactions, but careful selection of the Lewis acid and reaction conditions are needed to ensure that the correct stereochemical products (**28** and **29**) are obtained. Whilst their general utility is good, the disadvantages are in the recycling of the auxiliaries and in larger scale applications, the problem of disposing of the Lewis acid.

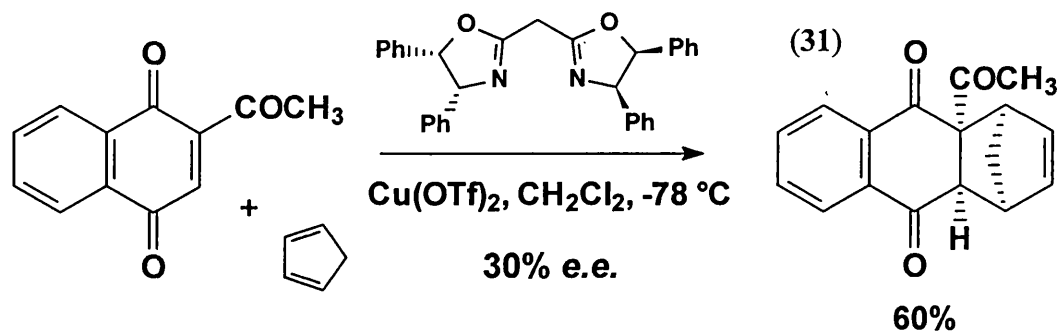
1.4.2 Chiral catalysts

This is illustrated in the reaction reported by Rebiere methacrolein and cyclopentadiene in the presence of a chiral catalyst derived from a chiral diol and ethylaluminium dichloride to yield cycloadduct **30** (scheme 1.20).¹⁴



Scheme 1.20: Chiral catalyst derived from a chiral diol and ethylaluminium dichloride

Brimble has reported the use of chiral ligands (scheme 1.21) to catalyse the Diels-Alder reaction between naphthoquinone derivatives and cyclopentadiene.³⁹



Scheme 1.21: The use of a chiral ligands and Lewis acid catalyst

The cycloadduct **31** was formed in a 60% yield, with a 30% $e.e.$. This has the advantage of avoiding the attachment and removal of auxiliaries from the desired product, which can reduce the overall isolated yield, however, recycling of the catalyst needs to be addressed.

1.5 Cyclodextrins versus Micelles

Cyclodextrins like micelles possess a hydrophobic core but unlike micelles, cyclodextrins are fixed structures and can be described as ‘molecular buckets’. Cyclodextrins are available in three different general forms: α , β and γ , with increasing cavity size (figure 1.5). Breslow explored the use of cyclodextrins in aqueous solutions to catalyse the Diels-Alder reaction between cyclopentadiene and methyl vinyl ketone (scheme 1.22).⁴⁰ He found that there was a significant rate enhancement if the substrates can fit within the cavity. Smaller cavities, which cannot accommodate larger reactive species, showed a reduced rate compared with substrates that fit in the hydrophobic cavity as shown in table 1.3.⁴¹

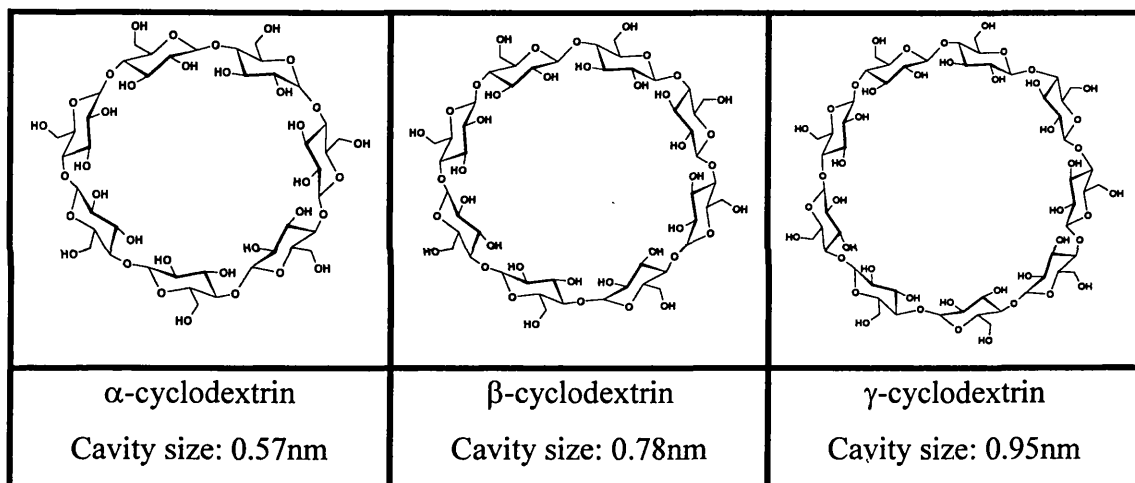
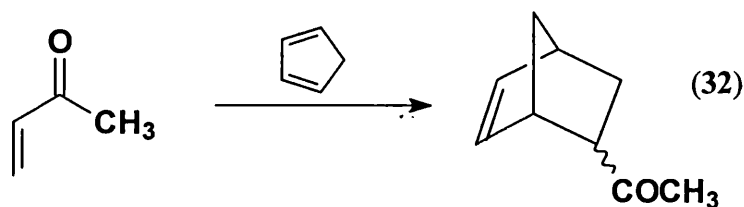


Figure 1.5: Different types of cyclodextrins with varying cavity diameters

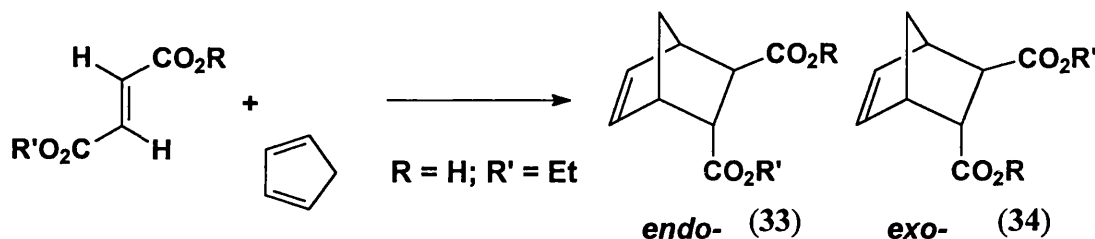


Scheme 1.22: Diels-Alder reaction catalysed by cyclodextrins

Solvent	Additive	Rate k_2 : $10^5 \text{ M}^{-1} \text{ s}^{-1}$
H ₂ O	α -cyclodextrin	47.9
H ₂ O	β -cyclodextrin	537.0

Table 1.3: Cyclodextrins increase rate of formation of cycloadduct (32), shown in scheme 1.22

One disadvantage, however, of using cyclodextrins is the high cost. Schneider and co-workers reported the influence of β -cyclodextrin on the diastereo- and enantioselectivity in the Diels-Alder reaction between cyclopentadiene and a fumaric acid half ester (scheme 1.23). Attributing the effect to 'an externally driven compression or packing of diene and dienophiles' in the cyclodextrin core altering the selectivity (see table 1.4).⁴² Although the enantioselectivity is not high, it clearly indicates that the size of the cyclodextrin core has an effect on rate of reaction.



Scheme 1.23: Diels-Alder reaction between fumaric acid half ester and cyclopentadiene

Diastereoselectivity (<i>endo/exo</i> products)		Enantioselectivity <i>e.e.</i> (%)	
H ₂ O	0.015 M* β -cyclodextrin	0.015 M*	β -cyclodextrin
1.10 \pm 0.05	2.2 \pm 0.08	<i>exo</i> -COOEt (34)	<i>endo</i> -COOEt (33)
		8.4 \pm 0.5	<2.0

* saturated solution of β -cyclodextrin in water

Table 1.4

It can be argued that micelles can effect reactions in an analogous fashion to cyclodextrins. The large increase in the amount of *endo* product in the reaction shown in scheme 1.23 was rationalised in terms of more Diels-Alder substrates adopting a more compact TS in the cavity of the cyclodextrin, which was not achieved with using water alone. Studies on the effect of micellar and cyclodextrin solutions as reaction media to date have indicated that they can enhance the rate of reaction and product selectivities. The reasons used to explain this, in both cases, are similar. However, one notable difference with micellar media is that there are a much greater variety of structural variations in the surfactants that can be used.

1.6 Solvent Effects on the Diels-Alder Reaction

Berson has correlated various solvent effects to the stereoselectivity of the Diels-Alder reaction between cyclopentadiene and acrylate derivatives.⁴³ Using solvents of different polarity, the ratios of the *endo/exo* (*N/X*) isomers of the cycloadducts were determined. He found that polar solvents conformed to the Alder or *endo* rule (see section 1.3.1) of “*maximum accumulation of unsaturates*”,² however, when non-polar solvents were used as a medium, the Alder rule was found to be flawed.

The Alder rule states that ‘there are secondary interactions between the non-participating molecular orbitals (non-bond making orbitals) in the diene and dienophile which stabilises the *endo* TS as mentioned in section 1.3.1. Irrespective of the solvent polarity, it might be predicted that similar *N/X* ratios would be observed, however results suggested otherwise. It was concluded that the *endo* rule is only of “minor importance” in determining the distribution of the isomers in the products in certain solvents.^{27, 43} Along with this premise, a new empirical measure of solvent polarity (Ω) was also introduced (equation 1).⁴³

$$\Omega = \text{Log} \left(\frac{\textit{endo}}{\textit{exo}} \right)$$

Equation 1: Empirical measure of solvent polarity

When methyl acrylate (**35**, figure 1.6) was reacted with cyclopentadiene in a range of solvent systems it gave a preference for the *endo* isomer, the kinetically favoured adduct, which was formed in preference to the *exo* product. Conversely, with methyl methacrylate (**36**), the *exo* addition was favoured in all systems. This reversal can be attributed to the lower activation energy of the *exo* adduct compared to the *endo* adduct. With *trans* methyl crotonate (**37**), a 1:1 product distribution was observed in all solvent systems. Here it is apparent that the *endo* rule applied to (**35**) but not (**36**) and (**37**) led to equivalent quantities of *endo* and *exo* products (figure 1.6).

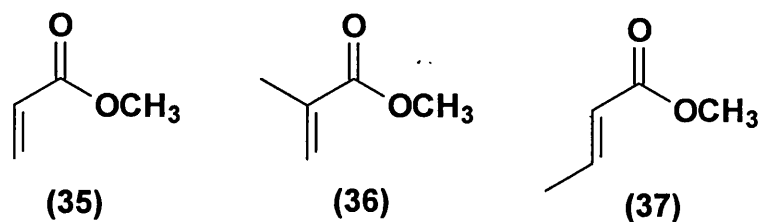
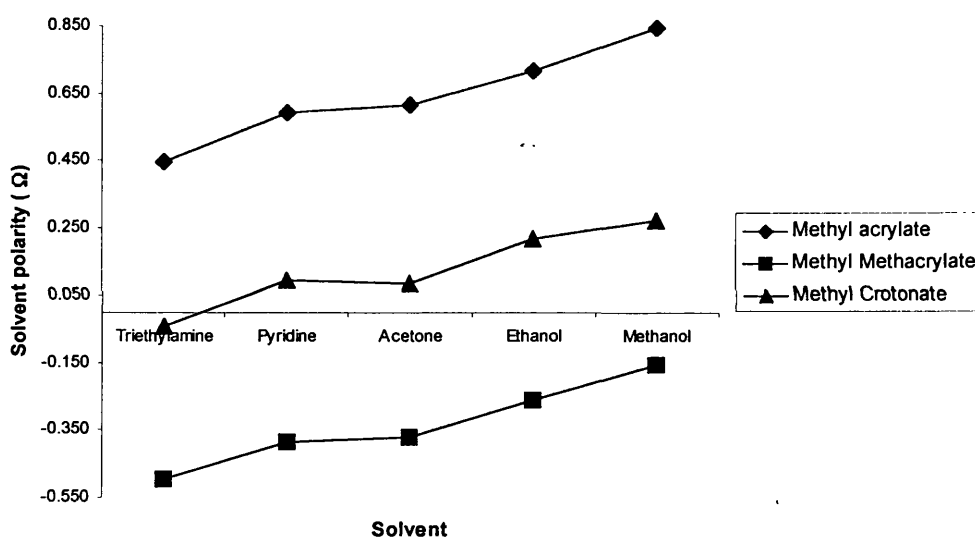


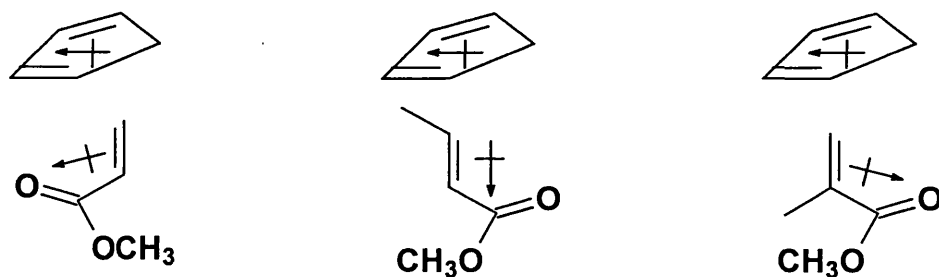
Figure 1.6: Structural differences between acrylate derivatives

With all three dienophiles, when increasing the solvent polarity from the non-polar triethylamine to the polar methanol, $\log(\textit{endo/exo})$ becomes more positive as shown in graph 1. The free energy change from the *endo* conformation into the *exo* TS is made more positive as the polarity of the solvent increases.



Graph 1: Solvent polarity (Ω) versus solvent type

There is also an electrostatic effect between the Diels-Alder substrates and during the molecular aggregation of the reactants, the dipoles of the substrates can become aligned in the TS (figure 1.7).⁴³



Methyl acrylate

trans-Methyl crotonate

Methyl methacrylate

Figure 1.7: Dipole moments found in methyl acrylate derivatives relative to cyclopentadiene

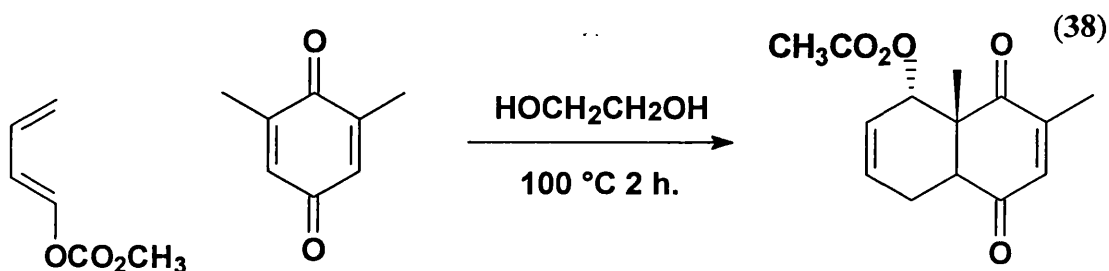
In the *endo* TS, the dipoles are roughly parallel, enforcing each other. In the *exo* TS, the dipoles are *anti*-parallel and have a destructive effect on both dipoles. Berson postulated that increasing the solvent polarity has the effect of polarising the substrate, particularly with methyl acrylate. Even though Ω of the product is very positive, in other words, predominately *endo*, Ω can be enhanced further by increasing the polarity of the solvent. There is a linear correlation between solvent polarity and distribution of *endo/exo* products with methyl acrylate as the dienophile but methyl methacrylate does not have a correlation whilst *trans* methyl crotonate showed only partial correlation. It was concluded that the dipole moment induced by the solvent polarity is not equal in each of the Diels-Alder substrates and therefore solvent polarity is not the only factor involved in the enhanced selectivity in the Diels-Alder adducts, but a contributing factor is also conveyed by the substrates' dipole moments.

1.7 Polar Solvents

1.7.1 Organic solvents

a) Ethylene glycol

Liotta and his co-workers have investigated the rate of the Diels-Alder reactions in ethylene glycol, using hydrophobic dienes and dienophiles (scheme 1.24).⁴⁵ A rate increase was observed which was attributed to the polarity of the solvent. They also inferred that the TS possessed a polar character.⁴⁴



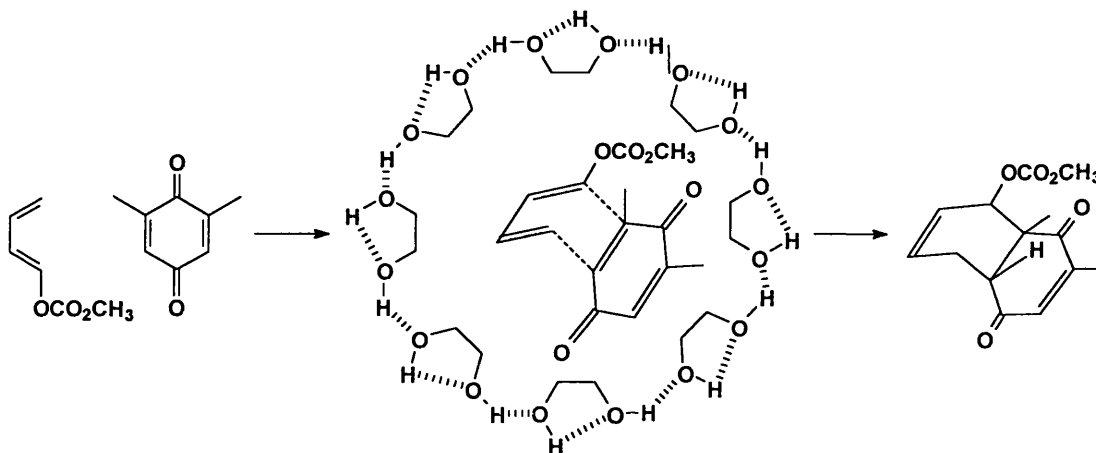
Scheme 1.24: 0% in benzene, 100% in ethylene glycol

The rate of reaction in ethylene glycol was also compared to the rate in other polar solvents, as determined by nuclear magnetic resonance (NMR), and is shown in table 1.5.

Solvent	Dielectric constant	Relative rate
Benzene	2.3	1.0
Methanol	32.6	4.1
Acetonitrile	36.2	1.8
Dimethylsulfoxide	46.6	3.1
Ethylene glycol	37.7	26.1
Water	78.0	no reaction

Table 1.5: Table showing dielectric constants of solvents and relative rate of reaction shown in scheme 1.24 for the formation of cycloadduct (38).

Liotta proposed that the increase in the rate of reaction was due to molecular aggregation, similar to the aggregation of hydrophobic molecules in an aqueous medium (scheme 1.25), such that ethylene glycol molecules are capable of forming aggregates by hydrogen bonding with each other. Within these aggregates, the diene and dienophile could enter and react.



Scheme 1.25: Encapsulation of the Diels-Alder substrate in the ethylene glycol 'complex'

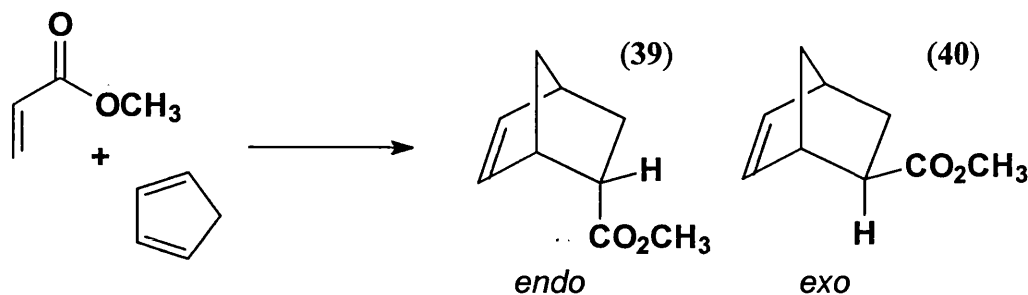
They performed the same reaction in water, but no product was observed. Thus it was concluded that the diene and the dienophile must be, at least, sparingly soluble in a solvent before a reaction can take place.⁴⁵

b) Formamide – water substitute

Realising the limitation of water to solubilise organic reactants, Lattes *et al.* investigated alternatives to water. They required a solvent:⁴⁶

- with **High polarity** – solvents with high polarities will be able to stabilise transition states in reactions,
- with **High solvating power** – dipole-dipole interactions between molecules,
- that was **Highly structured** – based on the solvents intermolecular forces between molecules, for example hydrogen bonding.

The Diels-Alder reaction between cyclopentadiene and methyl acrylate was investigated (scheme 1.26) using a range of appropriate solvents and the results compared to the use of water (summarised in table 1.6).



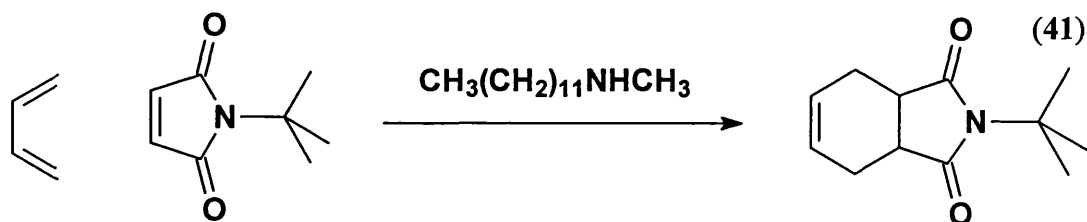
Scheme 1.26: A Diels-Alder reaction investigated in various solvents

Solvent	Dielectric constant (ϵ/ϵ_0)	Ω	<i>Endo</i> / <i>exo</i> ratio 39/40
Water	78.5	0.869	7.4
Formamide	109.5	0.825	6.7
<i>N</i> -methyl acetamide	182.4	0.672	4.7

Table 1.6: Table showing Ω versus *endo/exo* ratio for reaction in scheme 1.26

Using the Berson derived parameter Ω , they found that formamide had a lower Ω compared to water and did not follow Berson's empirical measure of solvent polarity.⁴³ Formamide has a higher dielectric constant than water, thus it was expected to give a higher Ω value but it was slightly lower. *N*-methyl acetamide has an even higher dielectric constant but gave an even lower Ω . Hence, it appeared that "solvophobic type interactions" can play an important role.^{9, 40, 47} Thus polarity is not the only criteria and that "internal forces" also present in the medium, such as surface tension, cohesion energy, internal pressure and charge dipole moment, are important. The surface tension of the polar solvent could also be lowered by the substrate if it is surface active.

1.7.2 Aqueous solvents

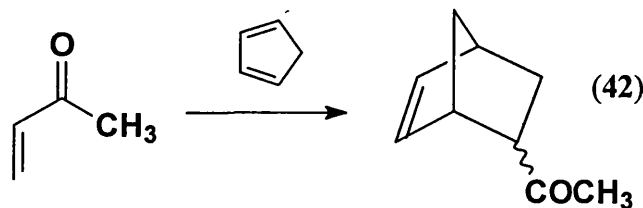


Scheme 1.27: Hopff and Rautenstrauch applied for a patent in 1938 covering reactions in water

Aqueous Diels-Alder reactions were first reported by Diels and Alder in the late 1920's but its potential was not realised until Hopff and Rautenstrauch applied for a patent in 1938 covering reactions in water.⁴⁸ They used dispersing or emulsifying agents, but only enough to solubilise their substrates in aqueous media. These agents were aptly named co-solvents. They reported several reactions including a reaction between *tert*-butyl maleimide and butadiene (scheme 1.27) in water 'treated' with methyl dodecylamine, which gave a quantitative yield of product (41). Since then, the use of such 'co-solvents' or surface active agents has received little attention until more recently.⁴⁹

1.7.2.1 Hydrophobic acceleration of Diels-Alder reactions

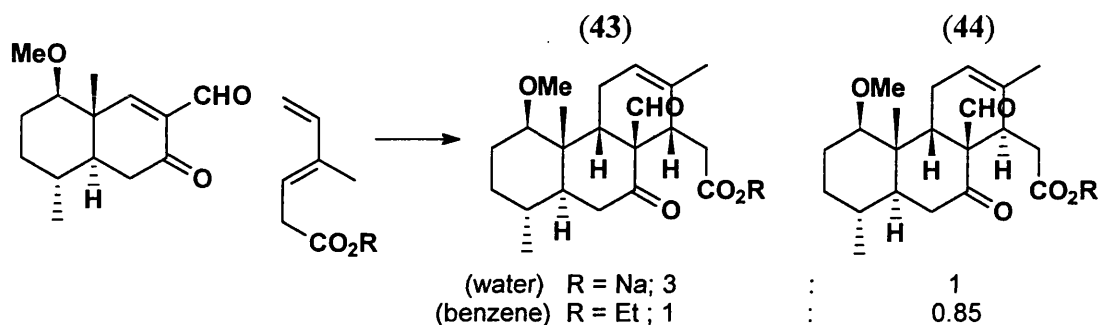
Breslow's investigations into the use of water as a solvent highlighted its usage. His earlier reports in this area described the reaction between cyclopentadiene and butenone (scheme 1.28) where he observed a 700-fold acceleration in water in the formation of cycloadduct (42) compared to the organic solvent 2, 2, 4-trimethylpentane.⁴⁰ The rate in methanol was intermediate but closer to the hydrocarbon solvent compared to water.



Scheme 1.28: Diels-Alder reaction: cyclopentadiene and butenone, a 700-fold acceleration in water

This result was rationalised using the *hydrophobic effect*, a concept introduced by Kauzmann.⁵⁰ In bulk water, apolar molecules have a tendency to aggregate together because of their hydrophobic properties. This increases their local concentration thus forcing the substrates into closer proximity with an increased chance of a reaction occurring.

Grieco has also explored the use of water as a reaction solvent and found it accelerated some Diels-Alder reactions together achieving good selectivities as shown in scheme 1.29.²⁴

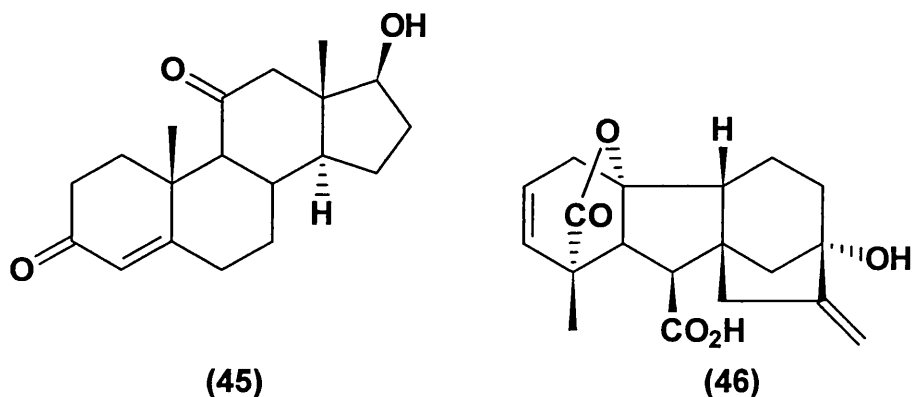


Scheme 1.29: Change in selectivity when water used as solvent

Breslow,^{9, 47} Grieco^{51, 52} and later others^{22, 49, 53-58} extended their research to demonstrate the advantages in using water as a solvent in terms of:

- Improved rates of reaction
- Improved yields of products and
- Different *endo/exo* selectivities.

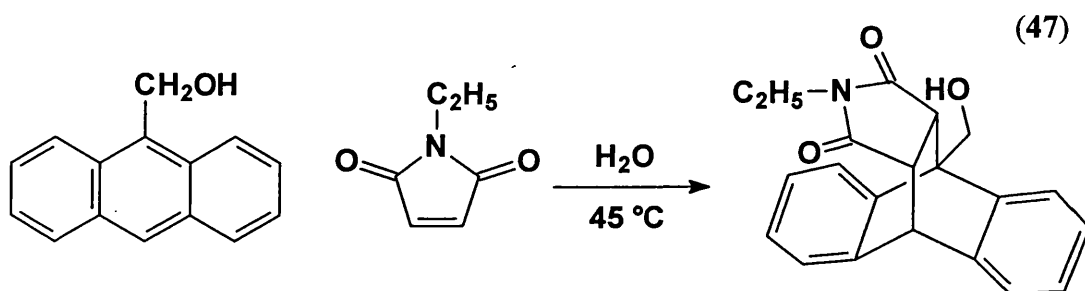
The use of water as a medium for Diels-Alder reactions has been successfully utilised for several complex syntheses for example, the synthesis of (+)-11-ketotestosterone (45) and (+/-)-gibberellins A₅ (46) (figure 1.8),⁵⁹ however the scope is invariably limited by the solubility of the substrates. That is the reacting substrates must have at least limited solubility in the solvent used.

Figure 1.8: (+)-11-ketotestosterone (45) and (+/-)-gibberellins A₃ (46)

1.7.2.2 “Salting out” and “salting in” agents

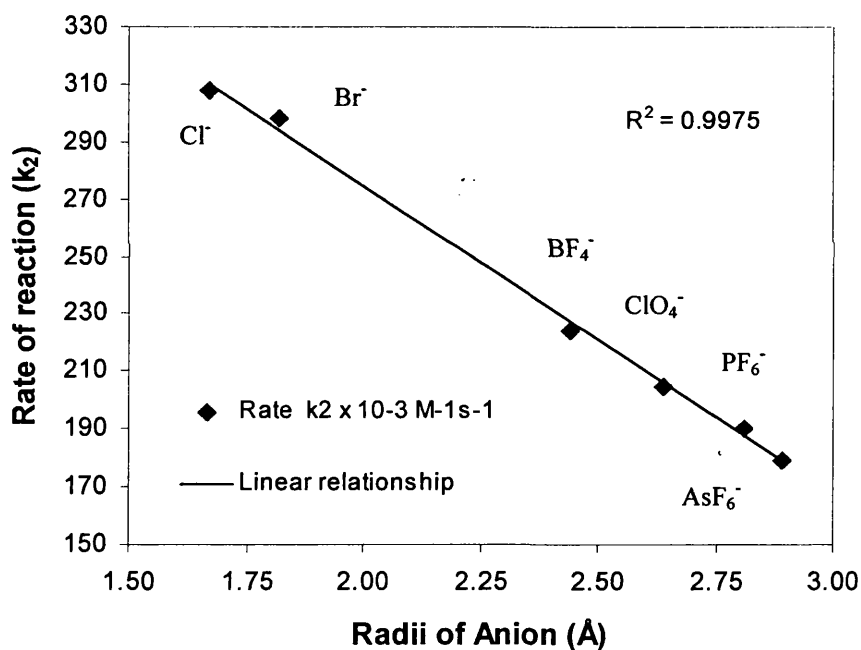
The use of salt additives in aqueous solutions has also been reported.^{60, 61} The presence of lithium chloride has been found to “salt out” the organic materials dissolved in water. Many organic molecules are sparingly soluble in water but in the presence of lithium chloride, the finite solubility is limited further due to an increase in the hydrophobic effect.

Breslow reported large rate accelerations for the Diels-Alder reaction between *N*-ethylmaleimide and hydroxymethyl anthracene in water, where it was 200 times faster than in acetonitrile (scheme 1.30).⁴⁷ However, in the presence of 4.86 M lithium chloride, the rate of reaction was increased 2.5 fold compared to water. Guanidium perchlorate as a solute decreased the reaction rate 3.0 fold compared to lithium chloride and guanidium salts are examples of “salting in” agents. They lower the hydrophobic effect by increasing the solubility of apolar molecules in water, the converse to lithium chloride.

Scheme 1.30: *N*-ethylmaleimide and hydroxymethyl anthracene accelerated reaction in water

This methodology was also applied to the reaction between cyclopentadiene and methyl vinyl ketone where it was found that the N/X ratio increased from 25 in water to 28 in aqueous lithium chloride solution and decreased to 22 in aqueous guanidium chloride. With an increase in hydrophobic effect, the *endo* TS is likely to be favoured since it reduces the interfacial interactions in the aqueous solution.⁴⁷

Rizzo also investigated the Diels-Alder reaction between *N*-ethylmaleimide and hydroxymethyl anthracene in aqueous salt solutions (scheme 1.30).⁶⁰ Using water as a reference he compared the rate of the Diels-Alder reaction in water and different sodium salt solutions. He reported that the reaction rate had a linear relationship (correlation coefficient $R^2 = 0.998$) with the size of the anion of the sodium salt. This salt solution order has become known as the Hofmeister series (graph 2).



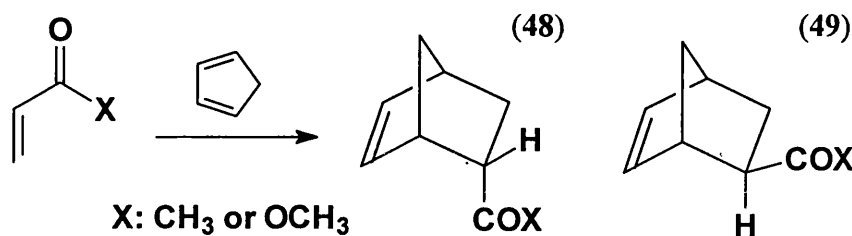
Graph 2: Hofmeister series

The linear relationship is most likely due to the effect of the salt on the hydrophobic effect, where larger anions reduce the effect and smaller ions increase the effect by decreasing the surface contact between the electrolyte and the organic solute.⁶⁰

1.7.2.3 The use micelle solutions for Diels-Alder reactions

The use of micelle solutions can be dated back to the original 1939 patent concerning aqueous Diels-Alder reaction (see section 1.5.2).⁴⁸ The co-solvents used to emulsify the apolar molecules are known today as detergents or surfactants. These type of molecules have long alkyl chains attached to polar 'head' groups that can form micelles in aqueous solutions (see section 2.2-2.4).

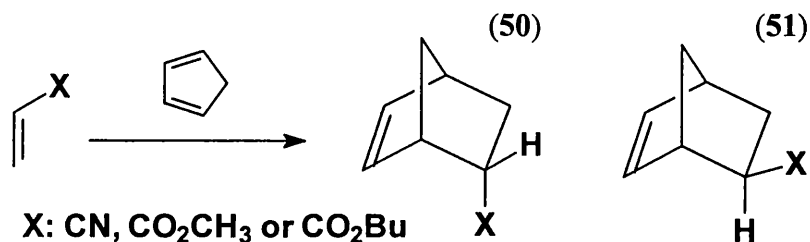
Breslow has examined Diels-Alder reactions between cyclopentadiene and selected dienophiles in detergent (micelle) solutions (scheme 1.31).⁴⁷ He reported that sodium dodecyl sulfate (SDS) and cetyltrimethylammonium bromide (CTAB) (*cmc* of SDS and CTAB is 8.32 mM⁶² and 1mM,¹⁰⁸ respectively (see section 2.3)) had little or no effect on cycloadduct (48)/(49) ratio of Diels-Alder reactions. Furthermore, rough rate studies on 0.02 M SDS as a reaction media gave only a slight increase on the rate velocity (*ca.* 15%). However, the concentration of the SDS solution used by Breslow was well above the *cmc*. They concluded that, in their systems, the use of detergent additives gave no advantages in terms of yield or selectivity.



Scheme 1.31

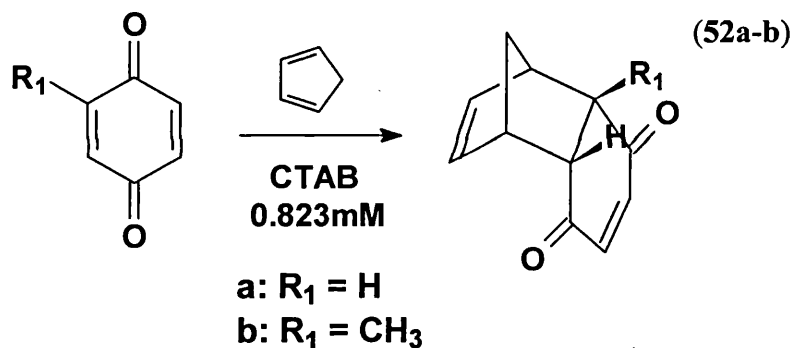
Sauer has looked at Diels-Alder reactions involving cyano groups and ester derivatives (scheme 1.32) and he observed rate accelerations accompanied with a change in selectivity when using SDS solutions.⁶³ When using dioxan as solvent, the rate constant (k_2) of the reaction was 1.18×10^5 mol/s but when using SDS solution, the k_2 increased to 100×10^5 mol/s. The (50)/(51) ratio was 3:1 in dioxan but increased to 9:1 in SDS solution. Sauer clearly demonstrated that SDS solution influenced the selectivity of the reaction. He also used other surfactants (*N*-dodecylpyridinium chloride and dodecyltrimethylammonium bromide) and observed similar results to

SDS, however omitted information on the concentration (*cmc*) of the solutions and reactants that they had used in their work.



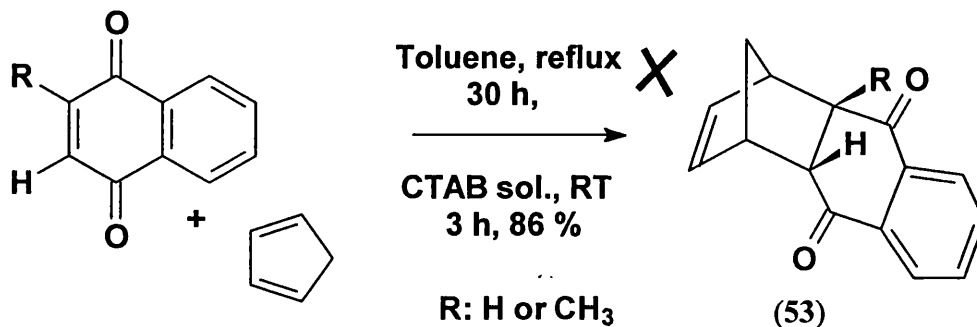
Scheme 1.32: Sauer observed rate acceleration in the Diels-Alder reaction

Singh has reported Diels-Alder reactions between quinones and spirocyclopentadienes in CTAB solutions.⁶⁴ He observed Diels-Alder reactions that proceeded in aqueous micelle solutions but not in organic media (scheme 1.33, reaction **52b**).



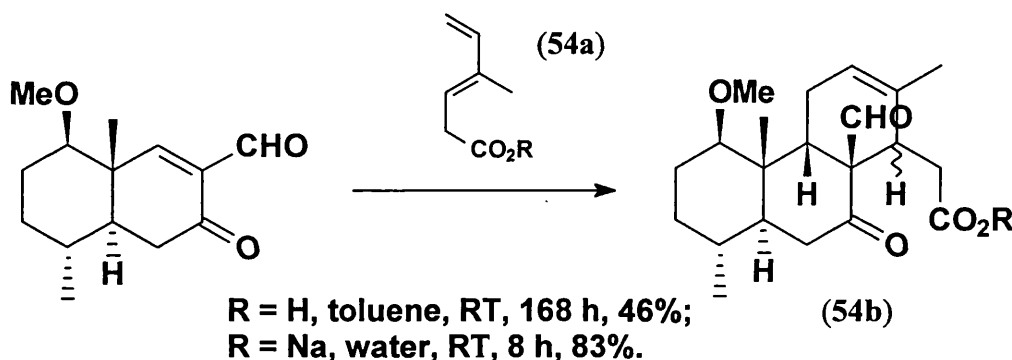
Scheme 1.33: Spirocyclopentadienes in CTAB solutions

When the Diels-Alder reaction was performed at ambient temperatures (3 hours at 30 °C) in CTAB solution, adducts (**52a**) and (**52b**) gave better yields (68 and 86% respectively) compared with conventional Diels-Alder reaction conditions using toluene and heating at reflux for 10-12 hours (50 and 0% respectively). The micellar solutions led to reactions that were faster, requiring only ambient temperature and furnishing the cycloadducts (**53**) in better yields compared to the conventional Diels-Alder conditions. Scheme 1.34 highlights these differences in reaction outcome.



Scheme 1.34

Grieco has used the sodium salt of a diene in water (scheme 1.35) and proposed that the rate acceleration was due to the diene molecules forming micelles and solubilising the dienophile.⁵¹



Scheme 1.35: The use of a sodium salt of a diene in water, which leads to higher product yields

The premise was supported by the fact that the reaction went to completion when the diene concentration was doubled, suggesting that the micelle forming diene (54a) formed larger or more micelles thus accelerating the reaction further.

To summarise, Breslow concluded that surfactant solutions had little or no effect on the rate of the Diels-Alder reaction (scheme 1.31) but Sauer found rate enhancements as well as different selectivities when surfactant solutions were used as a reaction media (scheme 1.32). This observation by Sauer was later confirmed by Singh and also observed in a Diels-Alder reaction that proceeded in aqueous surfactant media but not in organic media (scheme 1.33). However, all researchers demonstrated that aqueous media, including surfactant solutions, can be a viable non-organic medium for the Diels-Alder reaction.

1.8 Conclusion

Due to the large amount of Diels-Alder type reactions reported in the literature, it is impossible to review each one. This introduction has given a short account of the versatility of the Diels-Alder reaction in ring construction. In addition, enantioselective Diels-Alders have been achieved using chiral auxiliaries³⁴ and chiral Lewis acid¹⁴ or ligand methodology.^{65, 66} More recently, the solvents used for the Diels-Alder reactions has been an area of interest amongst researchers,⁶⁷⁻⁶⁹ water being an alternative solvent.^{55, 70} In a world where commercial application and low environmental impact increasingly go hand in hand, using water as the reaction media is both cheap and potentially less damaging to the environment. A number of reports have appeared in the literature concerning this area,^{54, 58, 71, 72} however, it is still limited by the problem of substrate solubilisation in aqueous media, and the use of surfactants may provide a possible solution.

2 Introduction: Surfactants and Micelles

In recent years, interest has focused on the use of alternative, more environmentally friendly solvent systems to either replace or, at least, reduce the consumption of conventional toxic organic solvents especially chlorinated solvents such as dichloromethane and chloroform.⁷³ Aqueous micellar solutions are one such possibility. The surfactants that make up the micelles can be derived from naturally occurring starting materials, designed to be biodegradable or, alternatively by careful choice of molecular structure, designed to be recyclable.

2.1 General Molecular Structure of Surfactants

Surfactants (surface active agents or detergents) are molecules that contain both non-polar 'hydrophobic' and polar 'hydrophilic' groups. Below is shown a schematic representation of a surfactant molecule (figure 2.1).

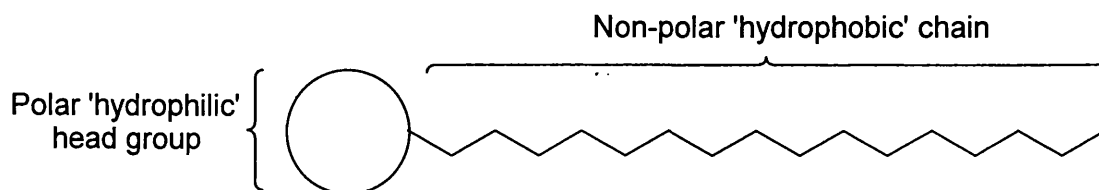


Figure 2.1: Schematic representation of a surface active agent

The typical hydrophobic region of a surfactant can possess up to 3 alkyl chains each containing between 8-18 carbon atoms and frequently of similar lengths. This is because surfactants with hydrophobic chains having less than 8 carbons have little or no surface activity, while those with more than 20 carbons are often insufficiently soluble in water to generate micelles.⁷⁴

Surfactants are generally classified according to the type of 'hydrophilic' head group present. The classes of surfactant are:

2.1.1 Zwitterionic surfactant

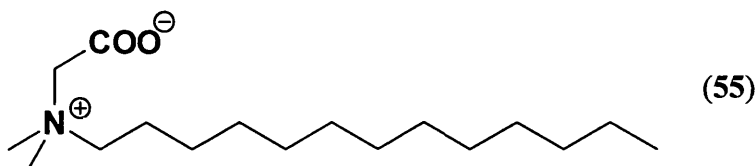


Figure 2.2: Zwitterionic surfactant *e.g.* *N*-Dodecyl-*N,N*-dimethyl betaine

These types of surfactants have a zwitterionic head group (figure 2.2) and can behave as anionic, non-ionic or cationic depending on the pH of the solution and the pKa's of the groups present.

2.1.2 Non-ionic surfactant

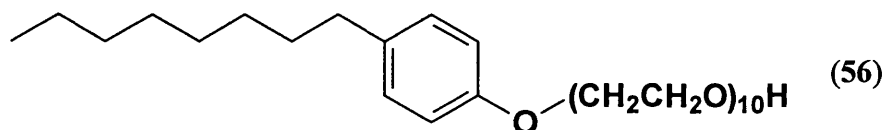


Figure 2.3: Non-ionic surfactant e.g. polyoxyethylene *p*-tert-octylphenyl ether

In this case the head group carries no formal charge over a wide range of pH. Frequently the head group is polymeric in nature; for example polyoxyethylene chains (figure 2.3) are the most commonly encountered non-ionic head group.

2.1.3 Cationic surfactant

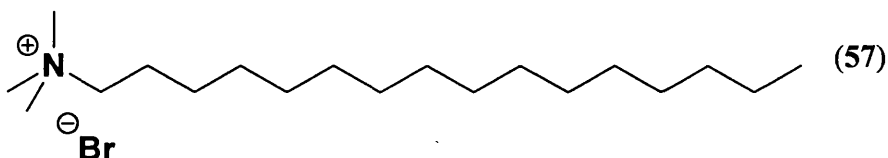


Figure 2.4: Cationic surfactant e.g. cetyltrimethylammonium bromide (CTAB)

Here the surface active species is a cation (figure 2.4). The bromide ion is known as the counter-ion and in solution dissociates from the surface-active species.

2.1.4 Anionic surfactant

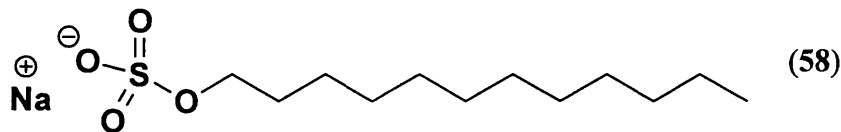


Figure 2.5: Anionic surfactant e.g. sodium dodecyl sulphate (SDS)

Here the surface active species is an anion. The sodium ion is the counter-ion in this case (figure 2.5).

The last two groups are collectively known as ionic surfactants due to the presence of a formal charge on the head group.⁶²

2.2 Concept of the Critical Micelle Concentration (cmc)

The series of events that occur when a surfactant is dispersed in water is depicted in figure 2.6. When a surfactant is dissolved in water at very low concentrations, it exists in solution as a monomeric entity (III). Once the surfactant has reached its monomeric solubility, any further increase in surfactant concentration results in the formation of a surfactant monolayer at the air-water interface (I), which lowers the surface tension of the water. Once this monolayer formation is complete, any further surfactant added starts to associate to form micellar aggregates (II) in the bulk of the solution. In the aggregate, the hydrophobic portion of the surfactant is buried deep within the core and removed from the contact with water, while the hydrophilic head groups are exposed on the outside in contact with the aqueous phase. The concentration at which the aggregate starts to form is called the *critical micelle concentration* or *cmc*, regardless of the nature of the aggregate form.

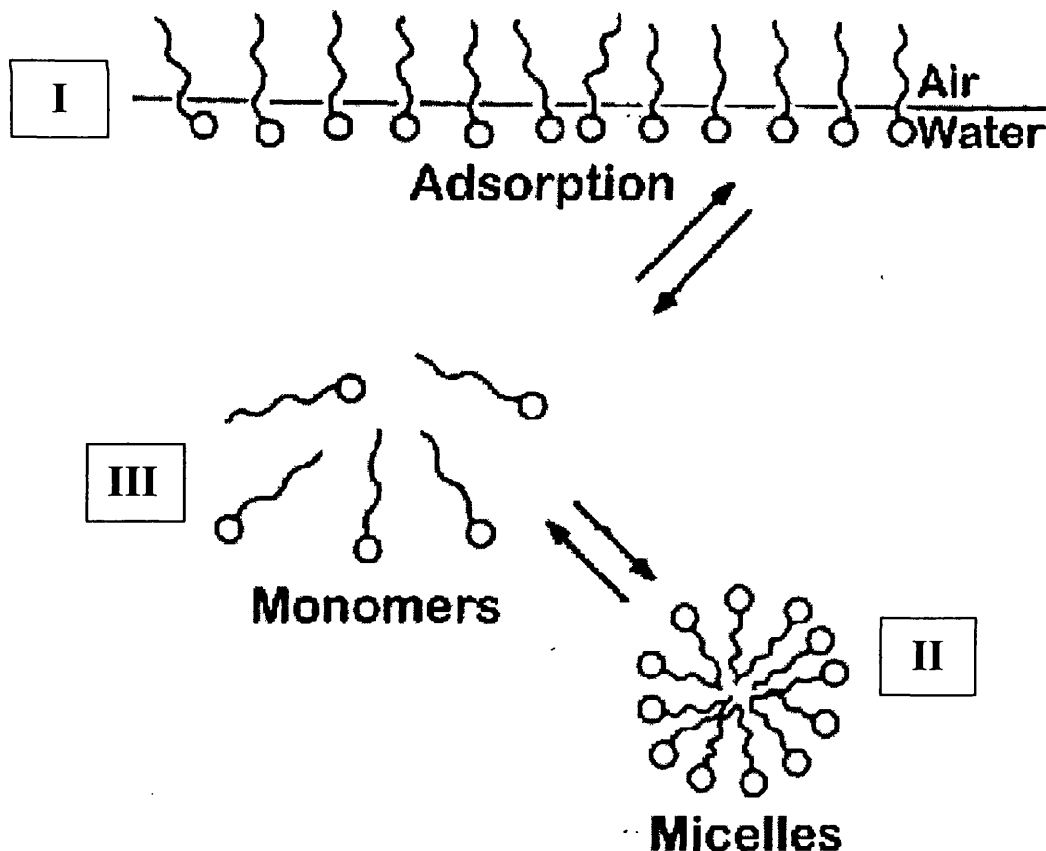


Figure 2.6: Adsorption of surfactants on air/water interface in aqueous solutions

The most frequently encountered aggregate is the micelle. A micelle typically contains between 50-100 individual monomers but other aggregates could be present at higher concentration and it is depicted in figure 2.7.⁷⁵ The co-operative aggregation of the individual surface active agent monomers into larger associated species is often described using a phase separation model where the micelles are considered to form a separate phase from the bulk phase of surrounding medium.⁷⁶ It has been widely observed that the *cmc* depends on the type of counter-ion present (for ionic surfactants), the hydrocarbon chain length, the nature of the polar head group and temperature.

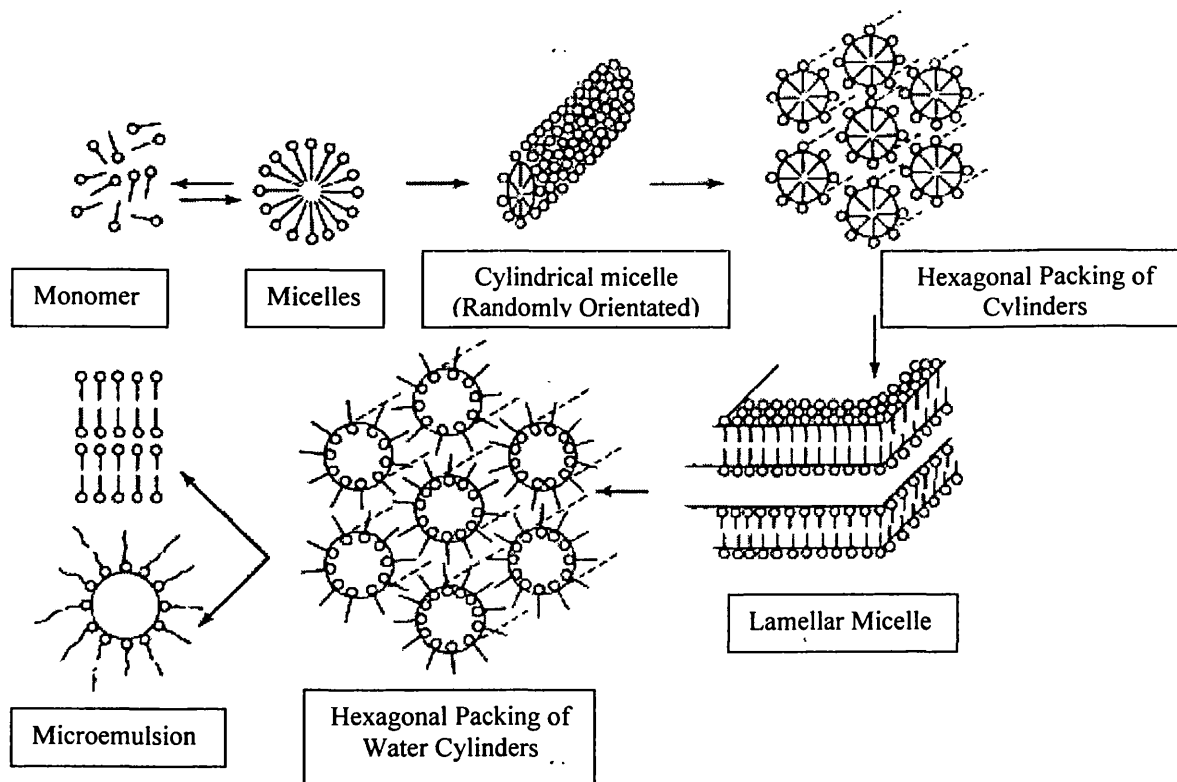
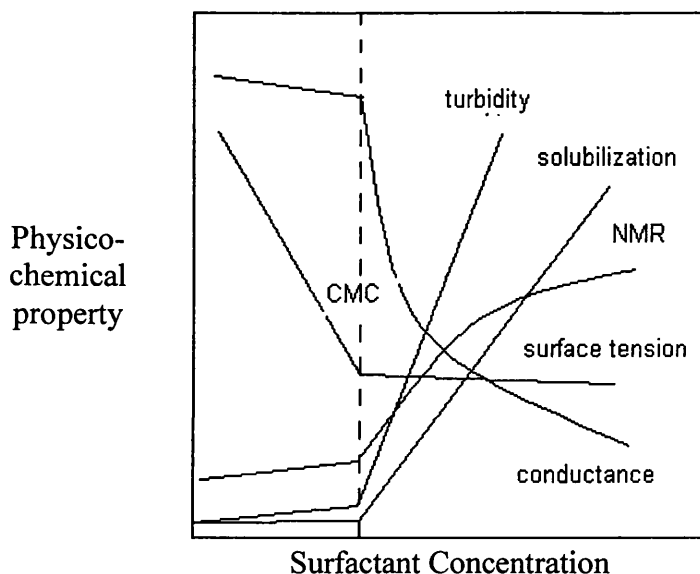


Figure 2.7: Other possible aggregates in surfactant solutions⁶²

The *cmc* is usually determined experimentally by plotting the change in a physico-chemical property, which occurs with increasing surfactant concentration. Some of the physico-chemical techniques used to determine the *cmc* are shown in graph 2.1. The concentration at which the break occurs is considered as the *cmc*.



Graph 2.1: The variation in physico-chemical properties with surfactant concentration

It should be noted that the *cmc* determined by different various methods listed above, are not generally coincident, as each technique is measuring a different property of the solution. Of the most commonly used techniques to determine the *cmc* of surfactants, the most frequently used are the solubilisation, conductance, and surface tension methods. Mukerjee and Mysels have compiled one of the most complete catalogues of *cmc* data available,⁷⁷ determined by different research groups using various techniques.^{78, 179}

2.3 The Micelle at Concentrations above the *cmc*

Hartley was the first to propose the model of a spherical micelle (figure 2.8).⁸⁰ It is now generally accepted that most surface active agent form micelles, which are spherical or slightly asymmetric in shape, at least at or just above the *cmc*. Furthermore in a micelle, the polar moiety of the surfactant remains in contact with the aqueous phase while the non-polar hydrocarbon forms the central core of the micelle.

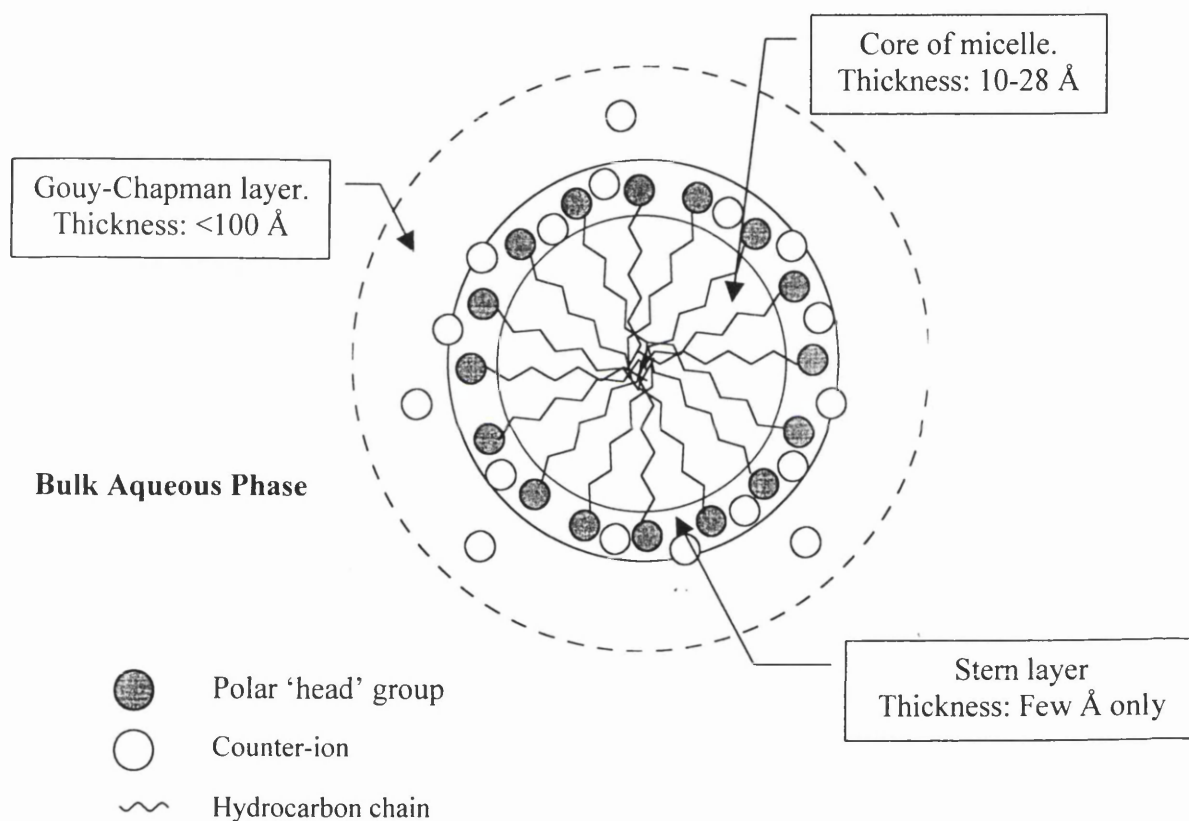


Figure 2.8: The classical schematic representation of a Hartley Model of a micelle⁸⁰

An ionic micelle, formed from either an anionic or cationic surfactant, consists of three distinct regions, namely the hydrocarbon core, the Stern layer and the diffuse Gouy-Chapman layer, the latter two comprising the double layer.

The **hydrocarbon core** contains the long, hydrophobic, alkyl chains of the surfactant. The hydrophobic core is thought to be liquid-like in nature and is shielded

from the aqueous phase by the head group of the **Stern layer**.⁸¹⁻⁸³ This layer contains the polar, hydrophilic ionised head groups, which constitute the inner region of the electrical double layer surrounding the micelle. This layer also contains about 80% of the tightly bound counter-ion. The outer region of the double layer is known as the **Gouy-Chapman layer**, and is a diffuse region containing a predominance of counter-ions (in order to neutralise the charge on the micelle). Beyond the double layer is the bulk solution. In a non-ionic surfactant micelle, there is no double layer. For example, with polyoxyethylated non-ionic micelles, a layer of polyoxyethylene chains surrounds the core with water molecules hydrogen bonded to them. Because of the geometry of the micelles, the polyoxyethylene chains nearest the core is least hydrated while those towards the outside are most hydrated. This outer layer is commonly termed as the **palisade layer** or **mantle** (figure 2.9).^{84, 85}

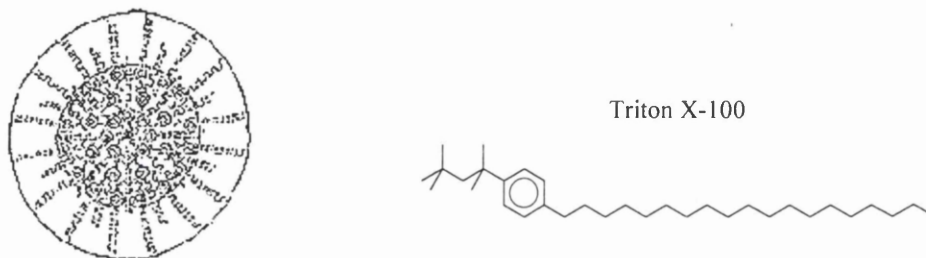


Figure 2.9: Non-ionic micelle: The micelle of Triton X-100.

2.4 Physical Properties of Micelles

McBain first observed that the physico-chemical properties of surfactants showed distinct concentration dependence.⁸⁶ The physico-chemical properties generally used to observe this concentration dependence are osmotic pressure,⁸⁷ turbidity (or Light Scattering),⁸⁸⁻⁹⁰ solubilisation,⁹¹⁻⁹³ magnetic resonance (¹³C NMR),⁹⁴ and surface tension.^{95, 96}

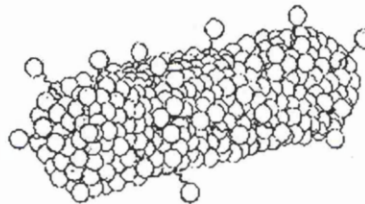
As mentioned above, micelles are generally believed to be spherical (see figure 2.10a) at their *cmc* but may form ellipsoidal aggregates such as 'rod' shaped micelles at higher concentrations (see figure 2.10b).^{84, 97} A reduction in the interfacial interaction of the hydrophobic regions of the surfactant from the bulk aqueous phase

can only be achieved by forming elongated structures to accommodate the ‘extra’ surfactants dissolved in solution.

At low temperatures, surfactants have very low solubility in water but above a certain temperature, their solubility increases dramatically. This temperature is referred to as the ‘critical micelle temperature’ (cmt) or the Krafft point.^{98, 99} The solubility of many organic compounds increases gradually in water as the temperature rises. For a surfactant at the Krafft temperature, there is a rapid rise in solubility with little change in temperature and is the point at which micelles are formed. Below this temperature, no micelles are formed and the solubility of the monomeric surfactant is limited; indeed the surfactants frequently exists as hydrated crystals in solution.⁸¹



a: Micelle just above the *cmc*



b: Micelle at higher surfactant concentration

Figure 2.10⁷⁵

When envisaging micelles, it is important to note that they are in a dynamic equilibrium with the monomeric species in solution. In addition, individual surfactant molecules are also able to dissociate from the aggregate and re-associate back into the micelle. This process occurs at a faster rate than the overall breakdown of the micelle (figure 2.11).

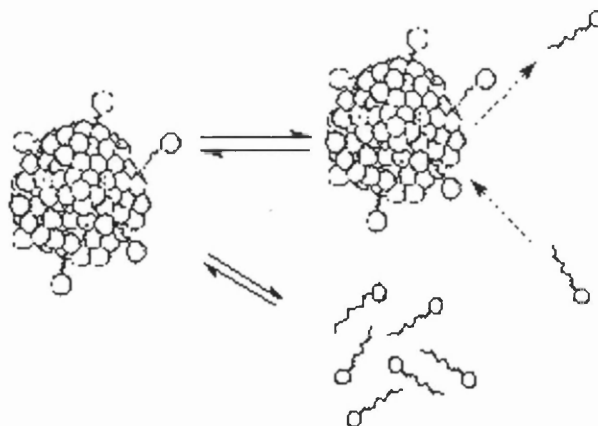


Figure 2.11: Association, dissociation of surfactant molecules and overall breakdown of a micelle in solution

The formation of micelles is generally regarded to be a result of the *hydrophobic effect*, a concept originally used by Kauzmann, to describe how proteins that have a high carbon content are able to dissolve in an aqueous media.^{50, 98} As mentioned in section 2.1, surfactants have a hydrophilic and hydrophobic region. The increase in concentration of surfactant molecules in solution increases the hydrophobic effect, which forces the hydrophobic and hydrophilic regions to aggregate. In aqueous media, the hydrophobic regions exclude water molecules while the hydrophilic region will hydrogen bond with the water molecules surrounding the head group. The result is the generation of micellar aggregates.

2.5 Location of Solutes in Micelles

Within a micellar aggregate, it is generally accepted that an apolar solute for example a hydrocarbon, will predominately be located in the hydrocarbon core of the micelle.⁶² The location of the solute depends upon the physico-chemical properties of the compound.^{100, 101} For example, with non-ionic micelles, polar solutes such as alcohols can be deeply buried in the micelle core or located near the micelles head group.⁶² The different sites (figure 2.12) in the micelle where a solute can be solubilised are:

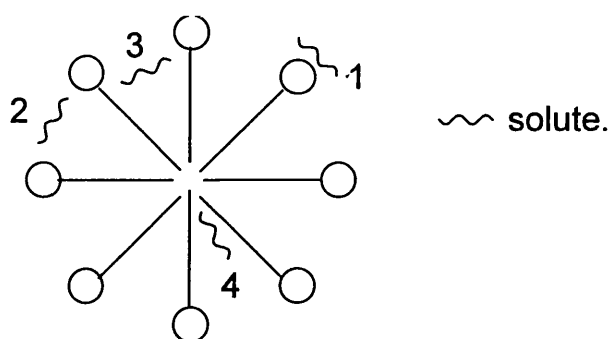


Figure 2.12: Location of solutes in a micelle

1. On the surface of the micelle,
2. Within the hydrophilic head group region,

3. At the interface between the head group region and the first few carbon atoms of the hydrophobic chain, ..
4. In the core of the micelle.

Micelles have regions of varying polarity, from the very polar 'head' group, which is in contact with the surrounding aqueous phase to a less polar hydrocarbon core. The physico-chemical properties of these regions will closely match the solutes that dissolve in that region of the micelle.^{97, 102}

Many techniques have been employed to investigate the exact location of a solute in a micelle. For example, Philipoff *et al.* has used X-ray diffraction to measure changes in micellar dimensions caused by the presence of solutes.¹⁰³ Eriksson *et al.* utilised NMR spectroscopy to determine the environment of the solutes in a micellar solution, for example, whether the solute is in an aqueous or in an organic-like environment.⁹⁴ Both group of workers independently determined that saturated aliphatic and alicyclic hydrocarbons lie deep within the core of the micelle while benzene and other polarisable hydrocarbons are located close to the water-micelle interface.^{94, 103} Small polar molecules such as short chain alcohols, in contrast, were found to be exclusively located in the outer palisade layer of the micelle as the spectra of these materials indicated that they are in a polar environment. By comparison, larger molecules, *e.g.* long chain alcohols or dyes, were believed to be interchelated between surfactant molecules with the polar moiety of the solutes oriented towards the polar head group region of the micelle and the non-polar group oriented toward the core of the micelle.

Mukerjee has investigated the solubilisation of benzoic acid derivatives within a series of non-ionic polyoxyethylene surfactants. He described the solubilisation of the solutes in terms of their distribution between two loci namely the hydrophilic head group and the hydrocarbon core regions.¹⁰⁴ Mukerjee found that the amount of solute solubilised within the core and the head group region was found to be proportional to the number of equivalents of the alkyl chain (C_R), and the number of equivalents of oxyethylene, C_{EO} .

The total amount solubilised S' was described by the equation:

$$S' = aC_{EO} + bC_R \quad \text{Equation: 2.1}$$

where a and b are constants.

Rearrangement of equation 2.1 gives: ..

$$\frac{S'}{C_{EO}} = a + b \frac{C_R}{C_{EO}} \quad \text{Equation: 2.2}$$

Hence a plot of $\frac{S'}{C_{EO}}$ against $\frac{C_R}{C_{EO}}$ for a surfactant, is linear with an

intercept of a , representing the solubilisation in the head group region, and a slope of b , representing solubilisation in the micellar core.

2.6 Solubilisation of Dyes in Surfactant Solutions

Measurements on the solubility of a dye that naturally has a low solubility in water, in the presence of varying concentrations of surfactant is a technique frequently used to determine the *cmc* of the surfactant.⁷⁷ Mukerjee and Mysels have investigated the colour changes of dyes, particularly pinacyanol, upon changing the SDS surfactant concentration.⁷⁸ They reported that the change in colour at low SDS concentration was due to the formation of a dye-surfactant complex, which was insoluble in water. At surfactant concentrations above the *cmc*, a blue colour was observed which was characterised by two ultraviolet (UV) absorption bands. The spectrum was similar to that of the dye when dissolved in an organic solvent. While centrifugation completely removed the red salt complex it did not affect the blue colour, implying that the blue colour was not due to a complexation of the surfactant with the dye but rather solubilisation of the monomeric dye molecule in the hydrocarbon core of the micelle. Dyes that contain an apolar, a polar moiety and a π -ring system in the same molecule have the tendency to π -stack when in an aqueous medium. This means that the non-

polar groups align themselves in an orientation so as to minimise hydrocarbon-water interfacial interactions, thereby forming a ‘pseudo’ aggregate. This aggregate can interact with surfactants to form mixed micelles. The first initial colour change from red to blue was well below the *cmc* and only the insight of knowing the true *cmc* prevented the result being acknowledged as the *cmc* of the surfactant. Therefore such solubilisation experiments were not advocated as a true measure of the *cmc* and were later defined as ambiguous.⁷⁹

Improvements in the understanding of dye-surfactant interactions gave the solubilisation method a new lease of life for the determination of the *cmc*. Mateo and co-workers reported a detailed study on the incorporation of acridine orange (**59**, figure 2.13) into anionic micelles such as SDS. These workers found that below the *cmc* of SDS, large aggregates were formed, by a ‘mutually induced aggregation’ mechanism resulting from the strong interaction between the hydrocarbon chains of the surfactant and the dye.⁹¹

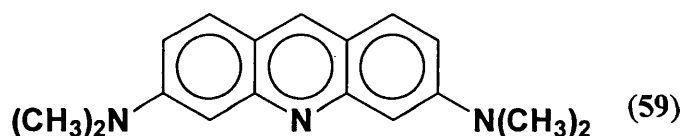


Figure 2.13: Acridine Orange

This interaction between the surfactant and the dye molecules was apparent from the UV spectrum of (**59**). Below the *cmc*, the UV spectrum of (**59**) exhibited a ‘monomer’ peak at 492 nm but as the surfactant concentration increased above the *cmc*, the monomeric peak decreased while a new second peak appeared. This observation was similar to the UV spectrum observed when (**59**) binds to DNA.

Klotz has reported that the binding of a highly branched water-soluble polymer, *e.g.* polyethylamine, causes a change in the UV absorption of methyl orange (figure. 2.14). For example, the binding of methyl orange to polyethylamine results in a shift of the UV absorption maxima of methyl orange, from 464 nm in aqueous solution to 375 nm. The blue shift of the methyl orange from 464 to 375 nm has been attributed to the binding of the anionic dye to the water-soluble polymer leading to the creation of strong binding sites on the polymer for subsequent attachments of

anions.¹⁰⁵ However, Klotz attributed this behaviour to ‘the stacking of the methyl orange molecules on the apolar groups present in the polymer’, a result of a co-operative interaction of the dye and polymer.

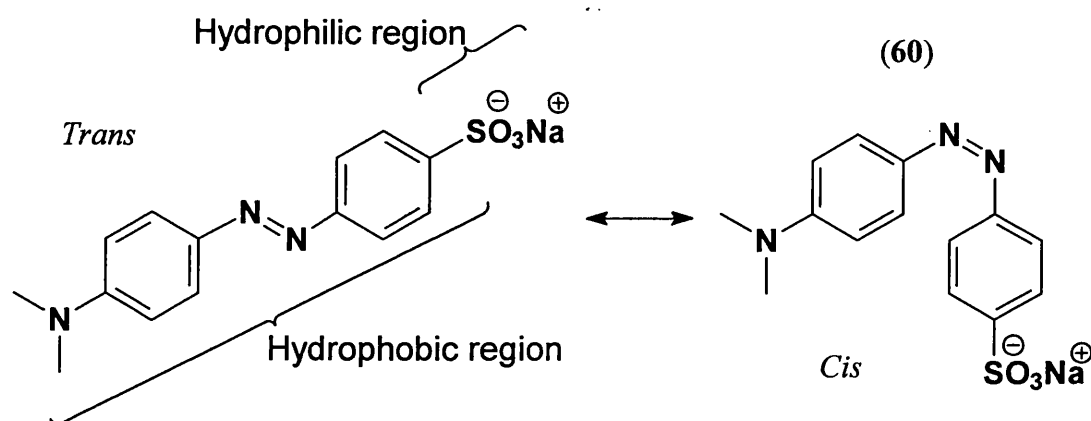


Figure 2.14: Methyl Orange molecule

Quadrifoglio and co-workers subsequently investigated the spectral behaviour of methyl orange (60) in the presence of the polyelectrolyte, poly (N-methylvinyl pyridinium chloride). These workers too, observed a blue shift similar to that seen with polyethylamine.¹⁰⁶ Unlike (59) used by Mateo, (60) does not exhibit the tendency to dimerise or self-aggregate in water. Furthermore the spectra observed for (60) with the polyelectrolyte did not correspond to dye aggregation. Quadrifoglio postulated that the appearance of the band at 368 nm, could in part be due to the binding of (60) to the positive binding sites on the polyelectrolyte. Although these workers considered that the largest component of the change in the UV spectrum (460→368 nm) was due to a conformational change of the bound dye molecule, from the thermally stable *trans* isomer to the unstable *cis* isomer (figure 2.14).

It was proposed that this change in conformation was elicited by the formation of “ion-pairs” between the dye and a hydrophilic binding site on the polyelectrolyte. As such, the polyelectrolyte stabilised the ‘unstable’ *cis* conformation of the methyl orange (figure 2.15) by slowing down the *cis-trans* conversion due to of hydrogen bonding and/or van der Waals forces within the “ion-pair”.

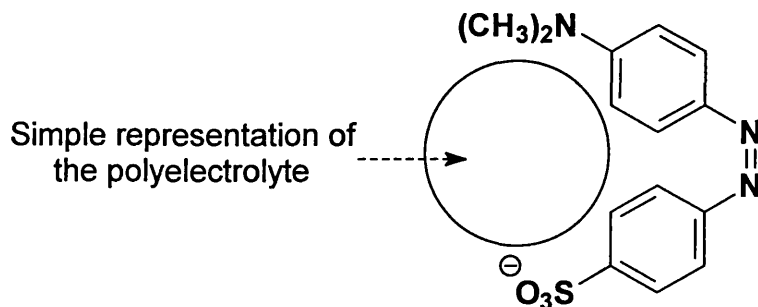


Figure 2.15: Association of polyelectrolyte and a methyl orange dye molecule

Later, Lovrien found that when methyl orange was bound to proteins, principally serum albumin, the rate of *cis-trans* isomerisation was reduced from 4.7×10^{-2} (the rate in bulk aqueous solution) to $1.7 \times 10^{-2} \text{ sec}^{-1}$, supporting Quadrifoglio's premise of *cis-trans* conformer present in the presence of electrolytes.¹⁰⁷

Dutta *et al.* have reported the existence of an interaction between methyl orange and the cationic surfactant CTAB, by using UV spectroscopy and recording the changes in the UV spectra of methyl orange.¹⁰⁸ Unlike Quadrifoglio's premise that the change in absorbance was due to presence of the *cis* conformer of methyl orange, these workers found that the visible spectra of methyl orange varied with increasing concentration of CTAB up to its known *cmc*. The change in absorbance was attributed to the interaction of methyl orange with the CTAB surfactant. Methyl orange exhibited a λ_{max} of 463 nm, which decreased in intensity as the concentration of CTAB increased. This decrease in intensity of the peak at 463 nm was accompanied by an increase in absorbance at a λ_{max} of 375 nm, caused by a reduced conjugation (blue shift) across the methyl orange molecule and the association of CTAB and methyl orange molecules (figure 2.17). This decrease in conjugation was visualised by the change in the colour of the methyl orange/surfactant solution from orange to yellow.

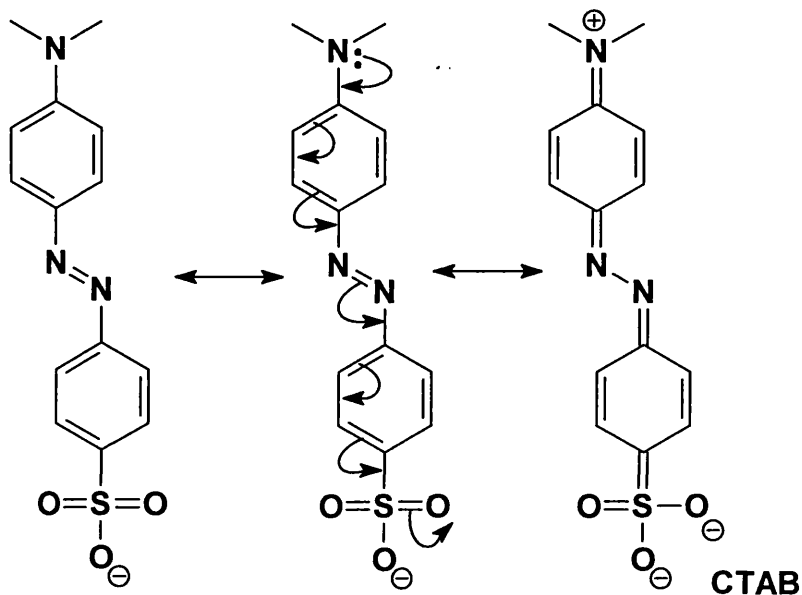


Figure 2.16: Delocalisation of electrons across the methyl orange molecule

Below the *cmc*, CTAB molecules can interact freely with methyl orange (figure 2.16). However at concentrations above the *cmc* when micelles are present in solution, the methyl orange which possess a hydrophobic and hydrophilic regions (see figure 2.14) could be embedded within a micelle to generate a mixed micelle structure (figure 2.17).

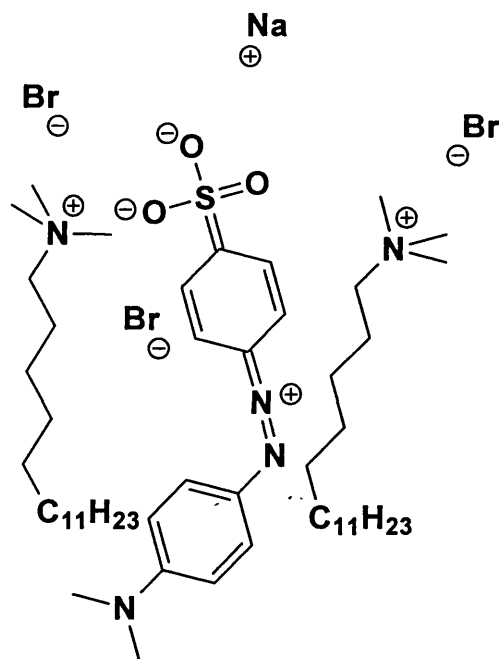


Figure 2.17: Proposed arrangement of methyl orange and CTAB

In a micelle, the degree of conjugation across the methyl orange will be less as the charge at the terminal nitrogen within a micellar core will not be favoured as shown in figure 2.17.

Kawashima has investigated the interaction of 4-phenylazo-1-naphthol-2,3'-disulfonate (PNDS) with surfactant solutions of polyethylene glycol *n*-dodecyl ether (figure 2.18).⁹³

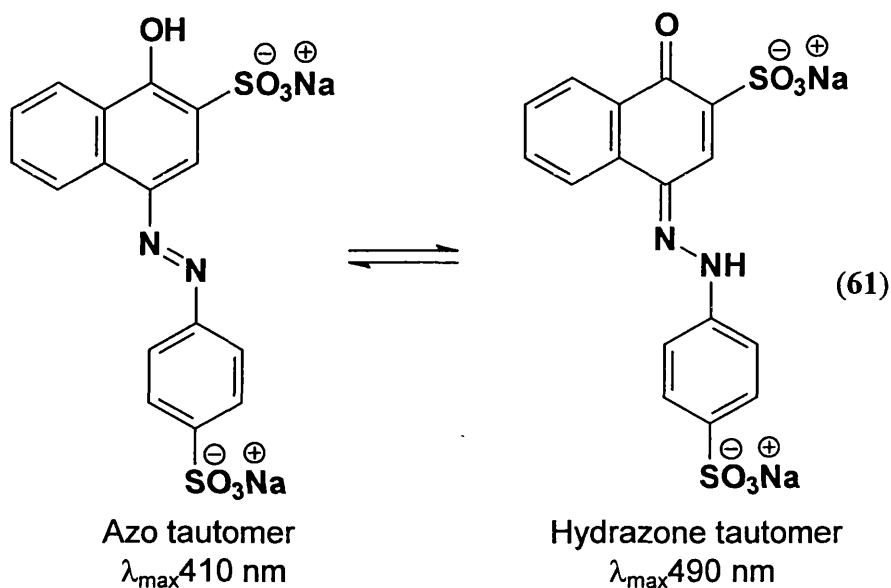


Figure 2.18: Azo and Hydrazone tautomer of PNDS

He observed that PNDS (61) exists completely as the hydrazone tautomer with a λ_{\max} at 490 nm when dissolved in water, however when dissolved in a polar solvent like ethanol, PNDS exists as the azo tautomer with a λ_{\max} of 410 nm. When the spectra of PNDS was examined in the presence of increasing amounts of polyethylene glycol *n*-dodecyl ether surfactant above the *cmc*, it was similar to the spectra of ethanol, indicating that PNDS was present in the azo tautomer. However, this method was shown to be limited to non-ionic surfactants, as SDS failed to elicit a change the absorbance of PNDS, even at concentrations above its *cmc*.

2.7 Water Penetration in an Ionic Micelle

Although there has been considerable debate about the structure of an ionic micelle, the Hartley model (figure 2.8) is the generally accepted model having three distinct regions, the hydrocarbon core, the Stern and the Gouy-Chapman layer as discussed above.⁸⁰ However, one question still eludes a definitive answer; that of how much water is contained in a micelle? Implicit in Hartley's model is that water is completely excluded from the core of the micelle due to its hydrophobic nature. Recently, however, several alternative models have been proposed. It should be noted that the more recent models are not intended to replace the Hartley model but rather to improve on it. For example, Menger has proposed that water can penetrate into the micelle and is not excluded by the hydrophobic core (figure 2.19).⁸⁴

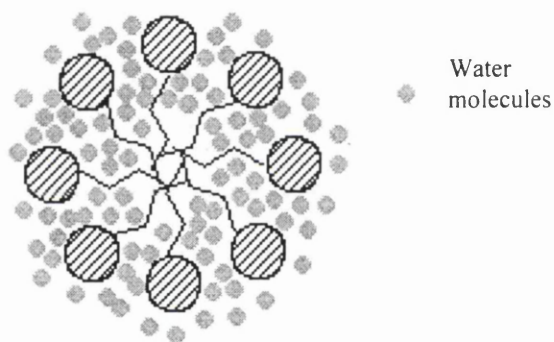


Figure 2.19: Menger's model of a micelle

Other micelle models include the "fjord" model, which is similar to Menger's "porous" micelle in that it allows water to penetrate right down to the micelle core. The "reef" model allows water to penetrate past the first few methylene groups of the alkyl chain.^{84, 97, 99}

In many micelle models, the alkane chains are shown to adopt a *trans* conformation, but this is inconsistent because this would make the centre of the micelle filled with terminal methyl groups. Dill and Flory proposed an alternative to the Hartley model based on lattice models (figure 2.20), providing evidence by the use of statistical theory that methylene groups are close to the Stern layer and even predicts that some chains are outside the lattice.¹⁰⁹ As a consequence it is considered

that the earlier experimental evidence showing the penetration of water is flawed as the terminal methyl group can 'curl' up to the surface of the micelle and as a result may sample the bulk aqueous phase.

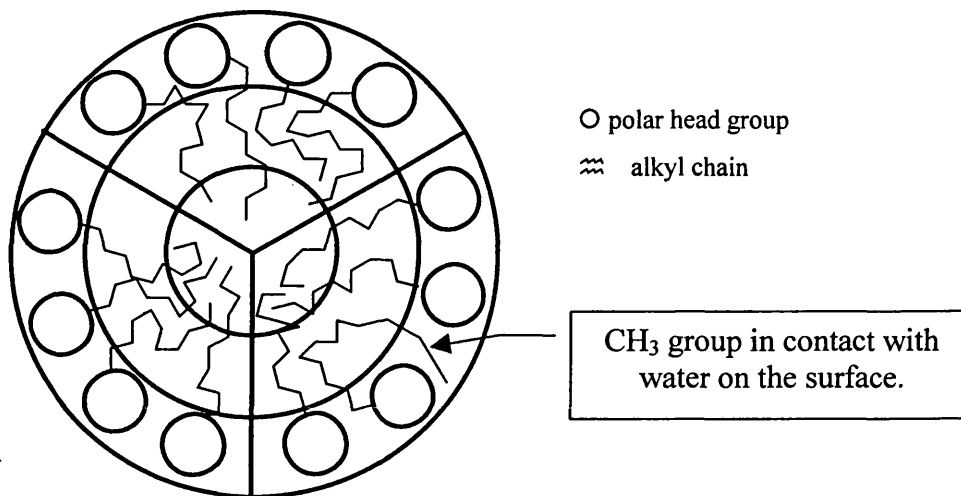


Figure 2.20: Lattice model of a micelle using statistical theory.

The formation and collapse of micelles is a dynamic process. The balance between the hydrophobic attractions of the long hydrocarbon chain and the repulsive forces that arise from the polar head groups that possess identical charges governs their life-time (10^{-7} seconds). The rapid formation and breakdown of micelles in aqueous media can lead to the conclusion that water is not excluded from the interior of the micelle and that some water molecules are trapped in the hydrophobic core, which adds credibility to Menger's 'porous' micelle model.^{84,97}

2.8 Micelles Interior

Investigations into the physico-chemical nature of the interior of the micelle have been carried out by Shinitzky.¹¹⁰ These workers measured the fluorescence depolarisation of 2-methylanthracene in an attempt to determine the microviscosity inside the micelle. Cationic surfactants, dodecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, CTAB and octadecyl, dimethylbenzylammonium bromide solutions were investigated at 27 °C. The results indicated that

the viscosity of the micelle interior (microviscosity) ranged from 17-50 cP. By comparison, the viscosity of water, decane and 1-octanol are 1.0, 1.3 and 8.9 cyclopentadiene, respectively. Thus the micelle interior is considered to be liquid-like but not as 'fluid' as other hydrocarbons of the equivalent or similar length, suggesting that the core is under pressure from the external bulk.¹¹⁰ This hypothesis was further substantiated by Menger who used ^{13}C NMR spin-lattice relaxation times to establish that the microviscosity of the ω -phenyldecanoate micelle was approximately 8.3 cP at 23 °C.¹¹¹

Povich applied an ESR spin-label method to study the physical state of CTAB in its micellar form by measuring the changes in the rotational correlation ($\tau_c \sim 10^{-7}$ sec) time of the nitroxide-free radical (62, NFR) in several different concentrations of surfactant solutions (figure 2.21). A change in τ_c was seen to occur just above the *cmc* of CTAB when the NFR is solubilised in the surfactant solution.¹¹²

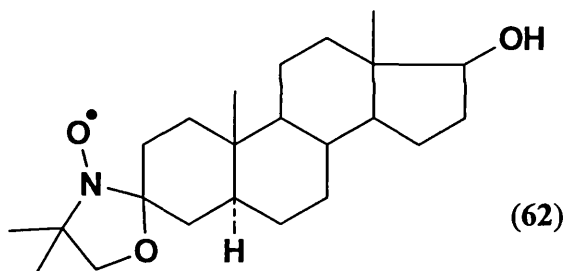


Figure 2.21: Nitroxide-free radical

These results suggested that the micellar hydrocarbon core exhibit a similar microviscosity to hexadecane (the equivalent hydrocarbon) at -22 °C, 40 °C below the melting point of hexadecane (m.pt: 17-19 °C¹¹³), inferring that the micelle interior would be consider to be solid-like in nature.

Thomas *et al.* has investigated the fluorescence of pyrene-3-carboxaldehyde (figure 2.22) in various solvents ranging from the non-polar *n*-hexane to methanol.¹¹⁴

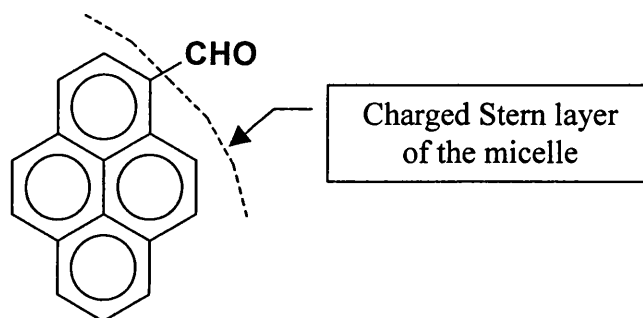


Figure 2.22: Orientation of pyrene-3-carboxaldehyde in a micelle

These workers found that the aldehyde had a very weak quantum yield (Q) of <0.001 in *n*-hexane but had a very strong Q yield in methanol. They also reported that the Q yield of the aldehyde varied in a linear manner with the solvents' dielectric constant. Using this relationship, the fluorescence of pyrene-3-carboxaldehyde in the presence of micelles was utilised to estimate the polarity of a micelle-water interface. Micellar solutions above the *cmc* were seen to solubilise the aldehyde in its hydrocarbon core with the hydrophobic moiety buried amongst the alkyl chains and the polar CHO group near the charged Stern layer of an ionic micelle. The same group of workers also investigated the site of solubilisation of pyrene derivatives using proton magnetic resonance and reported that pyrene, being hydrophobic in nature, was solubilised in the core of the CTAB micelle (figure 2.23).

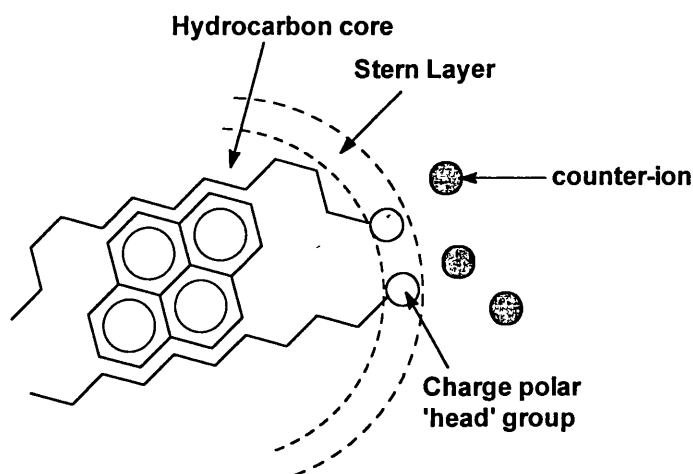
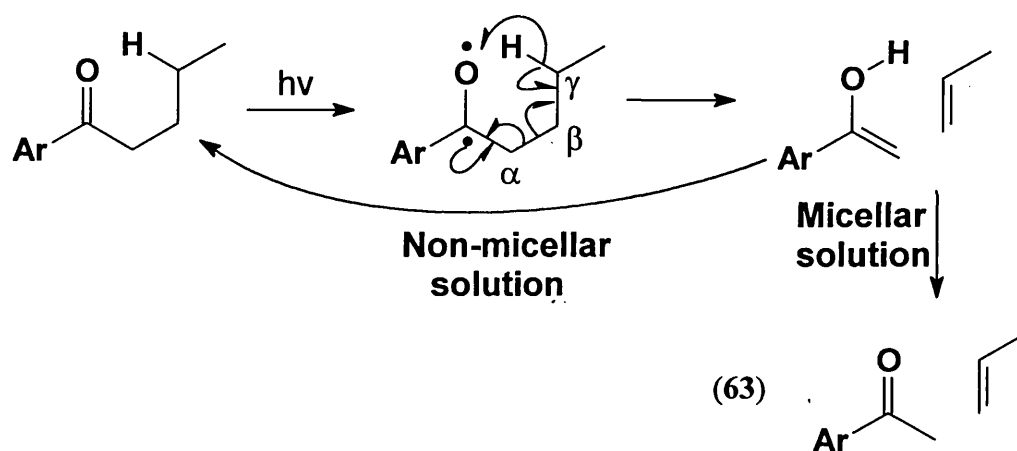


Figure 2.23: Solubilisation of a pyrene molecule in the hydrocarbon core of a micelle

2.9 Effects of Micelles on Organic Reactions

Aqueous micellar media have been employed as a solvent system for the five effects they can confer on an organic reaction.⁷⁵

Firstly the **cage** effects which result from the ability of a micelle to ‘hold’ reactants within the core of the micelle, thereby forcing the reactants to react. This effect has been observed in particular with photochemical reactions that are media sensitive. For example, Wagner *et al.* reported the abstraction of γ -H from an excited aryl ketone with the resultant hydroxyl intermediate being stabilised by the micelle (scheme 2.1).¹¹⁵ This stabilisation prevented the reverse reaction to give starting material.



Scheme 2.1: Micelle stabilised radical reaction

Secondly, the **local concentration** effect which results from the high concentration of reactants in the small volume of the micelle.^{40, 71} This effect has been observed for bimolecular reactions between apolar substrates, cyclopentadiene and methyl acrylate. The high local concentration of reactants in the presence of micelles accelerates the rate of reaction when compared to organic solvents.

Thirdly, **microviscosity** effect, which results from the higher viscosity within the micellar core compared to the surrounding bulk solution. Like the cage effect, the viscous liquid-like core can effectively “hold” the substrates together for long enough

for the reaction to take place. The micelle viscosity of commercially available surfactants can vary from 6-19 cP for SDS and 18-151 cP for CTAB as discussed above.¹¹⁰

Fourthly the **electrostatic** effect, which results from the charged head groups in the Stern layer. The charge on the head groups can stabilise charged, partially charged, or radical intermediates by hydrogen bonding and/or the formation of a complex with the head group. This effect can also align molecules in a favourable TS creating a facile micro-reaction environment for the reaction (figure 2.23).⁷⁵

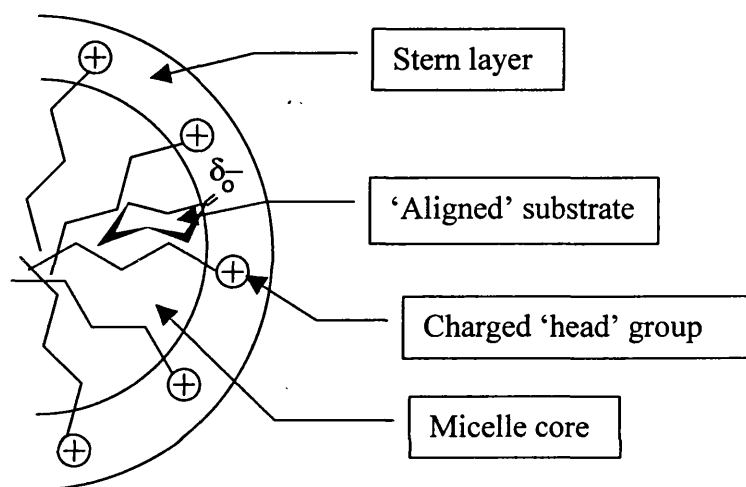
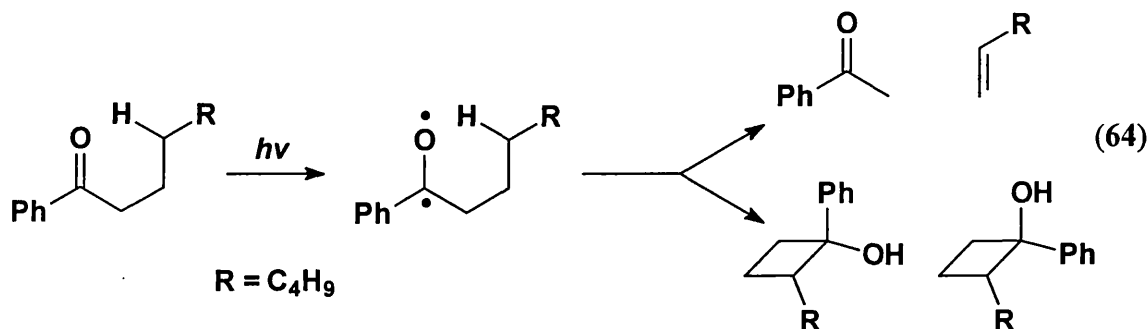


Figure 2.23: Orientation of substrates by the action of the charged Stern Layer

Finally, **polarity** effects arise because the interior of a micelle is less polar than the bulk aqueous phase but is more polar than a hydrocarbon solvent.⁷⁵ Solvent polarity can have a significant effect on γ -H abstraction in a radical reaction by $h\nu$. Turro *et al.* have investigated the effects of polarity on the decomposition of octaphenone by $h\nu$ (scheme 2.2).¹¹⁶



Scheme 2.2: Solvent effect on γ -H abstraction.

2.10 Techniques to Study Surfactants & their Micelles

2.10.1 Light scattering

"Light scattering results from the electric field association with the incident light inducing oscillation of the electron clouds of the atoms of the material in question. Then acts as a secondary source and radiate scattered light".

Introduction to Colloids & Surface Chemistry, Duncan J. Shaw, 4th Edition.

The Tyndall Effect is a phenomenon exhibited by all materials that are capable of scattering light with varying intensity.¹¹⁷ Perfectly homogenous systems would not scatter light and are the only exceptions. Even very pure liquids or gases that are dust-free are still able to scatter light due to density fluctuations and appear turbid with the aid of specialised equipment, *i.e.* powerful lasers, even if not to the naked eye.

The turbidity of a sample is defined as:

$$\frac{I_t}{I_0} = \exp[-\tau l]$$

Equation: 2.3

where:

- I_0 = intensity of the incident light
- I_t = intensity of the transmitted light beam
- l = length of the sample and
- τ = turbidity of the sample.

2.10.2 *Measurement of scattered light*

The intensity, polarisation and angular distribution of scattered light is highly dependent on the *size* and *shape* of the scattering particles present in the sample, with large asymmetric particles producing the greatest scattering. It is, therefore, essential that dust is removed from the sample by filtration or centrifugation under an inert nitrogen atmosphere as these large particles would scatter light more strongly than the sample, introducing errors into the results.^{90, 118, 119}

2.10.3 *Light scattering theory*

Rayleigh applied the electromagnetic theory of light to the scattering of light by small, non-absorbing (insulating) spherical particles in a gaseous medium. When an electromagnetic wave of intensity I_0 and wavelength λ is passed through a solution of known concentration containing particles of polarisability α , a dipole is induced in the particle.¹¹⁷

Relative molecular masses of micelles can be obtained directly from light scattering measurements without the need for calibration, as the results obtained are absolute. It is referenced using a sample of toluene, which is considered to be a 'pure' homogenous system. The total amplitude of the resultant light scattered from a sample, is proportional to the volume of the micelle and hence, its observed mass.

$$\text{Total intensity of light scattered (TILS)} \propto (\text{particle mass})^2$$

Debye later formulated a relationship between the total intensity of scattered light with the particles mass in the sample.¹²⁰

$$\text{TILS} \propto \text{number of particles (n)} \times \text{mass (m)}^2$$

As n_m is proportional to the concentration (c) of the solution,

$$TILS \propto cm$$

Using the formula derived by Debye from Rayleighs' electromagnetic theory, we have,

$$\frac{K_1 c}{R_{90}} = \frac{1}{M} + 2Bc \quad \text{Equation: 2.4}$$

where:

- K_1 = an optical constant^{62, 121}
- c = concentration
- R_{90} = Rayleigh ratio of sample relative to toluene
- M = molecular weight of the scattering unit
- B = second virial coefficient

At low concentrations, the virial coefficient can be ignored and equation 2.4 may be simplified to:

$$\frac{K_1 c}{R_{90}} = \frac{1}{M} \quad \text{Equation: 2.5}$$

Therefore,

$$M = \frac{R_{90}}{K_1 c} = \frac{R_{90(\text{benzene})}}{K_1 c} \quad \text{Equation: 2.6}$$

Re-arrangement and further simplification gives equation:

$$M = A \frac{1}{\left(\frac{\partial RI}{\partial c}\right)^2} \cdot \frac{S_{90}}{c} \quad \text{Equation: 2.7}$$

where: M = aggregate mass

A = temperature dependent constant, $1.2095 \text{ cm}^3 \text{ mol}^{-1}$ at $25 \text{ }^\circ\text{C}$ ^{62, 121}

$\left(\frac{\delta RI}{\delta c}\right)^2$ = gradient from refractive index of micelle solution of varying concentrations

$\frac{S_{90}}{c}$ = gradient of S_{90} of surfactant solutions at various surfactant concentration

Measuring the refractive index of micelle solutions at different concentrations, the value of $\left(\frac{\delta RI}{\delta c}\right)^2$ can be determined by plotting refractive index *versus* concentration and determining the gradient of the curve.

By calculating the aggregate mass and knowing the relative molecular mass (RMM) of the surfactant, it is possible to calculate the aggregation number (N) of a micelle.

2.10.4 *Surface tension*

“Surface tension is the property of a liquid surface to act as if it were an elastic membrane. It mainly depends upon the solutes or gases in contact with it in solution”.

Webster’s Third New International Dictionary

Surface tension, by definition, is the force acting in the plane of the surface of the liquid (figure 2.24). Pure water, uncontaminated by solutes or gases, has a surface tension value of 72.75 mN/m (0.07275 J/m²) at 20 °C.⁹⁵ This value is lowered when solutes, like surfactants, are dissolved in the water. Water molecules have a high cohesive nature; attractive forces (hydrogen bonding and van der Waals forces) result in binding water molecules with each other in solution. These forces are independent of one another and may be assumed to be additive.

Air

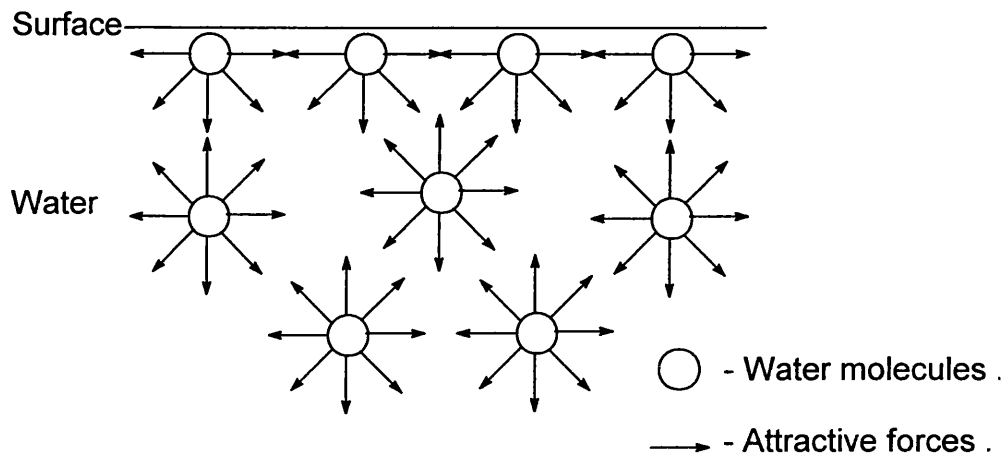


Figure 2.24: Attractive forces between water molecules and the surrounding water

However, these attractive forces are disrupted when solutes, like surfactants, are dissolved in the water.

The orientation of the surfactants at the surface of the water is known as surface activity. At low surfactant concentrations (well below the *cmc*), surfactant molecules orientate towards the air-water interface, allowing the hydrophilic groups of the surfactant to be in contact with the water and the hydrocarbon chains to be out of the surface of the water or lying flat on the surface.

Air

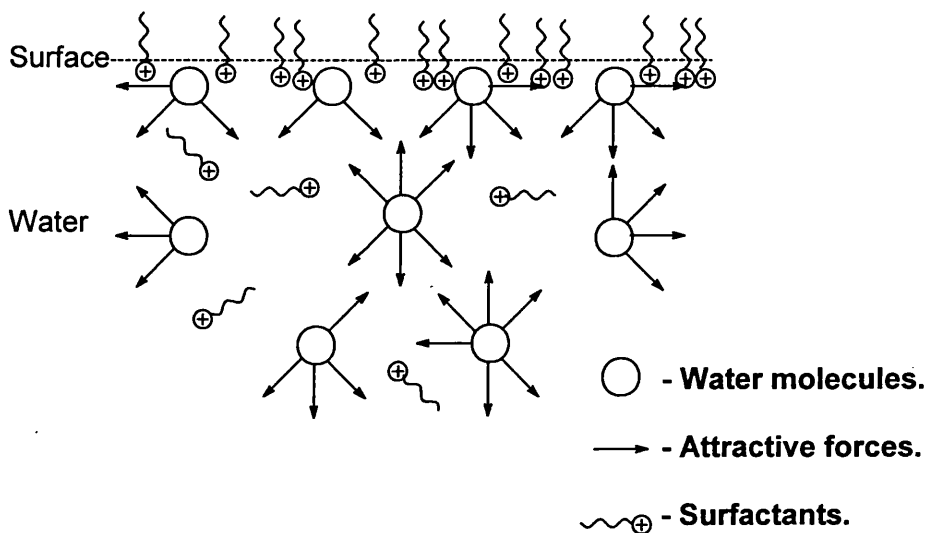


Figure 2.25: Orientation of surfactants at the air-water interface

The monolayer formed by the surfactant molecules at the air-water interface has a disruptive interference on the forces between adjacent water molecules on the surface (figure 2.25). This phenomenon has the affect of lowering the surface tension of the solution. This has led to the formulation of the Gibb's-Duhem equation in which the relationship between the change in surface tension ($d\gamma$) and the change in composition at the air-water interface is described (equation 2.8). The change in surface tension is dependent on surfactant concentration and can be determined using the Wilhelmy Plate method.

Application of the Gibb's surface tension equation:¹²²

$$\Gamma = -\frac{\text{slope}}{2RT} \quad \text{Equation: 2.8}$$

The slope can be determined by plotting surface tension versus natural log of concentration. Hence, from the surface excess (Γ), the micelle's surface area at the air-water interface can be calculated.

2.11 Conclusion

It is a misconception to imagine that surfactants are static entities that do not participate in the organic mechanisms. Studies have shown that surfactants and the micelles that form from these discreet molecules are able to accelerate organic reactions⁵¹ and influence stereoselectivity in organic reactions.^{53, 56}

Results and Discussion

3 Diels-Alder Reactions

3.1 Introduction

Initially, our first aim was to evaluate the efficiency of the Diels-Alder reaction in aqueous media with respect to a range of standard dienophiles. We wanted to assess the reactions and contrast the reaction selectivities in aqueous systems with a range of organic solvents of different polarity.

The acrylate series (**65a-d**) were selected as our dienophiles since they readily react with a range of dienes and we could increase the lipophilicity of the dienophile by extending the length of the alkyl chain on the ester moiety. Previous work has been carried out in this area using methyl acrylate (see section 1.5).^{43, 153}

3.2 Acrylate Derivative Synthesis

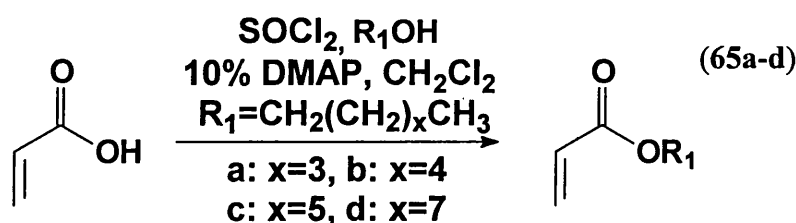
3.2.1 General approach

Acrylate derivatives are commercially available up to and including butyl acrylate. However, since we required longer ester chain lengths, it was necessary to synthesise them. Our initial synthetic work, therefore, included the synthesis of pentyl (65a), hexyl (65b), heptyl (65c) and nonyl acrylate (65d), which were then used in the Diels-Alder studies.

3.2.2 Synthesis of acrylate derivatives

3.2.2.1 Pentyl acrylate (65a)

Pentyl acrylate was first synthesised using the conventional method of combining acid and alcohol in the presence of a catalytic amount of concentrated sulphuric acid, which afforded the product in a crude yield of 33%, containing residual starting materials.¹²³ Purification of the product was achieved by distillation under reduced pressure to yield only 10% of the desired material due to the volatile nature of the product, so an alternative synthetic route was investigated and is outlined below.



Scheme 3.1: Standard ester synthesis of acrylate derivatives

The synthesis of these materials is seemingly straightforward and their particular synthesis is not elaborated in the literature. Amongst other methods used, the most successful is outlined above in scheme 3.1 and was a standard ester synthesis *via* the acid chloride. Neat acrylic acid was treated with thionyl chloride at 5 °C, then the corresponding alcohol was added and the reaction mixture heated at reflux

overnight. However, ^1H NMR analysis of the material isolated indicated the presence of the ethers, given in figure 3.1.

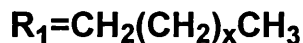
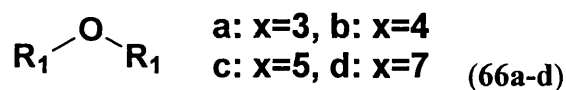
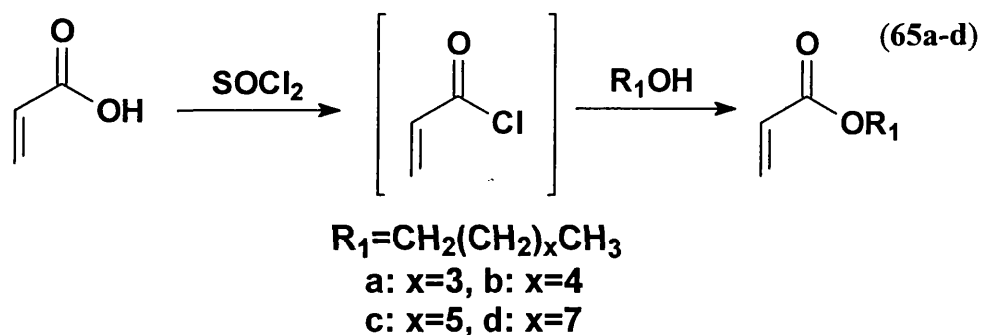


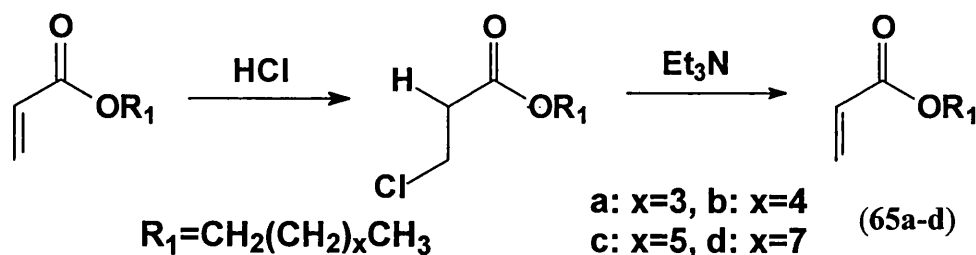
Figure 3.1: Additional product elucidated by ^1H NMR

A further product was also elucidated by ^1H NMR as the 3-chloropropanoate, which could be generated as shown in scheme 3.3. The desired acrylate product was not isolated at this stage but left as a mixture containing an impurity identified as the 3-chloropropanoate.



Scheme 3.2: Synthetic route to the acrylic ester *via* an acid chloride intermediate

The preparation of the acryloyl chloride and the corresponding ester results in the generation of hydrogen chloride, which can add *via* a Michael fashion to the acrylate double bond forming the 3-chloropropanoate derivative. The ether impurity (Figure 3.1) was removed by flash column chromatography at this stage, but as indicated above, the 3-chloropropanoate derivative was not separated from the acrylate product. Instead, the mixture containing the two was heated at reflux with triethylamine to yield the desired acrylate derivative by regenerating the double bond of the acrylate (scheme 3.3).



Scheme 3.3: Regeneration of the acrylate with triethylamine

Several methods were explored in an attempt to prevent chloride addition to the double bond. For example, nitrogen bases were added to the reaction which could form the corresponding hydrochloride salt such as pyridine hydrochloride. However, the yield did not increase and it did not completely remove the hydrogen chloride as 3-chloro propanoate was still formed in the reaction mixture. Therefore, it was decided to isolate the crude product containing the impurity (minus the ether) and heat at reflux with triethylamine present to effect the hydrogen chloride elimination, as described above. When this method used pentan-1-ol, it yielded pentyl acrylate (**65a**) in an overall yield of 55%.

3.2.2.2 Hexyl acrylate (**65b**)

A similar method was used as with pentyl acrylate (outlined in scheme 3.2) but using hexan-1-ol as the alcohol. The propanoate impurity contaminated the reaction mixture but when heated at reflux in the presence of triethylamine, it afforded the product, heptyl acrylate (**65b**), in 71% yield after purification.

3.2.2.3 Heptyl acrylate (**65c**)

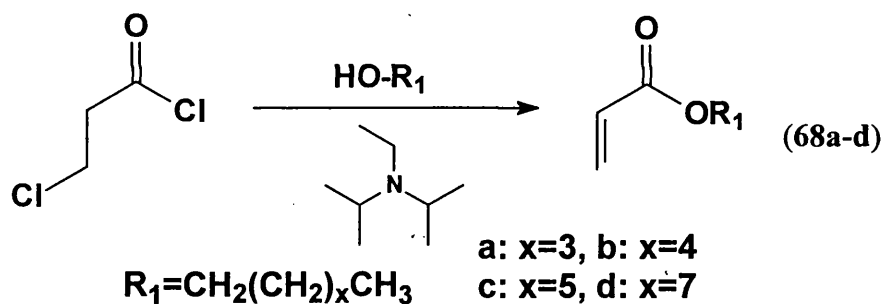
A similar method was used as with pentyl acrylate (outlined in scheme 3.2) but using heptan-1-ol as the alcohol. The propanoate impurity contaminated the reaction mixture but when heated at reflux in the presence of triethylamine it afforded, after purification, heptyl acrylate (**65c**) in 80% yield.

3.2.2.4 Nonyl acrylate (**65d**)

As with the synthesis of pentyl acrylate, nonan-1-ol was used to give a crude yield of 71% containing the propanoate impurity. This was converted through to the acrylate by heating at reflux in the presence of triethylamine. Final purification by flash column chromatography gave pure nonyl acrylate (**65d**) in 69% yield.

3.2.3 *Alternative approach*

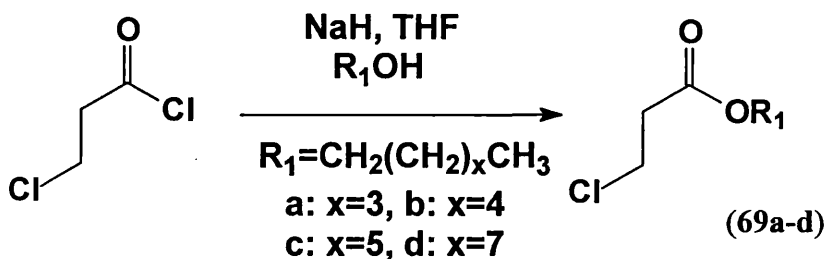
Initially we required the pentyl, heptyl and nonyl acrylates but for completion of the acrylate series we investigated an alternative synthetic route which avoided the highly toxic acid chloride intermediate.¹²⁴ One such method was using Hünigs base (quantitative), *N*-ethyldiisopropylamine and 3-chloropropionyl chloride, a commercially available compound, and the appropriate alcohol, as illustrated below in scheme 3.4.



Scheme 3.4: Acrylate synthesis using Hünigs base as a catalyst

This reaction was carried out at room temperature (RT) and heated at reflux (in diethyl ether or dichloromethane). However, the reaction did not go to completion (**68a**, 3%) or no product was isolated. Pyridine and triethylamine were also used as bases and in the case of nonan-1-ol, nonyl acrylate (**65d**) was isolated in 12% yield.

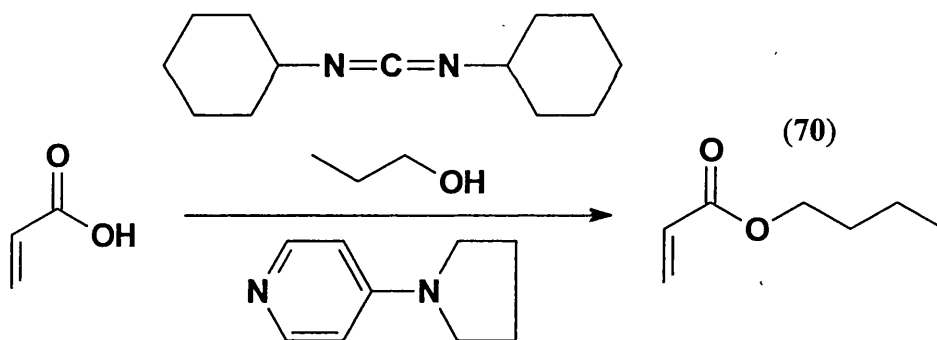
A further alternative strategy was explored and the anion of the alcohol was generated using sodium hydride as the base with pentan-1-ol (scheme 3.5a).



Scheme 3.5a: The route using sodium hydride as base

After heating the reaction mixture at reflux with triethylamine to eliminate the hydrogen chloride, pentyl acrylate (**69a**) was formed in a modest 35% yield after purification.

A 1, 3-dicyclohexylcarbodiimide (DCC) coupling was also investigated to synthesise the acrylate derivatives with the intention of avoiding the highly toxic acryloyl chloride intermediate and prevent hydrogen chloride gas evolution and subsequent addition across the acrylate double bond (scheme 3.5b).



Scheme 3.5b: DCC coupling of acrylic acid and butan-1-ol

Using butan-1-ol as a test starting material, the reaction resulted in an 88% yield of (**70**), the desired product.

Having investigated several routes, it was apparent that using acrylic acid, thionyl chloride with subsequent elimination of hydrogen chloride was a reproducible reaction for all acrylate derivative synthesis and hence this was used to give workable quantities of the acrylates (**65a-d**).

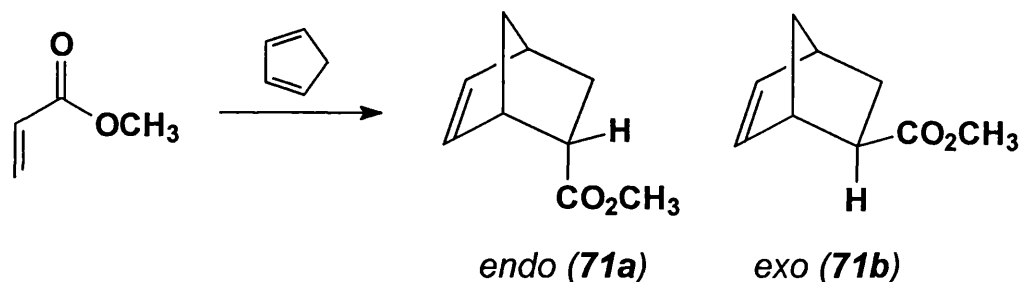
3.3 *Diels-Alder Reactions*

3.3.1 *Acrylate derivatives and cyclopentadiene*

Only five derivatives (methyl, ethyl, pentyl, heptyl and nonyl) were used to determine and hence illustrate if a trend exists in the series in terms of % yield of product and the *endo/exo* (*N/X*) ratio of the cycloadducts isolated from the Diels-Alder reactions. Some of these reaction systems were also used to explore other important parameters such as pH and salt addition.

3.3.2 5-Bicyclo[2.2.1]heptene-2-carboxylic acid methyl ester

(71a-b)



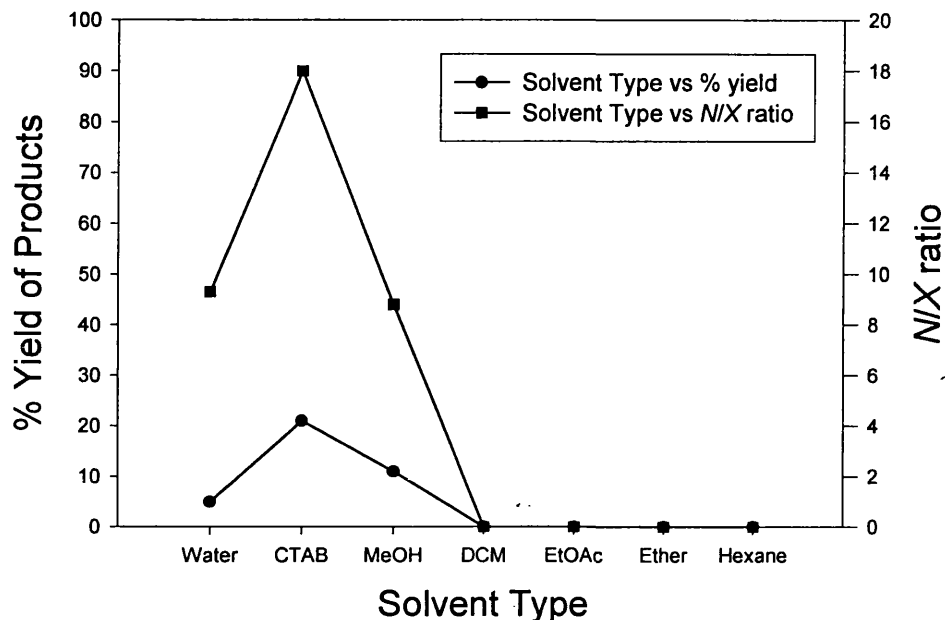
Scheme 3.6: Diels-Alder reaction between cyclopentadiene and methyl acrylate

As described in section 1.5, this reaction has been carried out by Breslow and Sauer who reported conflicting results on the effect of additive surfactants in solutions and the effects of solvent polarity on the Diels-Alder reaction. Our initial aim was therefore to investigate the solvent and surfactant (at their *cmc*, see section 2.2) effects on the Diels-Alder reaction.

Accordingly, methyl acrylate was reacted with 2 equivalents of cyclopentadiene in water, CTAB solution (1×10^{-3} mol dm⁻³), methanol, dichloromethane, ethyl acetate, diethyl ether and hexane for 4 hours.

Product analysis was carried out using ¹H NMR and the ‘methyl’ signal at 3.62 ppm and 3.55 ppm corresponding to the *endo* (71a) and *exo* (71b) products respectively (scheme 3.6). The alkene signals were also used to confirm the result. Although attempts were made to also analyse the reaction mixture using high-pressure liquid chromatography (HPLC), it was apparent that the Diels-Alder products underwent a ‘retro’ Diels-Alder reaction on the HPLC column. It was not due to the silica or solvents on the column since the material was stable to flash column chromatography, but was most likely to be caused by the high pressure experienced by the cycloadducts during the run. This observation was confirmed by injecting pure samples of *endo* (71a) and *exo* (71b) cycloadducts separated by flash column chromatography and the traces indicated a mixture of products and starting materials.

A graphical representation of the yields and N/X (**71a/71b**) ratio, plotted against decreasing solvent polarity (aqueous solvents→hexane) is shown below (graph 3.1).



Graph 3.1: Methyl acrylate + cyclopentadiene, 4 hours

After the 4 hours reaction, when using CTAB solution, the highest yield of 21% and an N/X (**71a/71b**) ratio of 18.0 (see graph 3.1 and appendix A1: table 3.1) was observed and was much higher compared to when organic solvents were used. This striking difference can be attributed to the solubilisation of organic solutes within the micellar core and concentration, caging and pre-orientation effects accelerating the reaction.¹²⁸

The experiment was repeated increasing the reaction times to 20 and 72 hours to investigate the solvent effects on the yield and an N/X (**71a/71b**) ratio and the product mixture was analysed as before.

Acceleration of the reaction in water based media is also accompanied by a high N/X ratio that can be rationalised in terms of **DIPOLE MOMENTS** as described in section 1.5.⁴³ When these two substrates approach each other, the dipole moment is

greater in the *endo* rather than that in the *exo* TS as they are pointing in the same direction as shown in figure 3.2.

In addition, when these substrates are solubilised in the interior of the micelles, the dipole moments can be enhanced because of the positively charged Stern Layer of the CTAB micelles. The substrates pre-orientate themselves near the charged region of the micelle with the dipole moment of both methyl acrylate and cyclopentadiene directed towards the positive charge, *i.e.* an *electrostatic effect* that stabilises the *endo* TS within the micelle interior.¹²⁵

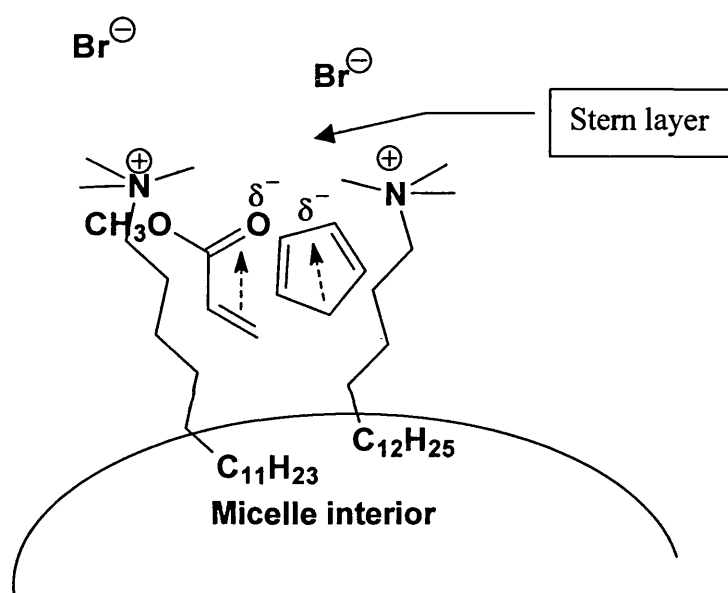
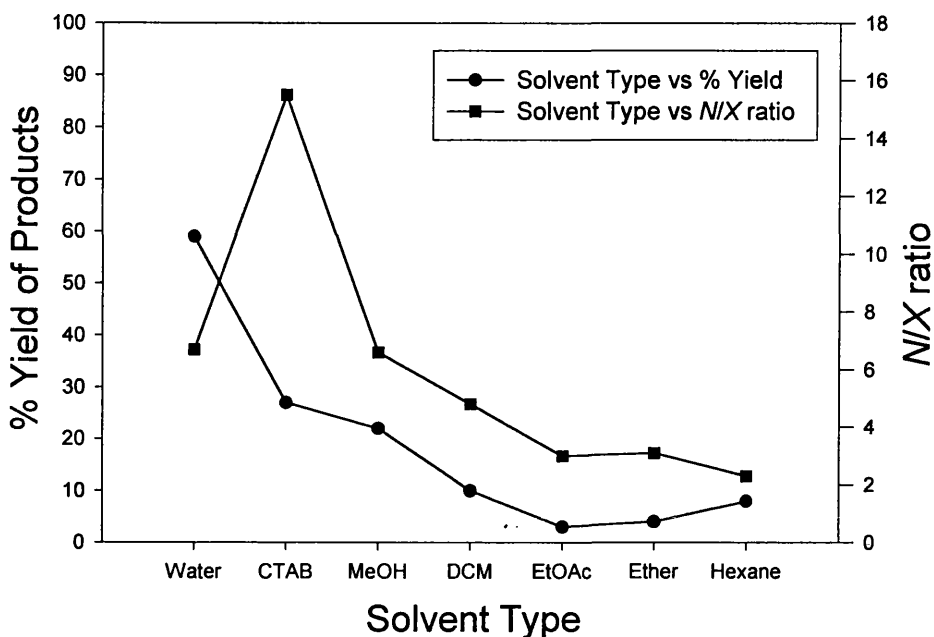


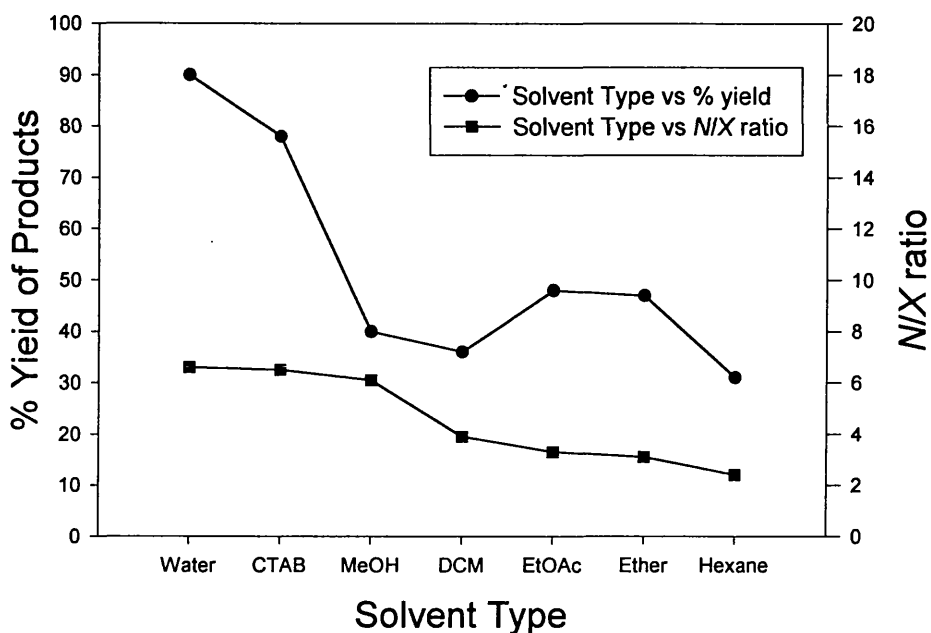
Figure 3.2: Proposed orientation of methyl acrylate and cyclopentadiene in the micelles' hydrocarbon core⁴³

It is likely that when using CTAB solutions, the substrates are solubilised within the micellar core. Methyl acrylate and cyclopentadiene are only sparingly soluble in water and this will reduce the rate of reaction between the substrates compared to CTAB thus, in general, resulting in lower yields. The use of organic solvents led to the production of no cycloadducts over short reaction times, other than when methanol was used. 'Mixed' solvents could explain this peculiarity. Non-anhydrous methanol will be saturated with water, which could influence the reaction by virtue of the 'mixed solvents' present in solution.



Graph 3.2: Methyl acrylate + cyclopentadiene, 20 hours

When carrying out the reaction over 20 hours a 59% yield of products was observed in water with an N/X (**71a**/**71b**) ratio of 6.7 compared to 18.0 over 4 hours (graph 3.2 and appendix A1: table 3.2). Increasing the reaction time will lead to the formation of more of the thermodynamic *exo* (**71b**) product and also the ‘retro’ Diels-Alder reaction will occur. The N/X (**71a**/**71b**) ratio when using CTAB and methanol was also lower compared to 4 hours, again, most likely due to thermodynamic *exo* (**71b**) product formation. As mentioned above, organic molecules tend to aggregate together in the aqueous media thus reducing the water and organic interfacial interactions and this is known as the *hydrophobic effect*.^{50, 126, 127} The reduction in interfacial interaction is usually accompanied by an increase in the amounts of *endo* (**71a**) isomer formed, as the *endo* TS is more compact compared to the *exo* TS.



Graph 3.3: Methyl acrylate + cyclopentadiene, 72 hours

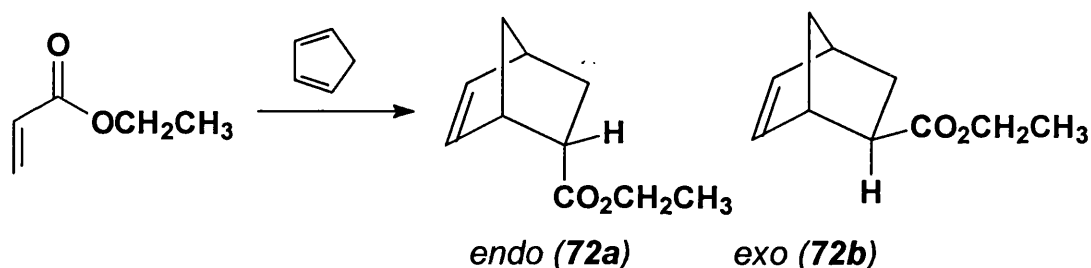
After 72 hours, (graph 3.3 and appendix A1: table 3.3) the aqueous solvents, water and CTAB mediated reactions gave a similar *N/X* (**71a/71b**) ratio but lower than at 20 hours due to the thermodynamically determined *exo* product formation. Water gave the highest yield of 90%, followed by CTAB solution in 78% and the organic solvents all gave <50% product.

Overall enhanced yields have been observed in the aqueous solutions compared to organic solutions and this was accompanied by higher *N/X* (**71a/71b**) ratio.^{9, 40, 47, 63} CTAB solution appears to be a better solvent for short reaction times since it can solubilise organic substrates, while water gives higher yields over long reaction times probably due to the hydrophobic effect. It is notable that we obtained a much higher *N/X* (**71a/71b**) ratio of 18.0 when CTAB solution was used at its *cmc* compared to Breslow's reported value of 8.8. Breslow used 20 mM solutions of CTAB and the *cmc* is 1×10^{-3} mM.¹⁰⁸ This suggests that surfactant concentrations can dramatically affect the product selectivity. This could be attributed to the shape of micellar aggregates, which are often spherical at just above its *cmc* and are known to become ellipsoidal or rod shape at higher concentrations.¹²⁸ Overall, aqueous solvents

like water and CTAB solutions gave higher yields and *N/X* selectivities over organic solvents for both short and long reaction times.

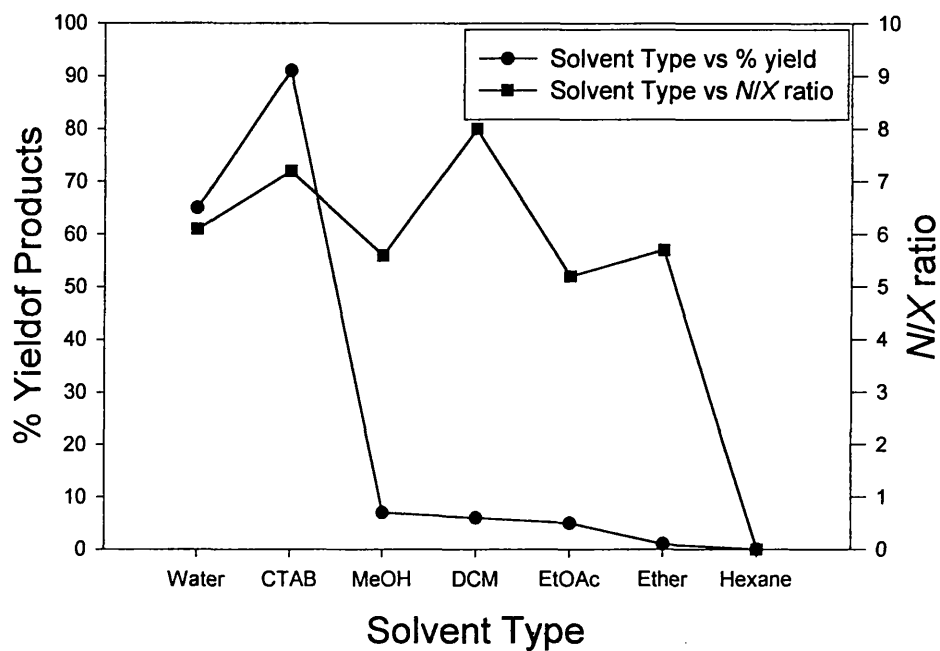
3.3.3 5-Bicyclo[2.2.1]heptene-2-carboxylic acid ethyl ester

(72a-b)

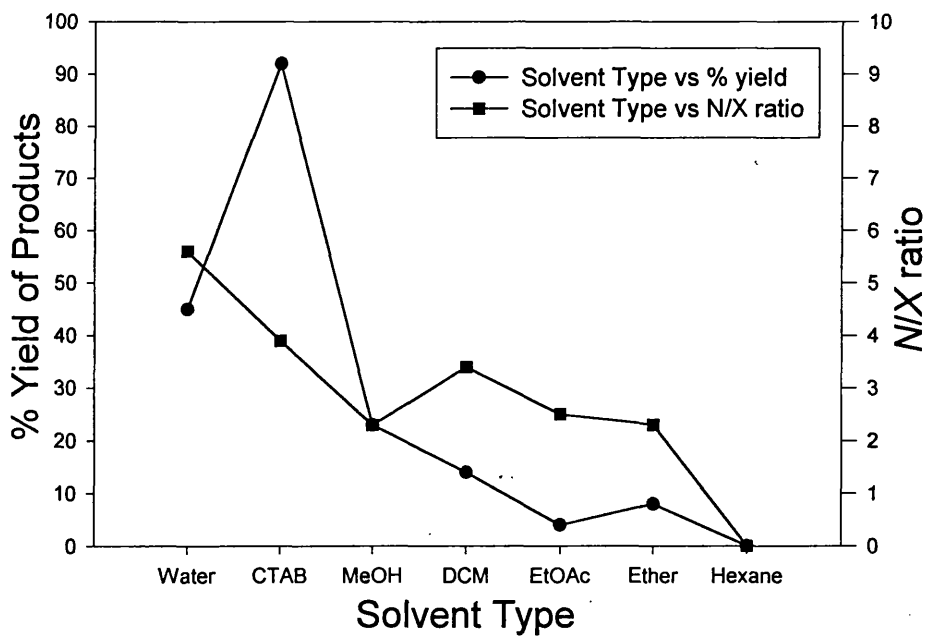


Scheme 3.7: Ethyl acrylate + cyclopentadiene

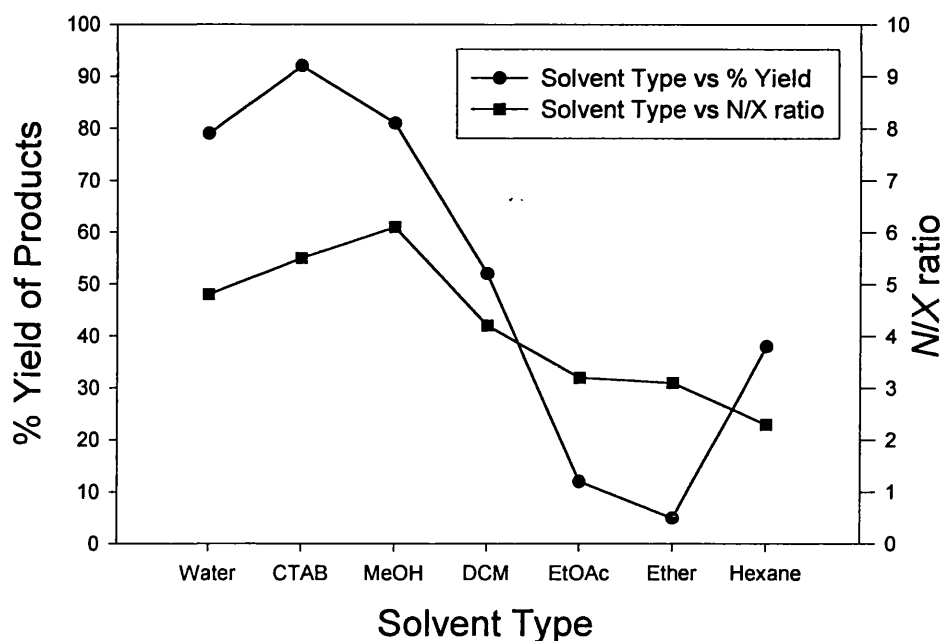
As mentioned above, we are investigating Diels-Alder reactions in 'alternative' media and we wished to assess the effect of increasing chain length for several reasons. Firstly, Berson only covered the acrylate series up to and including butyl acrylate. Secondly, we wished to explore the pre-orientation effects of micellar media as applied to the Diels-Alder reactions. Finally, longer chain acrylates were to be used with chiral surfactants and it was necessary to assess the acrylates behaviour in a non-chiral micellar media. Therefore, initially, reactions with ethyl acrylate as the dienophile were investigated. We envisaged little differences in the reaction outcome between methyl acrylate and ethyl acrylate. Again NMR was used to determine the *N/X* (72a/72b) ratio for the same reasons as with methyl acrylate and the results are represented graphically below (graphs 3.4-3.6, appendix A2: table 3.4-3.6).



Graph 3.4: Ethyl acrylate + cyclopentadiene, 4 hours



Graph 3.5: Ethyl acrylate + cyclopentadiene, 20 hours

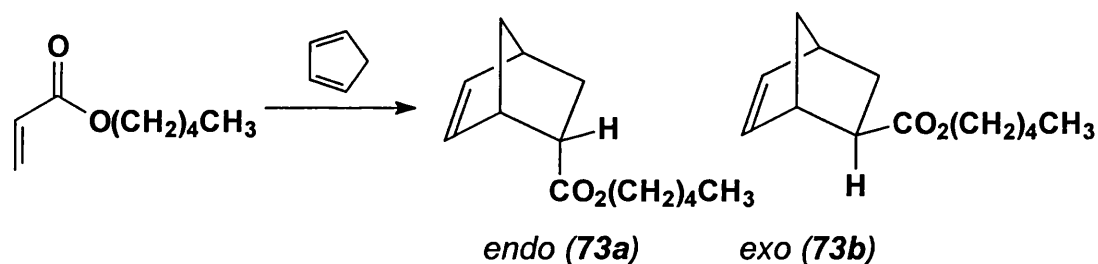


Graph 3.6: Ethyl acrylate + cyclopentadiene, 72 hours

For the 4 hour reaction, again when CTAB solution was used, the highest yield (90%) was observed followed by water (65%) and the organic solvents (<10%). The N/X (**72a/72b**) was variable but the use of CTAB solution gave a higher value than with water or methanol. Over longer reaction times, the highest yields were in CTAB solutions. The N/X (**72a/72b**) varied with different reaction times as with methyl acrylate, but aqueous solvents and methanol still gave the highest values. This can again be attributed to the solubilising, concentration and electrostatic effects that can be found in the micellar core or the hydrophobic effect in water. The lowering of the N/X ratios observed was again most likely due to the thermodynamic *exo* product being generated over longer reaction times.

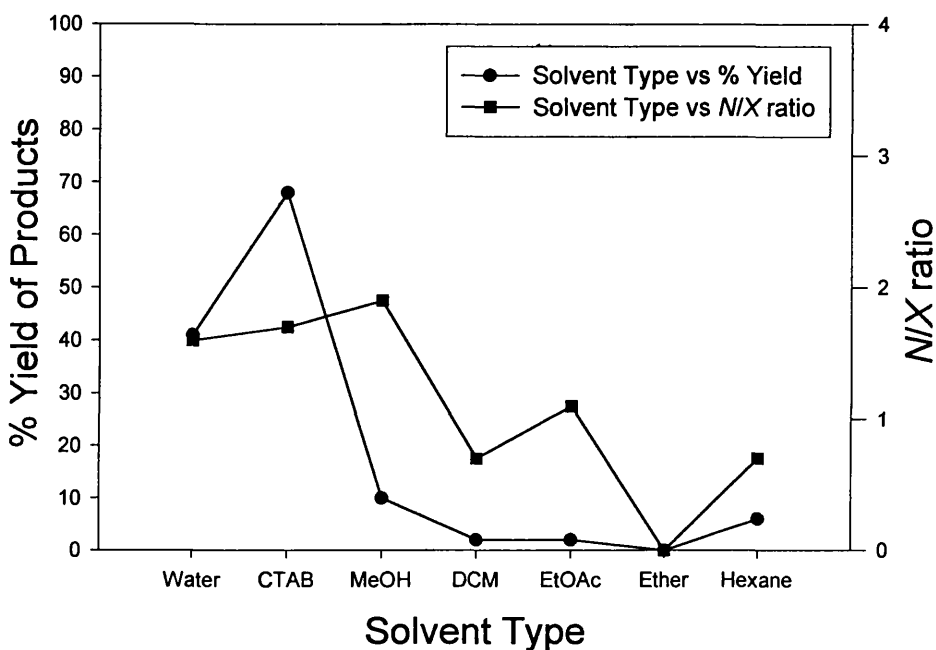
3.3.4 5-Bicyclo[2.2.1]heptene-2-carboxylic acid pentyl ester

(73a-b)

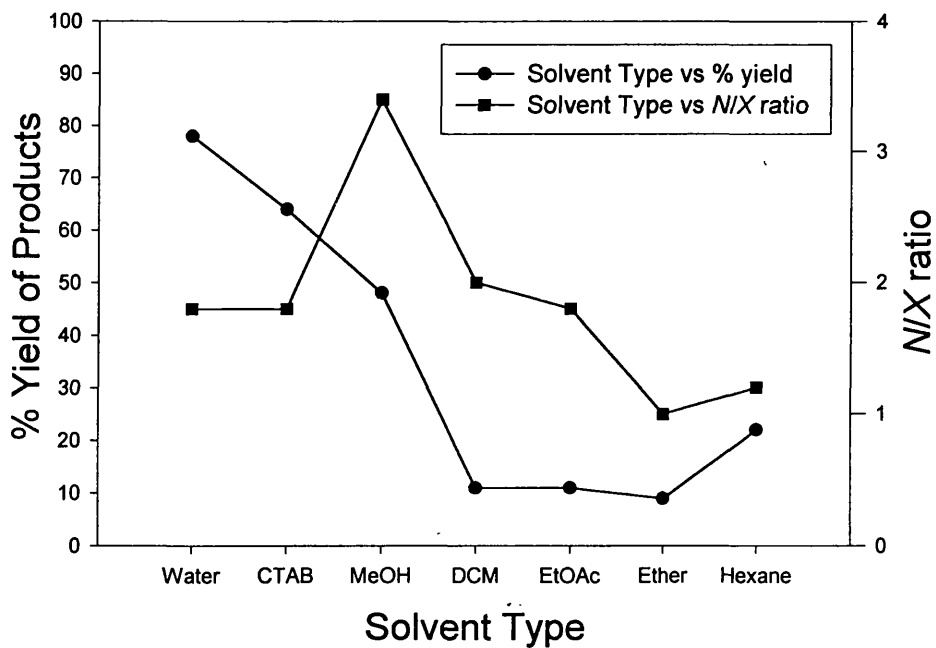


Scheme 3.8: Pentyl acrylate and cyclopentadiene

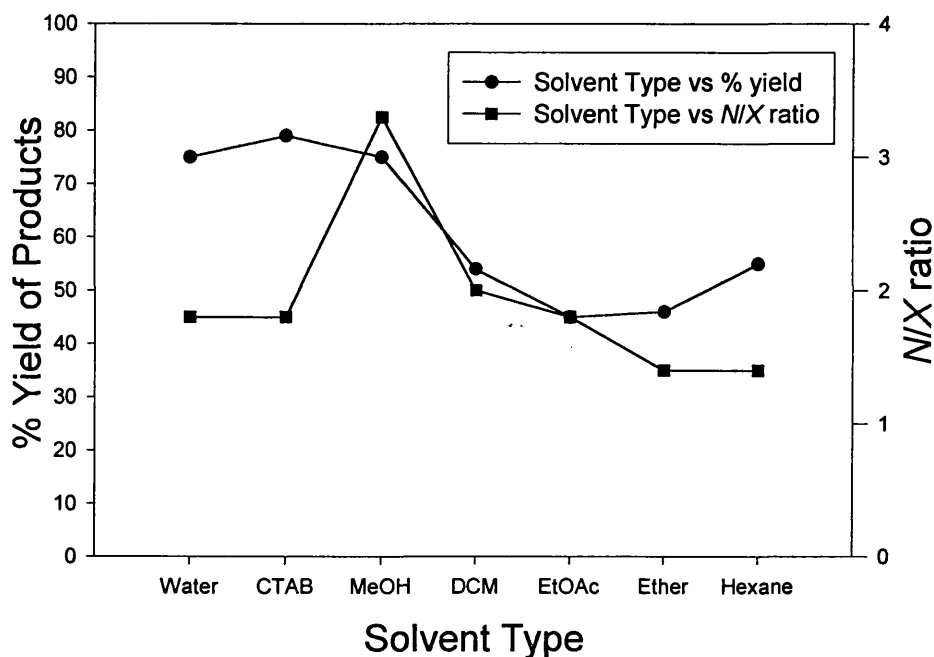
The pentyl acrylate was reacted with cyclopentadiene in a range of solvents as before and the results are summarised in the graphs below (graphs 3.7-3.9 and appendix A3: table 3.7-3.10). The *N/X* ratios and yield of products were determined by HPLC and not by ¹H NMR. The Diels-Alder adducts from the methyl acrylate, ethyl acrylate and cyclopentadiene reaction underwent a *retro* Diels-Alder on the HPLC column. This observation was confirmed by separating the *endo* (73a) and *exo* (73b) isomers by flash column chromatography then co-injecting a 1:1 ratio of (73a) and (73b) isomers in the HPLC column. It was found that the 1:1 ratio of isomers degenerated into more than two peaks, which corresponded to the starting materials (cyclopentadiene and acrylate substrates). This procedure was repeated with the pentyl acrylate adducts after reacting it with cyclopentadiene, and HPLC revealed that the pentyl acrylate adducts were stable under HPLC conditions where as methyl and ethyl acrylate cycloadducts were not. As a result of these findings, subsequent analysis of the Diels-Alder cycloadducts above the C₅ chain length were made using HPLC.



Graph 3.7: Pentyl acrylate + cyclopentadiene, 4 hours



Graph 3.8: Pentyl acrylate + cyclopentadiene, 20 hours



Graph 3.9: Pentyl acrylate + cyclopentadiene, 72 hours

Overall for all reaction times, N/X ratios were lower than that for the short chain analogues. For the 4 hour reaction, CTAB and then water gave the highest yields with methanol giving the highest N/X (**73a/73b**) ratio (followed by CTAB and water).

Increasing the reaction time to 20 hours and 72 hours gave reaction and selectivity trends (graphs 3.8 and 3.9, respectively) similar to methyl and ethyl acrylates. Water again gave the highest percentage yield, which can be attributed to the hydrophobic effect. The hydrophobic effect is effectively increased as the alkyl chain on the acrylate derivative is increased, making the acrylate more non-polar compared to the methyl and ethyl derivatives.

One notable result was that when methanol was used as the solvent, it gave a higher N/X (**73a/73b**) ratio than water and CTAB. This anomaly, as mentioned above, may have been due to the use of 'wet' methanol, so that it is acting as a mixed solvent media in the Diels-Alder reactions. In essence, the hydrophobicity of pentyl

acrylate in water results in greater packing into the *endo* TS within this methanolic media. This can be investigated by comparing dry methanol to wet methanol, to establish whether a difference is noticeable.

The lower *N/X* (**73a**/**73b**) ratios in organic media may be because the alkyl chain of the acrylate is sufficiently long to form 'reverse' micellar aggregates. The acrylate derivative has a polar carbonyl head group covalently bonded to an alkyl chain. This alkyl chain is sufficiently hydrophobic and will tend to orientate itself to point towards the bulk organic medium, while the polar head group will tend to aggregate in order to reduce the interfacial interactions between the organic medium and itself. The reverse micellar structure could be formed as illustrated below in figure 3.3.

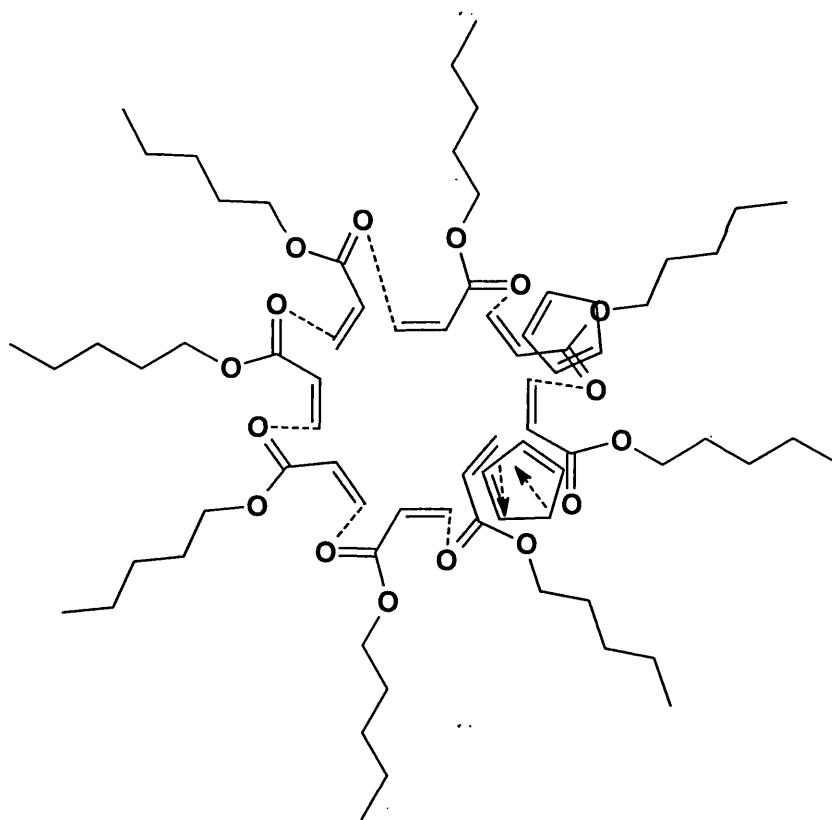


Figure 3.3: Reverse micelle in organic solvent media

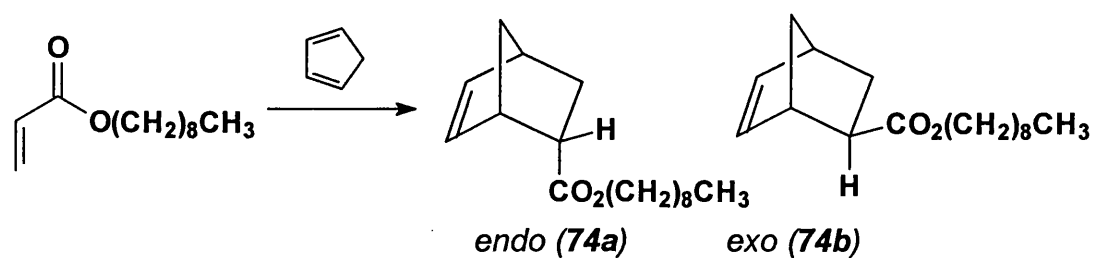
Another notable result is the high yield of products in water and CTAB after 4 h, compared to the shorter chain acrylates. As mentioned above, pentyl acrylate can form reverse micelles in organic solvents. Similarly, according to Menger's model,⁸⁴

'normal' (not reverse) micelles may assemble in the aqueous solvent. The higher yields with CTAB can be due to the electrostatic effect offered inside the micelle that can accelerate the reaction (see section 1.2.8). In solvents with low dielectric constants (polarity) only the *exo* isomer was identified to be present by HPLC. Again this result can be due to the formation of reverse acrylate aggregates in the organic solutions (figure 3.3).

Similar trends were observed with the hexyl and heptyl acrylates (appendix A4: table 3.10-3.12) when reacted with cyclopentadiene in different solvents. Again, notably, aqueous solvents gave better yield and higher selectivity or yields and selectivities comparable to the organically mediated Diels-Alder reactions.

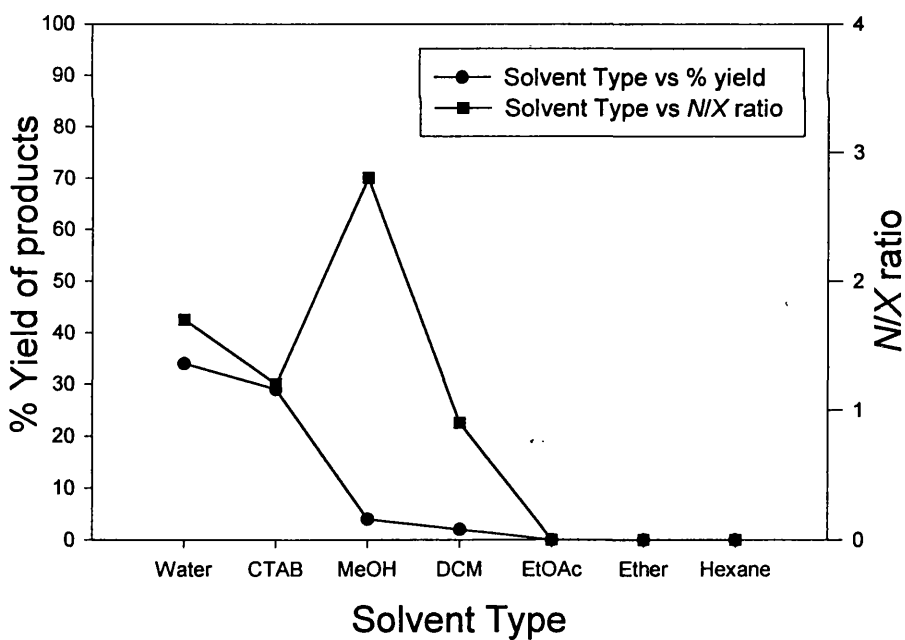
3.3.5 5-Bicyclo[2.2.1]heptene-2-carboxylic acid nonyl ester

(74a-b)

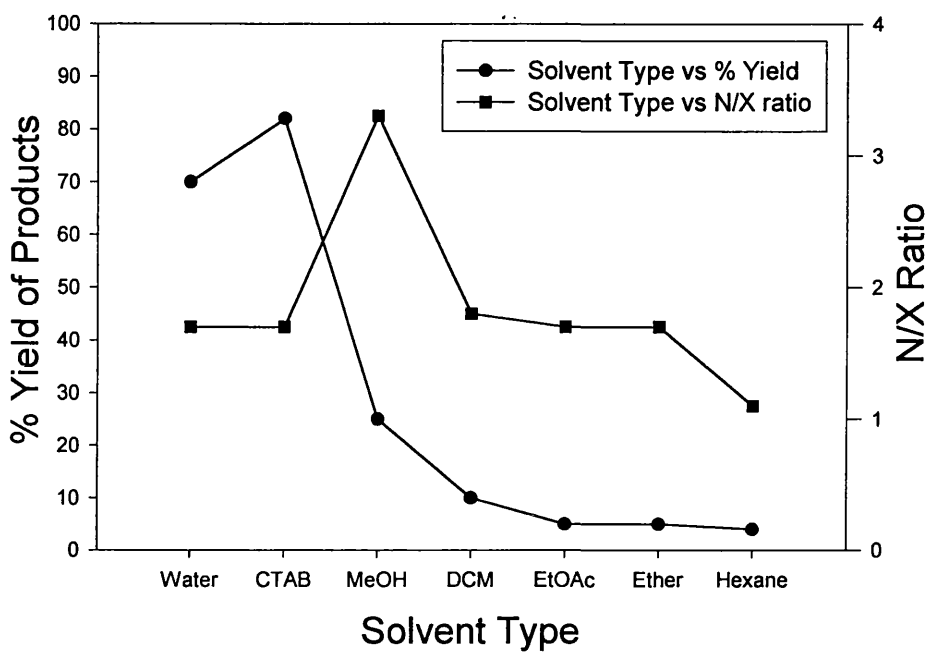


Scheme 3.9: Nonyl acrylate + cyclopentadiene

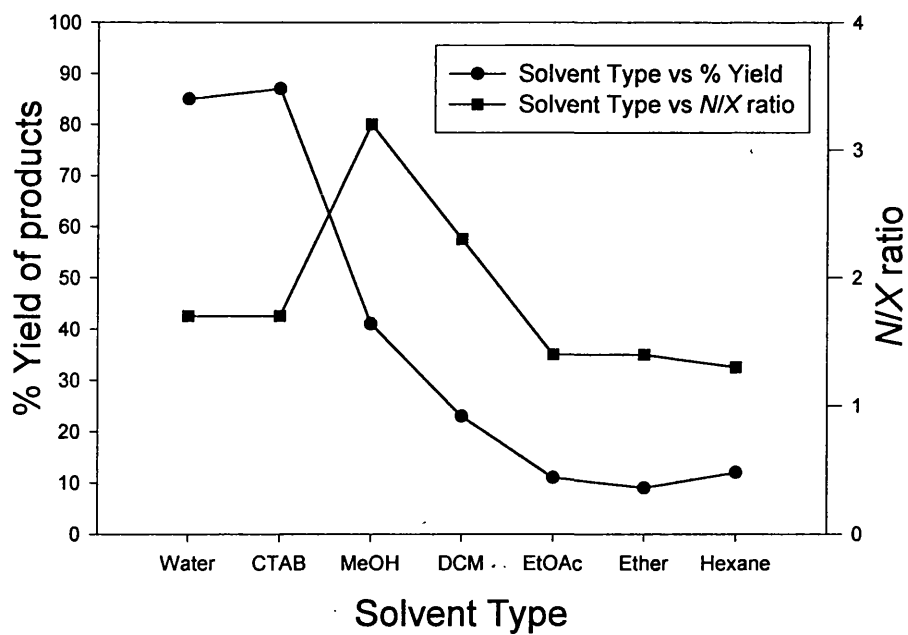
As with the other acrylate derivatives, the Diels-Alder reaction was investigated with nonyl acrylate as the dienophile. The results are summarised below (graphs 3.10-3.12 and appendix A5: table 3.13-3.15).



Graph 3.10: Nonyl acrylate + cyclopentadiene, 4 hours



Graph 3.11: Nonyl acrylate + cyclopentadiene, 20 hours



Graph 3.12: Nonyl acrylate + cyclopentadiene, 72 hours

There are several key features that are notable. As before, the use of water and CTAB led to higher yields than with organic solvents. The yields were again similar to pentyl acrylate when using both these media. When carrying out the reaction in water only, as with pentyl acrylate, the long chain acrylates can aggregate to form non-ionic micellar type assemblies or bilayers (figure 3.4 and section 2.2). With a surfactant present in solution, mixed micellar aggregates could be formed. The N/X (**74a**/**74b**) ratios for both water and CTAB solution were similar but dropped from approximately 2 to 1.6, indicating the effect of the long alkyl chain on the preference for the formation of the thermodynamic *exo* (**74b**) product with its pseudo equatorial carboxylate group compared to the shorter alkyl chains.

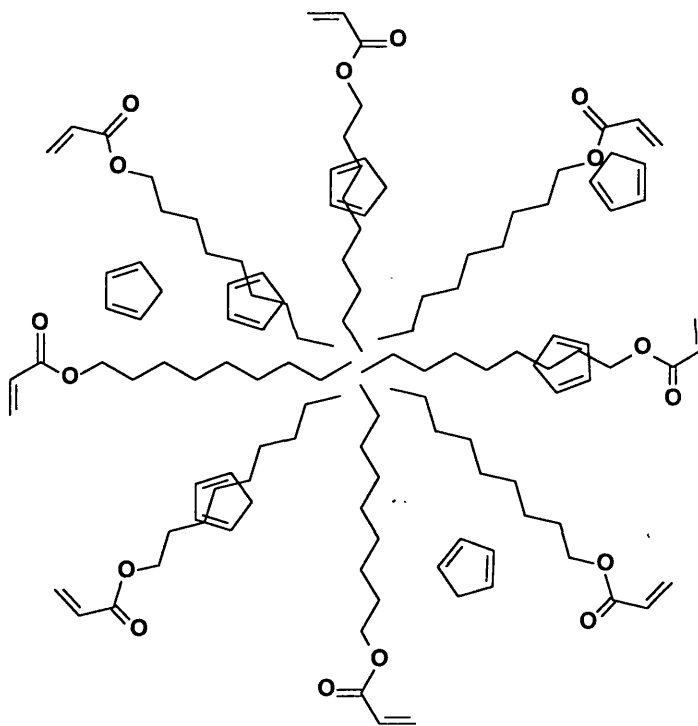


Figure 3.4: Aggregation of the nonyl acrylate in water?

3.3.6 Aqueous solutions as solvents in organic reactions

The successful results obtained when using water and CTAB solutions demonstrated that aqueous media are a feasible alternative as solvents for this reaction system. However, we wished to ascertain whether the reaction could be carried out at high substrate concentrations in an aqueous medium.

To this end, nonyl acrylate was reacted with cyclopentadiene at 10 times the original concentration used in the Diels-Alder reactions discussed earlier, *i.e.* 38 mM of nonyl acrylate in 25 ml of solvent (see table 3.16 below). In addition to water and CTAB solution, two other surfactant solutions were used, SDS and hexadecylpyridinium bromide (CPB).

Solvent	[Nonyl acrylate] 3.8 mM		[Nonyl acrylate] 38 mM	
	%yield	N/X ratio	% yield	N/X ratio
H ₂ O	85	1.7	71	2.4
CTAB	87	1.7	38	2
SDS	-	-	79	2.1
CPB	-	-	51	2.0
Et ₂ O	9.3	1.4	37	2.1

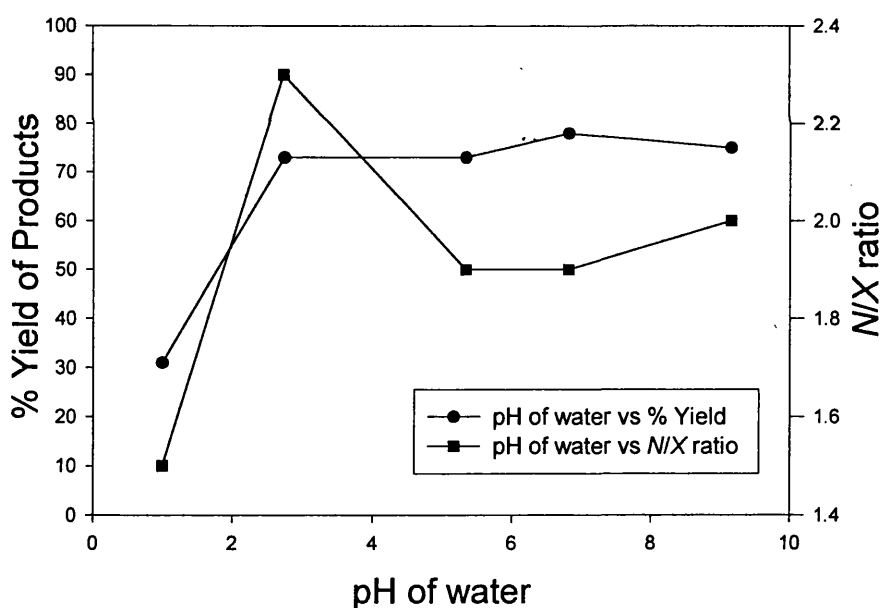
Table 3.16: Diels-Alder reaction in different surfactant solutions

Again the use of aqueous systems resulted in higher yields than diethyl ether. Of the surfactant solutions investigated, SDS gave the highest yield of products (79%), which is in agreement with previous observations that SDS micelles are more porous when compared to CTAB micelles.^{75, 125} Overall, these results suggest that the use of aqueous solvents does not mean a high dilution system is required to perform these reactions. Interestingly, the *N/X* ratios are marginally higher at higher substrate concentration, perhaps reflecting that the nonyl acrylate substrates are packing more efficiently into the surfactant micelle/aggregates resulting in the preference for the more compact *endo* transition state.

3.3.7 pH effects on the Diels-Alder reactions

3.3.7.1 Water as a solvent

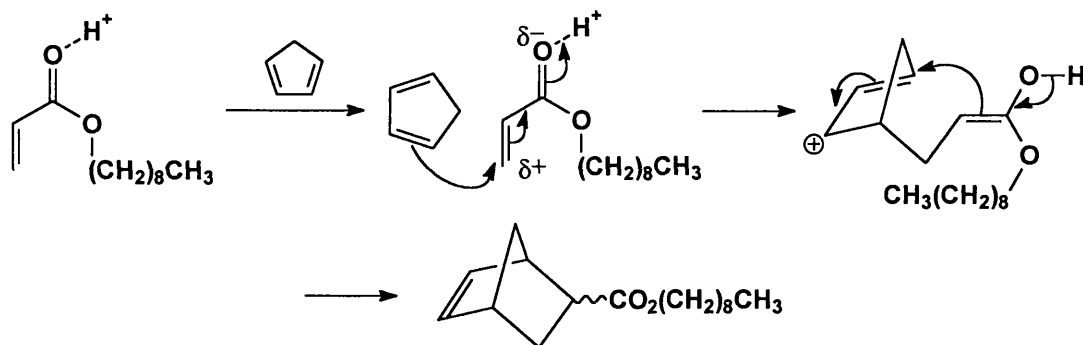
We proposed that the pH of the aqueous solution could have a significant effect on the reaction outcome and we set out to investigate this reaction parameter. In aqueous systems this has received little attention in the literature. Initially we explored the reaction in the absence of surfactant and de-ionised water was used in all of the aqueous media reactions, which has a pH of 6.7. Using 1M hydrochloric acid and 2M sodium hydroxide, the pH's of five water samples were adjusted to pH 1, 3, 5, 7 and 9, respectively, and used as solvents in the Diels-Alder reaction between nonyl acrylate and cyclopentadiene. The results are summarised below (graph 3.13, appendix A6: table 3.17).



Graph 3.13: Showing the effects of pH on the yields and selectivities of Diels-Alder reaction between nonyl acrylate and cyclopentadiene.

It is obvious that these reactions are pH dependent and it is notable that with a pH of 3 the highest N/X ratio of 2.3 was observed with a good yield, compared to a lower ratio at pH 7 (although the yield was marginally higher). This may be that at

acidic pH, protonation of the acrylate moiety of the dienophile will lower the LUMO, in a similar way to the effect of Lewis acids (scheme 3.10).

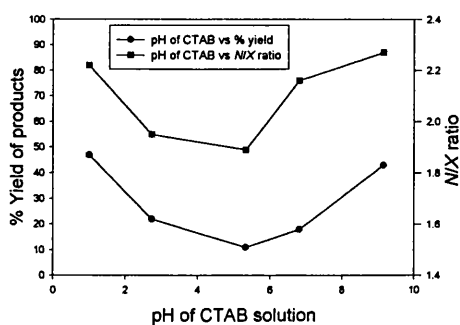


Scheme 3.10: Lewis acid type mechanism

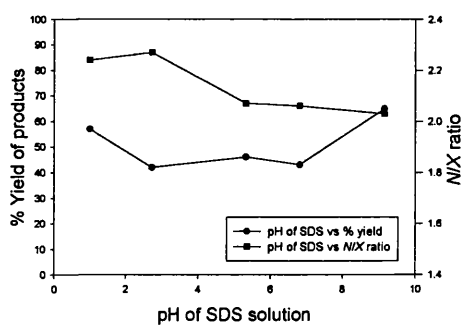
The low yield of products and N/X ratio at pH 1 could be attributed to the breakdown of nonyl acrylate micellar aggregates in the presence of high H^+ ion concentration.

3.3.7.2 CTAB and SDS at different pH solutions

The pH experiments were repeated with CTAB and SDS solutions at their respective *cmcs* with the pH adjusted again with 1M hydrochloric acid and 2M sodium hydroxide. The results are described below (graphs 3.14 and 3.15)



Graph 3.14: pH of CTAB solution against % yield and N/X ratio



Graph 3.15: pH of SDS solution against % yield and N/X ratio

When CTAB is dissolved in de-ionised water the resulting pH is 6.7. Overall, it was notable that with SDS and CTAB solutions there were similar trends with a high *N/X* ratio at pH 1 and 9 but the percentage yield decreased with increasing pH.

For both surfactant solutions, at low pH, the heteroatom of the acrylate can be protonated thus increasing the polarity of the head group and stabilising the micelles it forms in the aqueous solution or mixed micellar aggregates (as shown in figure 3.5). Counter-ion effects can also be used to rationalise the changes in yield and *N/X* ratio. The CTAB micelle has a bromide counter-ion in the Gouy-Chapman layer, which can be replaced by the hydroxide ion at pH 9 and/or the formation of sodium salt from the addition of sodium cation to bromide present in solution. Salts can have extreme effects on micelles in solution by lowering the *cmc* and increasing the hydrophobic effect of the organic molecules dissolved in solution. As mentioned earlier, increasing the hydrophobic effect increases the rate of reaction, accounting for the increased yield at pH 9 with CTAB solution. The higher *endo/exo* selectivities at low pH could also be explained by the formation of mixed micelles where steric crowding favours the more compact *endo* TS.

One notable result is the *N/X* ratio of 2.1, with SDS solution at pH 9. These results could be due to the orientation of the cyclopentadiene molecule in the micelle. Nonyl acrylate can form micelles with surfactant molecules to generate *mixed micelles*,^{130, 131} thereby, 'self' catalysing the reaction with its own micelles.

The high *N/X* ratio in the SDS solution could be attributed to the increased formation of the *endo* product or conversely the decreased formation of the *exo* product. The cyclopentadiene molecule, being hydrophobic, will preferably locate itself within the interior of the micelle (see section 2.5) and at pH 9 could be deprotonated to generate a stable, aromatic cyclopentadienyl anion. This charge will be directed towards the charged Stern Layer. . .

This orientation can be achieved by adopting the *endo* TS in the micelle, with the nonyl acrylate then adopting the relative position within the micelle as shown in figure 3.5, and the cyclopentadiene moiety directed towards the Stern layer, a preference for the *endo* TS may exist.

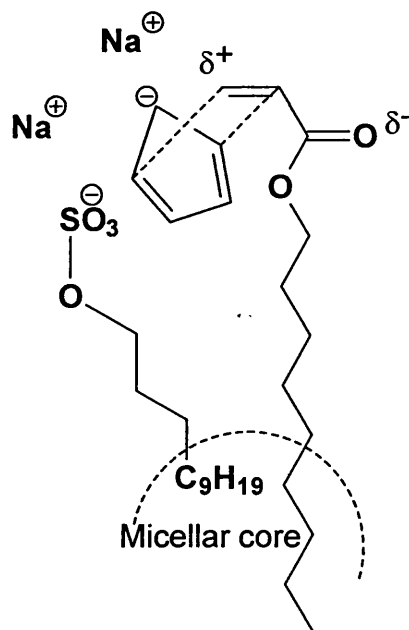


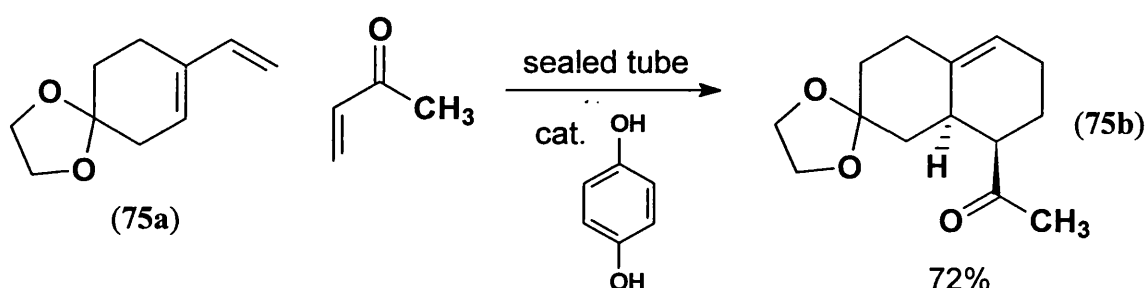
Figure 3.5: Proposed orientation of the cyclopentadiene molecule in a mixed SDS and nonyl acrylate micelle

Overall we have synthesised Diels-Alder cycloadducts from nonyl acrylate and cyclopentadiene using water alone or surfactant/micelle solutions to compare with organic solvents. It is worthwhile to reiterate that aqueous/micelle mediated Diels-Alder reactions afforded better yields and *endo/exo* selectivities compared with organically mediated reactions. In addition, highly concentrated substrates in aqueous solutions did not hinder the reaction but increased the *endo/exo* ratio of the cycloadducts isolated. Addition of acid or base to the aqueous solvents has given us an insight into other important parameters such as the pre-orientation of molecules within the micellar core.

4 Hydroquinones in Organic Reactions

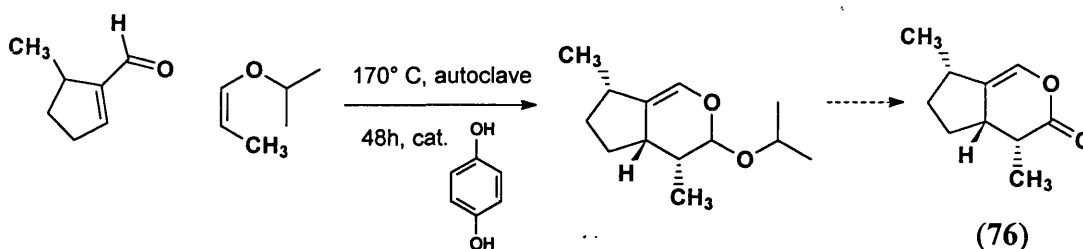
4.1 Introduction

Hydroquinone is not known to undergo a classical $4\pi+2\pi$ cycloaddition. However, it has been used as a catalyst; for example, Vig's synthesis of *dl-trans*- ϵ -cadinene (**75b**) describes hydroquinone as a catalyst in the Diels-Alder reaction between methyl vinyl ketone and diene **75a** (scheme 4.1).¹³²



Scheme 4.1: Vig's synthesis of *dl-trans*- ϵ -cadinene

Korte's synthesis of *dl*-isoiridomyrmecin (**76**) is another example of using hydroquinone as a catalyst (scheme 4.2).¹³³



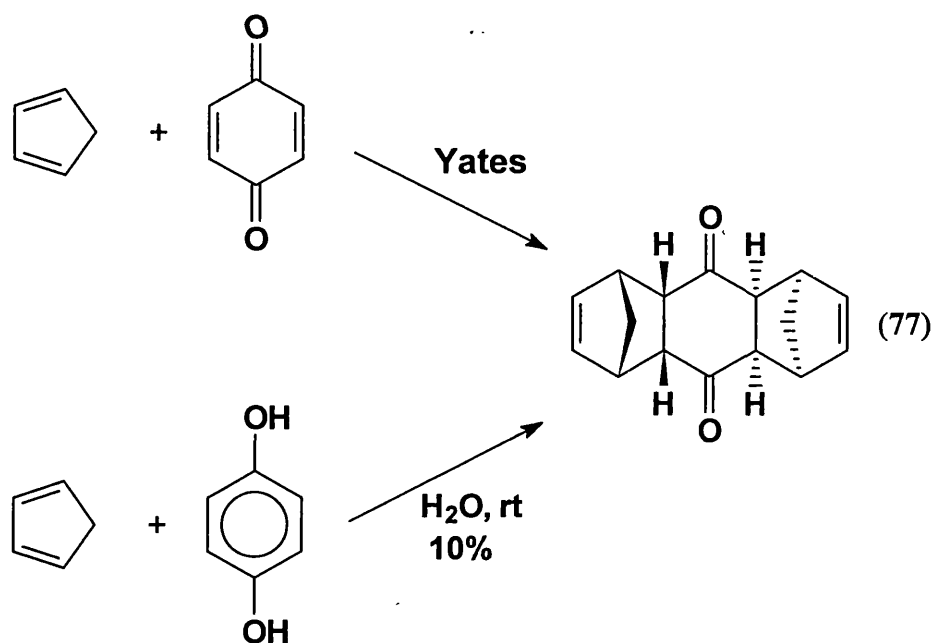
Scheme 4.2: Korte's synthesis of *dl*-isoiridomyrmecin

When hydroquinone was present only in catalytic amounts, it could be reasoned that it stabilised the polar transition state of the Diels-Alder reaction, in a similar fashion to Liotta's mechanism of the aggregation of ethylene glycol molecules around substrates.⁴⁵ Hydroquinone has two polar hydroxy sites and an electron rich π ring system, which can hydrogen bond and ' π -stack' respectively with the substrates, forming a pseudo aggregate stabilising the transition state.

The use of hydroquinone has been described in many processes but is oxidised to the corresponding quinone using either added oxidants or electrochemical routes.¹³⁴ For example, Putter reported the transformation of hydroquinone to benzoquinone using peroxide enzymes, which resulted in a mixture of quinones and quinhydrone products.^{135, 136}

4.2 Hydroquinone in Diels-Alder Reactions

Whilst investigating the reaction of benzoquinone systems with dienes (which will be described below) a chance observation was made whereby in water based media, if hydroquinone was present, a bis-cycloadduct was isolated in a 2-10% yield. This was later identified as *endo-anti-endo*-1,4,4a,5,8,8a,9a,10a-octahydro-1,4:5,8-dimethanoanthracene-9,10-dione (77) (scheme 4.3) from Yates' work on the 1:1 and 2:1 adducts of cyclopentadiene and *p*-benzoquinone. Yates reported extensive ¹H and ¹³C data, which enabled a straightforward assignment of the structure.¹³⁷



Scheme 4.3: Hydroquinone reacts with cyclopentadiene in water

As mentioned above, hydroquinone has been converted '*in situ*' to the corresponding benzoquinone in reactions with oxidising agents, for example, silver carbonate.¹³⁶ However, there was no obvious oxidising source and we sought to find

out what it was. To this end, hydroquinone was reacted with cyclopentadiene in various aqueous solvents, water and surfactant solutions and an organic solvent, diethyl ether, for comparative purposes (table 4.1). We reasoned that if hydroquinone is being oxidised then some oxidant must be present in water but not in an organic media, since when the reaction was repeated in diethyl ether no product was detected.

Solvent/20 hour reaction time	% yield (isolated)
Diethyl ether	0
Ethyl acetate at 50 °C	0
De-ionised Water	10
4.86M lithium chloride sol. (72 hours)	11
Surfactant Solutions (CTAB and 85)	5
Buffered water at pH 7.01	11-14

Table 4.1: Conditions to determine hydroquinone oxidant

The use of further organic solvents did not lead to any cycloadduct formation even at 50 °C. Aqueous media gave consistent yields of around 10% after a 20 hours reaction. The addition of lithium chloride, a salting-out agent solution, gave a slightly higher yield of 11%. It was noted that the use of the surfactant solutions, CTAB and (2*S*)-*N*-hexadecyl-(1-hydroxy-3-phenylpropyl)-*N,N*-dimethyl-2-ammonium bromide (**85**) (figure 4.1) depressed the yield to 5% from 10% and a supposition was made that the hydroquinone requires an aqueous environment around it for the oxidation to occur.

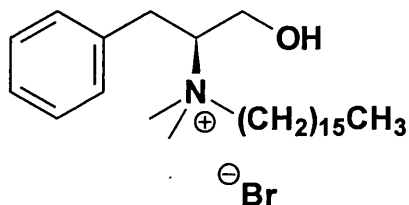
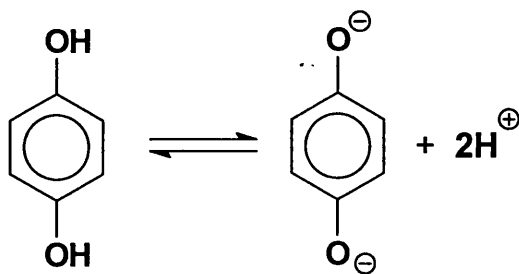


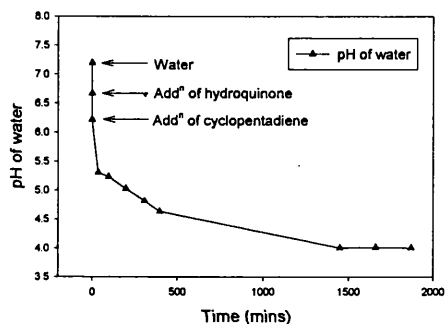
Figure 4.1: (2*S*)-*N*-Hexadecyl-(1-hydroxy-3-phenylpropyl)-*N,N*-dimethyl-2-ammonium bromide (**85**)

Hydroquinone is soluble in water by the dissociation of hydrogen ions to form diphenoxyl anions and renders the solution mildly acidic (scheme 4.4).⁸³

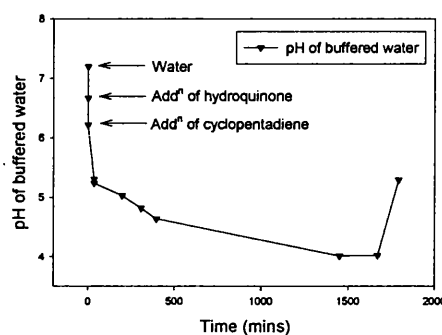


Scheme 4.4: Dissociation of hydroquinone in water

The pH profile of the Diels-Alder reaction between cyclopentadiene and hydroquinone was monitored over 24 hours (graphs 4.1 and 4.2).



Graph 4.1:
pH profile of the Diels-Alder reaction between hydroquinone and cyclopentadiene in water



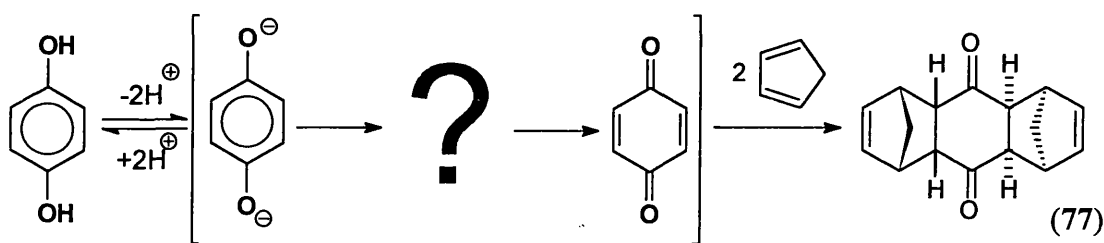
Graph 4.2:
pH profile of the Diels-Alder reaction between hydroquinone and cyclopentadiene in buffered water

The pH of de-ionised water is approximately 7.0, and after the addition of hydroquinone the pH drops to 6.7 as the hydroquinone dissociates into the phenoxy anions and H^+ ions then upon the addition of cyclopentadiene the pH decreased further to 6.2. The reaction was quenched and the product extracted after 31 hour, when the pH had stabilised at 4.0. The reaction was repeated in a phosphate buffer solution at pH 7.01 and again the reaction's pH was monitored (graph 4.2).

The reaction was observed to proceed further in the buffered solution, giving a yield of 14% compared to 10% in water alone. After 29 hours the pH had increased to 5.3.

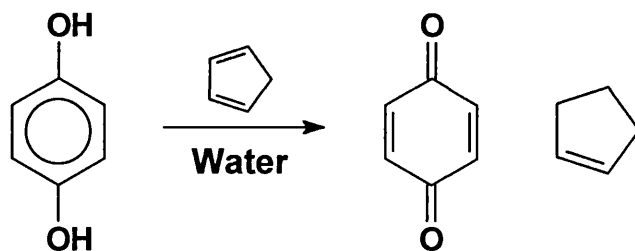
The reaction did not go to completion. Long reaction times involving cyclopentadiene are often complicated since the cyclopentadiene in solution will dimerise over time. Increasing the concentration of cyclopentadiene at the start of the reaction was found to depress the yield. This may be due to an increase in the 'organic' environment present as observed with the surfactant media.

The decrease in the reaction pH suggests that the hydroquinone may have dissociated more readily into the phenoxy dianion in the presence of cyclopentadiene and that the formation of the di-substituted cycloadduct will slowly push the reaction equilibrium towards the dissociation of more hydroquinone molecules into H^+ and phenoxy ions (scheme 4.5).



Scheme 4.5: Proposed route for the oxidation of hydroquinone in water

Other reaction conditions were also employed to investigate the source of the oxidant present in water. Oxygen that is dissolved in the water was considered first. Oxygen, a para magnetic molecule, is a well-known oxidant that can elicit the oxidation of hydroquinone *via* a radical route. Therefore we excluded oxygen in the reaction by degassing the water with nitrogen gas prior to use and maintaining the reaction under nitrogen. Degassing, freezing and thawing the ice under nitrogen was also attempted to ensure oxygen was excluded in the system. Light was also excluded in the reaction by doing the reaction in a 'blacked out' flask, however, in both cases product was isolated in similar yields to the reaction under normal conditions (light and oxygen present). A premise was made that the cyclopentadiene itself was the oxidising agent, oxidising the hydroquinone to benzoquinone, itself being reduced to cyclopentene (scheme 4.6). However no cyclopentene was detected.

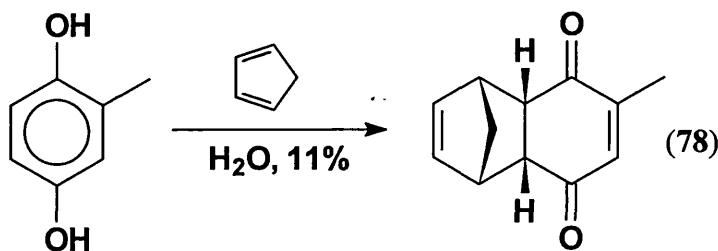


Scheme 4.6: Cyclopentadiene oxidising hydroquinone to benzoquinone?

Further subsequent work within the group has indicated that the reaction proceeds much more readily in water (10% yield) than deuterated water (2-3% yield), illustrating the importance of the hydrogen bonding in the process, due to a detectable kinetic isotope effect.¹³⁸ Also, when trace amounts of EDTA were added, no product was detected. This suggests that trace amounts of a metal ion, for example Fe^{3+} , are present either in the de-ionised water or from washing up and contact with, for example, spatulas. Future work will confirm this result.

4.3 Diels-Alder Reactions with Hydroquinone Derivatives

We wished to investigate whether the observed reaction with hydroquinone was applicable to other derivatives of hydroquinone. To this end, we initially explored the reaction with methyl hydroquinone (scheme 4.7).

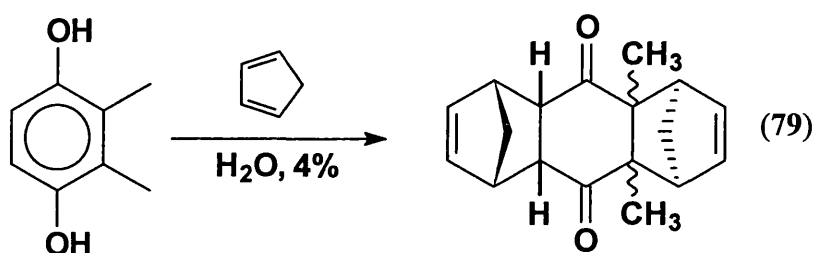


Scheme 4.7: Methylhydroquinone and cyclopentadiene reaction in water

This afforded a mono-substituted cycloadduct (78) in 11% yield as shown in scheme 4.7. The formation of the mono-substituted product exclusively over the di-substituted product could be attributed to the methyl group creating hindrance for attack of the cyclopentadiene to the second side of the benzoquinone. Spectral

analysis and comparison to Yates' data in the literature indicated it to be, not surprisingly, the *endo* isomer.¹³⁷

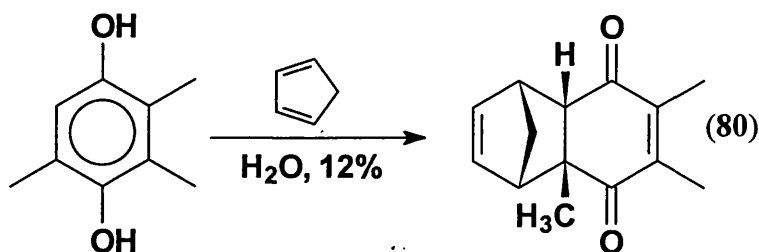
When 2, 3-dimethylhydroquinone was used as the substrate (scheme 4.8) no mono-substituted product was formed but instead the di-substituted cycloadduct (**79**) was isolated in 4% yield. This result was unexpected since it was envisaged that, with two methyl groups present, the mono-substituted adduct would be preferred due to the steric hindrance from the methyl groups.



Scheme 4.8: 2, 3-Dimethylhydroquinone and cyclopentadiene reaction in water

This material has not been reported in the literature previously, however, a comparison of the spectral data of the cycloadduct suggests the *endo-anti-endo* stereochemistry.¹³⁷

When using 2, 3, 5-trimethylhydroquinone and cyclopentadiene, the mono-substituted cycloadduct (**80**) was isolated in a 12% yield. A comparison of the spectral data with the methyl hydroquinone cycloadduct suggested it was the *endo* isomer with the cyclopentadiene attached to the less hindered side (scheme 4.9).



Scheme 4.9: 2, 3, 5-Trimethylhydroquinone and cyclopentadiene reaction in water

The assignment of this product was not surprising since the cyclopentadiene will attack the less hindered side of the hydroquinone derivative but does not go far to explain why the cyclopentadiene attacked both sides of the 2, 3-dimethylhydroquinone.

4.4 Benzoquinone in Diels-Alder Reactions

Benzoquinone derivatives were used as dienophiles in Diels-Alder reactions for several reasons. Firstly, to confirm the nature of some of the products formed above. Secondly, with our reactions in surfactant media, we were exploring systems that would react well under micellar conditions, but poorly in organic media or water alone. This would then enable us to assess the impact of the presence of a surfactant more accurately, in particular a chiral surfactant, where a competing water reaction would not 'dilute' the enantioselectivities observed.

Whilst initial work only was carried out, it highlighted potential systems for future investigations.

4.4.1 Cyclopentadiene and 2, 6-dimethylbenzoquinone

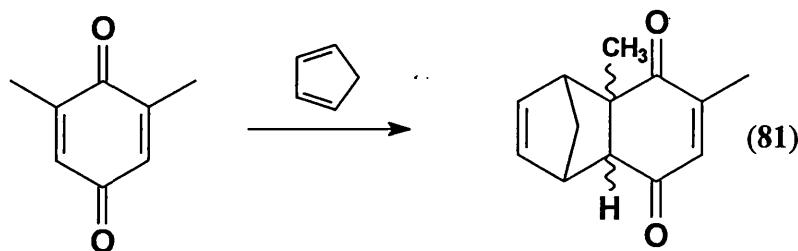


Figure 4.10: Diels-Alder reaction between cyclopentadiene and 2, 6-dimethylbenzoquinone

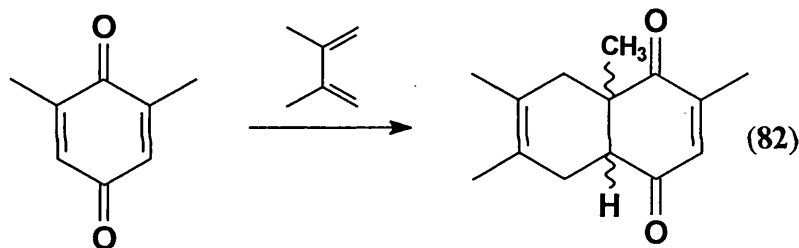
When using 2, 6-dimethylbenzoquinone and cyclopentadiene, (scheme 4.10) the mono-substituted cycloadduct (**81**) was isolated in a 51, 78 and 34% yield when using diethyl ether, de-ionised water and phenylalanine-derived (**85**) surfactant solution (at its *cmc*) respectively (see table 4.2). These results compared favourably to Singh's results.⁶⁴ A comparison of the spectral data with the other cycloadducts

reported by Yates could not confirm the product to be *endo* or *exo*, although the formation of the *endo* product is more likely.

Solvent	% yield of product
Diethyl ether	51
Water, deionized	78
Phenylalanine-derived (85) surfactant solution (0.02mM)	34

Table 4.2

4.4.2 2, 3-Dimethyl-1, 3-butadiene and 2, 6-dimethyl benzoquinone



Scheme 4.11: Diels-Alder reaction between isoprene and 2, 6-dimethylbenzoquinone

Due to the ability of cyclopentadiene to dimerise when in solution, we sought to investigate the effects of longer reaction times on the reaction illustrated in scheme 4.11. Preliminary results suggest that the Diels-Alder reaction between isoprene (which is stable and does not dimerise in solution) and 2, 6-dimethylbenzoquinone afforded the mono-substituted cycloadduct (**82**) in surfactant media only. For example, we observed that in organic media and water no cycloadduct was formed, but in surfactant a 5% yield of the product was isolated.

This aspect of our project is worthy of further investigation as time constraint compelled us to broaden our investigations to other compounds.

5 Surfactant Synthesis and Characterisation using Dyes

5.1 Introduction

One of the key aspects of the project was to test the feasibility of using chiral surfactants and whether chiral induction can be achieved. As a starting point we decided to synthesise surfactants utilising low cost materials using reported standard synthetic procedures for immediate access to our materials.

Generally, two types of chiral surfactants could be envisaged; those with the chirality positioned at the head group or with it further down the alkyl chain. The former was selected as a starting point since the acrylates, our test substrates, are more likely to be positioned around at the Stern layer of the micelles, with their alkyl chains directed into the core.⁶²

Amino acids were selected as the starting materials for the synthesis of cationic surfactants. This would provide the surfactants with an available hydroxy group for hydrogen bonding purposes (figure 5.1).

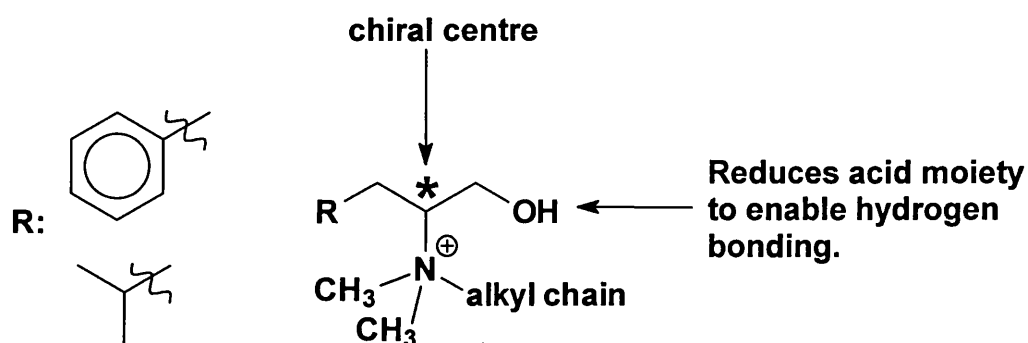
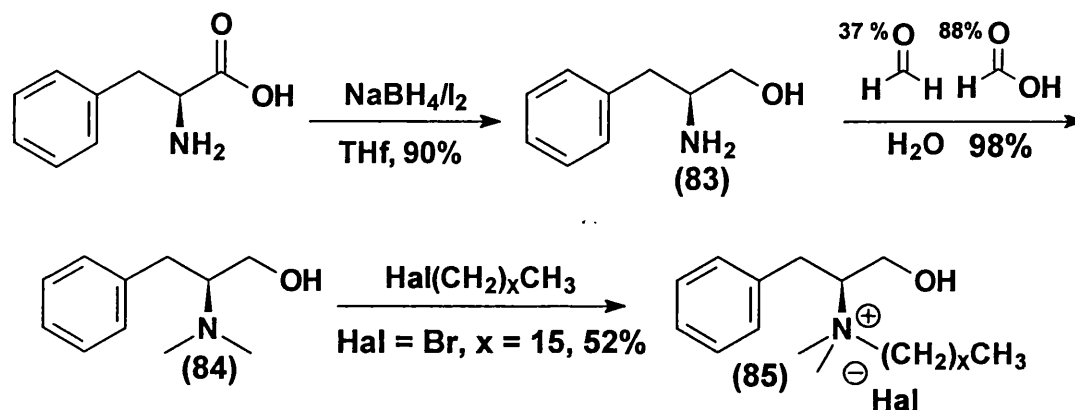


Figure 5.1: R = Phenyl or $(CH_3)_2CH$; alkyl chain = 16 carbons.

By synthesising a couple of surfactant analogues, we hope to formulate some ideas on the effect of different groups on the chiral induction achieved.

5.2 Synthesis of Phenylalanine (85) and Leucine (89) Derived Surfactants

Initially the phenylalanine-derived surfactant was selected due to the presence of the bulky aromatic ring and the synthesis is outlined in scheme 5.1.



Scheme 5.1: Synthesis of a chiral surfactant derived from phenylalanine with a bromide counter-ion

This methodology was first attempted with the racemic *RS*-phenylalanine and when satisfied with the procedure, chiral (*S*)-phenylalanine was used. (*S*)-Phenylalanine was reduced with sodium borohydride and iodine to afford the alcohol, (*S*)-phenylalaninol (83) in excellent yield (90%) using the Meyer's procedure outlined in scheme 5.1.¹³⁹ Methylation of the amine was carried out using the Eschweiler-Clarke reaction with 37% formaldehyde, 88% formic acid and the product (*S*)-*N,N*-dimethylphenylalaninol (84) was isolated in 98% yield.¹⁴⁰ Formation of the salt and introduction of the long alkyl chain was achieved by the reaction of (*S*)-*N,N*-dimethylphenylalaninol with a long chain alkyl bromide, 1-bromohexadecane under anhydrous conditions. The quaternary ammonium salt (85) with the bromide counter-ion formed readily and was recrystallised to give an isolated yield of 52% (scheme 5.2). The spectral analysis of (85) confirmed the identity of the material, however it was notable that the FAB mass spectrum gave a peak at $2\text{M}^+ - \text{Br}$. This suggested that the salt might exist as a dimer containing a bromine bridge (figure 5.2).

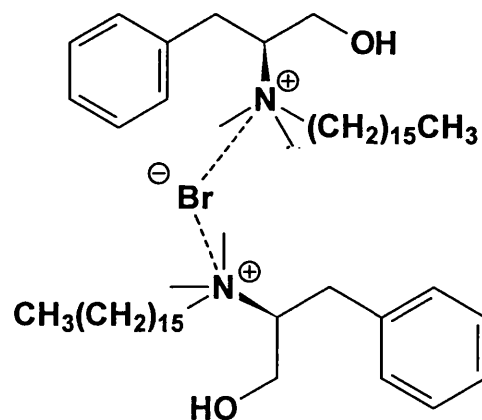
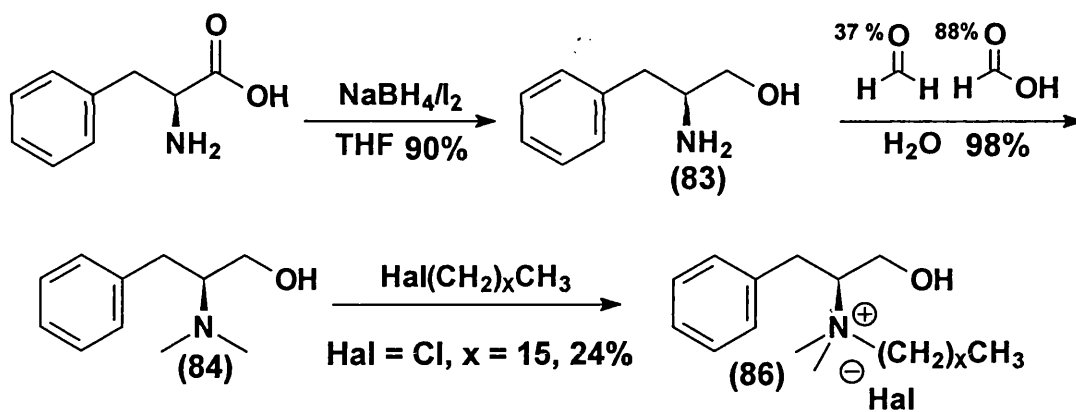


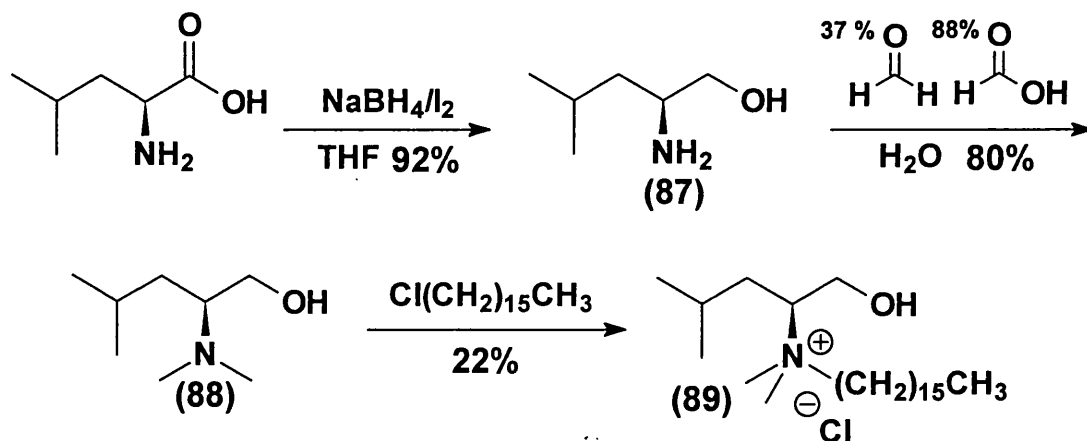
Figure 5.2: Surfactant 'dimer' with a bromine bridge

The chloride counter-ion derived surfactant (**86**) was also synthesised using 1-chlorohexadecane and (*S*)-*N*, *N*-dimethylphenylalaninol (**84**) to the desired material in 24% yield (scheme 5.2). The yield is most likely lower than the formation of (**85**) because of the chloride being a poor leaving group compared to the bromide.



Scheme 5.2: Synthesis of a chiral surfactant derived from phenylalanine with a chloride counter-ion

Having established the viability of the synthetic route, different amino acids were utilised and accordingly the (*S*)-leucine-derived (**89**) surfactant was prepared as shown in scheme 5.3.



Scheme 5.3: Synthesis of a chiral surfactant derived from leucine.

Using the same method as for phenylalanine, (*S*)-leucine was reduced to yield the alcohol (87) in 92% yield. Dimethylation of the amine with formic acid and formaldehyde was again straightforward and high yielding giving 80% of the required product (88). Finally the coupling of the long alkyl chain was achieved with 1-chlorohexadecane to yield 22% of the isolated salt (89) after recrystallisation. The chloroalkane was used in preference to the bromo derivative because by this stage we had established that the molecular dynamic calculations required for modelling of the micellar structure can only account for chloro and not the bromo counter-ion.

Both salts were purified rigorously with multiple re-crystallisation using ethyl acetate and hexane and their purity scrutinised with the use of NMR spectroscopy and melting points. As soon as there was no change ($< \pm 0.5$ °C) in melting point and the NMR spectra confirmed the purity of the product, the salts were dried in a freeze drier at 0.1mm Hg (20 °C) to ensure that the surfactant salts contained minimal organic solvent impurities.

Leucine and phenylalanine were selected as they are structurally similar differing only in one side group, phenylalanine having an aromatic phenyl ring and leucine having a (CH₃)₂CH group. Prior to using these in any cycloaddition reaction, an approximate *cmc* of the surfactants had to be determined (see section 2.2), to ensure that we used them within the concentration range where micelles are present.

5.3 Determination of the Critical Micelle Concentration of Chiral Surfactants

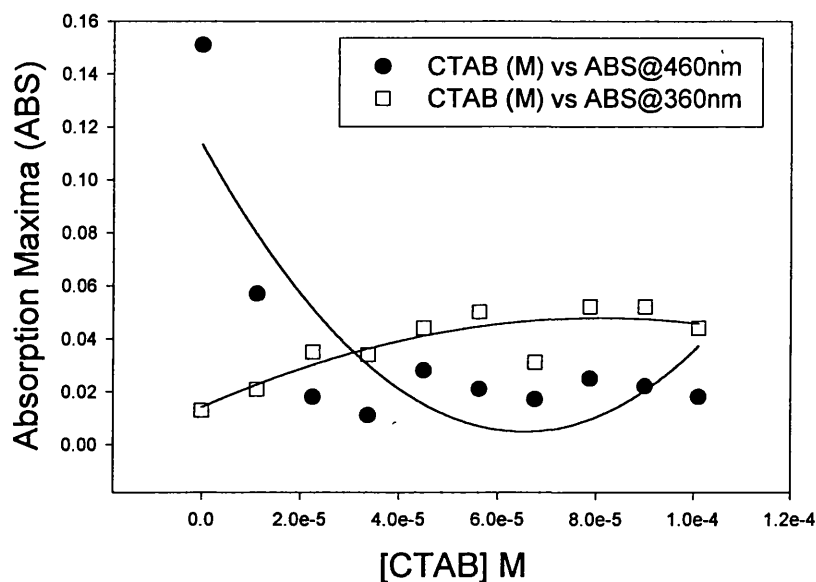
There are many methods currently available to determine the *cmc* of surfactants, which include surface tension^{95, 96, 141} and NMR spectroscopy.¹⁰² However, in the early stages of the project, we did not have access to surface tension apparatus and wished to explore the use of a method that would include the presence of another chemical compound such as a dye.¹⁰⁸ This would then tend to mimic the reaction media when reacting species (such as an acrylate and cyclopentadiene) are present as well as the micelles. Dye methods have been used to determine the *cmc* of surfactants since the 1950s.^{85, 93} This method was ideal since it required only a small quantity of surfactant and an ultraviolet (UV) spectrometer.

From McBain's work which indicated that surfactants' physico-chemical properties depended on their concentration, initially the effects of CTAB on the dye methyl orange were measured.⁸⁶ Therefore, the UV spectra were monitored for ten solutions of CTAB with increasing concentration in the presence of methyl orange (5 mg/100 ml of water), as shown below in table 5.1.

CTAB Solution (ml)	Methyl Orange (ml)	Water (ml)	[CTAB] M
0	1	9	0.00E+00
1	1	8	1.12E-05
2	1	7	2.25E-05
3	1	6	3.37E-05
4	1	5	4.50E-05
5	1	4	5.62E-05
6	1	3	6.75E-05
7	1	2	7.87E-05
8	1	1	9.00E-05
9	1	0	1.01E-04

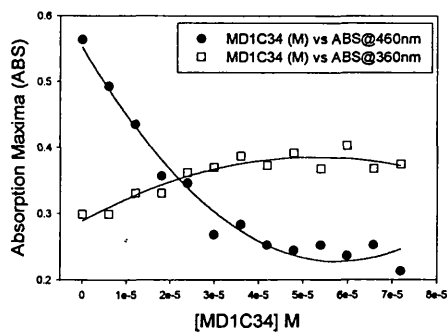
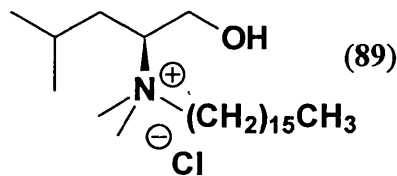
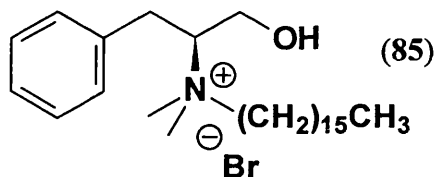
 Table 5.1: Methyl orange solution of determine *cmc*

A visual examination of the solution indicated a colour change from orange to yellow as the surfactant concentration increased. The change in the absorption maxima at 360 and 460 nm were monitored¹⁰⁸ and compared to the increase in surfactant concentration (see graph 5.1).

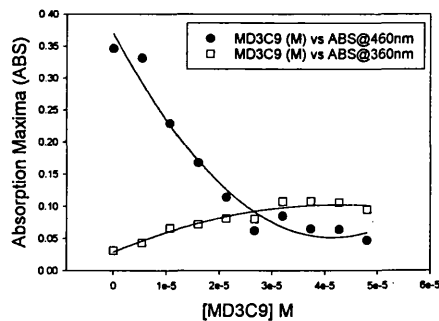


Graph 5.1: The *cmc* of CTAB with methyl orange
 Range: 3.2E-5 – 7.0E-5 M (12 – 26 mg/L)

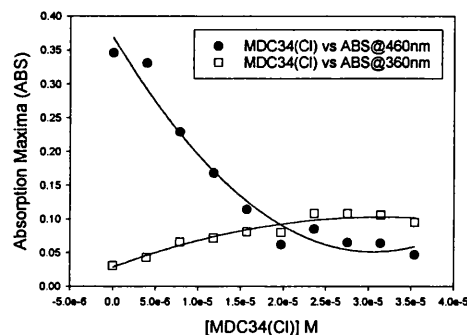
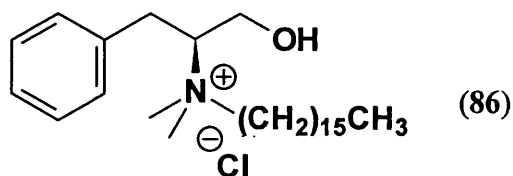
From the graph, the approximate *cmc* of CTAB in the presence of methyl orange was taken to be at the cross over point between the line of best fit for the decrease of absorption maxima at 460 nm and the increase in absorption maxima at 360 nm. A previous report noting the blue shift that we observed in methyl oranges' visible spectrum at different concentrations was attributed to "the change in chromophore microenvironment",^{108, 143} characteristic of the methyl orange's interactions with CTAB aggregates.^{130, 131} Whilst the range observed (12 – 26 mg/L) is lower than the *cmc* of CTAB alone, the *cmc* is known to vary depending on the presence of other compounds and we felt that this method gave us a suitable *cmc* 'starting point' for mixed micellar systems. In addition, conductivity measurements carried out within the group using novel surfactants indicated a correlation with the *cmc* determined by the dye method.¹⁴⁴ This method was repeated to determine the *cmc* of the synthetic surfactants derived from phenylalanine (**85** and **86**) and leucine (**89**). The *cmc* of the surfactant was given as a range because the critical concentration is a dynamic value and not a constant. It can be varied with temperature and even water hardness (due to dissolved salts and impurities). The range, especially the upper most value was used to ensure micelles are present in solution and not just surfactant monomers in the reaction media.



Graph 5.2:
Phenylalanine-derived bromide counter-ion
(**85**) surfactant *cmc* range:
2.3E-5 – 5.5E-5 M (11 – 27 mg/L)



Graph 5.3:
Leucine-derived chloride counter-ion
(**89**) surfactant *cmc* range:
2.8E-5 – 4.0E-5 M (11 – 16 mg/L)



Graph 5.4:
Phenylalanine-derived (86) chloride counter-ion surfactant *cmc* range:
2.0E-5 – 3.0E-5 M (9 - 13 mg/L)

Two different phenylalanine-derived surfactants were synthesised containing different counter-ions, the chloride and bromide as mentioned above. The *cmc* of these surfactants were found to be different using the same dye method. This difference can be attributed to the difference in size of the counter-ions.^{146, 151} Counter-ions can stabilise micelles by ‘neutralising’ the overall charges on the Stern layer, by passing around and through the micelle surface in the Gouy-Chapman layer. In the case of the bromide ions, more surfactant molecules are required to form a micelle to accommodate the larger counter-ion. In addition, the electron cloud around the bromide ions may require a ‘larger space’ to exist in the micelles Gouy-Chapman layer to effectively reduce the interactions between the ions of similar charges.

Surfactant	<i>cmc</i> (M)	<i>cmc</i> (mg/L)
(85)	2.3E-5 – 5.5E-5	11 – 27
(86)	2.0E-5 – 3.0E-5	9 – 13
(89)	2.8E-5 – 4.0E-5	11 – 16
CTAB	3.2E-5 – 7.0E-5	12 – 26

Table 5.2: Summary of the *cmc*'s of synthetic surfactant (85), (86), (89) and CTAB.

As mentioned above, the ultraviolet spectrum of the methyl orange in water has an absorption peak at 460 nm, but when surfactants are present there is a decrease in the absorption maxima observed at 460 nm while at the same time an increase at 360 nm. It is possible that the blue shift is due to the methyl orange molecules becoming embedded in the micellar type aggregates as shown below in figure 5.3.

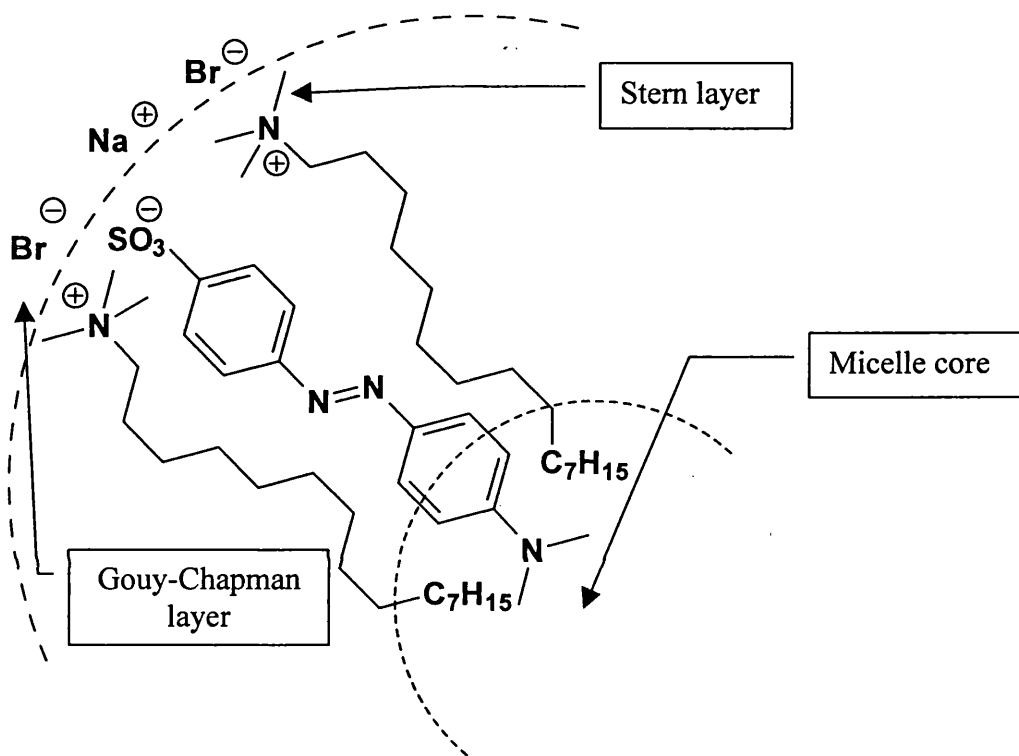


Figure 5.3: Diagrammatic representation of a methyl orange molecule embedded in a CTAB aggregates.

Methyl orange can behave as an amphiphile because it possesses a hydrophobic, hydrocarbon region, which is covalently linked to a hydrophilic, polar head group (figure 5.4)

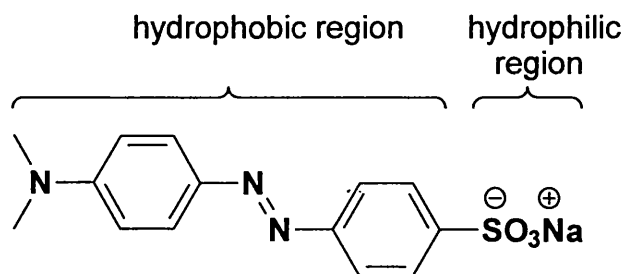


Figure 5.4: Methyl orange can behave as an amphiphile

A reduction in the absorption maxima is indicative of a decrease in the delocalisation of charge in the molecule and this would be expected with the aromatic 'tail' in a hydrophobic 'uncharged' medium. When the methyl orange molecule is embedded in the micelle there is likely to be a reduction in the extent of the delocalisation across the molecule, *i.e.* a blue shift in the UV spectrum, compared to the UV of the methyl orange when it is 'free' in solution.

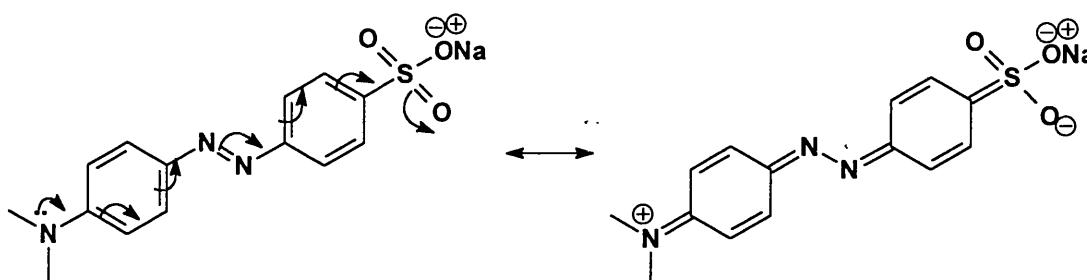


Figure 5.5: Delocalisation of electrons across the methyl orange when 'free' in aqueous solution giving rise absorbance@460 nm

The terminal nitrogen is in a very non-polar environment in the micelles' hydrocarbon core and cannot be stabilised when it has a formal positive charge. Therefore, the degree of delocalisation is decreased resulting in the observed blue shift in the UV-vis spectrum of methyl orange.^{108, 143}

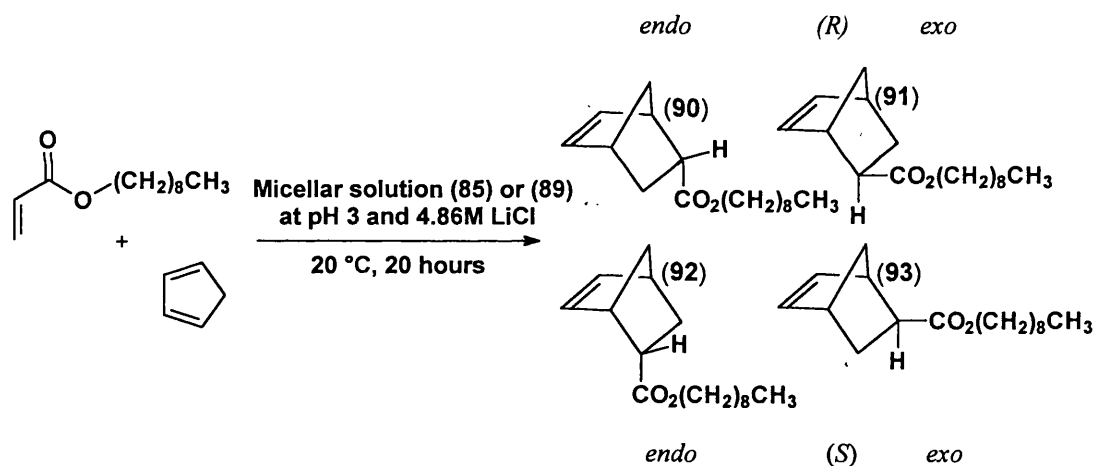
5.4 Summary

Overall, we synthesised two chiral surfactants derived from α -amino acids and determined an approximate *cmc* as a starting point using methyl orange. Further studies on the determination of *cmc* via surface tension experiments are discussed and described in chapter 7 and in the experimental, part II.

6 Diels-Alder Reactions in 'Chiral' Aqueous Media

6.1 Diels-Alder Reaction between nonyl acrylate and cyclopentadiene in surfactant solutions derived from (S)-phenylalanine (85) and (S)-leucine (89)

Nonyl acrylate was selected for our studies when using chiral micellar solutions as reaction media, since the pre-orientation effects exerted by the micelle are likely to be greater than with shorter chained acrylate. Our initial experiments indicated that their cycloadducts with cyclopentadiene were stable under HPLC conditions and we therefore planned to monitor any enantioselectivity observed using chiral HPLC.



Scheme 6.1: Four possible enantiomers from a Diels-Alder reaction between nonyl acrylate and cyclopentadiene

The racemic cycloadducts of the Diels-Alder reactions between nonyl acrylate and cyclopentadiene were separated out into the *endo* and *exo* isomers (scheme 6.1). These isomers were then analysed by chiral HPLC to determine the retention times of each enantiomeric pair and confirm any *N/X* selectivities.

Having established how to monitor for any enantioselectivities by looking for enhancements in either the *endo* or *exo* peaks, experiments were carried out using the chiral surfactants prepared as described in chapter 5.

Initially we explored a number of different reaction conditions with the phenylalanine-derived (**85**) surfactant including a variation in pH (1-9), the addition of 'salting out' agents, the addition of other additives (*e.g.*, sodium chloride and copper nitrate) and different reaction times. Notably, copper salts have been reported to accelerate rates in certain Diels-Alder reactions.¹⁵⁴ Individually, these additives did not induce any notable enantioselectivities although at pH 3 and with lithium chloride present, an *e.e.* in the *exo* adduct of between 5-10% was noted. This is not surprising since our earlier work highlighted good *N/X* selectivity at a pH of 3. Also the addition of the 'salting out' agent (see section 1.6.2.2) lithium chloride will increase the *hydrophobic effect* of the organic molecules in the aqueous medium.²⁶ This will 'force' the acrylate/cyclopentadiene substrates to be solubilised in the micelles present rather than in solution, therefore reducing the likelihood of the cycloaddition reaction occurring in the bulk aqueous media. When these conditions were then used in combination with the phenylalanine-derived (**85**) surfactant, the cycloadducts were analysed by chiral HPLC (0.1% IPA/hexane). It was found that again, the *endo* isomers did not have any enantiomeric excess (*e.e.*) but that the *exo* isomer had an *e.e.* of 16-18%. When these conditions were used with the leucine-derived (**89**) surfactant, at pH 3, it gave an *e.e.* of 13% only in the *endo* isomer (with negligible *e.e.* in the *exo* isomer). The leucine-derived (**89**) surfactant, at pH 3 with 4.86 M lithium chloride, a 15% *e.e.* was monitored. With the leucine-derived (**89**) surfactant alone at half the *cmc* (from the dye experiment), a 7% *e.e.* was noted, at the *cmc*, a 10% *e.e.* and at twice the *cmc*, a 12% *e.e.* was observed, all in the *endo* isomer. Increased surfactant concentration beyond this had no effect. The Diels-Alder reactions were repeated to ensure the *e.e.* values were reproducible for both phenylalanine and leucine surfactants and in addition were verified by repeating the reaction without surfactant but only water and the *e.e.* for the *endo* and *exo* isomers were less than or around 1%.

6.2 Determination of the Enantiomeric Excess (e.e.) of the Diels-Alder Reaction between nonyl acrylate and cyclopentadiene

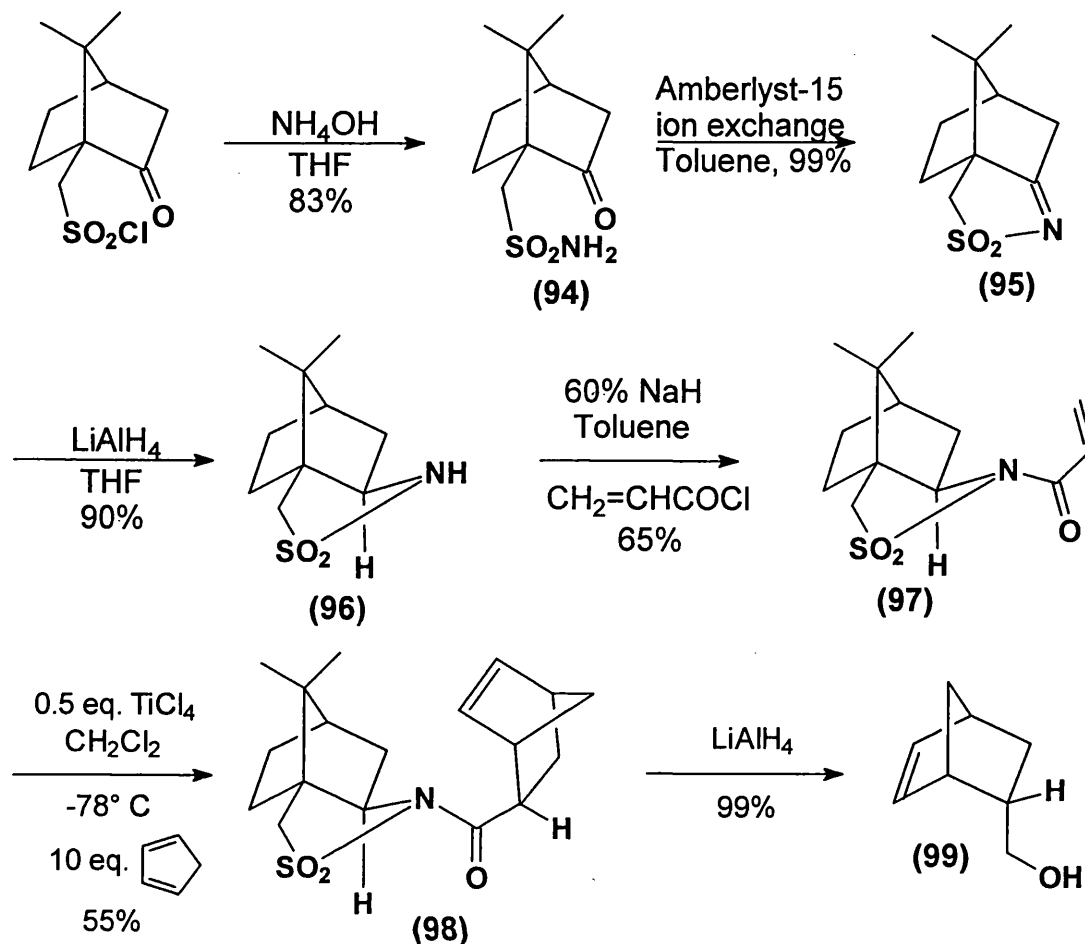
6.2.1 Endo isomers

The synthesis of enantiomerically pure Diels-Alder adducts were required to determine the cycloadduct generated preferentially in the Diels-Alder reaction between nonyl acrylate and cyclopentadiene in the presence of the leucine-derived (**89**) surfactant described above.

The camphor sultam route devised by Oppolzer was selected.¹⁴⁷⁻¹⁴⁹ Using this methodology, one enantiomerically pure camphorsultam auxiliary, the *R* or the *S*, when coupled to an acrylate moiety will only generate the *R-endo* or the *S-endo* enantiomer, respectively.

Accordingly, (*S*)-camphorsulfonyl chloride (scheme 6.2) was reacted with ammonia solution in tetrahydrofuran (THF) to yield 83% of the desired amide (**94**) as colourless crystals. This material was used without further purification and the NMR showed little impurities due to starting materials. This was then heated in a Dean-Stark apparatus overnight in the presence of an ion exchange resin, Amberlyst-15, to give the imine (**95**), and again this was used without further purification. The imine was reduced with lithium aluminium hydride to give the secondary amine (**96**) in a 90% yield. The acryloyl moiety was coupled to the nitrogen centre using sodium hydride and acryloyl chloride (which was prepared *in situ* as described in chapter 3) and the desired product (**97**) was isolated, as an oil, in good yield (65%) having been purified by flash column chromatography (*n*-hexane/ethyl acetate, 4:1).

The (*R*)-enantiomer was also synthesised using the same method, starting with the (*R*)-camphorsulfonyl chloride, and the required product was isolated in a 74% yield over 4 steps.



Scheme 6.2: Ompolzer's camphorsultam chiral auxiliary

These chiral dienophiles were then reacted with excess cyclopentadiene in the presence of the Lewis acid, titanium (IV) chloride, at -78°C for 20 hours. The cycloadducts (such as **98**) were extracted and purified to give the *R-endo* and *S-endo* enantiomers respectively. The camphor sultam auxiliary was then removed by reduction with lithium aluminium hydride to generate the corresponding alcohol (**99**). We required materials with a strong chromophore for HPLC analysis. Therefore, the alcohols (**99-R** and *S*) were coupled with benzoyl chloride to generate the corresponding benzoyl esters (**100**) (figure 6.1).

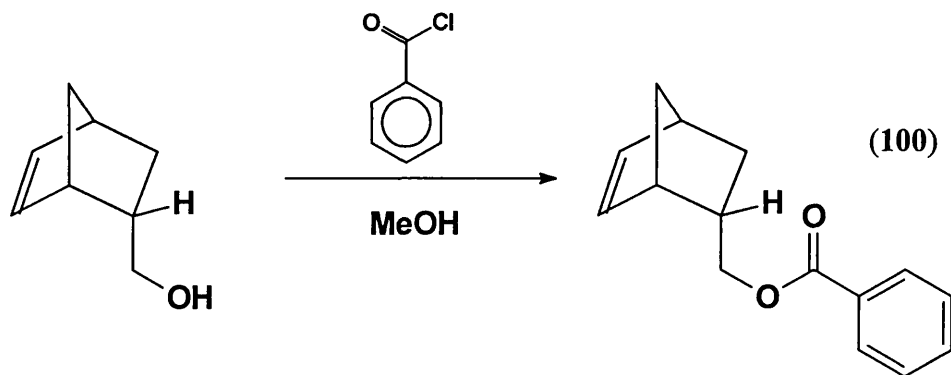
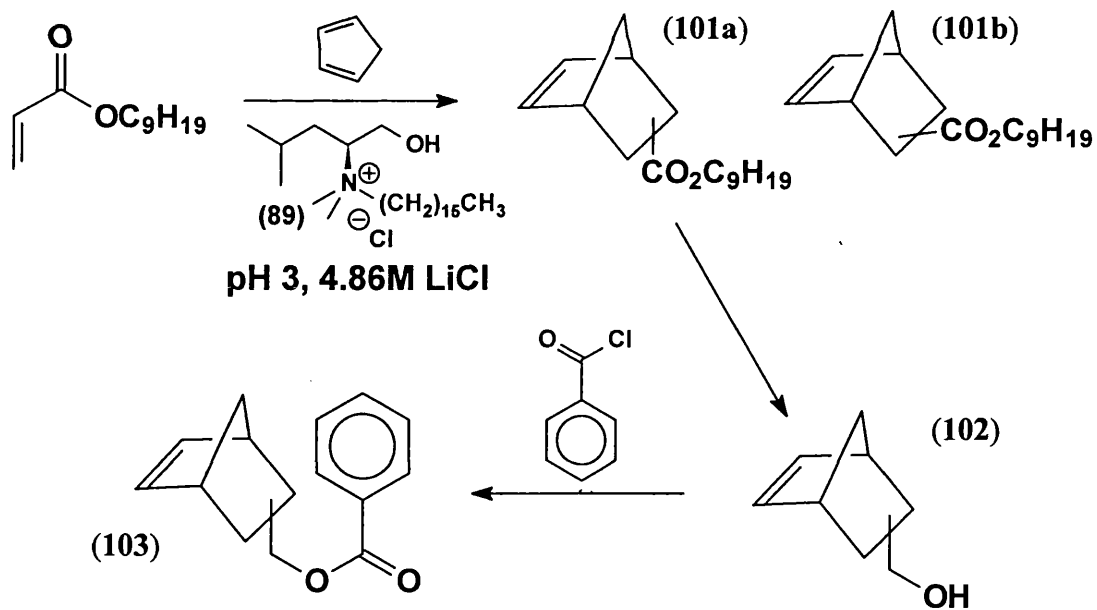


Figure 6.1: Coupling of the benzoyl moiety to aid in the HPLC analysis

The Diels-Alder adducts from the reaction between cyclopentadiene and nonyl acrylate in the presence of the leucine-derived surfactant were separated into their *endo* and *exo* isomers by flash column chromatography (4% Et₂O/hexane). Immediate reduction of (101a) and coupling of the benzoyl moiety using the same method as with (100) completed the synthesis of the surfactant catalysed cycloadducts.



Scheme 6.3: Synthesis, separation and derivatisation of the nonyl acrylate adduct

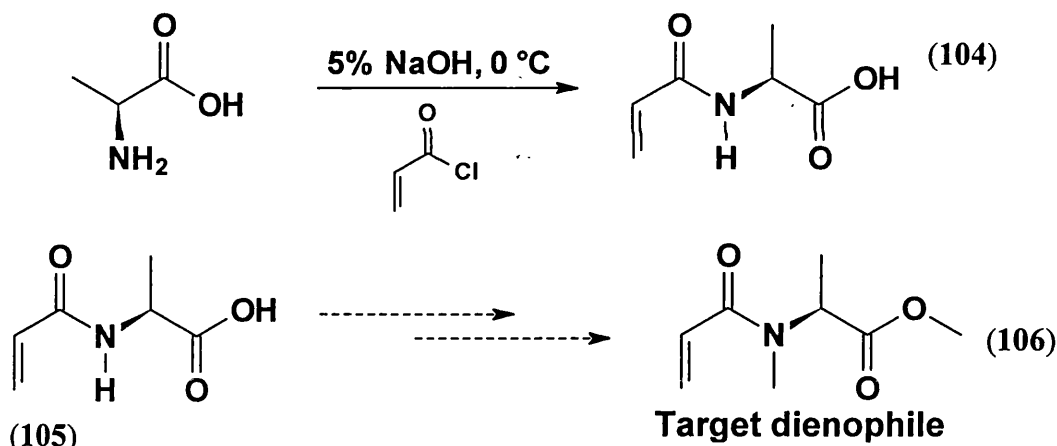
Using 0.5% isopropanol/hexane as eluent and a UV detector at 254nm, the cycloadducts from the titanium (IV) chloride reaction were compared with the cycloadduct isolated from the leucine-derived (89) surfactant catalysed Diels-Alder reaction. The *endo*-(*R*)-enantiomer from the Lewis acid catalysed reaction had a 4.8

minutes retention time and the *endo*-(*S*)-enantiomer had a 7.0 minutes retention time. Comparing the retention time of the cycloadduct isolated from the aqueous media reaction, we observed that the major *endo* isomer at 4.7 minutes retention time was produced in the aqueous chiral micellar media. Therefore the (102) *R* isomer was formed in excess.

The Oppolzer methodology provided us with a straightforward method to determine the enantiomer generated in excess, which was the (102-*R*)-enantiomer.

6.2.2 *Exo* isomers

Correlation of the *exo* adducts proved more difficult. A search revealed only a few methods in the literature.³⁴ One possibility using an amino acid auxiliary was considered.

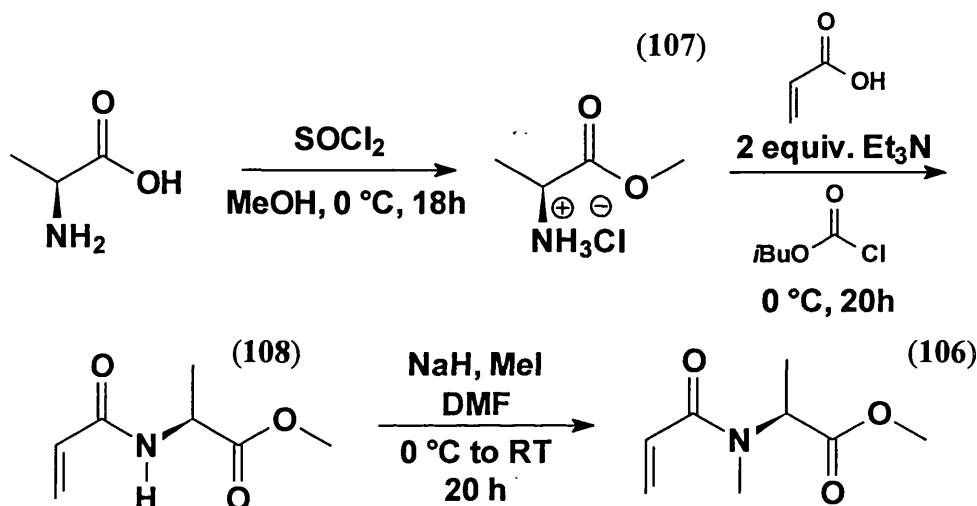


Scheme 6.4: Synthesis of target dienophile derived from (*S*)-alanine

The first step reported in the literature involved the formation of an amide (104) using 5% sodium hydroxide, (*S*)-alanine and acryloyl chloride at 0 °C (scheme 6.4).³⁴ Despite repeating the reaction several times using the conditions reported, no product was formed and therefore a different synthetic route to the target dienophile (106) was applied.

To a solution of (*S*)-alanine in methanol, 2 equivalents of thionyl chloride were added. The (*S*)-alanine methyl ester ammonium chloride (107) product (scheme 6.5) was isolated in quantitative yield (>99%). The second step in the synthesis

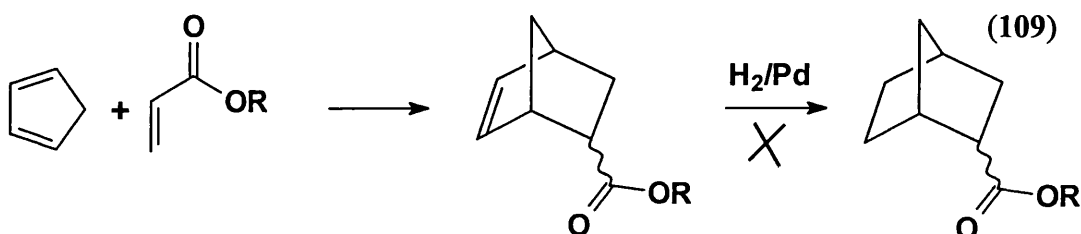
involved attaching an acryloyl moiety to the amide. This was achieved using acrylic acid, *isobutyl* chloroformate and 2 equivalents of triethylamine (**108**). The final step towards the **target dienophile (106)** was achieved by methylating the amide with sodium hydride and methyl iodide in dimethylformamide (23%) but the (**106**) dienophile bearing the chiral auxiliary did not result in any chiral induction using the condition reported.³⁴



Scheme 6.5: Synthesis of a chiral auxiliary derived from alanine

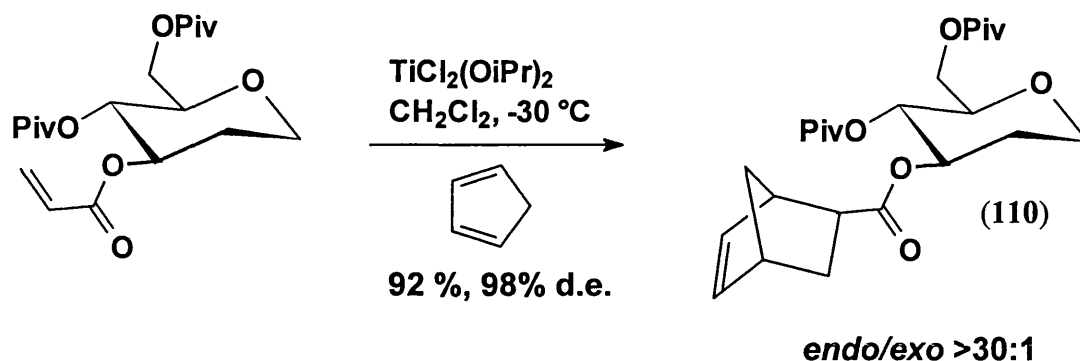
The results at this stage looked bleak and due to the lack of time we were forced to abandon this route. However, it was felt that since not one of the steps reported was reproducible, this was the wisest strategy.

Alternative methods were considered such as the correlation to literature compounds using polarimeter measurements. Accordingly, the *exo* isomer was treated with H₂/Pd to reduce the double bond to prevent the cycloadduct (**109**) from under-going a ‘retro’ Diels-Alder reaction (scheme 6.6).¹²³ Unfortunately, under these conditions the materials degraded and so again this route was abandoned.



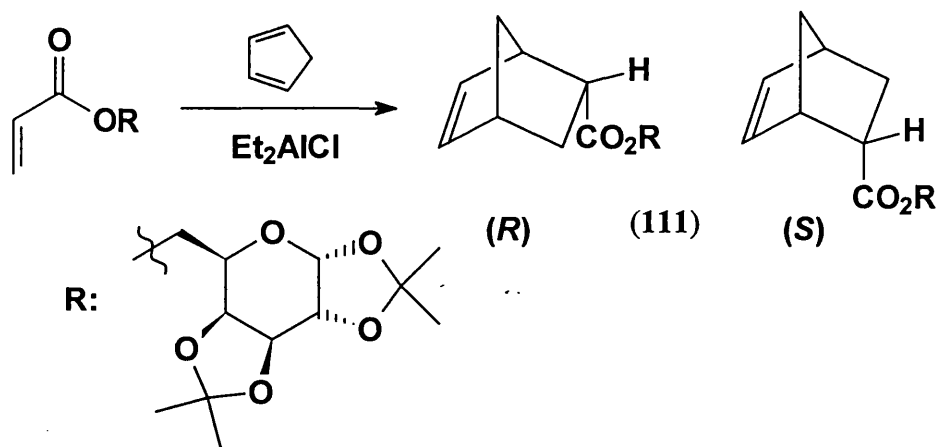
Scheme 6.6: Hydrogenation of the Diels-Alder adducts proved a non-viable route

Despite initial attempts to establish the *R* or *S* nature of the *exo* isomer, we were unsuccessful. Future work should tackle this using one of the other reported routes such as the use of carbohydrates (110) as ‘chiral templates’ (as shown in schemes 6.7 and 6.8).^{150, 151}



Scheme 6.7: Stähle's carbohydrate chiral templates

Ferreira's chiral template can affect the formation of the *R* and *S* enantiomers (111) by virtue of the solvent used as the reaction media (scheme 6.8).¹⁵¹ Toluene gives a >98:2 *endo/exo* ratio with a 7:3 (*R*)/(*S*) ratio, however, when dichloromethane was used, the *endo/exo* ratio remained the same but the (*R*)/(*S*) ratio was reverse to 3:7. Although the *exo* isomers are formed as the minor product, their presence in the reaction can be detected by chiral HPLC. Their retention times could be recorded and then compared with cycloadducts (90-93) isolated from our aqueous chiral induction experiments.



Scheme 6.8: Ferreira's carbohydrate chiral templates

7 Physical Chemistry Studies on Chiral Surfactants

7.1 Proposed Encapsulation and Chiral Induction Mechanism for the Diels-Alder Reaction between nonyl acrylate and cyclopentadiene

By using a combination of 2D NMR and analysing the data generated by surface tension and light scattering experiments, we were able to consider possible explanations for the selective addition of cyclopentadiene to nonyl acrylate in a micelle catalysed aqueous media.

7.1.1 Leucine-derived surfactant/micellar media

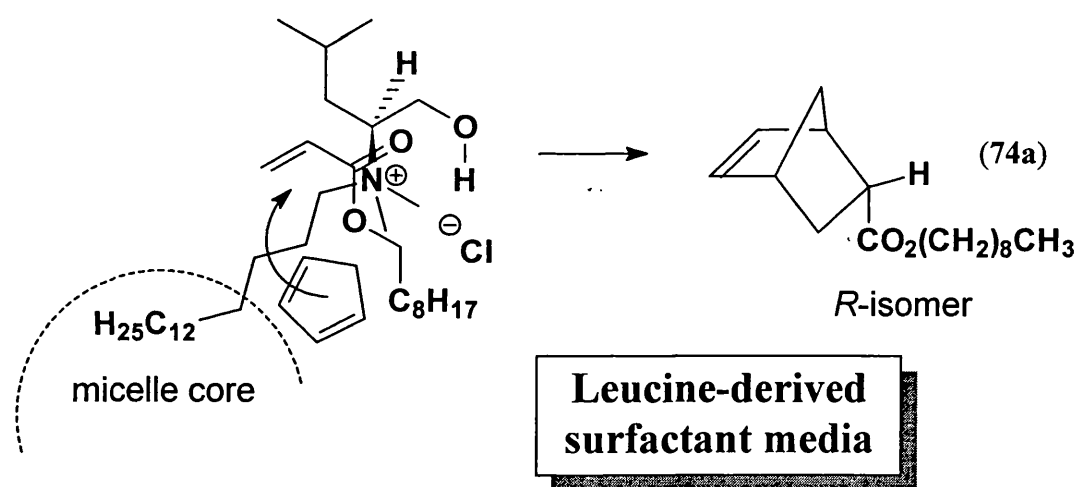


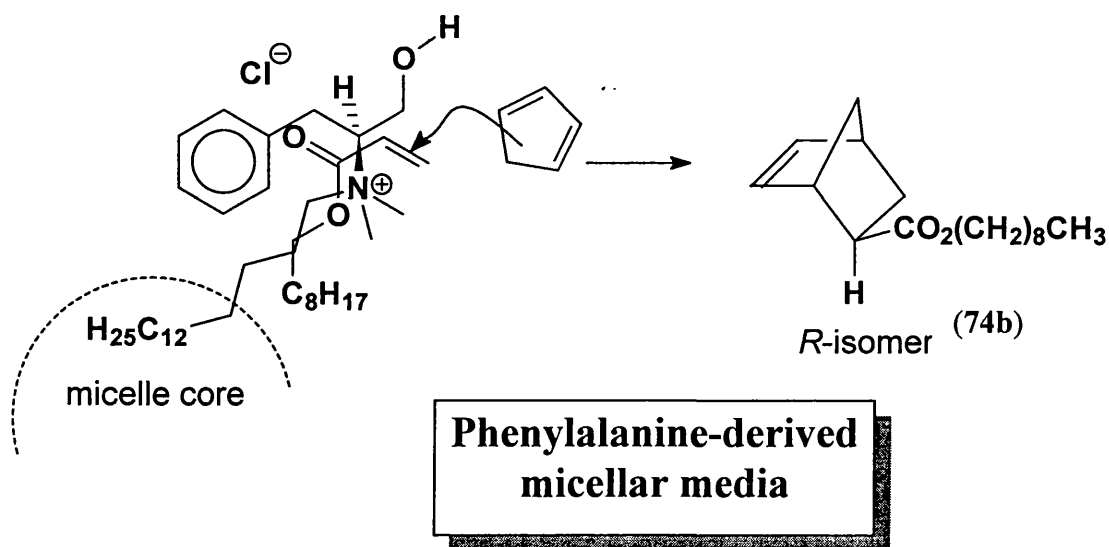
Figure 7.1: *Endo*-(*R*)-cycloadduct

Since surfactants are dynamic in nature, a number of surfactant conformations could be considered and the one shown in figure 7.1 is one such example. In order to formulate a reason for the selectivity of addition of the cyclopentadiene to the acrylate double bond, a simplistic model of the surfactant/substrate will help to visualise the observed preference. From our nOe experiment, it was apparent that the isopropyl

group was not in close proximity to the alkyl chain and therefore a possible conformation of the surfactant in an aqueous solution above its *cmc* features a more hindered top face of the molecule as shown in figure 7.1 with the isopropyl group directed away from micellar core. Nonyl acrylate will be likely to align with the underside of the leucine-derived surfactant (**89**), which results in the cyclopentadiene having to approach from below the acrylate. The carbonyl moieties can complex with the nitrogen and hydrogen bond to the hydroxy group with the double bond beneath the isopropyl group leading to the formation of the *R*-isomer (**74a**) preferentially.

Surface property studies (see experimental, part II) on this surfactant just below the *cmc* indicated that the area occupied by the molecule is 54.6 Å². With water in the micelles, adopting Menger's 'porous' model (see section 2.7), the partially soluble cyclopentadiene molecules will be dispersed in the micelle but not exclusively at the core, giving the *impetus* to attack from below the acrylate double bond (see figure 7.1).

7.1.2 Phenylalanine-derived surfactant/micellar media

Figure 7.2: *Exo-(R)*-cycloadduct

The surface property studies of the phenylalanine-derived (**86**) surfactant (see experimental part II), just below the *cmc* indicated that the molecule occupied an area of 43.6 \AA^2 . This value is lower than the leucine-derived (**89**) surfactant and even by virtue of the larger head group, the phenyl ring should occupy more ‘space’ than the isopropyl group on the leucine. This anomaly could be attributed to the conformation the phenyl ring could adopt in space and indeed, initial investigations into their conformation by nOe experiments suggest that the phenyl ring is in close proximity to the alkyl chain of the surfactant as shown in figure 7.2. This will lead to the conclusion that the overall area the molecule can occupy is lessened by adopting a ‘tighter’ conformation. This tighter conformation by the phenylalanine-derived (**86**) surfactant could lead to, by inference, a less porous micelle. A less porous micelle will have a less ‘aqueous’ but more organic core, solubilising the cyclopentadiene and acrylate to react to give an *exo* cycloadduct (**74b**) (which is preferred in organic media) (see section 3)

The leucine-derived micelle resulted in *e.e* for the *endo* isomer. This could, by inference, be attributed to a more porous micelle, explained by the larger area per molecule (54.6 \AA) and lower aggregation number (19 molecules per micelle) compared to the phenylalanine-derived (**86**) surfactant (43.6 \AA , 23 molecules per

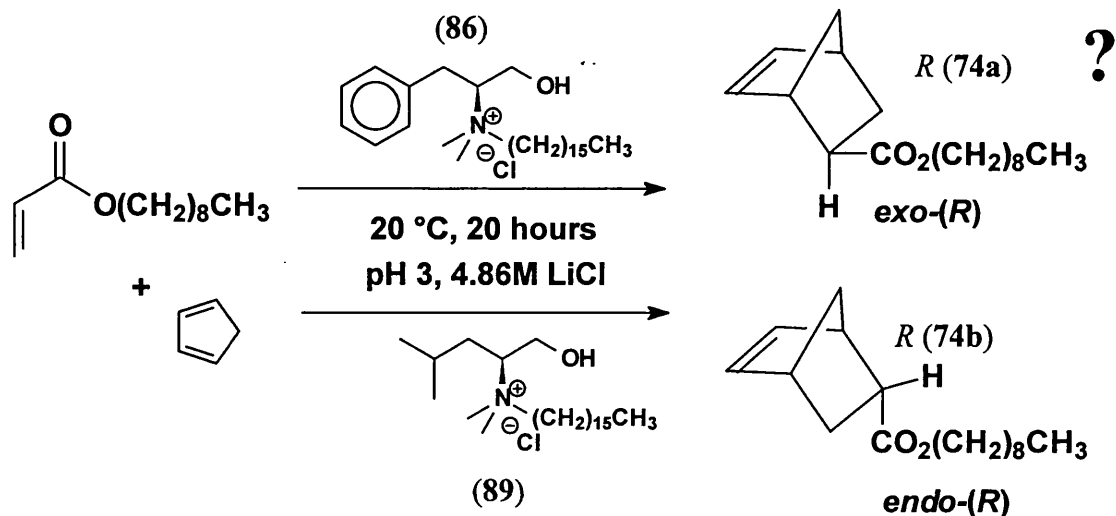
micelle). In summary, the core of the leucine-derived micelle is more 'aqueous-like' compared to the phenylalanine-derived (**86**) micelle due to the conformations adopted. Following the same reasoning, we would predict that the *exo-R*-isomer is the major one formed when using the phenylalanine-derived (**86**) surfactant, as shown in figure 7.2.

7.2 Conclusion

In this thesis, the efficacy of surfactant/micellar solutions as an organic reaction media for selected Diels-Alder substrates has been demonstrated. We have also performed the first Diels-Alder reaction in a chiral aqueous micellar media using cheap, commercially available starting materials.

Acrylate derivatives reacting with cyclopentadiene fared better in terms of yields in aqueous solvents at shorter reaction times. Increased *endo* selectivity and therefore higher *endo/exo* ratios also accompanied the rate of reaction. Both the observed results were attributed to the micelles' ability to encapsulate, orientate and concentrate substrates in the micellar core (see section 2.9).^{55, 97, 152}

We have shown the chiral induction (12-18% *e.e.*) can be achieved using chiral micellar media using micelle forming surfactant which are derived from amino acids (**85**, **86** and **89**) as shown in scheme 7.1.



Scheme 7.1: Chiral induction by micelles formed by chiral surfactants

The reversal in the *endo* and *exo* selectivity was achieved by changing the surfactants head group from phenyl to isopropyl.

Future Work

The *exo*-enantiomer observed from the aqueous Diels-Alder reaction with the phenylalanine-derived surfactants (**85** or **86**) has not been confirmed experimentally even though we have rationalised it is likely to be the *exo*-(*R*)-enantiomer (**74b**) from the NMR experiments and data generated from the surface property studies. This issue has to be addressed in any future work and can be tackled using α -amino acids or carbohydrates as chiral auxiliaries in the presence of Lewis acids as outlined in section 6.2.2.

Finding a Diels-Alder substrate that is compatible with aqueous media and react well with micellar solution but slowly in water will enable the issue of chiral induction by chiral micellar media to be investigated without competing water reaction.

The type of surfactants used can also be further investigated, for example, the structure of the head group. In particular the use of surfactants with available sites for hydrogen bonding, but a rigid or fixed structure. This will reduce the possible number of conformation it can adopt in the micelle.

The effect of counter-ions of the surfactants that can form micellar aggregates, for example, divalent ions like sulfates (SO_4^{2-}), could also be explored. These ions can form bridged aggregates as shown in figure 7.3, which will effectively form 'gemini surfactants' with twin alkyl chains and more complex micelles (figure 7.4).¹⁵⁵

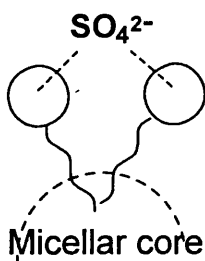


Figure 7.3: 'Gemini' surfactants

The vast number of possible dienophiles that can be selected for the Diels-Alder reaction must be limited to the ones that can investigate the micelle's properties (see section 2.9), so that individually as well as collectively can lead to a better understanding on the effects the micelles have on organic reactions.

8 Experimental Section

General Procedures

All NMR spectra were recorded using a Varian VXR-400 or a Bruker AC 300 (400 MHz or 300 MHz for ^1H and 100.6 MHz for ^{13}C) spectrometer: the solvent was CDCl_3 , unless otherwise stated. In most NMR experiments, residual proton in the deuteriochloroform (δ_{H} 7.25) was used as an internal standard for the chemical shifts. Coupling constants J are given in Hz. Infrared (IR) spectra were recorded in a Perkin Elmer 983 G or FT-IR 1605 spectrometer using KBr disc or a liquid film. The major peaks are reported in cm^{-1} .

Elemental analyses were performed by the Chemistry Department (University College) microanalytical department service.

Mass spectra were obtained using EI (electron impact) ionisation on a VG 7070 at University College and FAB (fast atomic bombardment) ionisation and 'accurate mass' MS were performed by Mike Cocksedge School of Pharmacy, University of London service.

Melting points was determined using a Büchi Model 510 melting point apparatus and are uncorrected.

Optical rotations were measured using an AA Series Polaar 2000 automatic polarimetry instrument using a quartz 1 dm pathlength cell.

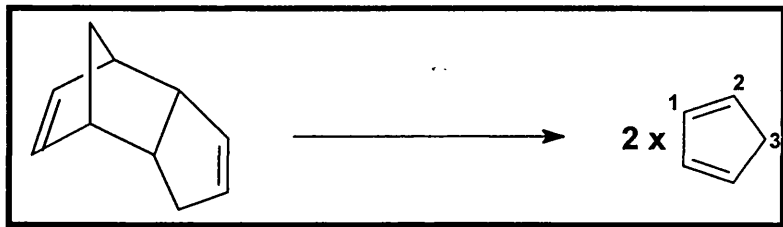
All solvents and reagents were used as received or purified by standard methods. All reactions performed under anhydrous conditions were under an atmosphere of nitrogen by means of a balloon or a gas line. All glassware was oven-dried prior to use.

All 'aqueous' reactions were performed in de-ionised water. HPLC grade water was used in all chiral induction experiments.

Reaction progress was monitored by thin layer chromatography, which was performed on Merck Kieselgel 60 F₂₅₄ glass-backed pre-coated plates, visualised by

UV (254nm). They were developed using iodine or an anisaldehyde stain which was prepared from anisaldehyde (8.0 cm³), conc. sulphuric acid (8.0 cm³) in absolute ethanol (250 cm³), or a potassium permanganate stain which was prepared from potassium permanganate (3.0 g), potassium carbonate (20.0 g), a 5% sodium hydroxide (5.0 ml) in water (300 ml), or a vanillin stain which was prepared from vanillin (15.0 g), conc. sulphuric acid (2.5 ml) in absolute ethanol (250 ml). Flash column chromatography was performed using BDH Silica gel (particle size 40-63 μm).

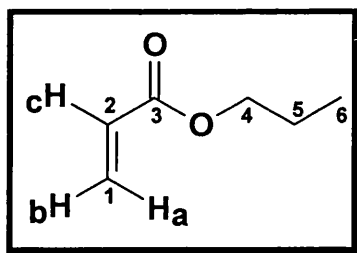
Enantiomeric excesses were determined by chiral phase HPLC using a Gilson Model M303 with a 25cm x 5cm Chiralcel columns using a UV detector at 226nm coupled to a Hewlett Packard Integrator model HP3396A.

Part I: Synthetic Methods**Cyclopentadiene (114)**

Dicyclopentadiene (50.0 g, 0.41 mol) was ‘cracked’ at 190 °C until the cyclopentadiene readily distilled over at 38-41 °C and was collected over an ice bath (42.8 g, 86%). It was used within 2 days of preparation.

δ_{H} (400 MHz; CDCl_3) 6.62 (2H, m, 1-H), 6.51 (2H, m, 2-H), 3.02 (2H, br s, 3-H).

δ_{C} (400 MHz; CDCl_3) 130.28 (C-2), 128.71 (C-1), 36.65 (C-3).

Propyl acrylate (115)

Thionyl chloride (4.49 ml, 61.9 mmol) was added dropwise to a stirred solution of acrylic acid (4.24 ml, 61.9 mmol) and vigorous stirring was continued for 1 h at RT. A solution of propan-1-ol (4.10 g, 68.1 mmol) in dichloromethane (25 ml) was added, followed by a solution of 4-dimethylaminopyridine (0.76 g, 6.20 mmol) in dichloromethane (10 ml). The mixture was heated at reflux overnight. The reaction mixture then was washed with saturated sodium hydrogen carbonate (2 x 50 ml) and

the product was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were dried over magnesium sulfate and the solvent removed *in vacuo* to give propyl acrylate as brown oil.

Note: Thin layer chromatography (tlc) analysis (hexane) indicated the presence of two products with an R_f of 0.44 and 0.02. The material was dissolved in hexane (20 ml) and filtered through a pad of silica gel to yield a product with R_f 0.44 (3.80 g). This was then heated at reflux for 48 h in dichloromethane (50 ml) with excess triethylamine (3.40 g, 33.30 mmol). The solvent was removed *in vacuo* and the product was purified by flash column chromatography (4% Et₂O/hexane) to give the titled compound propyl acrylate as a brown oil (3.80 g, 38%).

ν_{\max} (film) 2945s, 2867s, 1730s, 1635m, 1461s cm^{-1} .

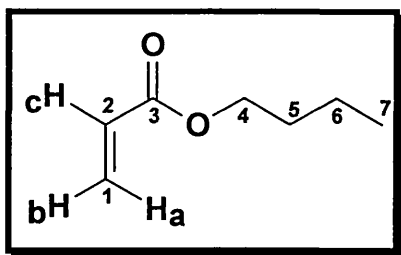
δ_{H} (400 MHz; CDCl₃) 6.41 (1H, d, J 17.4 Hz, H_a), 6.13 (1H, dd, J 17.4 and 10.4 Hz, H_c), 5.81 (1H, d, J 10.4 Hz, H_b), 4.11 (2H, t, J 6.7 Hz, CH₂O), 1.68 (2H, m, CH₂), 0.94 (3H, t, J 7.4 Hz, CH₃).

δ_{C} (100 MHz; CDCl₃) 165.12 (C-3), 130.31 (C-1), 128.60 (C-2), 69.24 (C-4), 22.80 (C-5), 10.21 (C-6).

m/z (E.I.) 115 (MH⁺, 15%), 100 (M⁺-CH₃, 59), 86 (M⁺-C₂H₅, 13), 60 (C₃H₇OH⁺, 69), 56 (M⁺-C₃H₇O, 100).

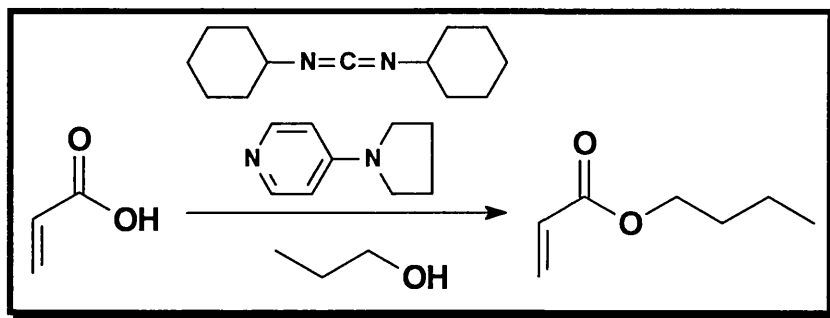
Butyl acrylate (116)

Procedure 1:



Thionyl chloride (4.13 ml, 57.0 mmol) was added dropwise to a stirred solution of acrylic acid (3.91 ml, 57.0 mmol) and vigorous stirring was continued for 1h at RT. A solution of butan-1-ol (4.60 g, 62.7 mmol) in dichloromethane (25 ml) was added, followed by a solution of 4-dimethylaminopyridine (0.64 g, 5.24 mmol) in dichloromethane (10 ml). The mixture was heated at reflux overnight. The reaction mixture was then washed with saturated sodium hydrogen carbonate (2 x 50 ml) and the product was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were dried over magnesium sulfate and the solvent removed *in vacuo* to give a brown oil. The material was dissolved in hexane (20 ml) and filtered through a pad of silica gel to yield one product by tlc. This was then heated at reflux for 48 h in dichloromethane (50 ml) with excess triethylamine (2.68 g, 26.5 mmol). The solvent was removed *in vacuo* and the product was purified by flash column chromatography (4% Et₂O/hexane) to give the titled compound butyl acrylate as a brown oil (3.41 g, 34%).

Procedure 2: (70)



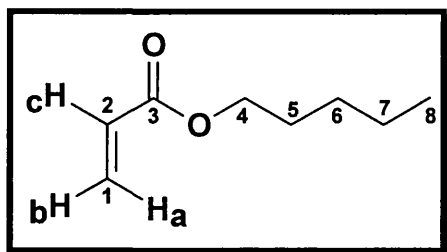
To a solution of acrylic acid (5.00 ml, 72.9 mmol), *N,N*-dicyclohexylcarbodiimide (16.6 g, 80.2 mmol), butan-1-ol (7.34 ml, 80.2 mmol) and 4-pyrrolidinopyridine (1.08 g, 7.30 mmol) in diethyl ether (50 ml) was added and the mixture stirred for 20 h at RT. The urea salt was removed by filtration and the filtrate was washed with water (3 x 50 ml), 5% acetic acid (3 x 50 ml) and water again (3 x 50 ml). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to give the desired product, butyl acrylate as a brown oil (11.3 g, 88%). The product was subsequently used without purification.

ν_{\max} (film) 2942s, 2871s, 1730s, 1630m, 1465s cm^{-1} .

δ_{H} (400 MHz; CDCl_3) 6.43 (1H, d, J 17.3 Hz, H_a), 6.10 (1H, dd, J 17.3 and 10.2 Hz, H_c), 5.80 (1H, d, J 10.2 Hz, H_b), 4.12 (2H, t, J 6.7 Hz, CH_2O), 1.73 (2H, m, OCH_2CH_2), 1.63 (2H, m, CH_2CH_3), 0.88 (3H, t, J 7.4 Hz, CH_3).

δ_{C} (100 MHz; CDCl_3) 165.01 (C-3), 130.21 (C-1), 128.50 (C-2), 66.52 (C-4), 32.12 (C-5), 19.01 (C-6), 13.52 (C-7).

m/z (E.I.) 128 (MH^+ , 10%), 115 ($\text{MH}^+ - \text{CH}_3$, 43), 100 ($\text{M}^+ - \text{C}_2\text{H}_5$, 4), 73 ($\text{C}_4\text{H}_9\text{O}$, 15), 55 ($\text{M}^+ - \text{C}_4\text{H}_9\text{O}$, 84).

*Pentyl acrylate*¹²³ (65a)

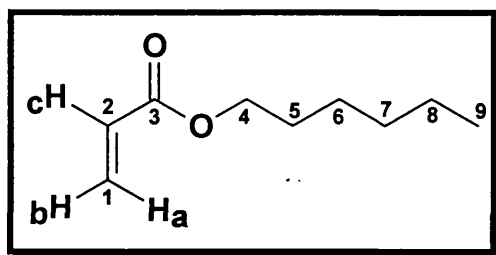
Thionyl chloride (5.00 ml, 69.3 mmol) was added dropwise to a stirred solution of acrylic acid (4.76 ml, 69.3 mmol) and vigorous stirring was continued for 1h at RT. A solution of pentan-1-ol (8.30 ml, 76.3 mmol) in dichloromethane (25 ml) was added, followed by a solution of 4-dimethylaminopyridine (0.77 g, 6.30 mmol) in dichloromethane (10 ml). The mixture was heated at reflux overnight. The reaction mixture was then washed with saturated sodium hydrogen carbonate (2 x 50 ml) and the product was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were dried over magnesium sulfate. The solvent was removed *in vacuo* to give a brown oil. The crude product was dissolved in hexane (20 ml) and filtered through a pad of silica gel to yield one product by tlc. The crude product was heated at reflux for 48 h in dichloromethane (50 ml) with triethylamine (3.54 g, 35.0 mmol). The solvent was removed *in vacuo* and the product was purified by flash column chromatography (4% Et₂O/hexane) to give the titled compound *pentyl acrylate* as a brown oil (4.98 g, 55%).

ν_{\max} (film) 2942s, 1729s, 1461.5m, 1295.9s, 1056s cm⁻¹.

δ_{H} (400 MHz; CDCl₃) 6.40 (1H, d, *J* 17.4 Hz, H_a), 6.12 (1H, dd, *J* 17.4 and 10.3 Hz, H_c), 5.81 (1H, d, *J* 10.3 Hz, H_b), 4.15 (2H, t, *J* 6.7 Hz, CH₂O), 1.67 (2H, m, OCH₂CH₂), 1.35 (4H, m, (CH₂)₂CH₃), 0.90 (3H, t, *J* 6.3 Hz, CH₃).

δ_{C} (100 MHz; CDCl₃) 165.02 (C-3), 130.31 (C-1), 128.60 (C-2), 66.50 (C-4), 29.71 (C-5), 28.61 (C-6), 22.83 (C-7), 14.10 (C-8).

m/z (E.I.) 143 (MH⁺, 23%), 127 (M⁺-CH₃, 20), 114 (MH⁺-C₂H₅, 31), 100 (M⁺-C₃H₇, 58), 87 (C₅H₁₁O⁺, 12), 71 (C₅H₁₁⁺, 13), 55 (M⁺-C₅H₁₂O, 42), 27 (CH₂CH⁺, 100).

*Hexyl acrylate*¹²³ (65b)

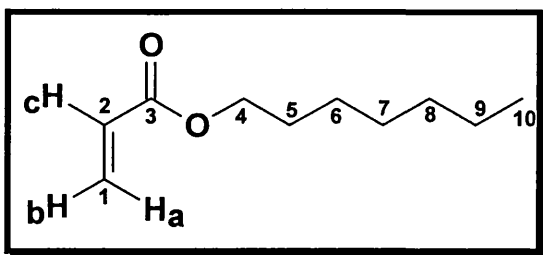
Thionyl chloride (4.64 ml, 64.0 mmol) was added dropwise to a stirred solution of acrylic acid (4.38 ml, 64.0 mmol) and vigorous stirring continued for 1 h at RT. A solution of hexan-1-ol (9.64 ml, 70.4 mmol) in dichloromethane (25 ml) was added, followed by a solution of 4-dimethylaminopyridine (0.75 g, 6.20 mmol) in dichloromethane (10 ml). The mixture was heated at reflux overnight. The reaction mixture was then washed with saturated sodium hydrogen carbonate (2 x 50 ml) and the product was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were dried over magnesium sulfate. The solvent was removed *in vacuo* to give a brown oil. The material was dissolved in hexane (20 ml) and filtered through a pad of silica gel to yield one product by tlc. This was heated for 48 h at reflux in dichloromethane (50 ml), with excess triethylamine (4.50 g, 44.0 mmol). The solvent was removed *in vacuo* and the product was purified by flash column chromatography (4% Et₂O/hexane) to give the titled compound *hexyl acrylate* as a brown oil (7.08 g, 71%).

ν_{\max} (film) 2642s, 1638s, 1280s, 1061s, 901m cm⁻¹.

δ_{H} (400 MHz; CDCl₃) 6.40 (1H, d, *J* 17.4 Hz, H_a), 6.12 (1H, dd, *J* 17.4 and 10.4 Hz, H_c), 5.80 (1H, d, *J* 10.4 Hz, H_b), 4.25 (2H, t, *J* 6.4 Hz, CH₂O), 1.65 (2H, m, OCH₂CH₂), 1.32 (6H, m, (CH₂)₃CH₃), 0.88 (3H, t, *J* 5.7 Hz, CH₃).

δ_{C} (100 MHz; CDCl₃) 165.51 (C-3), 130.50 (C-1), 128.62 (C-2), 66.83 (C-4), 30.11 (C-5), 26.20 (C-6), 32.13 (C-7), 23.12 (C-8), 14.04 (C-9).

m/z (E.I.) 157 (MH⁺, 11%), 141 (M⁺-CH₃, 83), 128 (MH⁺-C₂H₅, 19), 113 (M⁺-C₃H₇, 37), 101 (C₆H₁₃O, 5), 56 (MH⁺-C₆H₁₃O, 1).

*Heptyl acrylate*¹²³ (65c)

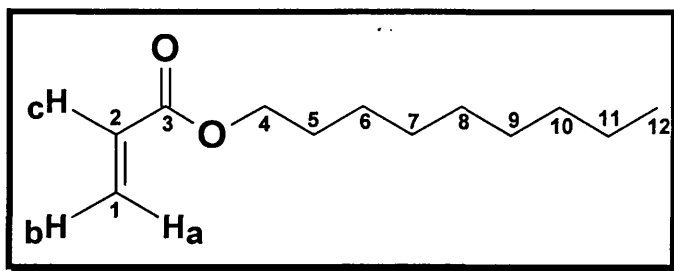
Thionyl chloride (4.28 ml, 59.0 mmol) was added dropwise to a stirred solution of acrylic acid (4.05 ml, 59.0 mmol) and vigorous stirring was continued for 1 h at RT. A solution of heptan-1-ol (7.51 g, 64.6 mmol) in dichloromethane (25 ml) was added, followed by a solution of 4-dimethylaminopyridine (0.66 g, 5.40 mmol) in dichloromethane (10 ml). The mixture was heated at reflux overnight. The reaction mixture was then washed with saturated sodium hydrogen carbonate (2 x 50 ml) and the product was extracted with dichloromethane (2 x 50 ml) and the combined organic extracts were dried over magnesium sulfate. The solvent was removed *in vacuo* to give a brown oil. The material was dissolved in hexane (20 ml) and filtered through a pad of silica gel to yield one product by tlc. This was heated at reflux for 48 h in dichloromethane (50 ml) with excess triethylamine (5.00 g, 49.4 mmol). The solvent was removed *in vacuo* and the product was purified by flash column chromatography (4% Et₂O/hexane) to give the titled compound *heptyl acrylate* as a brown oil (8.00 g, 80%).

ν_{\max} (film) 2932s, 1729s, 1617s, 1269m, 981s cm^{-1} .

δ_{H} (400 MHz; CDCl₃) 6.40 (1H, d, J 17.4 Hz, H_a), 6.13 (1H, dd, J 17.4 and 10.4 Hz, H_c), 5.80 (1H, d, J 10.4 Hz, H_b), 4.12 (2H, t, J 5.1 Hz, CH₂O), 1.73 (2H, m, OCH₂CH₂), 1.35 (8H, m, (CH₂)₄CH₃), 0.88 (3H, t, J 5.5 Hz, CH₃).

δ_{C} (100 MHz; CDCl₃) 165.02 (C-3), 130.22 (C-1), 128.51 (C-2), 66.80 (C-4), 30.11 (C-5), 26.50 (C-6), 29.73 (C-7), 32.50 (C-8), 23.12 (C-9), 14.02 (C-10).

m/z (E.I.) 171 (MH⁺, 12%), 155 (M⁺-CH₃, 11), 142 (MH⁺-C₂H₅, 4), 128 (MH⁺-C₃H₇, 32), 98 (C₇H₁₄, 2), 56 (MH⁺-C₇H₁₅O, 39).

*Nonyl acrylate*¹²³ (65d)

Thionyl chloride (3.63 ml, 50.0 mmol) was added dropwise to a stirred solution of acrylic acid (3.43 ml, 50.0 mmol) and vigorous stirring was continued for 1 h at RT. A solution of nonan-1-ol (7.94 g, 55.0 mmol) in dichloromethane (25 ml) was added, followed by a solution of 4-dimethylaminopyridine (0.56 g, 4.58 mmol) in dichloromethane (10 ml). The mixture was heated at reflux overnight. The reaction mixture was then washed with saturated sodium hydrogen carbonate (2 x 50 ml) and the product was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were dried over magnesium sulfate. The solvent removed *in vacuo* to give a brown oil. The material was dissolved in hexane (20 ml) and filtered through a pad of silica gel to yield one product by tlc. This was heated at reflux for 48 h in dichloromethane (50 ml) with excess triethylamine (3.00 g, 30.0 mmol). The solvent was removed *in vacuo* and the product was purified by flash column chromatography (4% Et₂O/hexane) to give the titled compound *nonyl acrylate* as a brown oil (7.09 g, 71%).

Alternative procedure¹²³

Thionyl chloride (3.63 ml, 50.0 mmol) was added dropwise to a stirred solution of acrylic acid (3.43 ml, 50.0 mmol) and vigorous stirring was continued for 1 h at RT. A solution of nonan-1-ol (7.94 g, 55.0 mmol) in pyridine (50 ml) was added, followed by a solution of 4-dimethylaminopyridine (0.56 g, 4.58 mmol) in dichloromethane (10 ml). The mixture was heated at reflux overnight. The reaction mixture was then washed with saturated sodium hydrogen carbonate (2 x 50 ml) and the product was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were

dried over magnesium sulfate. The solvent removed *in vacuo* to give a brown oil. The material was dissolved in hexane (20 ml) and filtered through a pad of silica gel to yield one product by tlc. The solvent was removed *in vacuo* and the product was purified by flash column chromatography (4% Et₂O/hexane) to give the titled compound *nonyl acrylate* as a brown oil (1.19 g, 12%).

(Found: M^+ 199.1693, C₁₂H₂₂O₂ requires M 199.1698);

ν_{\max} (film) 2932s, 2857s, 1729s, 1638m, 1622s, 1467s cm⁻¹.

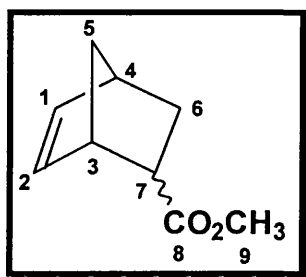
δ_{H} (400 MHz; CDCl₃) 6.41 (1H, d, J 17.4 Hz, H_a), 6.14 (1H, dd, J 17.4 and 10.4 Hz, H_c), 5.84 (1H, d, J 10.4 Hz, H_b), 4.15 (2H, t, J 6.7 Hz, CH₃O), 1.68 (2H, m, CH₂CH₂O), 1.32 (12H, m, (CH₂)₆CH₃), 0.88 (3H, t, J 6.7 Hz, CH₃).

δ_{C} (100 MHz; CDCl₃) 165.01 (C-3), 130.30 (C-1), 128.64 (C-2), 66.82 (C-4), 30.02 (C-5), 26.50 (C-6), 30.03 (C-7), 32.51 (C-8), 30.32 (C-9), 30.05 (C-10), 23.11 (C-11), 14.00 (C-12).

m/z (E.I.) 199 (MH⁺, 99%), 184 (M⁺-CH₃, 16), 170 (MH⁺-C₂H₅, 31), 156 (MH⁺-C₃H₇, 11), 127 (M⁺-C₅H₁₁, 10), 126 (CH₂(CH₂)₈⁺, 59), 85 (M⁺-C₈H₁₇, 4), 73 (MH₂²⁺-C₉H₁₉, 59), 55 (M⁺-C₉H₁₉O, 100), 41 (CH₃CH₂C⁺, 57), 27 (CH₃C⁺, 52).

5-Bicyclo[2.2.1]heptene-2-carboxylic acid methyl ester^{29, 43}

(71a-b)



Organic solvents:

Cyclopentadiene (0.251 g, 3.80 mmol) was added to a stirred solution of methyl acrylate (0.164 g, 1.90 mmol) in *solvent* (25 ml). The mixture was stirred for \underline{x} h at RT. The mixture was washed with distilled water (2 x 50 ml), brine (2 x 50 ml) and then dried over magnesium sulfate. The solvent was removed *in vacuo* to give an *endo/exo* mixture of *5-bicyclo[2.2.1]heptene-2-carboxylic acid methyl ester* as a brown oil. The *endo* and *exo* isomers were separated by flash column chromatography (4% Et₂O/hexane).

Aqueous solutions:

Cyclopentadiene (0.251 g, 3.80 mmol) was added to a stirred solution of methyl acrylate (0.164 g, 1.90 mmol) in *n*-hexadecyltrimethylammonium bromide, CTAB, (25 ml, 1×10^{-3} mol dm⁻³). The mixture was stirred for \underline{x} h at RT. The product was extracted with dichloromethane (2 x 30 ml) and the combined organic extracts were washed with distilled water (2 x 50 ml), brine (2 x 50 ml) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give an *endo/exo* mixture of *5-bicyclo[2.2.1]heptene-2-carboxylic acid methyl ester* as a brown oil. The *endo* and *exo* isomers were separated by flash column chromatography (4% Et₂O/hexane).

(Found: C, 71.3; H, 8.1%; C₉H₁₂O₂ requires: C, 71.0; H, 8.0%);

ν_{\max} (film) 2964s, 2868m, 1739s, and 1435m cm⁻¹;

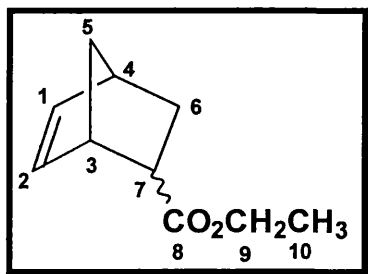
δ_{H} (400 MHz; CDCl_3) **Endo isomer:** 6.11 (1H, m, $\text{HC}=\text{CH}$), 5.85 (1H, m, $\text{HC}=\text{CH}$), 3.55 (3H, s, CH_3), 3.13 (1H, br s, 7-H), 2.89 (2H, m, 3-H, 4-H), 1.31 (2H, m, 5- H_2), 1.20 (2H, d, J 7.9 Hz, 6- H_2); **Exo isomer:** 6.05 (2H, m, $\text{HC}=\text{CH}$), 3.62 (3H, s, CH_3), 2.98 (1H, br s, 7-H), 2.88 (2H, m, 3-H, 4-H), 1.30 (2H, m, 6- H_2), 1.19 (2H, d, J 8.0 Hz, 5- H_2);

δ_{C} (100 MHz; CDCl_3) 176.09 (C-8), 131.70 & 131.68 (C-1, C-2), 50.73 (C-9), 46.04 (C-5), 44.41 & 44.29 (C-3, C-4), 37.58 (C-7), 24.61 (C-6).

m/z (E.I.) 152 (M^+ , 38%), 121 ($\text{M}^+ - \text{OCH}_3$, 2), 93 ($\text{M}^+ - \text{CO}_2\text{CH}_3$, 4), 66 (cyclopentadiene, 100).

5-Bicyclo[2.2.1]heptene-2-carboxylic acid ethyl ester^{29, 43}

(72a-b)



Organic solvents:

Cyclopentadiene (0.251 g, 3.80 mmol) was added to a stirred solution of ethyl acrylate (0.190 g, 1.90 mmol) in *solvent* (25 ml). The mixture was stirred for x h at RT. The mixture was washed with distilled water (2 x 50 ml) and brine (2 x 50 ml) and then dried over magnesium sulfate. The solvent was removed *in vacuo* to give an *endo/exo* mixture of 5-bicyclo[2.2.1]heptene-2-carboxylic acid ethyl ester product as a brown oil. The *endo* and *exo* isomers were separated by flash column chromatography (4% Et₂O/hexane).

Aqueous solutions:

Cyclopentadiene (0.251 g, 3.80 mmol) was added to a stirred solution of ethyl acrylate (0.164 g, 1.90 mmol) in CTAB (25 ml, 1×10^{-3} mol dm⁻³). The mixture was stirred for x h at RT. The product was extracted with dichloromethane (2 x 30 ml), and the combined organic extracts were washed with distilled water (2 x 50 ml) and brine (2 x 50 ml), and dried over magnesium sulfate. The solvent was removed *in vacuo* to give an *endo/exo* mixture of 5-bicyclo[2.2.1]heptene-2-carboxylic acid ethyl ester product. The *endo* and *exo* isomers were separated by flash column chromatography (4% Et₂O/hexane).

(Found: C, 72.0; H, 8.5 C₁₀H₁₄O₂ required C, 72.3; H, 8.5%);

ν_{\max} (film) 2974s, 2867m, 1729s, 1467m cm⁻¹.

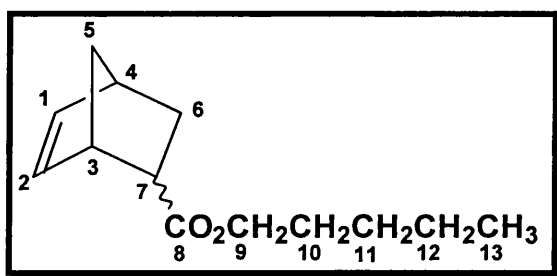
δ_{H} (400 MHz; CDCl₃) **Endo isomer:** 6.15 (1H, m, HC=CH), 5.88 (1H, m, HC=CH), 3.15 (1H, br s, 7-H), 2.85 (2H, m, 3-H, 4-H), 4.02 (2H, q, *J* 6.6 Hz, 9-H₂), 1.37 (2H, m, 5-H₂), 1.28 (2H, d, *J* 7.8 Hz, 6-H₂), 1.21 (3H, m, 10-H₃); **Exo Isomer:** 6.07 (2H, m, HC=CH), 2.98 (1H, br s, 7-H), 2.85 (2H, m, 3-H, 4-H), 4.00 (2H, q, *J* 6.6 Hz, 9-H₂), 1.37 (2H, m, 5-H₂), 1.28 (2H, d, *J* 7.8 Hz, 6-H₂), 1.21 (3H, m, 10-H₃);

δ_{C} (100 MHz; CDCl₃) 176.10 (C-8), 131.69 (C-1, C-2), 59.82 (C-9), 46.07 (C-5), 44.35 & 44.33 (C-3, C-4), 37.88 (C-7), 24.61 (C-6), 13.64 (C-10).

m/z (E.I.) 166.0 (M⁺, 36%), 137 (M⁺-CH₂CH₃, 21), 121 (M⁺-OCH₂CH₃, 1), 93 (M⁺-CO₂CH₂CH₃, 5), 66 (cyclopentadiene, 100).

5-Bicyclo[2.2.1]heptene-2-carboxylic acid pentyl ester^{29, 43}

(73a-b)



Prepared as for 5-bicyclo[2.2.1]heptene-2-carboxylic acid methyl ester using cyclopentadiene (0.27 ml, 3.80 mmol) and pentyl acrylate (0.24 ml, 1.90 mmol) generating the title compound *5-bicyclo[2.2.1]heptene-2-carboxylic acid pentyl ester* as a brown oil (86%).

(Found: M⁺ 209.1475, C₁₃H₂₁O₂ requires M 209.1538);

ν_{\max} (film) 2970s, 2867m, 1730s, 1467m cm⁻¹.

δ_{H} (400 MHz; CDCl₃) **Endo isomer:** 6.14 (1H, m, HC=CH), 5.90 (1H, m, HC=CH), 4.00 (2H, q, *J* 6.7 Hz, 9-H₂), 3.19 (1H, br s, 7-H), 2.90 (2H, m, 3-H, 4-H), 2.22 (2H,

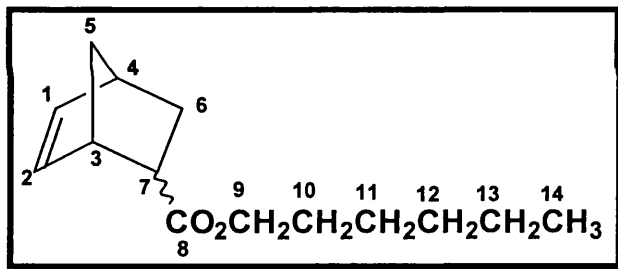
d, J 8.0 Hz, 6-H₂), 1.64 (2H, m, 10-H₂), 1.36 (2H, m, 5-H₂), 1.32 (4H, m, 11-H₂, 12-H₂), 0.90 (3H, t, J 6.7 Hz, 13-H₃); **Exo isomer:** 6.12 (2H, m, HC=CH), 4.12 (2H, J 6.7 Hz, q, 9-H₂), 3.02 (1H, br s, 7-H), 2.90 (2H, m, 3-H, 4-H), 2.22 (2H, d, J 8.0 Hz, 6-H₂), 1.64 (2H, m, 10-H₂), 1.36 (2H, m, 5-H₂), 1.32 (4H, m, 11-H₂, 12-H₂), 0.90 (3H, t, J 6.7 Hz, 13-H₃).

δ_C (100 MHz; CDCl₃) **Endo/exo isomers** 176.12 (C-8), 131.71 (C-1), 131.70 (C-2), 59.82 (C-9), 46.02 (C-5), 44.41 & 44.30 (C-3, C-4), 37.93 (C-7), 29.61 (C-10), 28.74 (C-11), 24.62 (C-6), 22.82 (C-12), 14.00 (C-13).

m/z (E.I.) 208 (M^+ , 54%), 66 (cyclopentadiene, 100).

5-Bicyclo[2.2.1]heptene-2-carboxylic acid hexyl ester^{29, 43}

(117)



Prepared as for 5-bicyclo[2.2.1]-heptene-2-carboxylic acid methyl ester using cyclopentadiene (0.27 ml, 3.80 mmol) and hexyl acrylate (0.27 ml, 1.90 mmol) generating the title compound *5-bicyclo[2.2.1]heptene-2-carboxylic acid hexyl ester* as a brown oil (56%).

(Found: M^+ 223.1622, C₁₄H₂₃O₂ requires M 223.1699);

ν_{\max} (film) 2971s, 2867m, 1729s, 1470m cm⁻¹.

δ_H (400 MHz; CDCl₃) **Endo isomer:** 6.14 (1H, m, HC=CH), 5.90 (1H, m, HC=CH), 3.98 (2H, q, J 6.7 Hz, 9-H), 3.20 (1H, br s, 7-H), 2.91 (2H, m, 3-H, 4-H), 2.22 (2H, d, J 8.0 Hz, 6-H₂), 1.64 (2H, m, 10-H₂), 1.38 (2H, m, 5-H₂), 1.30 (6H, m, 11-13-H), 0.91 (3H, t, J 6.7 Hz, 14-H₃); **Exo isomer:** 6.11 (2H, m, HC=CH), 4.10 (2H, q, J 6.7 Hz, 9-

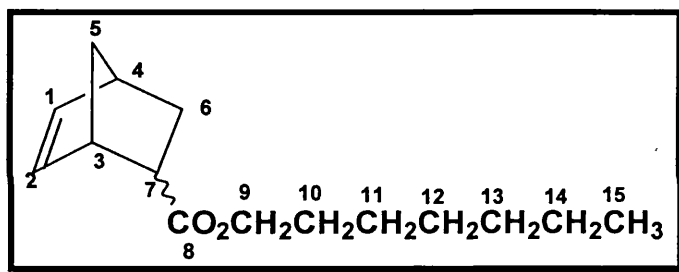
H), 3.02 (1H, br s, 7-H), 2.90 (2H, m, 3-H, 4-H), 2.22 (2H, d, J 8.0 Hz, 6-H₂), 1.64 (2H, m, 10-H₂), 1.36 (2H, m, 5-H₂), 1.30 (6H, m, 11-13-H), 0.91 (3H, t, J 6.7 Hz, 14-H).

δ_c (100 MHz; CDCl₃) 176.10 (C-8), 131.71 (C-1), 131.70 (C-2), 59.82 (C-9), 46.02 (C-5), 44.41 & 44.30 (C-3, C-4), 37.93 (C-7), 32.22 (C-12), 29.61 (C-10), 28.74 (C-11), 24.62 (C-6), 23.11 (C-13), 14.00 (C-14).

m/z (E.I.) 222 (M⁺, 88%).

5-Bicyclo[2.2.1]heptene-2-carboxylic acid heptyl ester^{29, 43}

(118)



Prepared as for 5-bicyclo[2.2.1]-heptene-2-carboxylic acid methyl ester using cyclopentadiene (0.27 ml, 3.80 mmol) and heptyl acrylate (0.31 ml, 1.90 mmol) generating the title compound *5-bicyclo[2.2.1]heptene-2-carboxylic acid heptyl ester* as a brown oil (83%).

(Found: MH^+ 237.1778, C₁₅H₂₅O₂ requires M.237.1855);

ν_{\max} (film) 2972s, 2868m, 1730s, 1467m cm⁻¹.

δ_H (400 MHz; CDCl₃) **Endo isomer:** 6.14 (1H, m, HC=CH), 5.92 (1H, m, HC=CH), 3.96 (2H, q, J 6.7 Hz, 9-H₂), 3.20 (1H, br s, 7-H), 2.90 (2H, m, 3-H, 4-H), 2.22 (2H, d, J 8.0 Hz, 6-H₂), 1.65 (2H, m, 10-H₂), 1.36 (2H, m, 5-H₂), 1.29 (8H, m, 11-14-H), 0.90 (3H, t, J 6.7 Hz, 15-H₃); **Exo isomer:** 6.12 (2H, m, HC=CH), 4.10 (2H, q, J 6.7 Hz, 9-H₂), 3.02 (1H, br s, 7-H), 2.90 (2H, m, 3-H, 4-H), 2.22 (2H, d, J 7.9 Hz, 6-H₂),

1.64 (2H, m, 10-H₂), 1.36 (2H, m, 5-H₂), 1.30 (8H, m, 11-14-H), 0.90 (3H, t, *J* 6.7 Hz, 15-H₃).

δ_C (100 MHz; CDCl₃) 176.00 (C-8), 131.71 (C-2), 131.70 (C-1), 59.80 (C-9), 46.00 (C-5), 44.42 & 44.30 (C-3, C-4), 37.93 (C-7), 32.25 (C-13), 29.91 (C-10), 29.71 (C-12), 26.74 (C-11), 24.62 (C-6), 23.11 (C-14), 14.00 (C-15).

m/z (E.I.) 236 (M⁺, 72%), 66 (cyclopentadiene, 100).

Note: The *endo/exo* ratios were determined by HPLC.

Column: Nucleosil 5 silica gel stationary phase.

Mobile phase: 40% dichloromethane, 60% hexane.

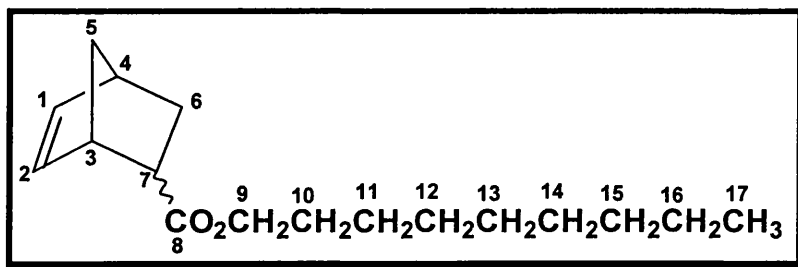
Flow rate: 1 ml/minute.

Detector: UV @ 226 nm.

Retention times: *exo*, 6.81 minutes and *endo*, 8.94 minutes.

pH Studies on the Diels-Alder reaction

5-Bicyclo[2.2.1]heptene-2-carboxylic acid nonyl ester^{29, 43} (**74a-b**)



Procedure 1:

Cyclopentadiene (2.51 g, 3.80 mmol) was added to a stirred solution of nonyl acrylate (3.77 g, 1.90 mmol) in CTAB (25 ml, 1×10^{-3} mol dm⁻³). The mixture was stirred for

x h at RT. The product was extracted with dichloromethane (2 x 30 ml), and the combined organic extracts were washed with distilled water (2 x 50 ml), brine (2 x 50 ml) and dried with magnesium sulfate. The solvent was removed *in vacuo* to give an *endo/exo* mixture of 5-bicyclo[2.2.1]heptene-2-carboxylic acid nonyl ester as a brown oil. The procedure was repeated for water, SDS (25 ml, 8.27 mM), CPB (25 ml, 0.02 mM) and diethyl ether (25 ml).

Procedure 2:

Cyclopentadiene (0.27 ml, 0.38 mmol) was added to a stirred solution of nonyl acrylate (0.36 ml, 0.19 mmol) in CTAB (25 ml, 1×10^{-3} mol dm⁻³). Its pH was adjusted to 1 with 1M HCl_(aq) and 2M NaOH_(aq). The mixture was stirred for x h at RT. The product was extracted with dichloromethane (2 x 30 ml), and the combined organic extracts were washed with distilled water (2 x 50 ml), brine (2 x 50 ml) and dried. The solvent was removed *in vacuo* to give an *endo/exo* mixture of 5-bicyclo[2.2.1]heptene-2-carboxylic acid nonyl ester as a brown oil. The procedure was repeated at pH 3, 5, 7 and 9. Also for SDS (8.27 mM) at pH 1, 3, 5, 7 and 9.

Endo/exo ratios were determined by HPLC.

(Found: MH^+ 265.2101, C₁₇H₂₉O₂ requires 265.2168);

ν_{\max} (film) 2972s, 2868m, 1729s, 1467m 1200m cm⁻¹.

δ_H (400 MHz; CDCl₃) **Endo isomer:** 6.25 (1H, m, HC=CH), 5.93 (1H, m, HC=CH), 3.96 (2H, q, J 6.7 Hz, 9-H₂), 3.21 (1H, br s, 7-H), 2.94 (2H, m, 3-H, 4-H), 2.21 (2H, d, J 4.5 Hz, 6-H), 1.64 (2H, m, 10-H₂), 1.57 (10H, m, 11-16-H), 1.35 (2H, m, 5-H₂), 0.88 (3H, t, J 6.8 Hz, 17-H₃); **Exo isomer:** 6.13 (2H, m, HC=CH), 4.10 (2H, q, J 6.7 Hz, 9-H₂), 3.04 (1H, br s, 7-H), 2.92 (2H, m, 3-H, 4-H), 2.21 (2H, d, J 4.5 Hz, 6-H₂), 1.64 (2H, m, 10-H₂), 1.57 (10H, m, 11-16-H), 1.35 (2H, m, 5-H₂), 0.88 (3H, t, J 6.8 Hz, 17-H₃).

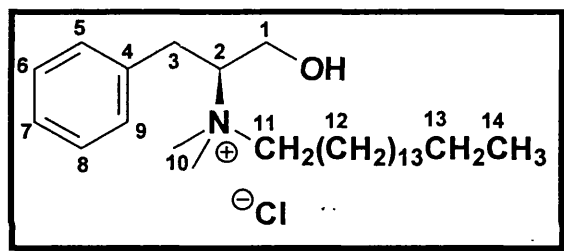
δ_C (100 MHz; CDCl₃) 176.00 (C-8), 131.71 (C-2), 131.70 (C-1), 60.12 (C-9), 46.02 (C-5), 44.34 & 44.32 (C-3, C-4), 37.90 (C-7), 32.52 (C-15), 30.25 (C-13), 30.12 (C-12), 29.99 (C-10), 26.50 (C-11), 24.62 (C-6), 30.10 (C-14), 23.11 (C-16), 14.00 (C-17).

δ_{H} (400 MHz; d_6 -DMSO) 6.87 (5H, m, Ph), 4.97 (1H, br t, J 4.4 Hz, OH), 3.33 (1H, m, CHHO), 3.09 (1H, m, CHHO), 3.00 (1H, m, 2-H), 2.80 (2H, m, 3-H), 2.68 (6H, s, 2 x 10-H₃), 2.50 (2H, t, J 8.0 Hz, 11-H), 1.23 (2H, m, NCH₂CH₂), 0.74 (30H, m, alkyl chain), 0.36 (3H, br s, 14-H);

δ_{C} (100 MHz; d_6 -DMSO) 142.15 (C-4), 134.59 (C-6, 8), 133.80 (C-5, 9), 132.08 (C-7), 78.62 (C-1), 68.35 (C-2), 61.48 (C-11), 54.42 and 54.27 (C-10), 36.48 (C-3), 35.88-27.28 (C-12s), 27.06 (C-13), 19.15 (C-14).

m/z (FAB) 404 (M^+ , 99%), 307 (MH^+ -C₇H₁₅, 34), 136 (MH^+ -C₁₈H₃₉N, 15).

(2*S*)-*N*-Hexadecyl-(1-hydroxy-3-phenylpropyl)-*N*, *N*-dimethyl-2-ammonium chloride¹⁴⁰ (**86**)



(*S*)-*N*, *N*-Dimethyl-2-amino-3-phenyl-1-propanol (5.74 g, 32.0 mmol) and 1-chlorohexadecane (8.36 g, 32.0 mmol) were stirred under anhydrous conditions at 90 °C for 40 hours, then cooled to RT. Addition of anhydrous diethyl ether (100 ml) and the mixture left to stand overnight. The precipitate of (*2S*)-*N*-hexadecyl-(1-hydroxy-3-phenylpropyl)-*N*, *N*-dimethyl-2-ammonium chloride was filtered under gravity and the colourless solid air-dried. The crude product was recrystallised from ethyl acetate and hexane, 1:5 to yield colourless crystals of the desired product (3.31 g, 24%).

Cmc (Dye): 9 – 13 mg/L.

Cmc (Surface tension): 44 mg/L

m.pt: 119-120 °C.

$[\alpha]_{\text{D}} = -54.0^\circ$ (25 °C), c 1.11 EtOH.

(Found: M^+ -Cl⁻ 404.3891, C₂₇H₅₀NO⁺ requires M 404.3892);

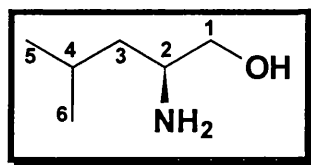
ν_{max} (KBr) 3296s, 2952s, 2851s, 1470s, 1454s, 1425m cm⁻¹;

δ_{H} (400 MHz; d_6 -DMSO) 6.87 (5H, m, Ph), 4.97 (1H, br t, J 4.4 Hz, OH), 3.30 (1H, m, CHOH), 3.10 (1H, m, CHOH), 3.00 (1H, m, 2-H), 2.80 (2H, m, 3-H₂), 2.68 (6H, s, 2 x 10-H₃), 2.65 (2H, t, J 8.0 Hz, 11-H₂), 1.25 (2H, m, NCH₂CH₂), 0.80 (30H, m, alkyl chain), 0.35 (3H, m, 14-H₃);

δ_{C} (100 MHz; d_6 -DMSO) 142.20 (C-4), 134.61 (C-6, 8), 133.92 (C-5, 9), 132.00 (C-7), 76.60 (C-1), 68.42 (C-2), 61.50 (C-11), 55.42 and 55.41 (2 x C-10), 36.55 (C-3), 35.88-27.06 (C-12), 27.01 (C-13), 18.45 (C-14).

m/z (FAB) 404 (M⁺, 100%), 307 (MH⁺-C₇H₁₅, 30), 136 (MH⁺-C₁₈H₃₉N, 19).

(2*S*)-2-Amino-4-methyl-1-pentanol¹³⁹ (87)



The experiment was performed under anhydrous conditions. To sodium borohydride (3.46 g, 92.0 mmol) in dry THF (100 ml) was added (*S*)-leucine (4.98 g, 38.0 mmol). The flask was cooled to 0 °C and iodine (9.65 g, 38.0 mmol) in dry THF (25 ml) was added over 15 minutes. When the addition of iodine was complete and the evolution of gas ceased, the flask was heated at reflux for 18 hours. Methanol (500 ml) was added slowly until the mixture became clear and then it was stirred for 30 minutes. The solvent was removed *in vacuo* and the resulting white paste was dissolved in 20% aqueous potassium hydroxide (100 ml), stirred for 4 hours and extracted with dichloromethane (3 x 150 ml). The organic extracts were then dried over sodium sulfate and concentrated *in vacuo* to afford (2*S*)-2-amino-4-methyl-1-pentanol as a colourless oil (4.04 g, 92%). The product was used without further purification.

(Found: MH⁺ 118.1240; C₆H₁₆NO requires M 118.1232);

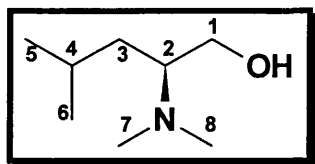
ν_{max} (film) 3281s, 2954s, 2361m, 1591s, 1468s, 1060m cm⁻¹;

δ_{H} (300 MHz; CDCl₃) 3.50 (2H, d, J 5.6 Hz, 1-H₂), 3.10 (2H, t, J 7.5 Hz, 3-H₂), 2.85 (1H, m, 2-H), 2.41 (2H, br s, NH₂), 1.62 (1H, m, 4-H), 0.85 (6H, d, J 6.6 Hz, 5-H₃ & 6-H₃).

δ_C (100 MHz; $CDCl_3$) 66.75 (C-1), 50.45 (C-2), 43.23 (C-3), 23.22 (C-4), 22.18 (C-5 & C-6),

m/z (E.I.) 118 (MH^+ , 100%), 116 (M^+-H , 95), 114 (M^+-3H , 100), 103 (M^+-CH_3 , 11), 100 (M^+-OH , 6), 101 (M^+-OH , 23), 87 (MH^+-NH_2OH , 45), 84 (M^+-NH_2OH , 44), 54 ($CHCH_2CHCH_2$, 23).

(2*S*)-*N, N*-Dimethyl-2-amino-4-methyl-1-pentanol¹⁴⁰ (**88**)



To (2*S*)-2-amino-4-methyl-1-pentanol (4.04 g, 35.0 mmol) in water (8.70 ml, 0.50 mol) was added 37% formaldehyde solution (3.90 ml, 0.14 mmol) followed by 88% aqueous formic acid (12.3 ml, 0.30 mol). The reaction mixture was stirred continually at RT for 5 h, then the temperature was increased to 95 °C and the mixture was heated at reflux for 18 hours. The mixture was cooled to RT and the pH adjusted to 12 with 2M potassium hydroxide (100 ml), extracted with diethyl ether (3 x 100 ml), washed with distilled water (3 x 100 ml) and brine (100 ml) then dried over sodium sulfate. The solvent was removed *in vacuo* to yield a pale yellow solid, which was recrystallised with ether/hexane, 1:4 to yield colourless crystals of the desired product, (2*S*)-*N, N*-dimethyl-2-amino-4-methyl-1-pentanol (4.00 g, 80%).

m.pt: 45-47 °C (ether/hexane, 1:4)

$[\alpha]_D = +0.052^\circ$, c:1.05 EtOH.

(Found: M^+-H 144.1380; $C_8H_{18}NO$ requires M 144.1388);

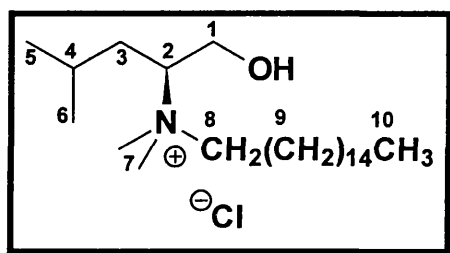
ν_{max} (film) 3405s, 2954s, 1462s, 1262s, 1367m, 1046s cm^{-1} ;

δ_H (300 MHz; $CDCl_3$) 3.46 (2H, d, J 5.6 Hz, 1- H_2), 3.10 (2H, t, J 10.4 Hz, 3- H_2), 2.62 (1H, m, 2-H), 2.21 (6H, s, 7-H & 8-H), 1.44 (1H, m, 4-H), 0.86 (6H, d, J 6.5 Hz, 5- H_3 & 6- H_3).

δ_c (100 MHz; CDCl_3) 62.24 (C-1), 61.10 (C-2), 39.65 (C-7, 8), 32.65 (C-3), 23.64 (C-4), 21.90 (C-5, 6).

m/z (E.I.) 144 ($M^+ - \text{H}$, 56%), 114 ($M^+ - \text{C}_2\text{H}_7$, 100), 98 ($\text{C}_6\text{H}_{12}\text{N}^+$, 8), 72 ($M^+ - \text{C}_4\text{H}_9\text{O}^+$, 76), 57 (C_4H_9^+ , 35).

(2*S*)-*N*-Hexadecyl-(1-hydroxy-4-methylpentyl)-*N*, *N*-dimethyl-2-ammonium chloride¹⁴⁰ (89)



(2*S*)-*N*, *N*-Dimethyl-2-amino-4-methyl-1-pentanol (4.00 g, 30.0 mmol) and 1-chlorohexadecane (8.40 g, 28.0 mmol) was stirred under anhydrous conditions at 90 °C for 40 hours, then cooled to RT. Diethyl ether (100 ml) was added and the mixture left to stand overnight. The precipitate of (2*S*)-*N*-hexadecyl-(1-hydroxy-4-methylpentyl)-*N*, *N*-dimethyl-2-ammonium chloride was filtered under gravity and the white solid air-dried. The crude product was recrystallised from ethyl acetate and hexane, 1:5 to yield colourless crystals of the desired product (2.70 g, 22%).

Cmc (Dye): 11 - 16 mg/L.

Surface tension: 130 mg/L

m.pt: 72-74 °C (EtOAc/Hexane, 1:5)

$[\alpha]_D = +0.070^\circ$ (25 °C), c 0.025 EtOH.

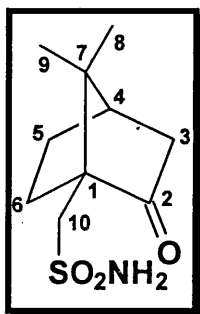
(Found: $M^+ - \text{Cl}^-$ 370.4106; $\text{C}_{24}\text{H}_{52}\text{ON}^+$ requires M 370.4149);

ν_{max} (KBr) 3237br, 2910s, 1632w, 1469s, 1376m, 1039s cm^{-1} .

δ_H (400 MHz; d_6 -DMSO) 3.46 (2H, d, J 5.6 Hz, 1-H), 3.34 (6H, s, 2 x 7-H₃), 3.01 (1H, m, 2-H), 1.65 (2H, m, 3-H₂), 1.22 (30H, br s, 9-Hs), 0.95 (3H, d, J 6.4 Hz, 5-H₃ or 6-H₃), 0.90 (3H, d, J 6.7 Hz, 6-H₃ or 5-H₃), 0.84 (3H, t, J 6.7 Hz, 10-H₃)

δ_C (100 MHz; d_6 -DMSO) 71.23 (C-1), 57.38 (C-2), 48.75 (C-8), 40.47 (C-3), 40.20 (C-7 x 2), 31.37-23.78 (C-9), 22.16 (C-4), 21.81 (C-6), 21.02 (C-5), 14.01 (C-10).
 m/z (FAB) 370 (M^+ , 100%), 72 ($M^+ - C_4H_9O$, 5), 57 ($C_4H_9^+$, 19).

(1*S*)-7, 7-Dimethyl-2-oxobicyclo[2.2.1]heptane-1-methane sulfonamide^{147, 149} (94)



To a solution of (1*S*)-10-camphorsulfonyl chloride (20.0 g, 79.8 mmol) in THF (200 ml), 97% ammonia solution (200 ml) was added dropwise at 0 °C over 30 minute. The resulting solution was stirred overnight at RT. Water (200 ml) was added and the product extracted with dichloromethane (2 x 200 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo* to yield the desired product (1*S*)-7, 7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonamide (15.3 g, 83%) as colourless crystals. Procedure repeated for (1*R*)-10-camphorsulfonyl chloride, (17.7 g, 96%). All spectroscopic data was identical to its enantiomer.

(Found: MH^+ 232.1020; $C_{10}H_{18}NO_3S$ requires M 232.1007);

m.pt: 131-133 °C (lit. 133-134 °C¹⁴⁸)

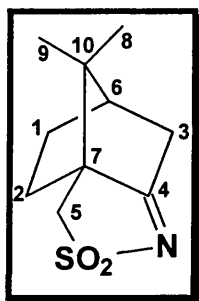
ν_{max} (KBr) 3312s, 2970s, 1735s, 1640s, 1413m, 1328s, 1151s cm^{-1} ;

δ_H (300 MHz; $CDCl_3$) 5.42 (2H, br s, NH_2), 3.31 (2H, m, 10-H), 2.36 (2H, d, J 10.3 Hz, 1-H), 2.03 (1H, m, 4-H), 1.74 (2H, t, J 9.1 Hz, 6-H), 1.44 (2H, dt, J 9.1 & 5.0 Hz, 5-H), 1.05 (3H, s, 8-H), 0.95 (3H, s, 9-H).

δ_C (100 MHz; $CDCl_3$) 195.51 (C-2), 64.40 (C-10), 49.34 (C-1), 47.90 (C-3), 44.52 (C-7), 35.80 (C-4), 28.32 (C-5), 26.54 (C-6), 19.30 (C-8), 18.82 (C-9).

m/z (E.I.) 232 (MH^+ , 100%), 214 (MH^+-NH_2 , 73), 151 ($M^+-SO_2NH_2$, 10), 137 ($M^+-CH_2SO_2NH_2$, 18), 123 ($C_8H_{12}O^+$, 6), 93 ($CH_3NO_2S^+$, 47), 80 ($SO_2NH_3^+$, 5).

(7*S*)-10, 10-Dimethyl-5-thia-4-azatricyclo[5.2.1.0]dec-3-ene-5, 5-dioxide^{147, 149} (**95**)



To a solution of (1*S*)-7, 7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methane sulfonamide (10.0 g, 43.0 mmol) in toluene (300 ml), amberlyst-15 ion exchange resin (1.0 g) was added. The mixture was heated at reflux in a Dean-Stark apparatus overnight. The reaction mixture was cooled to RT, dichloromethane (100 ml) was added, the resin was removed by filtration and the solvent was removed *in vacuo* to give the desired product, (7*S*)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]dec-3-ene-5, 5-dioxide (9.22 g, >99%) as a white solid. The product was used without further purification.

Repeated for (1*R*)-7, 7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methane sulfonamide, (9.02 g, 98%). All spectroscopic data was identical to its enantiomer.

(Found: MH^+ 214.0920; $C_{10}H_{16}NO_2S$ requires M 214.0902);

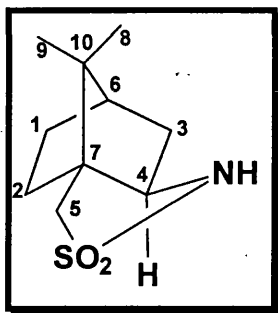
ν_{max} (KBr) 3010m, 2970s, 2889m, 1640s, 1317s, 1172m cm^{-1} ;

δ_H (300 MHz; $CDCl_3$) 3.13-2.97 (2H, m, 5-H), 2.38 (2H, d, J 10.0 Hz, 3-H), 2.03 (1H, m, 6-H), 1.74 (2H, t, J 9.3 Hz, 2-H), 1.44 (2H, dt, J 9.3 & 4.9 Hz, 1-H), 1.05 (3H, s, 8-H), 0.84 (3H, s, 9-H).

δ_C (100 MHz; $CDCl_3$) 195.42 (C-4), 64.40 (C-5), 59.30 (C-7), 47.91 (C-6), 44.52 (C-10), 35.80 (C-3), 28.34 (C-1), 26.50 (C-2), 19.32 (C-8), 18.80 (C-9).

m/z (E.I.) 214 (MH^+ , 18%), 157 ($MH^+ - C_4H_9$, 28), 115 (43), 108 ($C_8H_{12}^+$, 92), 93 ($CH_3NO_2S^+$, 21).

(7*S*)-10, 10-Dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5, 5-dioxide^{147, 149} (96)



Sodium borohydride (0.80 g, 21.0 mmol) was added to a stirred solution of (7*S*)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]dec-3-ene-5, 5-dioxide (3.00 g, 14.0 mmol) in THF (200 ml) at 0 °C. After addition the reaction was stirred vigorously overnight at RT. Methanol (100 ml) was added until the solution became clear and the mixture was stirred for 30 minutes. The solvent was then removed *in vacuo* to give the desired product, (7*S*)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5, 5-dioxide (2.09 g, 69%) as a white solid. The product was used and not purified further. Repeated for (7*R*)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]dec-3-ene-5, 5-dioxide, (2.21 g, 73%). All spectroscopic data was identical to its enantiomer.

(Found: MH^+ 216.1070; $C_{10}H_{18}NO_2S$ requires M 216.1058);

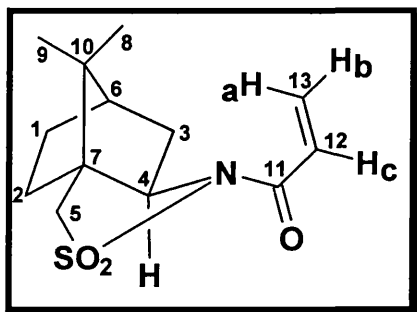
ν_{max} (KBr) 3292s, 2879s, 1473s, 1343s, 1217s, 1066m cm^{-1} ;

δ_H (300 MHz; $CDCl_3$) 4.12 (1H, br s, NH), 3.38 (1H, m, 4-H), 3.08 (2H, m, 5-H), 2.01 (1H, m, 6-H), 1.89 (2H, t, J 6.7 Hz, 3-H), 1.74 (2H, t, J 9.3 Hz, 2-H), 1.44 (2H, dt, J 9.3 & 4.9 Hz, 1-H), 1.10 (3H, s, 8-H), 0.90 (3H, s, 9-H).

δ_C (100 MHz; $CDCl_3$) 62.74 (C-5), 50.25 (C-4), 47.37 (C-10), 44.59 (C-7), 35.96 (C-6), 31.75 (C-3), 26.69 (C-2), 20.39 (C-1), 20.3 (C-8 & C-9).

m/z (FAB) 216 (MH^+ , 18%), 192 (23), 168 ($M^+ - NHSO_2$, 1), 154 ($M^+ - CH_2SO_2NH$, 13), 136 ($C_{10}H_{16}^+$, 5), 124 ($M^+ - (2CH_3) - CH_2SO_2NH$, 12), 108 ($C_4H_{14}^+$, 10).

N-Acryloyl-(7*S*)-10, 10-dimethyl-5-thia-4-azatricyclo
[5.2.1.0]decane-5, 5-dioxide^{147, 149} (97)



A solution of (7*S*)-(+)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5, 5-dioxide (2.00 g, 9.29 mmol) in toluene (50 ml), was added dropwise to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.56 g, 13.9 mmol). After 1 hour, a solution of acryloyl chloride (1.50 ml, 18.6 mmol) in toluene (50 ml) was added slowly and the mixture was stirred at RT for 3 hours. The addition of water (20 ml) and separation of the organic phase with dichloromethane (3 x 50 ml) yielded a yellow solid. Flash column chromatography with hexane/ethyl acetate, (4:1) gave the desired product *N*-acryloyl-(7*S*)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5, 5-dioxide as an oil (1.62 g, 65%).

Procedure repeated for (7*R*)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]dec-3-ene-5, 5-dioxide, (1.85 g, 74%). All spectroscopic data was identical to its enantiomer.

(Found: MH^+ 270.1180; $C_{13}H_{18}NO_3S$ requires M 270.1164);

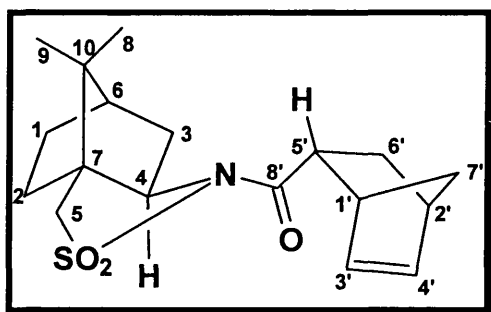
ν_{max} (KBr) 2919s, 2366m, 1675s, 1328s, 1131s, 1061m cm^{-1} ;

δ_H (300 MHz; $CDCl_3$) 6.85 (1H, dd, J 17.0 and 9.6 Hz, H_c), 6.50 (1H, d, J 17.0 Hz, H_a), 5.84 (1H, d, J 9.6 Hz, H_b), 3.98 (1H, m, 4-H), 3.08 (2H, m, 5-H), 2.05 (1H, m, 6-H), 1.99 (2H, t, J 6.7 Hz, 3-H), 1.74 (2H, t, J 9.3 Hz, 2-H), 1.44 (2H, dt, J 9.3 & 4.9 Hz, 1-H), 1.10 (3H, s, 8-H), 0.90 (3H, s, 9-H).

δ_C (100 MHz; $CDCl_3$) 164.80 (C-11), 131.28 (C-13), 127.76 (C-12), 53.09 (C-5), 52.89 (C-4), 48.54 (C-10), 44.68 (C-6), 44.56 (C-7), 29.31 (C-3), 26.45 (C-2), 22.65 (C-1), 19.86 (C-8 & C-9).

m/z (FAB) 270 (MH^+ , 45%), 269 (M^+ , 40), 214 ($M^+-C_3H_3O$, 5), 154 (76), 136 ($M^+-C_3H_3NO_3S$, 100), 107 (36), 91 (27), 55 (31).

4-(1'S, 5'R)-Bicyclo[2.2.1]hept-2-en-5'-carbonyl-(7S)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5, 5-dioxide^{147, 149}
(98)



The experiment was performed under anhydrous conditions. To *N*-acryloyl-(7*S*)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5, 5-dioxide (1.00 g, 3.71 mmol) in dry dichloromethane (20 ml), at $-78\text{ }^\circ\text{C}$, titanium chloride (0.21 ml, 1.86 mmol) was added. After 15 minutes, a solution of freshly distilled cyclopentadiene (2.48 ml, 37.10 mmol) also at $-78\text{ }^\circ\text{C}$, was added in one portion *via* a cannula and the mixture was stirred for a further 20 hours at $-78\text{ }^\circ\text{C}$. Subsequent addition of water at $-78\text{ }^\circ\text{C}$, extraction with dichloromethane (3 x 50 ml) and removal of the solvent *in vacuo*, gave a brown solid. This was dissolved in propan-2-ol (20 ml), filtered through celite and recrystallised from hot ethanol, to give the desired product 4-(1'*S*, 5'*R*)-bicyclo[2.2.1]hept-2-en-5'-carbonyl-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5, 5-dioxide as a yellow solid (0.72 g, 55%).

Procedure repeated for *N*-acryloyl-(7*R*)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5, 5-dioxide (0.72 g, 55%). All spectroscopic data was identical to its enantiomer.

(Found: M 335.1570; $C_{18}H_{25}NO_3S$ requires M 335.1555);
m.pt $187\text{-}188\text{ }^\circ\text{C}$; (Lit. $185\text{-}186\text{ }^\circ\text{C}$ ¹⁴⁸).

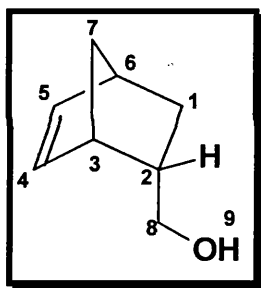
ν_{\max} (KBr) 1675s, 1328s, 1131s, 1061m cm^{-1} ;

δ_{H} (300 MHz; CDCl_3) 6.25 (1H, m, $\text{CH}=\text{CH}$), 5.85 (1H, m, $\text{CH}=\text{CH}$), 3.99 (1H, m, 4-H), 3.08 (2H, 2 x d, J 9.0 Hz, 5- $\text{H}_{1/2}$), 3.44 (1H, d, J 5.6 Hz, 5'-H), 2.89 (2H, m, 2'-H, 1'-H), 2.50 (1H, br s, 6'-H), 2.05 (1H, m, 6-H), 1.99 (2H, t, J 6.7 Hz, 3-H), 1.74 (2H, t, J 9.3 Hz, 2-H), 1.44 (2H, q, J 9.4 Hz, 1-H), 1.30 (2H, m, 7'-H), 1.22 (3H, s, 8-H), 0.95 (3H, s, 9-H).

δ_{C} (100 MHz; CDCl_3) 178.19 (C-8'), 131.35 (C-3', 4'), 54.75 (C-5), 50.30 (C-4), 46.16 (C-10), 45.13 (C-7'), 44.66 (C-1', 2'), 41.14 (C-6), 38.39 (C-7), 34.64 (C-5'), 29.66 (C-2), 26.45 (C-3), 25.19 (C-6'), 22.00 (C-1), 19.86 (C-8 & 9).

m/z (FAB) 335 (M^+ , 10%), 270 (MH^+ -cyclopentadiene, 40), 135 (54), 84 (14), 66 (cyclopentadiene, 100), 54 (18).

(2*S*)-5-Bicyclo[2.2.1]heptene-2-methanol¹²³ (99/102)



To a suspension of lithium aluminium hydride (0.070 g, 1.78 mmol) in diethyl ether (5 ml), a solution of *endo* 5-bicyclo[2.2.1]heptene-2-carboxylic acid nonyl ester (**101a**) (0.471 g, 1.78 mmol) in diethyl ether (2 ml) was added dropwise at 0 °C. The resultant mixture was allowed to warm to room temperature and stirred vigorously overnight. A saturated solution of sodium sulfate was added dropwise until a precipitate of aluminium hydroxide was formed. Then solid anhydrous sodium sulfate was added and the solution left to stand for 30 minutes. The solid sodium sulfate was removed by filtration and the filtrate was concentrated *in vacuo*. Flash column chromatography (ethyl acetate:hexane, 1:1) yielded the desired product, 5-bicyclo[2.2.1]heptene-2-methanol (0.21 g, 99%) as a colourless oil.

Repeated for 4-(1'*R*,5'*S*)-bicyclo[2.2.1]hept-2-en-5'-carbonyl-(7*S*)-(+)-10, 10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5,5-dioxide (**98**) (0.22 g, 95%). All spectroscopic data was identical to its enantiomer.

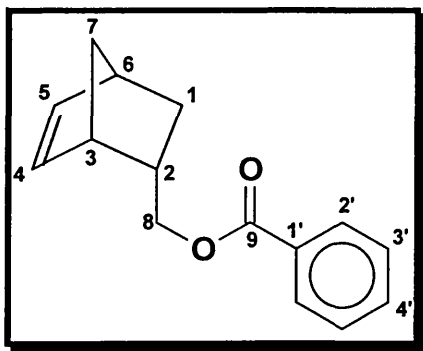
ν_{\max} (film) 3320br (OH) 2955s, 2600m, 1732s, and 1435m 1200 cm^{-1} ;

δ_{H} (300 MHz; CDCl_3) 6.15 (1H, m, $\text{HC}=\text{CH}$), 5.95 (1H, m, $\text{HC}=\text{CH}$), 3.15 (2H, d, J 3.6 Hz, 8- H_2), 2.98 (1H, br s, 2-H), 2.79 (2H, m, 3-H, 6-H), 1.30 (2H, m, 7- H_2), 1.19 (2H, d, J 7.8 Hz, 1- H_2);

δ_{C} (100 MHz; CDCl_3) 137.29 (C-4, 5), 67.89 (C-8), 47.35 (C-7), 45.08 (C-3), 44.88 (C-6), 35.50 (C-2), 25.77 (C-1).

m/z (E.I.) 125 (M^+ , 10%), 107 (M^+-OH , 7), 93 ($\text{M}^+-\text{CH}_2\text{OH}$, 7), 66 (cyclopentadiene, 46).

endo-(2*R*)-5-Bicyclo[2.2.1]heptene-2-methyl benzoate¹²³ (**100a**,
b/103)



To *endo*-(*R*)-5-bicyclo[2.2.1]heptene-2-methanol (**99**) (0.050 g, 0.40mmol) in dichloromethane (1.0 ml) at 0 °C was added benzoyl chloride (0.070 ml, 0.60 mmol) dropwise, maintaining the temperature at 0-2 °C. After addition, the reaction mixture was stirred at 0 °C for a further 1 hour and at RT overnight. The reaction mixture was quenched with saturated sodium hydrogen carbonate solution (50 ml), extracted with diethyl ether (2 x 50 ml), washed with distilled water (50 ml), brine (50 ml) and dried over sodium sulfate. The solvent was removed *in vacuo* give the desired product,

endo-(2*R*)-5-bicyclo[2.2.1]heptene-2-methyl benzoate (**100**) (0.049g, 54%) as a colourless oil.

Repeated for *endo*-(2*R*)-5-bicyclo[2.2.1]heptene-2-methanol (**102**) (0.049 g, 54%).

All spectroscopic data was identical to its enantiomer.

(Found: M^+ 228.1160; $C_{15}H_{16}O_2$ requires M 228.1150);

ν_{\max} (film) 2955s, 1732s, 1640s, 1435m, 1200 cm^{-1} .

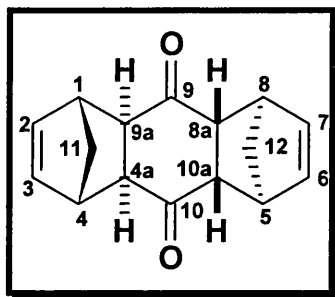
δ_H (300 MHz; $CDCl_3$) 8.16 (2H, d, J 7.8 Hz, 2'-H₂), 7.56 (2H, t, J 7.8 Hz, 3'-H₂), 7.42 (1H, t, J 7.8 Hz, 4'-H), 6.14 (1H, m, HC=CH), 5.99 (1H, m, HC=CH), 3.10 (2H, d, J 3.6 Hz, 8-H₂), 2.96 (1H, br s, 2-H), 2.75 (2H, m, 3-H, 6-H), 1.31 (2H, m, 7-H₂), 1.25 (2H, t, J 7.6 Hz, 1-H₂).

δ_C (100 MHz; $CDCl_3$) 167.09 (C-9), 132.65 (C-1'), 133.10 (C-4, 5), 130.55 (C-4'), 129.74 (C-3'), 128.58 (C-2'), 69.42 (C-8), 46.93 (C-7), 45.49 (C-3), 44.79 (C-6), 34.18 (C-2), 24.16 (C-1).

m/z (FAB) 229 (MH^+ , 18%), 123 (M^+ -PhCO, 16), 107 (M^+ -PhCO₂, 43), 77 ($C_6H_5^+$, 35), 66 (Cyclopentadiene, 10).

Diels-Alder reaction between Hydroquinone and Benzoquinone with Cyclopentadiene

*1,4,4a,5,8,8a,9a,10a-Octahydro-1,4:5,8-dimethano-anthracene-9, 10-dione*¹³⁷ (77)



Organic solvents:

Freshly distilled cyclopentadiene (0.52 ml, 7.60 mmol) was added to a stirred solution of hydroquinone (0.42 g, 3.80 mmol) in diethyl ether (50 ml). The mixture was stirred for 24 h at RT. The mixture was washed with distilled water (2 x 50 ml), brine (2 x 50 ml) and then dried (magnesium sulfate). The solvent was removed *in vacuo* to give starting material.

Aqueous solutions:

Freshly distilled cyclopentadiene (0.52 ml, 7.60 mmol) was added to a stirred solution of hydroquinone (0.42 g, 3.80 mmol) in phenylalanine-derived (85) surfactant solution (50 ml, 0.02 mM). The mixture was stirred for 24 hours at RT. The product was extracted with diethyl ether (2 x 50 ml), and the combined organic extracts were washed with distilled water (2 x 50ml), brine (2 x 50ml) and dried with magnesium sulfate. The solvent was removed *in vacuo* to give a mixture of product and starting material. This procedure was repeated again with deionized water (50 ml), lithium

chloride solution (50 ml, 4.86M) and buffered water (50 ml, pH 7.01). The desired product was isolated by flash column chromatography, chloroform/methanol (10:1).

Results:

Solvent	% yield (isolated)
Diethyl ether	0
Ethyl acetate at 50 °C	0
Water	2-10
4.86M LiCl (aq) (72 hours)	11
phenylalanine-derived (85) surfactant solution	5
Buffered water (pH 7.01)	11-14

(Found: M^+ 240.1135, $C_{16}H_{16}O_2$ requires 240.1150);

Found: C, 79.70; H, 6.73%; $C_{16}H_{16}O_2$ requires: C, 79.97; H, 6.71%;

m.pt: 149-151° C (EtOAc/Hexane, 1:2) (Lit: 153-154° C¹³⁷)

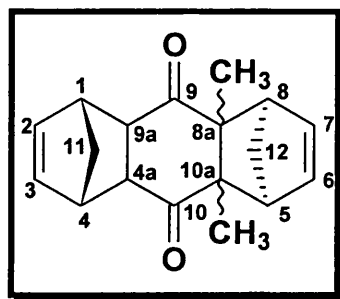
ν_{max} (KBr) 2900s, 1746s, 1635s, 1235m, 1100 cm^{-1} .

δ_H NMR (400 MHz; $CDCl_3$) 6.19 (4H, s, 2- H_4), 3.35 (4H, s, 1- H_4), 2.87 (4H, s, 4a- H_4), 1.44 (4H, m, 11- H_4).

δ_C (100 MHz; $CDCl_3$) 211.30 (C_{2-9}), 131.79 (C_{4-2}), 43.48 (C_{2-11}), 43.06 (C_{4-4a}), 39.89 (C_{4-1}).

m/z (FAB) (M^+ , 100%), 174 ($C_{11}H_{10}O_2^+$, 52), 109 ($C_6H_5O_2^+$, 8), 66 (cyclopentadiene, 100).

8a, 10a-Dimethyl-1,4,4a,5,8,8a,9a,10a-octahydro-1,4:5,8-dimethano-anthracene-9, 10-dione (79)



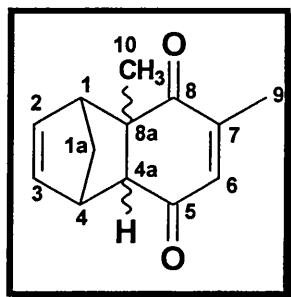
Procedure as for methylhydroquinone. Isolated a yellow solid (0.04 g, 4%)

ν_{\max} (KBr) 3312s, 1752s, 1735s, 1652s, 1356m, 1328s, 1151s cm^{-1}

δ_{H} (300 MHz; CDCl_3) 5.99 (4H, s, 2, 3, 6, 7-H), 3.51 (4H, s, 1, 4, 5, 8-H), 3.21 (2H, s, 4a, 9a-H), 1.92 (6H, s, 2 x CH_3), 1.44 (4H, m, 11, 12-H).

δ_{C} (100 MHz; CDCl_3) 218.45 (C-9, 10), 131.81 (C-2, 3, 6, 7), 53.50 (C-8a, 10a), 43.44 (C-1, 4), 43.12 (C-5, 8), 40.49 (C-11), 39.89 (C-4a, 9a), 38.40 (C-12), 14.60 ($\text{CH}_3 \times 2$).

7,8a-Dimethyl-1,4,4a,8a-tetrahydro-1,4-methano-naphthalene-5,8-dione (81)



Organic solvents:

Freshly distilled cyclopentadiene (0.05 g, 7.30 mmol) was added to a stirred solution of 2, 6-dimethylbenzoquinone (50.0 mg, 3.70 mmol) in diethyl ether (50 ml) containing 2% *tert* 2, 4, 6-tributylphenol (30.0 mg, 0.10 mmol). The mixture was stirred for 24 hours at RT. The mixture was washed with distilled water (2 x 50 ml) and brine (2 x 50 ml) and then dried over magnesium sulfate. The solvent was removed *in vacuo* to give a mixture of product and starting material.

Aqueous solutions:

Freshly distilled cyclopentadiene (0.05 g, 7.30 mmol) was added to a stirred solution of 2,6-dimethyl benzoquinone (50.0 mg, 3.70 mmol) in phenylalanine-derived (85) surfactant solution (50ml, 0.02mM) with 2% *tert* 2,4,6-tributyl phenol (30.0 mg, 0.10 mmol). This procedure was repeated again with deionized water (50 ml). The mixture was stirred for 24 hours at RT. The product was extracted with diethyl ether (2 x 30 ml), and the combined organic extracts were washed with distilled water (2 x 50 ml), brine (2 x 50 ml) and dried (magnesium sulfate). The solvent was removed *in vacuo* to give a mixture of product and starting material.

Results:

Solvent	% yield of product
Diethyl ether	51
Water, deionized	78
phenylalanine-derived (85) surfactant solution (0.02mM)	34

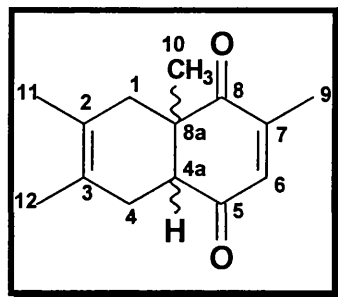
ν_{\max} (KBr) 2950s, 1766s, 1672s, 1246m, 1088 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) 6.45 (1H, s, 6-H), 6.00 (2H, m, 2-H, 3-H), 3.38 (1H, br s, 4a-H), 3.05 (1H, br s, 1-H), 2.78 (1H, d, 4a-H J 3.93 Hz), 1.90 (3H, s, 9-H₃), 1.55 (2H, dd, CH_2 J 9.2 and 12.0 Hz), 1.42 (3H, s, 10-H₃)

δ_{C} (100 MHz; CDCl_3) 203.48 (C-8), 200.17 (C-5), 151.58 (C-7), 135.00 (C-6), 133.49 (C-2, 3), 50.08 (C-4a), 48.05 (C-1), 46.88 (C-8a), 40.85 (C-4a), 39.90 (C-1a), 35.90 (C-4), 15.15 (C-9), 13.29 (C-10).

m/z (E.I.) 203 (M^+ , 21%), 188 ($\text{MH}^+ - \text{CH}_3$, 12), 175 ($\text{M} - 2\text{CH}_3$, 67), 66 (cyclopentadiene, 11).

2,3,7,8a-Tetramethyl-4a, 8a-tetrahydro-1, 4-methano-naphthalene-5, 8-dione (82)



Organic solvents:

2,3-Dimethyl-1,3-butadiene (0.05 ml, 0.44 mmol) was added to a stirred solution of 2,6-dimethylbenzoquinone (30.0 mg, 0.22 mmol) in *solvent* (25 ml). The mixture was stirred for \underline{x} h at RT. The mixture was washed with distilled water (2 x 50 ml), brine (2 x 50 ml) and then dried over magnesium sulfate. The solvent was removed *in vacuo* to give *2,3,7,8a-tetramethyl-4a, 8a-tetrahydro-1, 4-methano-naphthalene-5, 8-dione* as colourless oil.

Aqueous solutions:

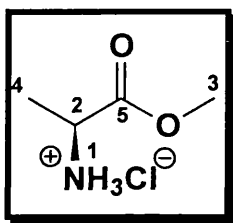
2,3-Dimethyl-1, 3-butadiene (0.05 ml, 0.44 mmol) was added to a stirred solution of 2,6-dimethylbenzoquinone (30.0 mg, 0.22 mmol) in CTAB (25 ml, 1×10^{-3} mol dm⁻³). The mixture was stirred for \underline{x} h at RT. The product was extracted with dichloromethane (2 x 30 ml) and the combined organic extracts were washed with distilled water (2 x 50 ml), brine (2 x 50 ml) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give *2,3,7,8a-tetramethyl-4a,8a-tetrahydro-1,4-methano-naphthalene-5,8-dione* as a colourless oil.

(Found: M^+ 218.1312; C₁₄H₁₈NO₂ requires M 218.1307);

δ_{H} (400 MHz; CDCl_3) 6.46, (1H, s, 6-H), 3.39 (1H, s, 4-H), 3.06 (1H, s, 1-H), 2.79 (1H, d, J 4.2 Hz, 4a-H), 1.90 (3H, s, 9- H_3), 1.51 (3H, s, 10- H_3), 1.20 (6H, s, 11- H_3 & 12- H_3)

δ_{C} (100 MHz; CDCl_3) 203.35 (C-5), 200.80 (C-8), 151.55 (C-7), 135.00 (C-6), 133.51 (C-2, C-3), 55.80 (C-4a), 47.59 (C-8a), 39.11 (C-1), 30.45 (C-4), 18.65 (C-11), 18.30 (C-12), 16.00 (C-10), 14.50 (C-9).

(2*S*)-Alanine methyl ester-2-(ammonium chloride)^{34, 123} (105)



To a solution of (*S*)-alanine (20.0 g, 0.22 mmol) in methanol (100 ml) cooled to 0 °C with ice/water (1:1), thionyl chloride (16.4 ml, 0.44 mmol) was added dropwise maintaining the temperature at 0-5 °C. After addition the resulting mixture was stirred overnight (*ca.* 18 h). The solvent was removed *in vacuo* to yield the titled product, (2*S*)-Alanine methyl ester-2-(ammonium chloride) as a white solid (31.3 g, >99 %).

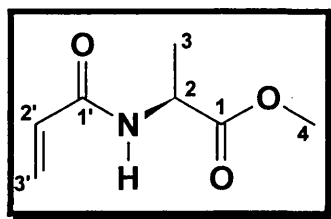
m.pt: 109-111 °C. (Lit 110°C³⁴)

ν_{max} (KBr) 3312s, 2970s, 1735s, 1632w, 1413m, 1151s cm^{-1} .

δ_{H} (300 MHz; CDCl_3) 8.63 (3H, br s, NH_3^+), 4.29 (1H, m, 2-H), 3.81 (3H, s, 3- H_3); 1.71 (3H, d, J 7.3 Hz, 4- H_3)

δ_{C} (100 MHz; CDCl_3) 168.20 (C-5), 50.61 (C-3), 45.73 (C-2), 13.54 (C-4).

m/z (E.I.) 104 (M^+ , 100%), 90 ($\text{M}^+ - \text{CH}_3$, 56), 73 ($\text{M}^+ - \text{OCH}_3$, 11), 72 ($\text{M}^+ - \text{NH}_2\text{CH}_3$, 31).

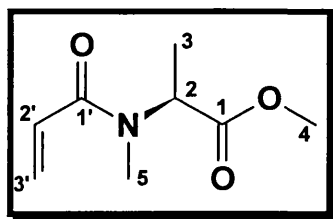
(2S)-*N*-Acryloyl alanine methyl ester^{34, 123} (106)

To a solution of acrylic acid (3.32 ml, 48.43 mmol) and triethylamine (13.5 ml, 96.9 mmol) in tetrahydrofuran (150 ml) at 0 °C was added *i*-butylchloroformate (6.29 ml, 48.4 mmol). The mixture was stirred for 1 hour and (*2S*)-alanine methyl ester-2-(ammonium chloride) (5.00 g, 35.8 mmol) was added in one portion and the reaction mixture stirred overnight. The solvent was removed *in vacuo* to yield a brown oil and the desired product, (*S*)-*N*-acryloyl alanine methyl ester was isolated by flash column chromatography (ethyl acetate/hexane, 1:1) to give a yellow oil (5.63 g, 55 %).

ν_{\max} (film) 3300s, 2970s, 1735s, 1632w, 1410m, 1100 cm^{-1} .

δ_{H} (300 MHz; CDCl_3) 6.56 (1H, br s, NH), 6.24 (1H, d, J 15.3 Hz, 3'-H), 6.09 (1H, dd, J 15.3 and 10.1 Hz, 2'-H), 5.61 (1H, d, J 10.1 Hz, 3'-H), 4.62 (1H, m, 2-H), 3.69 (3H, s, 4-H₃), 1.37 (3H, d, J 7.1 Hz, 3-H₃).

δ_{C} (100 MHz; CDCl_3) 173.48 (C-1), 164.91 (C-1'), 130.22 (C-3'), 126.94 (C-2'), 52.36 (C-2), 47.89 (C-4), 18.64 (C-3).

(2S)-*N*-Acryloyl-*N*-methyl alanine methyl ester^{34, 123} (104)

To a stirred solution of (*2S*)-*N*-acryloyl alanine methyl ester (4.14 g, 28.52 mmol) in dry dimethylformamide (40 ml) at 0 °C, sodium hydride (1.03 g, 25.75 mmol) was added in one portion and the mixture stirred was for one hour at 0 °C. Then methyl iodide (8.87 ml, 27.41 mmol) was added dropwise over 10 minutes and the mixture was stirred vigorously and stirred at RT overnight. The solvent was remove *in vacuo* to yield a yellow oil and the desired product, (*2S*)-*N*-acryloyl-*N*-methyl alanine methyl ester was isolated by flash column chromatography (ethyl acetate/hexane, 1:1) to give a colourless oil (1.82 g, 23 %).

(Found: M^+ -H 170.0810; $C_8H_{12}NO_3$ requires M 170.0817);

ν_{\max} (film) 3300s, 2970s, 1735s, 1632w, 1410m, 1100 cm^{-1} ;

δ_H (400 MHz; d_6 -DMSO) 6.22 (1H, d, J 17.3 Hz, 3'-H), 6.09 (1H, dd, J 17.3 and 10.3 Hz, 2'-H), 5.85 (1H, d, J 10.3 Hz, 3'-H), 3.61 (3H, s, 4-H₃), 2.70 (1H, m, 2-H), 2.26 (3H, s, 5-H₃), 1.18 (3H, d, J 7.1 Hz, 3-H₃);

δ_C (100 MHz; $CDCl_3$) 171.58 (C-1), 167.01 (C-1'), 130.60 (C-3'), 126.56 (C-2'), 54.86 (C-4), 51.19 (C-2), 30.67 (C-5), 14.22 (C-3).

m/z (EI) 170 (M^+ -H, 45), 156 (M^+ -CH₃, 5), 140 (M^+ -OCH₃, 12), 125 (M^+ -O(CH₃)₂, 6), 111 (M^+ -O(CH₃)₃, 5).

Part II: Physical Studies on Surfactant/Micelle Solutions

Light Scattering

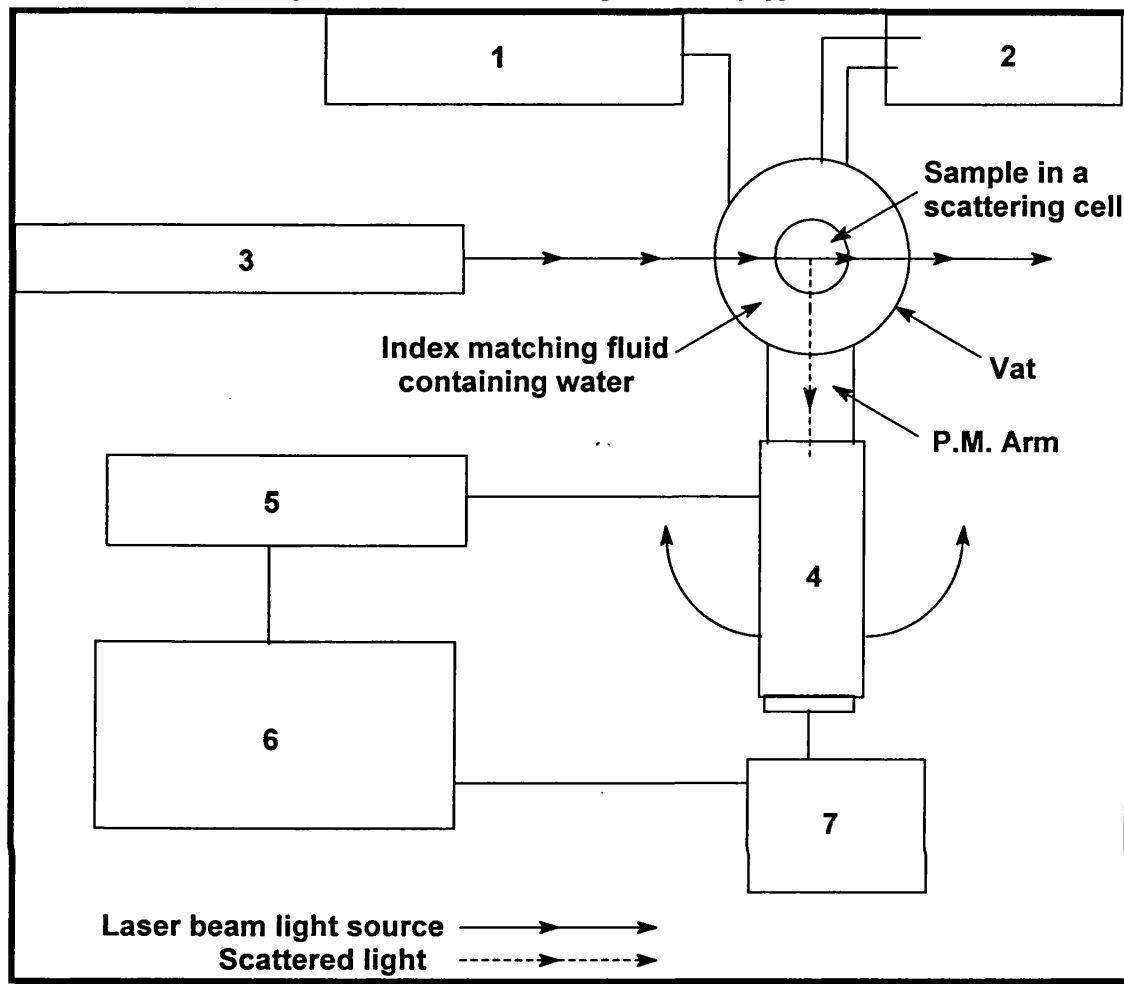
Total Intensity Light Scattering (TILS)

A Malvern 4700c digital auto-correlator was used to measure the scattered light emitted from the surfactant sample. The apparatus is illustrated in figure A.

A fan cooled high intensity 75-mW argon-ion laser was used as an incident light source for the experiment. All experiments were performed using polarised light of wavelength 488 nm.

Light was passed through a sample held in a vat containing water kept thermostatically at $25.0 \pm 0.1^\circ \text{C}$. The vat was attached to a filter pump to free the water in the vat from dust and dirt, to reduce errors introduced by dust scattering light and not by the sample. The scattered light emitted from the sample was detected and amplified by a photomultiplier (P.M.), which was controlled by a stepper motor allowing the operator to change the angle of the P.M. arm relative to the sample. The information collected by the P.M. tube was shunted into a correlator connected to a computer to display the information collected from the sample.

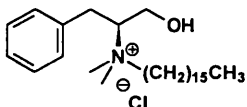
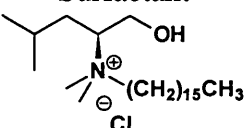
Figure A. Schematics of the Light Scattering apparatus



1. **Temperature Controller** maintains the **vat** at constant temperature of $25 \pm 0.1^\circ \text{C}$.
2. **Filter Pump** filters out the dust and dirt in the water.
3. **Laser** 'fires' a monochromatic light (488 nm) into the **Index matching fluid** housing the **sample**.
4. **P.M. (photomultiplier)** collects the scattered light emitted from the surfactant solution sample.
5. **Correlator** equates the information from the scattered light collected by the **P.M.**
6. **Computer** stores and displays the information from the **Correlator**.
7. **Stepper Motor Control** enables the operator to change the angle of the P.M. arm from $45 - 135^\circ$ with respect to the sample in the **vat**.

Method

The surfactant was dissolved in distilled water to give a 1% solution and filtered three times under pressure using nitrogen through two 0.1 μm "Millipore" filters. The fourth filtration was directly into a light scattering cell. The scattering cell and were washed profusely with distilled water, dried with acetone and stored inverted until needed. All solutions were prepared and diluted using weight. All surfactant solutions were filtered and re-filtered until the value of Z_{45} (ratio of scattered light at 45° to that of 135°) was lower than 1.10. The final filtrate of surfactant solution was collected directly into a light scattering cell and placed in a water bath at $25 \pm 0.1^\circ \text{C}$. The light from the laser beam was focussed in the centre of the cell, from which the scattered light was detected by a photomultiplier (P.M.) tube, converting the scattered light to a count of electron output. Dividing the count rate for the surfactant sample by the count rate for filtered toluene derived the scattering ratio at 90° angle, S_{90} . An average of three counts was taken for each concentration.

Surfactant	Amount of surfactant (g)	Amount of water (g)	%
Phenylalanine-derived (86) Surfactant 	0.2	20	1
Leucine-derived (89) Surfactant 	0.2	20	1

The TILS was determined at 6 different apertures, 500, 400, 300, 200, 150 and 100, for the surfactant sample and calibrating the scattering intensity of the sample with a liquid of known Rayleigh ratio (R_0), toluene was selected. The scattering of the surfactant sample and toluene at the 6 apertures were determined then the mean ratio (S_{90}) of all the apertures calculated.

This procedure was repeated for different % concentrations: 0.8, 0.6, 0.4 and 0.2. Light scattering of distilled water was taken to be 0 % of a surfactant solution. The results are presented as plot of S_{90} as a function on surfactant concentration.

TILS results:

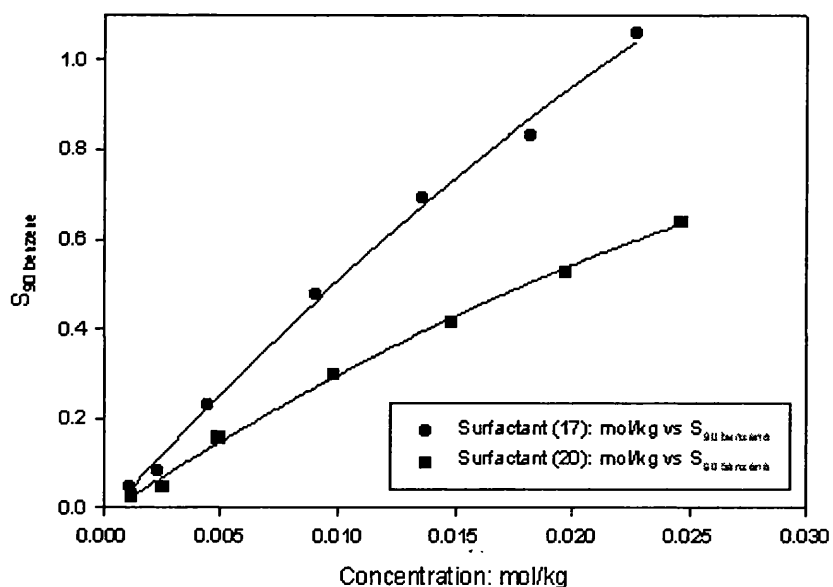
Phenylalanine-derived (86) surfactant

Conc. (%)	$S_{90 \text{ tol}}$	$S_{90 \text{ ben}}$	mol	mol/kg	$c/S_{90 \text{ tol}}$	$c/S_{90 \text{ ben}}$
1	0.953	1.059	0.00227	0.0227	0.0238	0.0215
0.8	0.749	0.832	0.00182	0.0182	0.0243	0.0218
0.6	0.621	0.690	0.00136	0.0136	0.0220	0.0198
0.4	0.430	0.478	0.00091	0.0091	0.0211	0.0190
0.2	0.209	0.232	0.00045	0.0045	0.0217	0.0196
0.1	0.075	0.084	0.00023	0.0023	0.0302	0.0272
0.05	0.043	0.048	0.00011	0.0011	0.0264	0.0238

Leucine-derived (89) surfactant

Conc. (%)	$S_{90 \text{ tol}}$	$S_{9 \text{ ben}}$	mol	mol/kg	$c/S_{90 \text{ tol}}$	$c/S_{90 \text{ ben}}$
1	0.576	0.640	2.46E-03	0.0246	0.0427	0.0385
0.8	0.476	0.529	1.97E-03	0.0197	0.0414	0.0372
0.6	0.376	0.418	1.48E-03	0.0148	0.0393	0.0354
0.4	0.270	0.300	9.85E-04	0.0098	0.0365	0.0328
0.2	0.143	0.159	4.92E-04	0.0049	0.0344	0.0310
0.1	0.044	0.049	2.46E-04	0.0025	0.0560	0.0504
0.05	0.026	0.029	1.23E-04	0.0012	0.0474	0.0426

Graph B shows the plot of S_{90} versus surfactant concentration. From this graph, a trend line was fitted for both surfactant curves and solved for x (e.g. $y = Ax^2 + Bx + C$) to determine the aggregate mass, hence the aggregate number of the respective surfactants by substituting x_{TILS} into equation 2.7 (see below).



Graph B: Plot of S₉₀ versus surfactant concentration (mol/kg)

Refractive Index

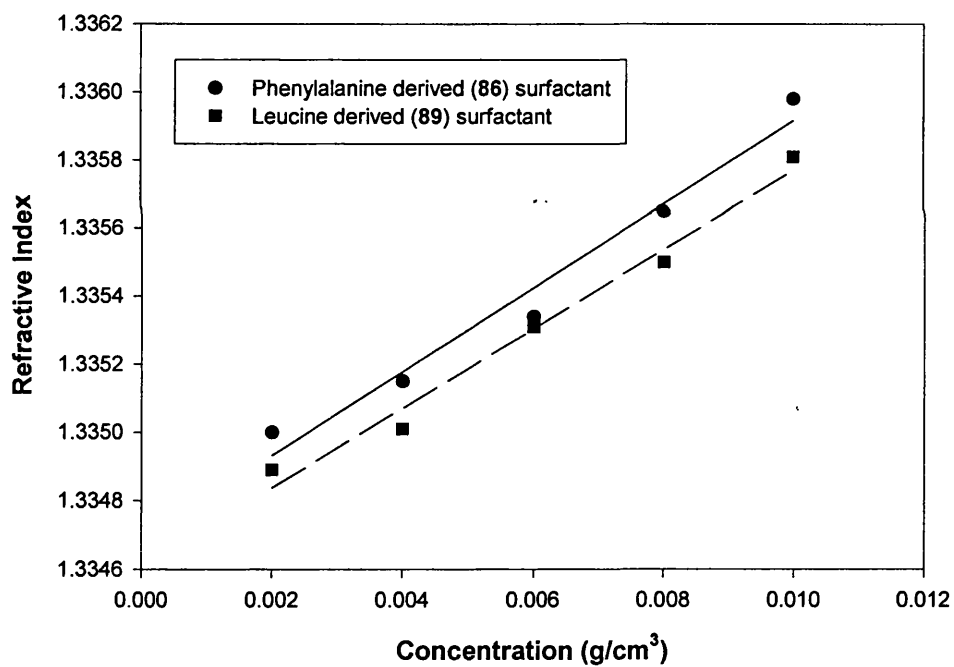
Another important property of a micelle solution is its Refractive Index (RI). The RI of a medium, in this case an aqueous solution, is the ratio of the speed of light in a vacuum to its speed in the medium at a particular concentration of solutes. The squared term $\left(\frac{\partial RI}{\partial c}\right)^2$ in the equation to determine micellar weight, is the change in the refractive index with respect to the concentration of surfactant in solution.

Taking a sample of surfactant solution at different percentage concentrations, the refractive index was determined by a sodium lamp operating at 589.6 nm and a refractometer.

Refractive index results:

Conc. (%)	Conc. (g/cm ³)	Refractive index (86) surfactant	Refractive index (89) surfactant
1.0	0.010	1.33598	1.33581
0.8	0.008	1.33565	1.33550
0.6	0.006	1.33534	1.33531
0.4	0.004	1.33515	1.33501
0.2	0.002	1.33500	1.33489

Pure water has a R_f of 1.3330 at 589.6 nm (sodium lamp) and 25 °C¹¹⁷



Like TILS, a trend line was fitted for both surfactant line and again solved for x_R and substituted into equation 2.7.

$$M = A \frac{1}{\left(\frac{\delta RI}{\delta c}\right)^2} \cdot \frac{S_{90}}{c} \quad \text{Equation 2.7}$$

Where, M = Aggregate mass
 A = Temperature dependent constant, $1.2095 \text{ cm}^3 \text{ mol}^{-1}$ at 25° C .⁶²

$\left(\frac{\delta RI}{\delta c}\right)^2 = x_R$ from refractive index of micelle solution of varying concentrations.

$\frac{S_{90}}{c} = x_{TILS}$ from TILS S_{90} of micelle solution of varying concentrations.

By calculating the aggregate mass and knowing the relative molecular mass (RMM) of the surfactant, it is possible to calculate the aggregation number (N) of a micelle.

Results from calculations:

Surfactant/RMM	Aggregate Mass/AU	Aggregate number
(86) surfactant /440.15	10123	23
(89) surfactant /406.13	7716	19

Surface Tension

Wilhelmy plate method

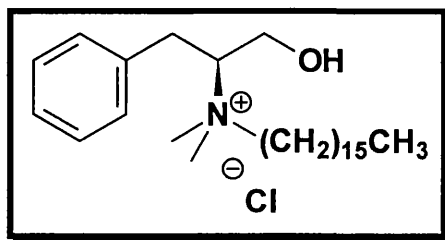
The surface tension of solutions like surfactants was determined experimentally using the Wilhelmy plate method. A thin glass plate that has been soaked in soap solution, washed with copious amounts of triple distilled water and dried with a hot gun was suspended over a surfactant solution of known concentration by a tensiometer connected to a millivolt (mV) meter. The surfactant solution in raised slowly until part of the plate was immersed in the surfactant solution. Then the surfactant solution was lowered slowly until the plate is completely out of the liquid. The 'energy' required to remove the plate from the solution or surface tension was recorded in milli volts (mV), which was converted into milli Newton per metre (mN/m) using the equation 2.8 below.

$$\text{Surface tension (mN/m)} = \frac{\text{mV} \times 980.665}{4.43} \qquad \text{Equation 2.8}$$

This was repeated with different surfactant concentrations by halving the mass of water and replacing the mass taken with triple distilled water, effectively halving the concentration. When the cmc of the solution is almost reached, less water is taken out and replaced. This procedure was repeated till the surface tension was close to the surface tension of water at 72.0 mNm^{-1} .

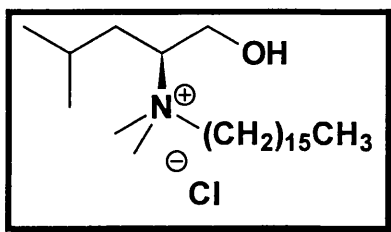
Surface tension results:

Phenylalanine-derived (86) surfactant

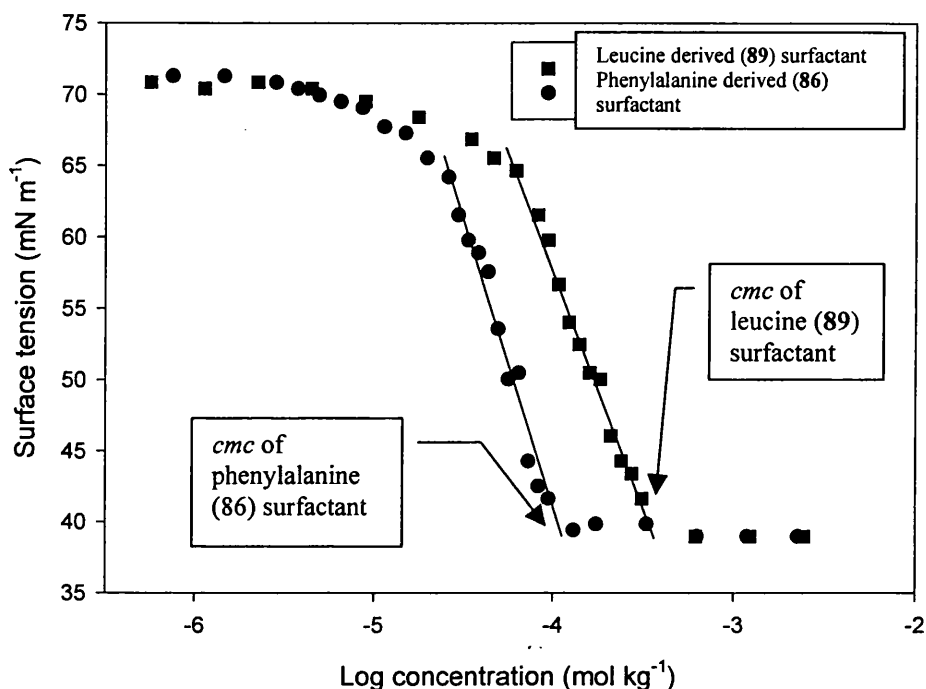


Water taken Out	Water added In	Mass of water	(17) in Solution (g)	% Conc.	Reading mV	(17) ST
-	+	40	4.00E-02	0.10000	0.176	38.96
18.996	19.008	40.012	2.10E-02	0.05249	0.180	39.85
19.006	19.014	40.02	1.10E-02	0.02755	0.176	38.96
18.991	19.009	40.038	5.79E-03	0.01447	0.176	38.96
18.989	19.018	40.067	3.05E-03	0.00760	0.180	39.85
9.9910	10.010	40.086	2.29E-03	0.00570	0.176	38.96
11.299	11.596	40.383	1.64E-03	0.00407	0.184	40.73
10.006	9.991	40.368	1.24E-03	0.00306	0.196	43.39
4.997	5.212	40.583	1.08E-03	0.00267	0.228	50.47
5.001	5.243	40.825	9.49E-04	0.00232	0.232	51.36
4.986	5.004	40.843	8.33E-04	0.00204	0.240	53.13
4.994	5.420	41.269	7.31E-04	0.00177	0.252	55.79
5.000	5.001	41.27	6.43E-04	0.00156	0.264	58.44
4.998	5.000	41.272	5.65E-04	0.00137	0.280	61.98
4.996	4.999	41.275	4.96E-04	0.00120	0.284	62.87
5.001	4.999	41.273	4.36E-04	0.00106	0.288	63.75
10.010	10.000	41.263	3.30E-04	0.00080	0.298	65.97
10.000	9.999	41.262	2.50E-04	0.00061	0.310	68.62
9.998	9.999	41.263	1.90E-04	0.00046	0.312	69.07
9.999	10.000	41.264	1.44E-04	0.00035	0.310	68.62
10.000	10.001	41.265	1.09E-04	0.00026	0.314	69.51
10.000	10.010	41.275	8.25E-05	0.00020	0.316	69.95
9.998	9.996	41.273	6.25E-05	0.00015	0.318	70.40
10.001	9.998	41.270	4.74E-05	0.00011	0.324	71.72
20.000	19.999	41.269	2.44E-05	0.00006	0.324	71.72
20.001	20.000	41.268	1.26E-05	0.00003	0.316	69.95

Leucine-derived (89) surfactant:



Water taken Out	Water added In	Mass of water	(20) in solution (g)	% Conc.	Reading MV	(20) ST
-	+	40.130	4.00E-02	0.09968	0.176	38.96
19.993	20.023	40.160	2.01E-02	0.04998	0.176	38.96
19.997	20.005	40.168	1.01E-02	0.02509	0.176	38.96
20.009	20.011	40.170	5.06E-03	0.01259	0.188	41.62
5.002	5.017	40.185	4.43E-03	0.01102	0.196	43.39
4.996	4.994	40.183	3.88E-03	0.00965	0.200	44.27
4.988	5.070	40.265	3.40E-03	0.00843	0.208	46.04
5.017	5.017	40.265	2.97E-03	0.00738	0.226	50.03
4.988	5.045	40.322	2.60E-03	0.00646	0.228	50.47
4.994	5.013	40.341	2.28E-03	0.00566	0.237	52.46
4.999	5.001	40.343	2.00E-03	0.00496	0.244	54.01
5.000	4.998	40.341	1.75E-03	0.00434	0.256	56.67
5.001	4.998	40.338	1.53E-03	0.00380	0.270	59.77
4.999	4.999	40.338	1.34E-03	0.00333	0.278	61.54
10.001	9.996	40.333	1.01E-03	0.00251	0.292	64.64
10.000	9.999	40.332	7.60E-04	0.00189	0.296	65.53
10.010	10.004	40.326	5.72E-04	0.00142	0.302	66.85
20.001	19.998	40.323	2.88E-04	0.00071	0.309	68.40
20.000	20.010	40.333	1.45E-04	0.00036	0.314	69.51
20.010	19.999	40.322	7.32E-05	0.00018	0.318	70.40
20.120	20.000	40.202	3.67E-05	0.00009	0.320	70.84
20.012	19.994	40.184	1.84E-05	0.00005	0.318	70.40
19.996	20.010	40.198	9.25E-06	0.00002	0.320	70.84



A graph of log concentration versus surface tension was plotted and from the graph, the slope can be determined and the surface excess (Γ) of the surfactant molecule calculated using the Gibbs surface tension equation shown below (equation 2.9).

$$\Gamma = -\frac{\text{slope}}{2RT} \quad \text{Equation 2.9}$$

Then the value Γ was substituted into equation 2.10 to determine area per molecule of each surfactant.

$$\sigma = \frac{1}{\Gamma N_a} \cdot 10 \times 10^{20} \quad \text{Equation 2.10}$$

where N_a = Avogadro's number (6.023×10^{23})

Results from calculations:

Surfactant	Area per molecule (\AA^2)
Phenylalanine-derived (86)	43.6
Leucine-derived (89)	54.6

Summary of Results

Type of Experiment	Surfactant	Aggregate mass	Aggregate number	Area/molecule (\AA)	cmc (mg/L)
TILS + Refractive index	Phenylalanine derived (86)	10123	23	43.6	35
Dye method					9-13
Surface tension	Leucine derived (89)	7716	19	54.6	88
Dye method					11-16

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Appendices

A1: Methyl acrylate + cyclopentadiene: 4 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	4	5	9.3
CTAB	>80	23	4	21	18.0
MeOH	32.7	23	4	11	8.8
CH ₂ Cl ₂	8.9	23	4	sm	-
EtOAc	6	23	4	sm	-
Et ₂ O	4.3	23	4	sm	-
Hexane	1.9	23	4	sm	-

Note: sm = Starting material isolated

Table 3.1

Methyl acrylate + cyclopentadiene: 20 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	21	20	59	6.7
CTAB	>80	21	20	27	15.5
MeOH	32.7	21	20	22	6.6
CH ₂ Cl ₂	8.9	21	20	10	4.8
EtOAc	6	21	20	3	3.0
Et ₂ O	4.3	21	20	4	3.1
Hexane	1.9	21	20	8	2.3

Table 3.2

Methyl acrylate + cyclopentadiene: 72 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	22	72	90	6.6
CTAB	>80	22	72	78	6.5
MeOH	32.7	22	72	40	6.1
CH ₂ Cl ₂	8.9	22	72	36	3.9
EtOAc	6	22	72	48	3.3
Et ₂ O	4.3	22	72	47	3.1
Hexane	1.9	22	72	31	2.4

Table 3.3

A2: Ethyl acrylate + cyclopentadiene: 4 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	4	65	6.1
CTAB	>80	23	4	91	7.2
MeOH	32.7	23	4	7	5.6
CH ₂ Cl ₂	8.9	23	4	6	8.0
EtOAc	6	23	4	5	5.2
Et ₂ O	4.3	23	4	1	5.7
Hexane	1.9	23	4	sm	-

Note: sm = Starting material isolated

Table 3.4

Ethyl acrylate + cyclopentadiene: 20 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	20	45	5.6
CTAB	>80	23	20	92	3.9
MeOH	32.7	23	20	23	2.3
CH ₂ Cl ₂	8.9	23	20	14	3.4
EtOAc	6	23	20	4	2.5
Et ₂ O	4.3	23	20	8	2.3
Hexane	1.9	23	20	sm	sm

Note: sm = Starting material isolated

Table 3.5

Ethyl acrylate + cyclopentadiene: 72 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	72	79	4.8
CTAB	>80	23	72	92	5.5
MeOH	32.7	23	72	81	6.1
CH ₂ Cl ₂	8.9	23	72	52	4.2
EtOAc	6	23	72	12	3.2
Et ₂ O	4.3	23	72	5	3.1
Hexane	1.9	23	72	38	2.3

Note: sm = Starting material isolated

Table 3.6

A3: Pentyl acrylate + cyclopentadiene: 4 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	4	41	1.6
CTAB	>80	23	4	68	1.7
MeOH	32.7	23	4	10	1.9
CH ₂ Cl ₂	8.9	23	4	2	0.7
EtOAc	6	23	4	2	1.1
Et ₂ O	4.3	23	4	0	0
Hexane	1.9	23	4	6	X 0.7

Table 3.7

Pentyl acrylate + cyclopentadiene: 20 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	20	78	1.8
CTAB	>80	23	20	64	1.8
MeOH	32.7	23	20	48	3.4
CH ₂ Cl ₂	8.9	23	20	11	2.0
EtOAc	6	23	20	11	1.8
Et ₂ O	4.3	23	20	9	1.0
Hexane	1.9	23	20	22	1.2

Table 3.8

Pentyl acrylate + cyclopentadiene: 72 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	72	75	1.8
CTAB	~ 80.2	23	72	79	1.8
MeOH	32.7	23	72	75	3.3
CH ₂ Cl ₂	8.9	23	72	54	2.0
EtOAc	6	23	72	45	1.8
Et ₂ O	4.3	23	72	46	1.4
Hexane	1.9	23	72	55	1.4

Table 3.9

A4: Heptyl acrylate + cyclopentadiene: 4 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	24	4	18	1.7
CTAB	>80	24	4	36	1.7
MeOH	32.7	24	4	38	2.6
CH ₂ Cl ₂	8.9	24	4	8	1.7
EtOAc	6	24	4	4	1.8
Et ₂ O	4.3	24	4	4	1.0
Hexane	1.9	23	4	2	X 1.9

Table 3.10

Heptyl acrylate + cyclopentadiene: 20 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	20	47	1.9
CTAB	~ 80.2	23	20	33	2.0
MeOH	32.7	23	20	23	3.3
CH ₂ Cl ₂	8.9	23	20	19	2.3
EtOAc	6	23	20	17	2.6
Et ₂ O	4.3	23	20	6	2.5
Hexane	1.9	23	20	6	1.8

Table 3.11

Heptyl acrylate + cyclopentadiene: 72 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	72	38	1.8
CTAB	~ 80.2	23	72	62	1.8
MeOH	32.7	23	72	55	3.1
CH ₂ Cl ₂	8.9	23	72	43	2.9
EtOAc	6	23	72	21	1.3
Et ₂ O	4.3	23	72	26	1.3
Hexane	1.9	23	72	18	1.1

Table 3.12

A5: Nonyl acrylate + cyclopentadiene: 4 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	4	34	1.7
CTAB	~ 80.2	23	4	29	1.2
MeOH	32.7	23	4	4	2.8
CH ₂ Cl ₂	8.9	23	4	2	0.9
EtOAc	6	23	4	sm	-
Et ₂ O	4.3	23	4	sm	-
Hexane	1.9	23	4	sm	-

Note: sm = Starting material isolated

Table 3.13

Nonyl acrylate + cyclopentadiene: 20 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	20	70	1.7
CTAB	~ 80.2	23	20	82	1.7
MeOH	32.7	23	20	25	3.3
CH ₂ Cl ₂	8.9	23	20	10	1.8
EtOAc	6	23	20	5	1.7
Et ₂ O	4.3	23	20	5	1.7
Hexane	1.9	23	20	4	1.1

Table 3.14

Nonyl acrylate + cyclopentadiene: 4 hours

Solvent	Polarity	Temp. °C	Time hr.	% yield	N/X ratio
H ₂ O	80.2	23	72	85	1.7
CTAB	~ 80.2	23	72	87	1.7
MeOH	32.7	23	72	41	3.2
CH ₂ Cl ₂	8.9	23	72	23	2.3
EtOAc	6	23	72	11	1.4
Et ₂ O	4.3	23	72	9	1.4
Hexane	1.9	23	72	12	1.3

Table 3.15

A6: pH effects on the Diels-Alder reaction

Water pH	% product Yield	N/X ratio
1.00	31	1.5
2.73	73	2.3
5.33	73	1.9
6.81	78	1.9
9.15	75	2.0

Table 3.17: pH effects on water in Diels-Alder reaction