

Selectivity in inter- and intra-molecular photocycloaddition of ethenes to benzenoid compounds

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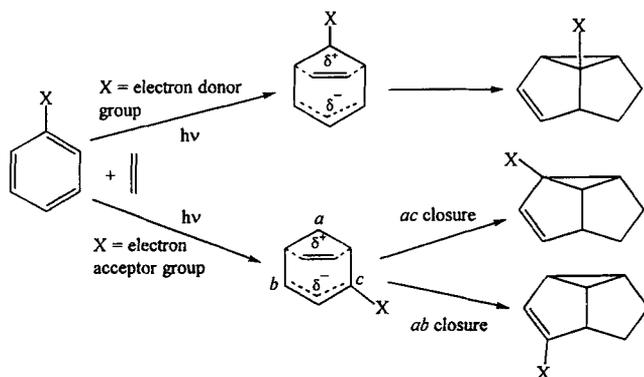
Abstract. The formation of isomers from the inter- and intra-molecular *meta* photocycloaddition of ethenes to the benzene ring has been specifically directed using the addend substituents in order to cause an asymmetric distortion of the C_6 ring during the reaction, and to induce non-synchronicity into the addition process. The latter influence in the intramolecular reaction is achieved by the presence of a heteroatom in the linking tether which also provides a convenient access to linear and angular heterotriquinanes. The *meta* photoaddition can be induced by sunlight exposure of appropriately substituted arene–ethene bichromophores.

Keywords. Photocycloaddition; sunlight; dihydrosemibullvalene; triquinanes.

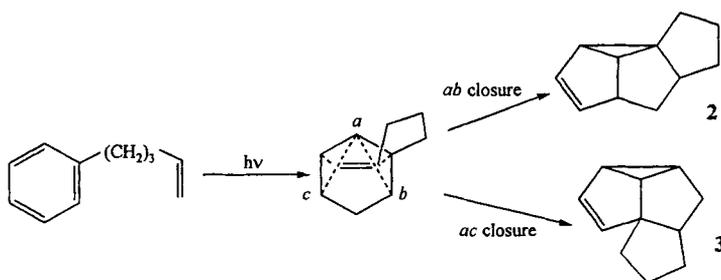
1. Introduction

Photoinduced processes of organic compounds have appreciable potential for exploitation as key steps in synthetic sequences, not only because the methodology is clean and does not involve aggressive reagents leading to toxic by-products, but also because such reactions can lead in one step to an appreciable increase in molecular complexity^{1,2}. Although the thermal chemistry of the benzene ring is dominated by substitution processes, in sharp contrast, the reactions of the photoexcited singlet state lead to a rich diversity of aliphatic products of potential elaboration towards biologically active compounds³. In particular, the photocycloadditions of ethenes to the benzene ring have attracted appreciable interest, both for their synthetic use as an access to polycyclic systems⁴ and for their intriguing mechanistic aspects⁵. Theoretical studies have been made of these cycloaddition processes^{5,6} and recently Clifford and co-workers⁷ have noted that the first step in the addition of ethenes to the benzene ring is the formation of one C–C bond without a barrier to give the low energy S_1/S_0 conical intersection 1. This species can then lead to adduct formation with the reaction mode selectivity being controlled by the substituent stabilisation of biradical intermediates. The major conclusions from other theoretical studies are that, in agreement with experimental observations, the *para* process giving bicyclo[2.2.2]octa-2,5-dienes is the least favoured mode of addition and that the formation of bicyclo[4.2.0]octa-2,4-dienes from *ortho* cycloaddition and tricyclo[3.3.0.0^{2,8}]oct-3-enes (dihydrosemibullvalenes) from *meta* cycloaddition arise respectively from a pathway involving a degree of charge transfer between the addends and from attack of the S_0 ethene onto the S_1 benzenoid compound.

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Scheme 1. *m*-Photocycloaddition of ethenes to mono-substituted benzenes.



Scheme 2. Intramolecular *m*-photocycloaddition of 5-phenylpent-1-enes

The *meta* photocycloaddition process has been used as a key step in the synthesis of a variety of naturally occurring compounds⁸⁻¹⁰, and has therefore, been the subject of a number of mechanistic studies¹¹. Both bicyclo[3.2.1]octenyl zwitterionic and biradical species have been postulated as intermediates in this convenient and versatile access to the dihydrosemibullvalene skeleton, but the high regioselectivity of the addition can be equally well accommodated by substituents on the arene stabilising the polarity which develops in the S_1 benzene ring on approach of the S_0 ethene as indicated in scheme 1¹²⁻¹⁴. Nevertheless, both from intermolecular attack of the ethene at the 2,4-positions of the benzene ring (scheme 1) and, more importantly for the synthetic applications, from the 1,3-intramolecular addition in 5-phenylpent-1-enes (scheme 2), linear and angular triquinane photoisomers 2 and 3 respectively, are produced resulting from the two directions of cyclisation to give the cyclopropane ring in the adduct. In both cases, the photoisomers can, in principle, be interconverted thermally and photochemically by an ethenylcyclopropane-cyclopentene rearrangement. Frequently, however, it has been found, that at best, enriched mixtures are obtained from such experiments and, in general, much involatile material is formed. There is thus a need to develop a methodology which can direct the intramolecular cyclisation in the C_6 ring of the addition intermediate in order to provide a discrimination between the formation of the photoisomers. The attainment of such control along the reaction pathway of *meta* photocycloaddition of ethenes to the benzene ring will

make the process more attractive as an established synthetic method, and will also provide useful information concerning the mechanistic details of this intriguing reaction.

In the present paper, we review and discuss how control over the closure to give the cyclopropane ring and hence over the isomer formation from both the inter- and intra-molecular *meta* photocycloaddition reactions can be achieved by using directing influences of the substituents on the benzene and ethene addends.

2. Results and discussion

The *meta* photocycloaddition of ethenes to the benzene ring occurs with high regioselectivity, and photoadduct isomers arise from the two, generally indiscriminate, directions of intramolecular cyclisation to give the cyclopropane ring. From studies into the influences of addend substituents on isomer formation, we have evolved approaches to attain the required control over isomer formation which, for the present purposes, can be conveniently divided into (i) asymmetric distortion of the C_6 ring in reaction intermediates, and (ii) non-synchronous addition of the ethene. Both approaches use substituents to force $C-1$ of the benzene to become closer to one or other of its *meta* carbon atoms during the addition, and cyclisation then occurs specifically between these sites.

2.1 Ring distortion effects

Our first attempts to direct the cyclopropane ring formation and hence control the photoisomer formation were formulated using steric interactions of the addend substituents to orient the molecules and electronic features to promote the intramolecular cyclisation¹⁵. From considerations of electron donor - electron acceptor properties, the benzonitrile - *trans* 1,2-dichloroethene (TDCE) addend pair is predicted to markedly favour the *meta* rather than the *ortho* cycloaddition process, and from consideration of substituent stabilisation of developing charge in the C_6 ring, the addition should occur at the 2,4-positions of the benzonitrile. We reasoned that the steric repulsions between the substituents would favour the orientation 4 for the addition and that the cyano group would influence the direction of cyclopropane ring formation by delocalisation of the anionic allylic moiety in the C_6 ring (i.e. preferred *ab* closure in 4). Irradiation of this system satisfyingly gives solely the 4-cyano-6-*exo*-7-*endo*-dihydrosemibullvalene 5. However, since the 6-*exo*-7-*endo*-stereochemistry of the dichloro substituents is also observed in *meta* cycloadditions of TDCE to benzenes having no electron withdrawing substituents, the direction of the cyclopropane ring formation is considered not to arise from an electronic feature of the substituent. Instead, the control is rationalised in terms of an asymmetric distortion of the C_6 ring arising from a repulsive interaction between the *endo*-chlorine atom and $C-3$, as depicted in 6^{16,17}. This distortion brings $C-1$ and $C-3$ into close proximity and thus favours cyclisation between these positions rather than between $C-1$ and $C-5$. It is, however, surprising that such control by distortion is specific rather than selective.

As noted previously, the intramolecular *meta* photocycloaddition of 5-phenylpent-1-enes has been used as the key step in a number of synthetic sequences towards polyquinanes and other naturally occurring compounds. In these arene - ethene bichromophores, it is necessary to be able to access, as required, either the linear or the angular triquinane photoisomers specifically in order to increase the chemical yield of

these key synthetic intermediates and to obviate the need for chromatographic separations. The *endo*-chlorine-induced distortion effect has been applied to this problem in the intramolecular addition and the required discrimination between the formation of the two triquinane photoadduct isomers has been achieved¹⁸. Thus, irradiation of 2-chloro-5-phenylpent-1-ene 7 yields products derived only from the linear isomer 8 with the solvent methanol, and the 1,3-shift product 9 of the angular triquinone adduct 10 comprises 70% of the product mixture from *E*-1-chloro-5-phenylpent-1-ene 11; the other photoisomers are derived from 2,6-cycloaddition.

The photoaddition of TDCE to phenols provides an interesting variant of this 'distortion' control and although the adducts are bicyclo[3.3.1]oct-2-en-8-ones 12, the stereochemistry of the chlorine atoms is consistent with the prior formation of the 1-hydroxy-6-*exo*-7-*endo*-dichloro-dihydrosemibullvalenes 13^{17,19}. Such 1-hydroxy compounds have been considered to rearrange readily to the ketones under acidic conditions but until recently their inherent thermal lability resulting from a facile homodienyl 1,5-hydrogen shift had not seemingly been appreciated. Following this realisation, we have investigated the possibility that as the ethene undergoes addition at the 2,6-positions of the phenol and induces non-planarity in the C₆ ring, an appropriate electronegative 3-substituent (e.g. the trifluoromethyl group) could interact with the hydroxy group. The effect of this intramolecular hydrogen bonding should then be to cause asymmetry in the non-planar C₆ ring and thereby bring C-1 and C3 closer together as depicted in 14. Thus, the hydrogen bonding may not only prevent the 1,5-hydrogen shift but also distort the C₆ ring sufficiently to promote 1,3-cyclisation in the intermediate species. It may also be considered that the preference for 1,3- as against 1,5-cyclisation would be further enhanced as a result of the 3-substituent, localising the charge in the allylic anionic moiety. This feature can indeed, be significant for the cyano group. For example, during the photoaddition of cyclopentene to 3-cyanoanisole, a 4:1 ratio is observed for 1,3- to 1,5-cyclisation^{20,21}. However, the effect of a 3-trifluoromethyl substituent is minor and the preference for the 1,3-cyclisation from the addition of cyclopentene to 3-trifluoromethylanisole is less than 10%²¹. In marked contrast, the irradiation of 3-trifluoromethylphenol and cyclopentene gives exclusively a 2.5:1 ratio of the *exo* and *endo* isomers of 1-hydroxy-11-trifluoromethyl[6.3.0.0^{2,11}.0^{3,7}]undec-9-ene 15 (i.e. solely 1,3-cyclisation)²². Since the trifluoromethyl group appears to exert little electronic influence over the intramolecular cyclisation, it is deduced that the cyclopropane ring formation is directed by the distortion of the C₆ arising from the intramolecular hydrogen bonding between the hydroxyl and trifluoromethyl substituents as depicted in 14. This feature also evidently inhibits the 1,5-hydrogen shift in 1-hydroxy-dihydrosemibullvalenes and thereby allows the isolation of these substituted *meta* photoadducts.

It is noteworthy that no accounts have appeared describing the photoaddition of ethenes to benzyl alcohol or its simple derivatives, and in particular, we have noted the total absence of adduct formation between cyclopentene and this benzenoid compound. The reason for this lack of reactivity remains obscure but in view of the results for the *meta* photocycloadditions to phenols, it was of interest to determine if hydrogen bonding of the hydroxyl group of benzyl alcohol would not only promote the photoaddition reaction but would also give rise to a sufficient distortion in the C₆ ring to induce the C-1 - C-3 cyclisation as depicted in 16. Satisfyingly, the presence of a 3-trifluoromethyl substituent on benzyl alcohol did indeed induce an efficient, regiospecific 2,6-photoaddition of cyclopentene to the benzene ring followed by specific

formation of the cyclopropane ring between the 1,3-positions. To determine whether the well-known attractive interaction between fluorine and silicon could be similarly employed to distort the six-membered ring during the photoaddition process and lead to specificity in adduct isomer formation, we examined the photoaddition of cyclopentene to 3'-trifluoromethylbenzyltrimethylsilane. Again, the direction of cyclopropane ring formation was specifically controlled giving solely the *exo* and *endo* isomers of 17. It is thus evident that distortion in the C_6 is a powerful and versatile method for controlling the isomer formation in the *meta* photocycloaddition of ethenes to the benzene ring. Furthermore, such distortion can be generated in several ways and result in selectivity of isomer formation in a predictable manner.

2.3 Control by non-synchronous addition

The first indications that control may possibly be achieved over the direction of cyclisation to give the cyclopropane ring by influencing the synchronicity of the ethene addition, were reported from studies on the selectivity of photocycloaddition of cyclopentene to disubstituted benzenes. For example, in 2-substituted anisoles, the methoxy group directs the regiochemistry of the ethene addition to the 2,6-positions and the 2-substituent then resides at either the 5- or 8-position of the dihydrosemibullvalene skeleton depending on the preference for either 1,5- or 1,3-intramolecular cyclisation respectively, in the addition intermediate. For a 2-methyl group, the 5-substituted *meta* photoadduct is greatly preferred over the 8-isomer (2:1 respectively)²³⁻²⁵, whereas only the 8-cyano substituted adduct is observed from 2-cyanoanisole²⁶. It is, however, to be noted that in this latter system, the *meta* cycloadducts comprise only 5% of the total product mixture. From these and other observations, it has been tentatively concluded that an electron acceptor substituent at the 2-position preferentially promotes the cyclisation between the 1,3-carbon atoms¹¹. This feature is proposed to originate as follows. It has been argued that during this addition there is a degree of electron flow from the ethene to the S_1 benzene and so an acceptor group at C-2 promotes bond formation between this carbon atom and the ethene²⁶. The result is that C-2 attains sp^3 character prior to C-6 and hence C-1 and C-3 are in closer proximity that C-1 and C-5 and undergo bond formation to give the cyclopropane ring. The situation is reversed with a donor group at the 2-position and bond formation to the ethene then occurs preferentially with C-6, and cyclisation is favoured between C-1 and C-5 to give the 8-substituted adduct. Thus, non-synchronicity of the ethene addition which, in these intermolecular processes is induced by electronic effects, can, in principle, be used to control the cyclopropane ring formation and discriminate between positional isomers of the *meta* photocycloadduct. The scope of this approach is, however, limited and cannot readily be applied to the synthetically more useful intramolecular *meta* process.

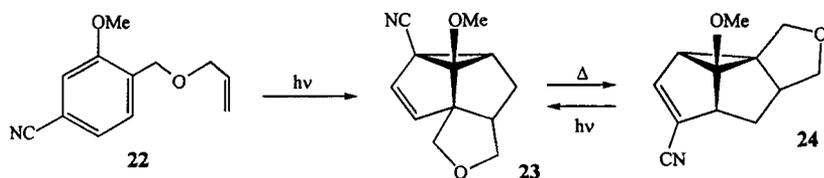
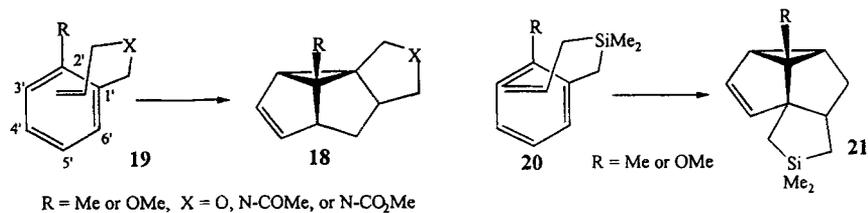
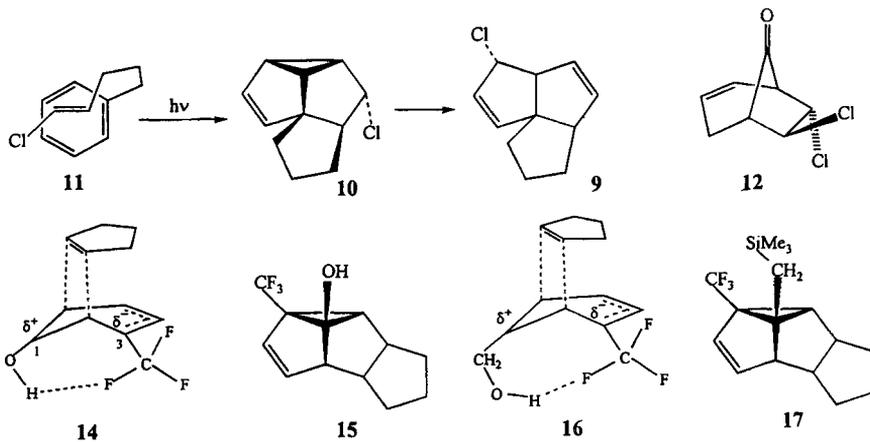
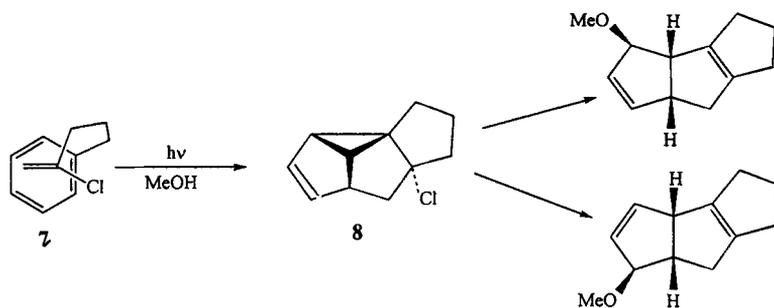
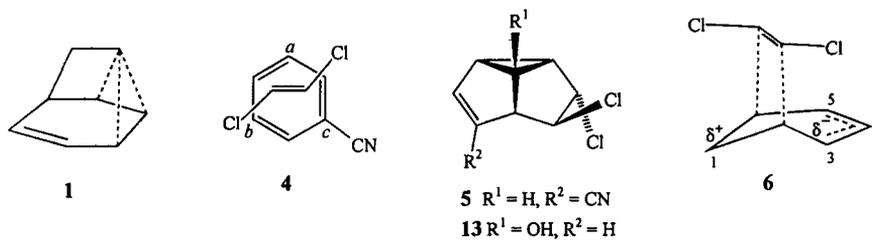
It was the need to evolve a method to discriminate between the linear and angular triquinane adduct isomers from 1,3-intramolecular photoaddition of arene-ethene bichromophores that led us to consider the potential of using the linking unit to control the orientation of the addends and to vary the distance between the addition centres of the ethene and the benzene ring. The latter feature was of particular interest as it would allow an assessment of the feasibility of inducing non-synchronicity into the addition of the ethene by using asymmetry in the orientation of the addends. Early attempts to control the conformation, using methyl groups in the connecting unit and cyclic

ethenes, produced little indication that these features would induce the required distortion which may discriminate between the formation of the two photoadduct isomers²⁷. However, from studies into the use of the intramolecular *meta* photocycloaddition to access heteropolycyclic systems we have been able to overcome this problem and induce the required asymmetry in the bichromophore orientation. Since the *meta* reaction does not occur with pyridines, and neither imines nor azo compounds undergo photoaddition to the benzene ring, the heteroatoms were incorporated into the linking unit.

In order to ensure that the intramolecular *meta* photocycloaddition occurred at the 1',3'-positions, it was necessary to incorporate the heteroatom (O, N) at the 4-position of the interconnecting tether of the 5-phenylpent-1-ene bichromophore since with oxygen at the 3- or 5-positions the reaction is non-selective²⁸ or occurs at the 2',6'-positions respectively²⁹, and no addition is observed in the corresponding aza compounds. Furthermore, with nitrogen at the 4-position, electron transfer and back electron transfer are highly favoured and no intramolecular cycloaddition occurs³⁰. This feature was, however, readily overcome by protecting the nitrogen in the 3-benzylazaprop-1-enes in an amide or urethane grouping. Incorporation of a 2'-methyl or 2'-methoxy substituent to direct the regiochemistry of the intramolecular addition to the 1',3'-positions resulted in the *meta* cycloaddition reaction yielding essentially solely the linear triquinane isomer 18 from both the oxa and aza bichromophores³¹. This remarkable selectivity in the direction of formation of the cyclopropane ring can be conveniently explained by the smaller bond angle and the shorter bond lengths in the $-\text{CH}_2-\text{X}-\text{CH}_2-$ tether compared to the hydrocarbon systems. The species then formed on interaction of the chromophores would have asymmetrical orientation of the S_1 benzene ring and S_0 ethene as depicted in 19. It is proposed that such asymmetry results in non-synchronous addition of the ethene and C-1' to C-2 bonding is thereby promoted in preference to C-3' to C-1 bonding. Thus C-1' attains a tetrahedral geometry prior to C-3' and hence the cyclopropane ring is formed between C-2' and C-6' to give the linear isomers with high selectivity. To determine the validity of this rationale of the findings, we examined the intramolecular photocycloaddition reactions of 3-benzyl(dimethylsila)prop-1-enes, since in these bichromophores the longer Si-C bonds compared to C-C bonds should give the orientation depicted in 20 for the addition precursor. If asymmetry in the intermediate species does control the synchronicity of the ethene addition, then bonding between C-3 and C-1 would be preferred in 20 and lead to selective formation of the angular triquinane isomer. In the unsubstituted bichromophore (20, R = H) the addition occurs exclusively at the 2',6'-positions as a result of the β -stabilising effect of silicon on the developing positive charge in the C_6 ring³². However, for both the 2'-methyl and 2'-methoxy derivatives the *meta* photoisomers have the angular triquinane structures 21 exclusively³³. It is concluded, therefore, that non-synchronicity in the ethene addition can be induced by asymmetry in the addition precursor species. The non-synchronicity leads to high selectivity in adduct isomer formation by promoting one of the two directions of intramolecular cyclisation which give the cyclopropane ring.

2.3 Sunlight-initiation

The first example of the cycloaddition of an ethene to the benzene ring in sunlight was reported in 1962 and involved excitation within the charge-transfer absorption band of the maleic anhydride-benzene system³⁴. Since then few other examples have been



described. Our particular interest has been to induce the *meta* cycloaddition in sunlight and thereby attain a 'clean' synthesis of the linear and angular triquinane isomers. To this end, the solar chemistry of benzenes having both electron donor and electron acceptor substituents has been investigated³⁵. For many of these systems, *ortho* cycloaddition is favoured but the substituents in 3-cyanoanisole act in concert on the stabilisation of the developing charges in the C_6 ring during *meta* addition and dihydrosemibullvalenes can be obtained albeit from long exposure times. The potential of this approach is illustrated with the ether-tethered bichromophore, 3-(2'-methoxy-4'-cyanobenzyloxy)prop-1-ene 22 which has λ_{\max} 294 nm with a tail \approx 340 nm. Exposure to both sunlight and the radiation from a medium pressure mercury arc lamp give essentially quantitative yields of the two photoisomers having the angular and linear structures 23 and 24 respectively in varying relative amounts. Experiments on the separated photoisomers showed that the variability in the relative yields arose from the ease of the thermally- and photochemically-induced ethenylcyclopropane-cyclopentene rearrangements in this system. Thus 23 readily isomerised to the linear isomer 24 on warming its solutions, and the retro process was accomplished in high yield by irradiation in the 260–280 nm region.

3. Experimental

For intermolecular systems, solutions of the benzenoid compound (0.3 mol dm^{-3}) and the ethene (1.0 mol dm^{-3}) in acetonitrile, dioxane or cyclohexane were irradiated under air in $50 \times 1.25 \text{ cm}$ (i.d.) quartz tubes. The bichromophores were irradiated as 1% w/v solution in the same solvents and under the same conditions. In both cases the reactor was fitted with six 18 w low pressure mercury arc lamps. The photoreactions were monitored by capillary gas chromatography and tlc. The photoadducts were separated by flash chromatography as described previously²² and the spectral data from which structures were assigned have been reported in detail elsewhere²². The apparatus used for the sunlight-initiated reactions has also been previously described³⁵.

Acknowledgements

A postgraduate studentship (to DMA) from the Engineering and Physical Sciences Research Council is gratefully acknowledged.

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