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Photocycloaddition

Photochemistry of Arenes—Reloaded

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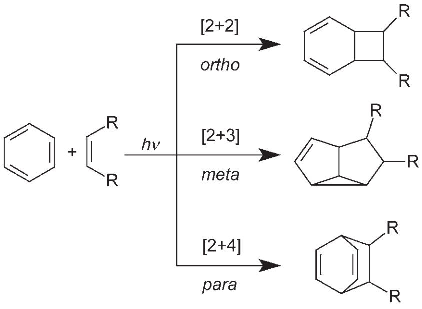
The chemistry of aromatic compounds is familiar to students after their first semester. Thus, when asked about the typical reaction of arenes, the common and (of course) right answer is: Substitution. However, there is more than one answer!

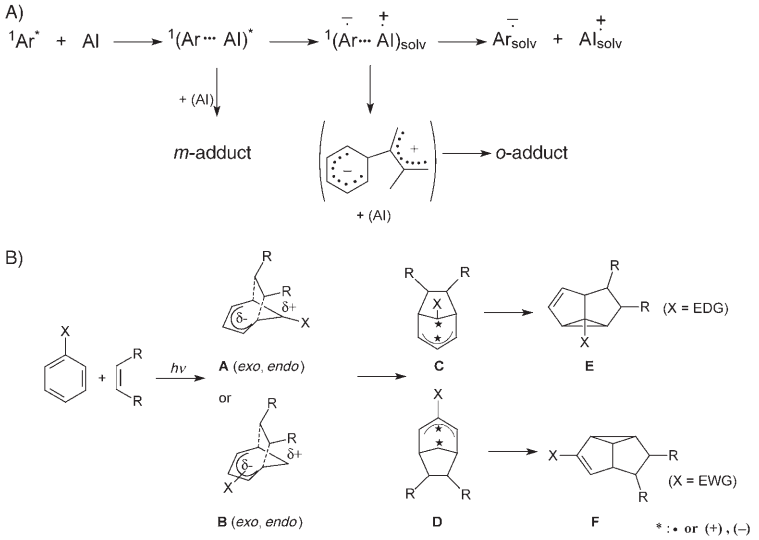
This year chemists have been able to celebrate a discovery that represents a milestone in arene chemistry: The *meta* photocycloaddition of alkenes to benzene, which was developed 40 years ago independently by Wilzbach and Kaplan as well as by Bryce-Smith, Gilbert, and Orger.[1] This discovery was preceded by a development at the end of the 1950s which was probably even more pioneering and expanded the range of general reactions of benzene and arenes extraordinarily: *ortho* photocycloaddition, which was also discovered by the pioneer of arene photochemistry, Bryce-Smith,[2] although Ayer and Büchi had already described it in a patent in 1957.[3] Interestingly, *para* photocycloaddition to benzene was later reported by Wilzbach and Kaplan.[4] Scheme 1 shows these three types of photocycloaddition at benzene. In most cases the common feature of the described reactions is the pathway via the first excited singlet-state of benzene ($^1B_{2u}$). Some special cases involve electron-donor–electron-acceptor (EDA) complexes, triplet states, and excited states of the reaction partners (alkenes or alkynes).



Scheme 1. *Ortho*, *meta*, and *para* photocycloaddition of alkenes to benzene.

The period after these developments, namely, the 1960s and 1970s, was characterized by high research activity, and involved many research groups. The reactions of benzene, as well as its simple and multiply substituted derivatives were investigated in detail. Of the great number of review articles concerning arene photochemistry, only a few shall be mentioned here, in particular the excellent reviews (in the author's opinion) by Cornelisse and Hoffmann,[5,6] who present a selection of important cycloadditions. The contributions from the Leiden research group provide a particularly discerning and very good insight to date into the long-discussed mechanism of photocycloadditions to benzene (Scheme 2).[5] The *meta* variation attracted the authors attention because of its unexpected pathway and its uncommon products. In the 1980s a universally valid model regarding the reaction mechanism was developed, and the effect of charge transfer on the periselectivity (*ortho* versus *meta*) as well as the influence of the substituents on the regio- and stereoselectivity could be resolved.[7]

Chemists did not become aware of the great potential of the *meta* photocycloaddition until the elegant work of



Scheme 2. A) Exciplex formation and deactivation processes, and B) mechanism of the *meta* photocycloaddition of alkenes to benzene and its derivatives—simplified illustration according to ref. [7] (**F**: only one regioisomer is shown, see Scheme 7). Ar: arene, Al: alkene, EDG: electron-donating group, EWG: electron-withdrawing group.

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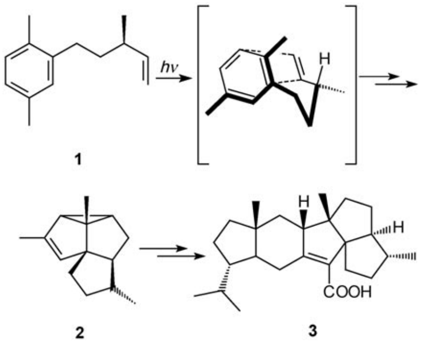
Wender et al. was published in the 1980s which showed an efficient way to synthesize numerous natural products.[8] Among these examples, the synthesis of (−)-retigeranic acid (**3**) involves the cycloaddition of the simple *para*-xylene derivative **1** as the key step to give the tetracyclic compound **2** (Scheme 3).[9]

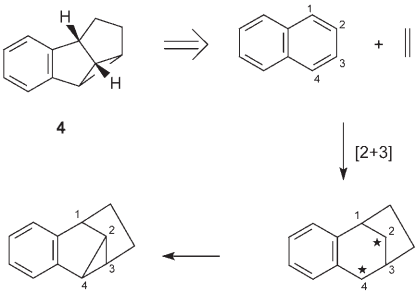


Scheme 3. Synthesis of (−)-retigeranic acid according to Wender and Singh.[9]

This step is remarkable because of the high atom economy[10] and the large increase in the structural complexity.[9] Hence, it is no surprise that the importance of *meta* photocycloaddition was often compared to that of the Diels–Alder reaction, although it has not reached such widespread application.[8]

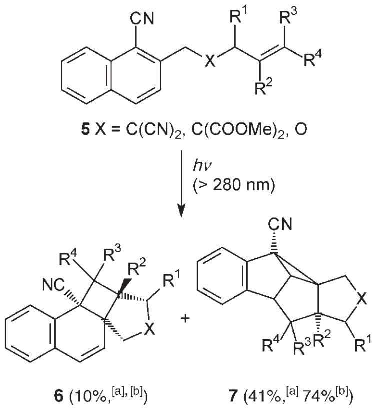
Photocycloadditions of alkenes to higher arenes such as naphthalene or anthracene, for example, were also reported very early on. Until now, priority has been given to [2+2], [4+2], and [4+4] cycloadditions, in most cases aiming for complex cage structures.[11] In this context, the fundamental work of Prinzbach and Weber should be noted, in which cycloadditions and dimerizations of two arenes were used to build Platonic hydrocarbons.[12]

Occasionally compounds of benzosemibullvalenes of type **4** were reported, which were formed by a di-π-methane rearrangement[13] from corresponding *para* cycloadducts.[14] Compound **4** is theoretically also accessible by *meta* photocycloaddition of ethene to naphthalene (Scheme 4). Such reactions, which have frequently been reported with benzene, have rarely been observed with naphthalene.



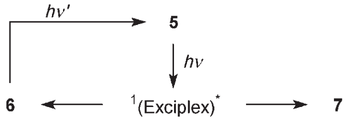
Scheme 4. Construction of the semibullvalene structure by *meta* photocycloaddition of ethene to naphthalene. ∗: · or (+),(−).

This is unexpected, because the wide knowledge of benzene photochemistry should have made this a known strategy. As often happens, there are other factors which play a decisive role: In this case the factors are the different properties of the *ortho* and *meta* cycloadducts of naphthalene under given reaction conditions. Mukae, Maeda, and Mizuno have achieved a breakthrough in the direct formation of naphthalene *meta* adducts recently when they described the intramolecular photocycloadditions of alkenes to cyanonaphthalenes and naphthalene carboxylic acid esters (Scheme 5).[15]



Scheme 5. Intramolecular photocycloaddition of alkenes to naphthalene derivatives; yields after a) 3 h and b) 10 h irradiation.

Why have the *meta* cycloadducts been overlooked so far? McCullough and co-workers[16] would have discovered them 25 years ago, if they had interpreted the facile cycloreversion of the *ortho* adducts correctly. However, the Mizuno group realised this fact and used it for the formation of the *meta* cycloadducts. Scheme 6 shows the proposed mechanism: Under the irradiation conditions of the naphthalene derivative **5** ($\lambda > 280$ nm) the product **7** shows only weak absorption (simple benzene chromophore), thus it is stable. The primary formed *ortho* adduct **6** (styrene chromophore) shows strong absorption at $\lambda > 280$ nm and undergoes cycloreversion easily. For this reason it is no surprise that at low reaction rates the *ortho* adducts are the main products. Only with longer irradiation times does the product ratio reverse and the *meta* adducts can be isolated in high yields (up to 85 %). The situation resembles to some extent those of benzene and its simple derivatives: Under commonly used conditions (use of a mercury low-pressure lamp at $\lambda = 254$ nm) the *ortho* adducts can also be excited, and are capable of cycloreversion and rearrangement to *para* adducts.[7]



Scheme 6. Mechanism of the formation of *meta* adducts **7** from **5**.

Some other aspects of these photocycloadditions need to be discussed, namely the periselectivity (*ortho* versus *meta*) and the regioselectivity (the position of the directing cyano group). It has been known for a long time that the charge-transfer character of the involved reaction partners (arene and alkene) determines the *ortho*/*meta* product ratio: High charge transfer in the exciplex favors *ortho* cycloaddition, whereas low charge transfer favors *meta* addition.[7] This charge transfer can be calculated easily from the electrochemically measurable redox potentials and the excitation energy by using the Weller Equation.[7,17] The discussed naphthalene derivatives **5** meet these criteria and favor *ortho* cycloaddition, and thus **6** is the main product, however only at low conversion.

The directing effect of cyano and ester groups can be deduced easily from the polar character of the exciplex and the polarized biradical, respectively (see Scheme 2B: Cornelisse denotes this intermediate as “bipolar bicyclo-[3.2.1.]octenyl biradical”, which some-

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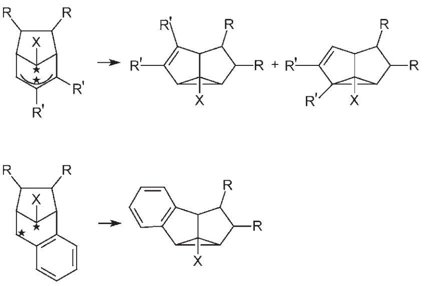
times is drawn as a zwitterion).[5a,7] The electron-withdrawing substituent (CN, COOMe) is always located at the benzylic bridgehead of the adduct **7**. Of course the geometric features of the intramolecular system also affect the regioselectivity of the cycloaddition.

If the empiric rules, which were originally developed for benzene,[7] can be applied to higher arenes, other synthetic routes could be predicted. For example, donor-substituted naphthalenes should provide *meta* adducts in the primary process. On the other hand, those combinations in which the photoinduced electron transfer is already exergonic (according to Weller) should preferably undergo substitutions, and these have often been observed.[18,19]

One may pose the question as to why, despite Wender's elegant work on the synthesis of natural products, *meta* photocycloaddition has hardly played a role in asymmetric synthesis.[20] The reason is the lack of regioselectivity during the formation of the cyclopropane ring (steps **C**→**E** and **D**→**F**, see Scheme 2). Thus, there is formation of either two constitutional isomers (Scheme 7: $R' \neq H$) or constitutionally identical compounds ($R' = H$). An attempt to control the ring closure by specific selection of the substituents R′ failed with the benzene system.[21] Naphthalene, however, forms a sharp contrast since only one ring closure is possible (Scheme 7, bottom). For this reason new ways for stereoselective *meta* photocycloaddition could be explored, especially in regard to diastereoselective and enantioselective synthesis.



Scheme 7. Low and high regioselectivity in *meta* photocycloaddition at benzene and naphthalene, *: · or (+),(−).

The latest studies from the Mizuno research group[15] in regard to *meta* photocycloaddition represents a breakthrough, which will gain high prominence for the construction of complex carbon frameworks. Furthermore, *ortho* photocycloaddition also offers high synthetic potential,[5,6,7,22] which has been overlooked in recent years. Hence it is hoped that this report will stimulate interest in these valuable synthetic methods, and the photochemistry of naphthalene and other arenes (including heteroarenes) will hopefully again be the subject of future research.

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[20] The synthesis of retigeranic acid is an exception, since the regioisomeric adducts can be isomerized later. Thus, the full synthesis is highly stereoselective (see Ref. [9]).

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