Selective alkylation by photogenerated aryl and vinyl cation

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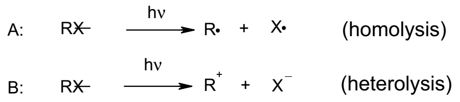
Citation
Slegt, M. (2006, May 18). *Selective alkylation by photogenerated aryl and vinyl cation*. Retrieved from https://hdl.handle.net/1887/4397

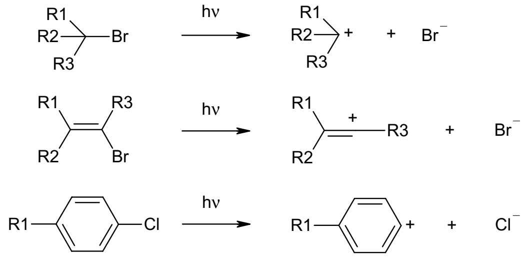
Chapter 1 | **Introduction**

Photochemistry, the breaking and making of bonds between atoms in molecules under the influence of light, is a very powerful method to execute chemical transformations. Using photons, reactions sometimes can be performed that cannot be achieved by heating and stirring. Ultraviolet (UV) light with a wavelength of 254 nm represents an energy of 112.6 kcal/mol photons, while light of 350 nm delivers 81.7 kcal/mol photons [1]. The energy of UV light is enough to cause fission of a single and sometimes even a double bond present in a molecule. In photochemistry textbooks the majority of bond-breaking reactions discussed are of the homolytic kind, yielding a pair of radicals[2] (Scheme 1A). Fission of the heterolytic kind, yielding a cation and an anion (Scheme 1B), is barely paid attention to, even though it is well-documented that the photolysis of alkyl, vinyl and some phenyl halides in solution gives ion-derived products[3,4] (Scheme 2).

Scheme 1: Homolysis and heterolysis upon irradiation.



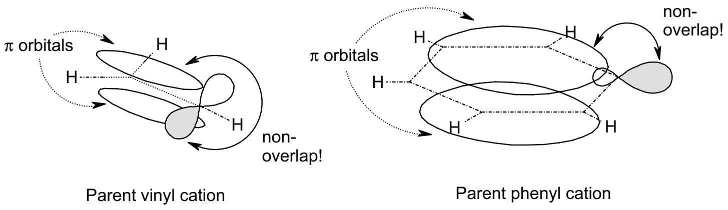
Scheme 2: The heterolytic photolysis of alkyl, vinyl, and phenyl halides.



Alkyl cations are quite common species, whereas vinyl and phenyl cations are not. These dicoordinated carbocations are among the most unstable intermediates known to organic chemists. Apart from the apparent electron-deficiency and the hybridisation, the instability originates from the inability of the π orbitals of these species to overlap with the vacant orbital of the C$^+$ atom[5] (Scheme 3). Further, the aryl and cyclic vinyl cations cannot adopt the preferred linear orientation around the C$^+$ atom.

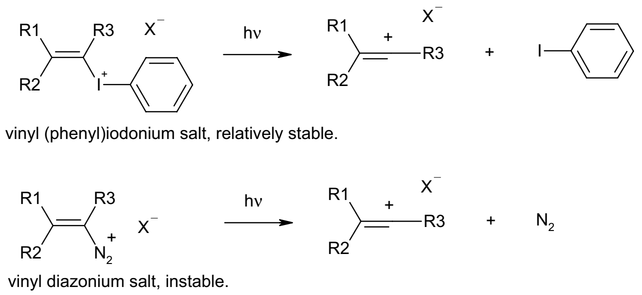
Photochemistry is especially suitable to effect the demanding reactions of Scheme 2. Employing photolysis of alkyl halides a broad range of alkyl cations has been generated under mild reaction conditions[3a,4]. The same is true for vinyl halides, which yield a score of vinyl cations[3b,4]. The photolysis of phenyl halides, however, only in exceptional cases proceeds through a heterolytic bond-cleavage mechanism[4]. In most cases photo-induced electron transfer (PET) from a donor to the phenyl halide yields a radical anion, which cleaves into a phenyl radical and a halide anion[6].

Scheme 3: Lack of overlap between electron rich and electron poor orbitals.



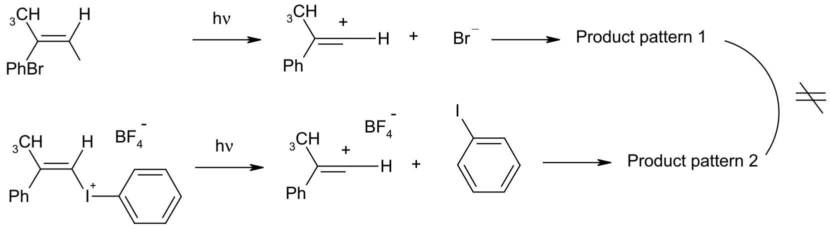
A new impulse to photo-induced heterolysis was the observation that vinyl pseudo-halides can be used as precursors to (highly unstable) vinyl cations[7] (Scheme 4). Iodobenzene is a far better leaving group than any halide anion[8]. The same is true for N_2 as leaving group, but unfortunately vinyldiazonium salts are considerably less stable than vinyl iodonium salts as precursors.

Scheme 4: Photoheterolysis of vinyl(phenyl)iodonium and vinyldiazonium salts.



The heterolytic bond cleavage reactions of the vinyl precursors in Schemes 2 and 4 yield ion pairs or free ions. In Scheme 2 the vinyl cations are generated next to a bromide leaving group, whereas for the precursors of Scheme 4 a non-nucleophilic counter-ion ($X^- = BF_4^-$) is chosen and photoheterolysis yields the vinyl cations amidst iodobenzene or N_2 leaving groups and the non-nucleophilic counter-ion. The leaving groups are neutral and less basic than halide anions and therefore interfere less with the reaction pathway of the cationic intermediates. This factor severely affects the outcome of the photochemical solvolysis reactions. For example, the primary vinyl cation in Scheme 5, prepared as an ion pair from its vinyl halide precursor, displays a distinctly different product pattern than the very efficiently prepared free cation accompanied by its neutral leaving group and non-nucleophilic counter-ion, generated from its pseudo-halide precursor[7b,9].

Scheme 5: Reactivity of an ion pair and an ion-molecule pair vinyl cation.

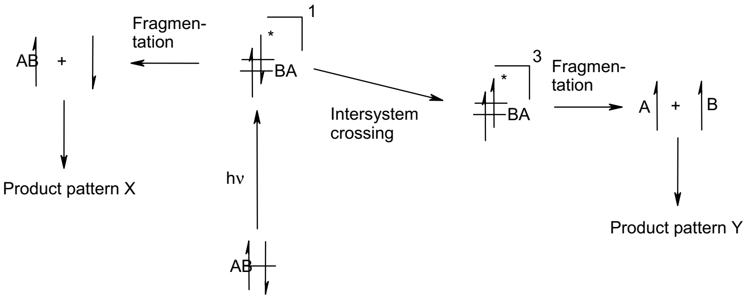


Phenyldiazonium salts are more stable than vinyldiazonium salts, therefore phenyl cations can conveniently be prepared by photoheterolysis[10], whereas this reaction is practically impossible to achieve with vinyldiazonium compounds. A range of substituted phenyl cations has been produced by this method. Also pseudo-halide leaving groups have been employed in the preparation of phenyl cations. The photolysis of diphenyliodonium salts, compounds that are known for over a century now, produces phenyl cations next to phenyl radicals[11]. The reaction has been extensively used by computer-chip manufacturers as a method to generate "photo-acid" using short wavelength UV irradiation, in their search for more refined, wavelength-dependent, patterning of the circuits[12].

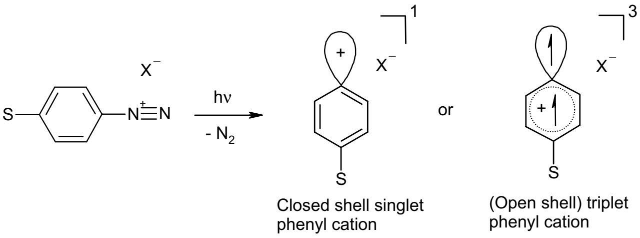
Using photons instead of heating not only allows to achieve high energy-demanding reactions, it also gives spin-selective (singlet or triplet) chemistry[13]. Normally, every chemical bond contains two electrons with anti-parallel spins, one spin-up and the other spin down. Electronic excitation produces a molecule in its singlet excited state. Thus, even though the light promotes one electron from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO), the spins of the electrons remain anti-parallel. If bond cleavage occurs faster than other possible processes, the two fragments formed, together, are of singlet nature: the principle of conservation of spin or Wigner's rule [14] (Scheme 6). If bond cleavage does not take place efficiently in the singlet excited state, the molecule may undergo intersystem crossing to its triplet excited state. In this process one of the electrons undergoes a spin inversion and the spins of the electrons are now both spin-up (or spin-down) and thus parallel. Bond cleavage from such a triplet state will yield the two fragments together as a triplet. Singlet and triplet fragments usually display different chemistry, hence the term spin-selectivity.

The picture of Scheme 6 should also be valid for the photogeneration of dicoordinated carbocations from halide and diazonium precursors. This was recently shown to be correct for a series of *para*-substituted phenyl cations generated from the corresponding benzene diazonium salts[15]. Depending on the substituents, the C-N bond cleavage occurs either from the singlet excited state, yielding a singlet phenyl cation and a molecule of nitrogen, or from the triplet state, yielding a triplet phenyl cation and nitrogen (Scheme 7).

Scheme 6: Spin-selective photochemistry: an adapted Jablonski-diagram.



Scheme 7: Singlet and triplet phenyl cations.



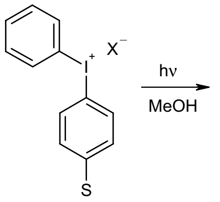
Variation of the leaving group should also enable spin-selective chemistry. Intersystem crossing, the conversion of an excited singlet state to its triplet state, is enhanced by the presence of so-called heavy atoms as bromine and iodine [16]. The utilisation of pseudo-halide iodonium salts in the photolysis of vinyl cation and phenyl cation precursors may direct the intermediate-forming pathway.

In this thesis various photochemical reactions are studied that produce phenyl, aryl and some vinyl cations through heterolytic cleavage of the bond between carbon and a leaving group. The primary goal is to understand and control the reactivity of these extremely reactive fragments. Further a sketch is offered on how the unique properties of these intermediates may be employed to the benefit of bioorganic and biological chemistry.

In all approaches reported in this thesis, product studies are the main tool to identify the (nature of the) product-forming intermediates. It is generally accepted that generation of the same intermediates through different chemical routes under similar reaction conditions leads to the same product profiles[17,18]. In many cases the product studies are complemented with quantum chemical studies.

In **Chapter 2** of this thesis the nature of the intermediates formed in the photolysis of phenyliodonium salts is probed. In a classical physical organic chemistry approach, the effects of variation of substituents at the photolabile compound on the formation of intermediates and ensuing products were studied (Scheme 8). An important goal was to clarify some unsatisfactory aspects of the mechanism of photolysis of these compounds proposed fifteen years ago[11a].

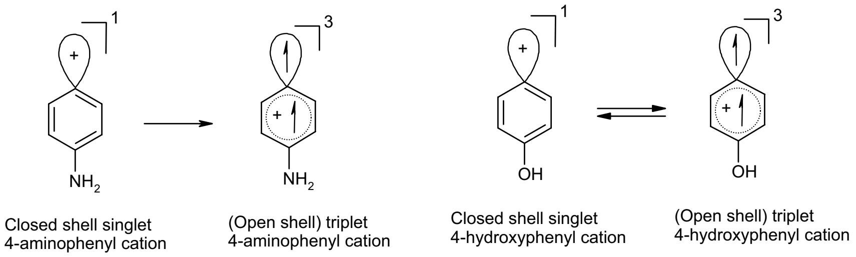
Scheme 8: Photochemical reactions studied in Chapter 2.



S = H, CH_3, OCH_2CH_3, CF_3, $C(O)OCH_3$, CN, $C(O)CH_3$, $N(CH_3)_2$

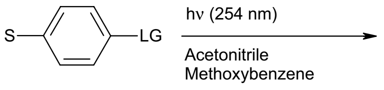
Chapter 3 of this thesis is devoted to the photogeneration of the singlet and the triplet 4-aminophenyl and 4-hydroxyphenyl cations (Scheme 9) from their iodonium salt precursors. For the 4-aminophenyl cation the singlet-triplet order of stability is calculated to be the reverse of the situation for the parent phenyl cation: its ground state is a triplet state[12]. For the 4-hydroxyphenyl cation a quite small singlet/triplet gap is calculated and reaction conditions may well determine whether the singlet or the triplet species is the ground state. The reactivity of the various intermediates was investigated and the circumstances were established under which either the singlet or the triplet state is the most stable.

Scheme 9: The 4-amino- and 4-hydroxy phenyl cations.



In **Chapter 4** a means is sought to profile the reactive intermediates produced in the photolysis of a series of phenyl cation precursors equipped with various substituents and leaving groups (Scheme 10). A method to fingerprint the singlet/ triplet cations is offered based on their chemoselectivity (Scheme 11) and regioselectivity toward the nucleophile methoxybenzene (Scheme 12).

Scheme 10: Photochemical reactions studied in Chapter 4.

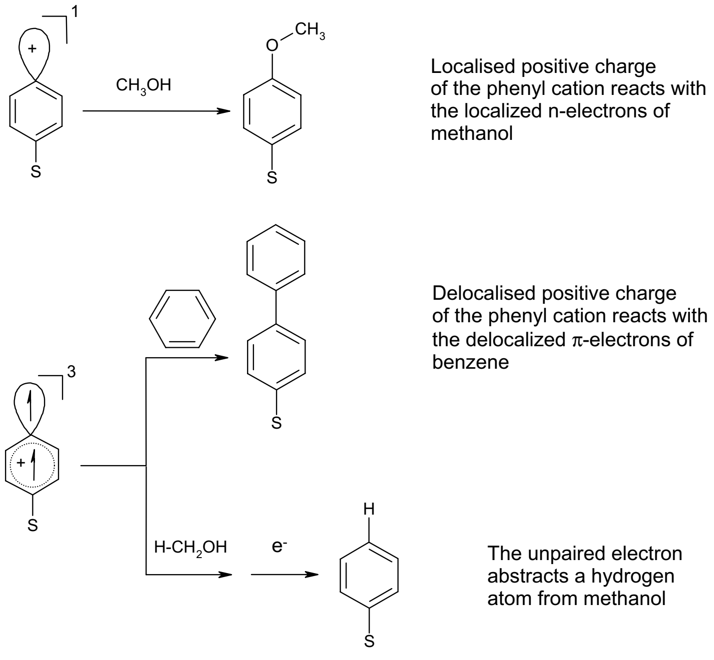


S = H	LG= $N_2^+BF_4^-$
NH_2	Cl
OH	Cl
$C(O)CH_3$	$N_2^+ BF_4^-$
NO_2	$N_2^+ BF_4^-$
$N(Et)_2$	$N_2^+ BF_4^-$
H	$I^+C_6H_5\ BF_4^-$

The two spin states (singlet and triplet), and consequently the electronic configurations of phenyl cations, (see Schemes 7 and 9) each are identifiable by their reactivity [20,3c]. The parent phenyl cation, which possesses a singlet ground state, and a highly localised positive charge, is a hard Lewis acid that preferably reacts with hard nucleophiles (following the Hard Soft Acid Base Principle[21]). To a lesser extent, it also reacts with soft Lewis bases such as aromatic rings. Phenyl cations with a triplet ground state, such as the 4-aminophenyl cation, possess a more dispersed positive charge, and behave as soft Lewis acids that react with soft nucleophiles more efficiently than with hard nucleophiles (Scheme 11).

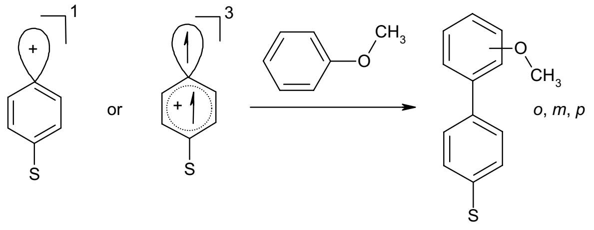
Triplet phenyl cations are also triplet carbene-like species, and are able to abstract a hydrogen atom. The electrophilicity of these cations, however, makes them better alkylating agents than hydrogen abstracting species[3c].

Scheme 11: Chemoselectivity.



The different spin states of the phenyl cations were shown to lead to distinguishable *ortho*, *meta*, *para* ratios of the biaryls produced (Scheme 12).

Scheme 12: Regioselectivity.



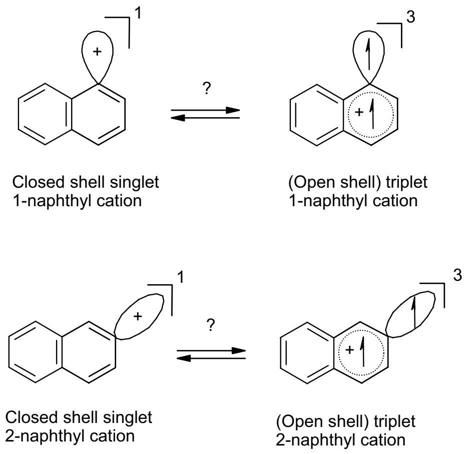
In **Chapter 5** the photogeneration of a 5-membered cyclic vinyl cation from its vinyl (phenyl) iodonium salt precursor is reported. Vinyl cations incorporated in a cycloalkenyl system cannot adopt the preferred linear orientation around the C^{+} atom, and are highly strained. Over time, many attempts have been made to generate small cyclic vinyl cations[22]. The report shows that the power of a photon in combination with the use of the exceptionally good leaving group iodobenzene[8] is needed to achieve this goal.

Beyond vinyl and phenyl cations lies the uncharted territory of polynuclear aromatic (aryl) cations, such as the naphthyl, anthryl, phenanthryl and pyrenyl cations. At best, the singlet or triplet nature and the S/T energy gap of some of these species have been studied by quantum chemical calculations[19e,23]. Experimental studies of the reactivity of these intermediates in solution have not yet been reported.

Aryl cations are expected to have a small S/T gap, or even an inverted S/T gap, for two reasons: the annelating rings act as electron-donating substituents and the rigidity of the systems hampers the cations to adopt the preferred linear structures of singlet cations.

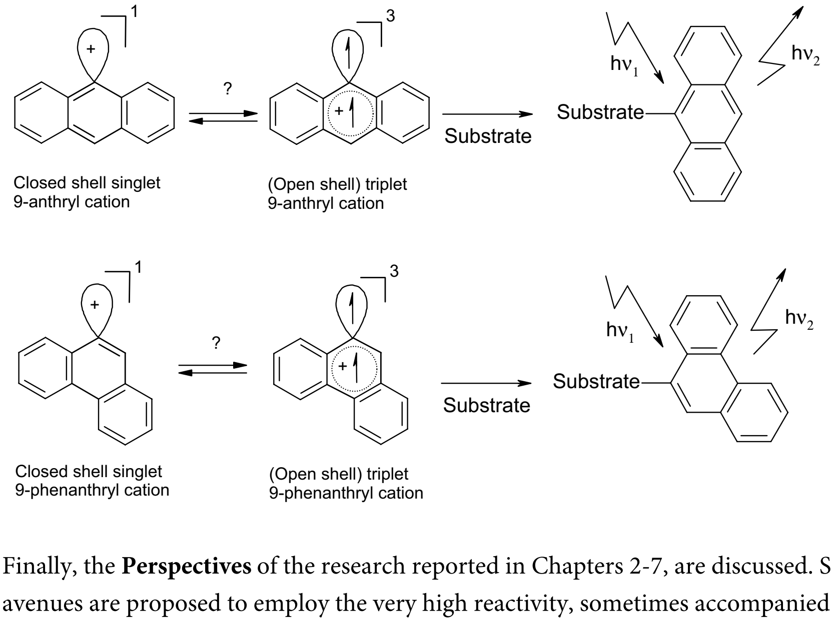
In **Chapter 6** the 1- and 2-naphthyl cations (Scheme 13) are prepared by photolysis of corresponding iodonium and diazonium salt precursors and their reactivity was studied. An assessment as to whether the singlet or triplet species is actually the lowest in energy was made through fingerprinting experiments and quantum chemical calculations in vacuum and in solution.

Scheme 13: The 1- and 2-naphthyl cations.



Chapter 7 reports the research performed to generate and employ the 9-anthryl and the 9-phenanthryl cation (Scheme 14). These cations are of particular interest because, if, after alkylation the substrate is to be retrieved by means of fluorescence recognition, both the anthryl and the phenanthryl group are avid fluorescers in the alkylated products but not in their precursors (i.e. the iodonium salts).

Scheme 14: The 9-anthryl and 9-phenanthryl cations.



Finally, the **Perspectives** of the research reported in Chapters 2-7, are discussed. Several new avenues are proposed to employ the very high reactivity, sometimes accompanied by high selectivity, of aryl and vinyl cations and to assess their initial (upon generation) and final (in product formation) multiplicity. Also the applicability of the photogenerated intermediates to alkylate nucleic acids and proteins is sketched and preliminary experimental results are presented.

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