Selective alkylation by photogenerated aryl and vinyl cation

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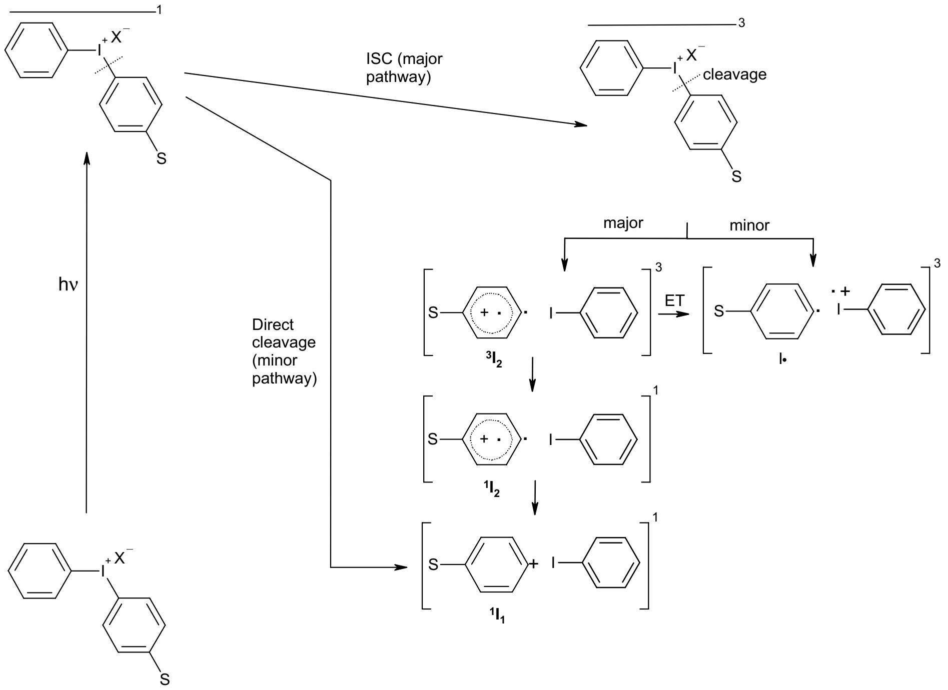
Summary

This thesis describes the results of a project to develop novel strategies for the alkylation of nucleobases and amino acids. The foundations of the project were the knowledge about and experience with highly reactive vinyl and aryl cations of the organic photochemistry group, and the knowledge about and the experience with nucleotide and peptide chemistry of the bio-organic synthesis group. The primary aim of the research was to obtain selectivity of reaction of aryl and vinyl cations via photolysis of especially developed precursors. Applications of new (and existing) methods of photoalkylation are to be found in the diagnostic toolbox of biochemists and biological chemists, and possibly in the treatment of DNA-based malfunction of specific cell groups (photodynamic therapy).

Scheme 1: Proposed mechanism of photolysis of diphenyliodonium salts.

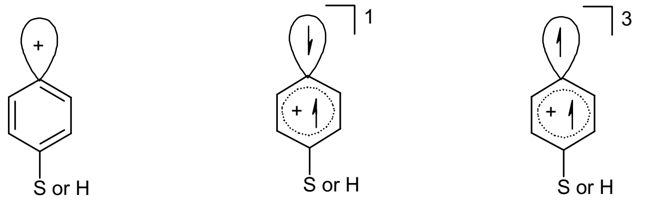


While charting the possibilities to apply diphenyliodonium salts, which are well-known as photo-acid generators (and anti-biotic agents), as photoalkylation agents, regio- and chemoselectivities were observed which led to the proposal for the mechanism of the photolysis of these compounds depicted in Scheme 1 (Chapter 2). The C-I$^+$ bond cleavage proceeds mainly from the triplet excited state. The ramifications of this proposal are that, compared to the widely embraced mechanism of the photolysis of diphenyliodonium salts, singlet excited state bond cleavage is less important and the triplet excited state predominantly produces a triplet phenyl cation ($^3\mathbf{I}_2$) instead of a phenyl radical (**I•**). However, it should be noted that neither direct homolysis (producing **I•**) nor direct heterolysis of the singlet excited state (yielding $^{1}\mathbf{I}_1$) can be excluded completely.

Singlet and triplet phenyl cations were expected to differ in their reaction selectivity. This was tested by generating singlet and triplet phenyl cations through different routes in the presence of various substrates. Since published quantum chemical calculations indicated that the only phenyl cation with a triplet ground state is the 4-aminophenyl cation, precursors supposedly leading to this cation were photolyzed.

The distinct regioselectivities and chemoselectivities observed demonstrate that the 4-amino phenyl cation is generated in different manifolds depending on the excited state from which the bond cleavage occurs (Chapter 3). The nature of the leaving group determines whether a singlet or a triplet phenyl cation is produced. With halogen as leaving group, cleavage occurs in the triplet excited state yielding triplet cation $^{3}\mathbf{I}_2$. With N_2 as leaving group, cleavage occurs in the singlet excited state yielding the closed-shell singlet cation $^{1}\mathbf{I}_1$ and the open-shell singlet cation $^{1}\mathbf{I}_2$ (Scheme 2). Photolysis of the corresponding iodonium salt yields both the triplet and the singlet phenyl cation.

Scheme 2: Isomers of phenyl cations.



Closed shell singlet
phenyl cation
S = NR_2 or OH

$\mathbf{I}_1$: $\pi^6\sigma^0$

Open shell singlet
phenyl cation
S = NR_2 or OH

$\mathbf{I}_2$: $\pi^5\sigma^1$

(Open shell) triplet
phenyl cation
S = NR_2 or OH

$\mathbf{I}_3$: $(\pi^5\sigma^1)^3$

According to quantum chemical calculations, the singlet and triplet species of the 4-hydroxyphenyl cation are of about the same stability. Observations of the reactivity of this cation as a function of its precursors were similar to those for the 4-aminophenyl cation. With (bromide or) chloride as leaving group the triplet cation $^{3}\mathbf{I}_2$ is produced, with nitrogen as leaving group the singlet cation(s) $^{1}\mathbf{I}_2$ and $^{1}\mathbf{I}_1$ are formed.

The study established a firm relation between the multiplicity of phenyl cations and the leaving group of their precursors. Additionally, it was shown that the 4-hydroxyphenyl cation does not deprotonate prior to its reaction with nucleophiles, as demonstrated by the generation and reactivity of that deprotonated species by photolysis of diazoquinone.

The photolysis of seven photolabile compounds, known to produce phenyl cations, in acetonitrile in the presence of anisole yields methoxybiaryls in four distinct *o*, *m*, *p* ratios (Chapter 4). The differences in regioselectivity are due to the different nature of the product-forming intermediates: a singlet closed shell cation, a singlet open-shell cation, an EDG-substituted triplet cation, and an EWG-substituted triplet phenyl cation, respectively. The differences in spin state of the cations, and consequently the differences in electronic configurations, result in different mechanisms of reaction. This spin-selective chemistry provides a tool to fingerprint the singlet/triplet nature of any aryl cation.

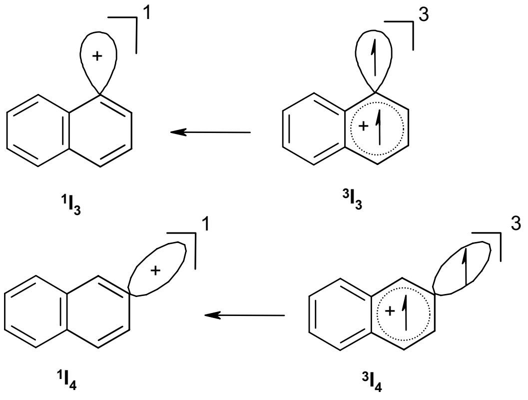
The fingerprint of the phenyl cation produced in the photolysis of diphenyliodonium tetrafluoroborate shows that the product-forming intermediate is a singlet species, despite the presence of the heavy atom iodine, which is expected to promote a triplet pathway. This finding complements the proposed mechanism depicted in Scheme 1, in which external nucleophiles only react with the cations after the complex has dissociated. This leaves time for the photogenerated phenyl cation to isomerise to its ground state.

The second pillar of the research in this thesis is the generation of vinyl cations. The project reported in Chapter 5 partook in an age-old quest for a "holy grail" of vinyl cation chemistry: the most unstable vinyl cation possible. For cyclic vinyl cations the most unstable species witnessed thus far was the 6-membered ring vinyl cation. Numerous attempts to thermally generate the 5-membered ring vinyl cation were unsuccessful. It is demonstrated that not only the C_6-ring vinyl cation, but also the C_5-ring vinyl cation is generated photochemically, under mild reaction conditions, from their iodonium salt precursors.

Next to trapping products of the C_5-ring vinyl cation also trapping products of the C_5-ring allyl cation were found. The hydride shift of a vinyl cation forming an allyl cation is a typical carbocationic process. The data presented constitute the first unambiguous case for the direct formation of a C_5-ring vinyl cation.

In pursuing the possibilities offered by the differences in chemo- and regioselectivity of singlet and triplet aryl cation species, the photogeneration of polyaromatic cations was attempted. The 1- and 2-naphthyl cations $\mathbf{I}_3$ and $\mathbf{I}_4$ were generated by photolysis of their iodonium and diazonium salt precursors and their reactivity was studied (Chapter 6). The naphthyl cations react (predominantly) through their singlet, closed shell isomer ($^1\mathbf{I}_{3,4}$) (Scheme 3). With the iodonium salt precursors, which fragment from the triplet excited state, a small contribution to the pattern of reactivity of their triplet naphthyl cations ($^3\mathbf{I}_{3,4}$) is found. Is is proposed that, under the experimental circumstances, the singlet closed shell naphthyl cations are lower in energy than their triplet isomers, even though high level quantum chemical calculations indicate that the singlet and triplet species are practically isoenergetic.

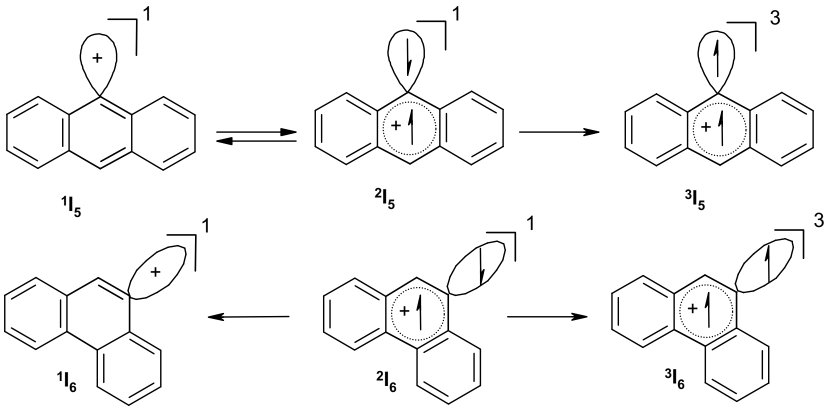
Scheme 3: The 1- and 2-naphthyl cations.



It appears that, using the naphthyliodonium salt precursors, the triplet naphthyl cations formed isomerise via a 1,2 hydrogen atom shift or lose a proton to the solvent producing triplet 1,2-naphthyne. These processes lead to the *cine*-substitution patterns observed in the photo-product mixtures. No *cine* substitution occurs upon irradiation of 1- and 2-napthyldiazonium tetrafluoroborate, which generates only the singlet 1- and 2-napthyl cations.

Venturing further on uncharted territory, for the first time the 9-anthryl cation $\mathbf{I}_5$ and the 9-phenanthryl cation $\mathbf{I}_6$ have been generated in solution and their reactivity has been studied (Chapter 7) (Scheme 4). Trapping studies indicate that the 9-anthryl cation, formed by means of photolysis of the corresponding iodonium salt, is produced in its open-shell singlet state ($^2\mathbf{I}_5$). Trapping studies of $\mathbf{I}_6$ show that it reacts in its closed-shell singlet state ($^1\mathbf{I}_6$) via both

Scheme 4: The 9-anthryl and the 9-phenanthryl cation.



methods by which the cation was produced: directly, by photolysis of the corresponding phenanthryl iodonium salt, or indirectly, by photolysis of the vinylic bromide 9-bromomethylene-*9H*-fluorene. The latter reaction first produces a primary vinyl cation that in turn forms $\mathbf{I}_6$ through a 1,2 phenyl shift.

The above results open perspectives for tagging of substrates with a fluorescent moiety. The iodonium precursors do not fluoresce, owing to the presence of a heavy atom in the molecule, but the tag after the alkylation event does. This offers the possibility to track the tagged substrate without interference of the pre-fluorescent photolabile group.

As an illustration of the perspectives of the research reported in this thesis, in Chapter 8 preliminary results are presented on the photoalkylation of guanosine and of phenylalanine in solution, using a variety of phenyl cation precursors. In general significant photoalkylation occurs.