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Helquats – Modular synthesis and properties of novel helical dications

PhD. Thesis Synopsis

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Prague 2010

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2. Introduction

Helicenes

Helicenes[1] are ortho-condensed polycyclic aromatic compounds, in which benzene rings or aromatic heterocycles are angularly annulated. When the number of rings is four and more, the system cannot be planar and adopts helical structure to relieve steric congestion. The helix assumes either a right- or left-handed helical shape, thus determining the chirality of the molecule as a whole. The enantiomers of helicenes are designated as (*P*) or (*M*) for the right- or left-handed isomer, respectively (Figure 1).

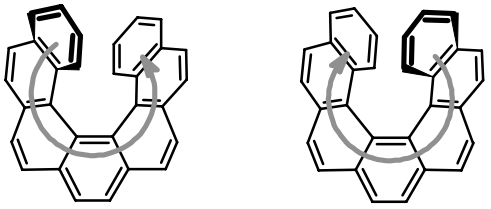
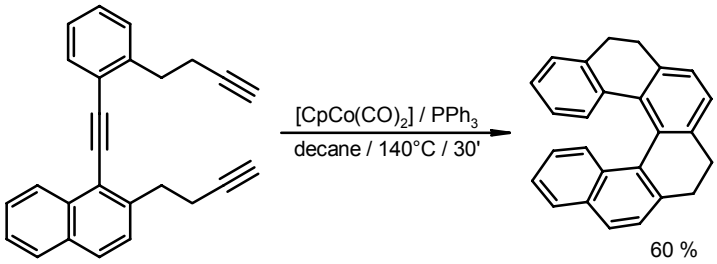


Figure 1 (*P*)- and (*M*)-[7]helicene.

The unique three-dimensional structure of helicenes together with their remarkable spectral and optical characteristics have drawn considerable attention to their development and research.

A favourable atom-economic synthetic route towards helicenes was developed by Starý and Stará based on transition-metal catalysed [2+2+2] cyclotrimerisation of aromatic triynes (Scheme 1). This versatile approach is inherently modular and proved to be very reliable as a number of fully aromatic helicenes and functionalised helicene-like molecules were prepared this way.



Scheme 1 [2+2+2] cyclotrimerisation in helicene synthesis.

Viologens

Viologens[2] are diquaternary derivatives of 4,4'-bipyridyl with paraquat[3] and diquat (Figure 2) the best-known examples utilised as herbicides produced in ton quantities every year.

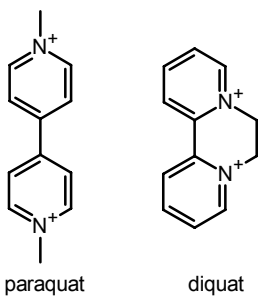
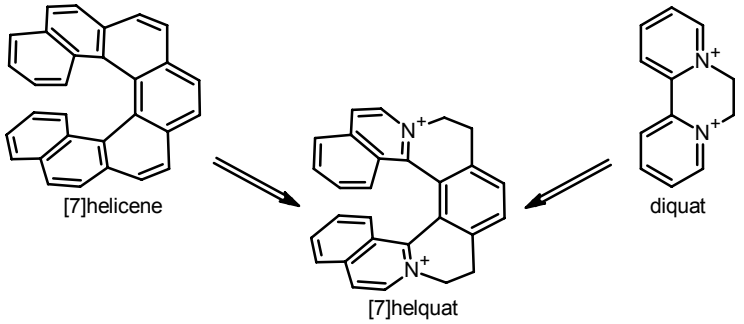


Figure 2.

A crucial feature of viologens is their ability to be reversibly reduced in a very fast process. They exist in three well-characterised oxidation states as the dication, the radical cation, and the neutral form. The importance of these properties projects into the applications of viologens, such as redox indicators in biological systems or electrochemical display devices, and also in their herbicidal activity.

Helquats as helicene-viologen structural hybrids

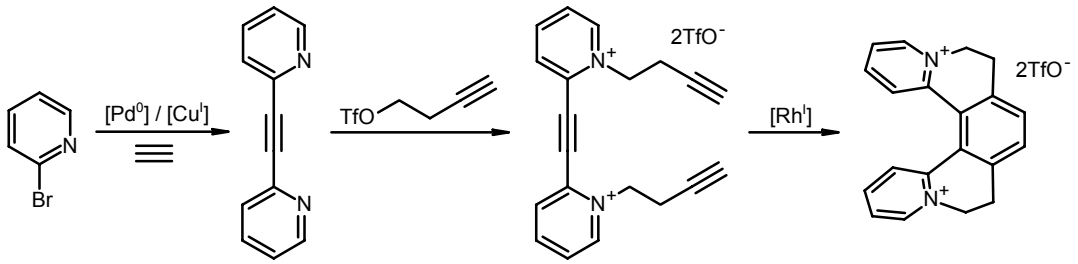
Helquats[4], or helical extended diquats, represent a structural combination of the dicationic viologens and uncharged helicenes (Scheme 2), thus putting together the powerful electron-accepting character of viologens with the electronic properties and pronounced chirality of helicenes.



Scheme 2 A combination of helicenes and viologens gives helquats.

As has been shown recently[5], helquats can be reversibly reduced in two one-electron steps with redox potentials parallel to simple viologens. The reduction is fast, which is relatively rare in organic redox systems, and the rate and reversibility together with their facile structural modification makes helquats promising candidates for applications as building blocks of monolayers at metallic surfaces or electron-transfer mediators.

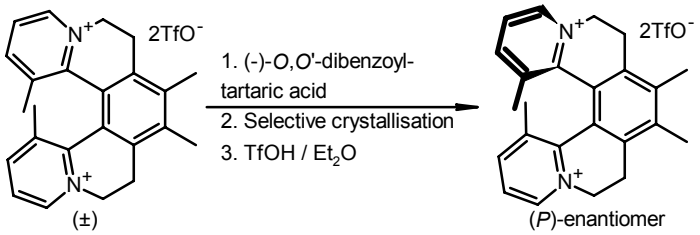
The synthesis of helquats is very straightforward as it typically consists of only three steps. First Sonogashira coupling is carried out with an N-heterocyclic halide and gaseous acetylene giving a symmetric product. Alternatively, 2-ethynylpyridine is subjected to Sonogashira coupling with N-heteroaryl halide opening access to unsymmetric products. In the following step the two unsubstituted nitrogens are quarternised by relevant triflates and finally, a key [2+2+2] cycloisomerisation furnishes the helquat. This approach is very efficient in terms of step- and atom-economy as all reactions are skeleton-building and thus, no steps including protective groups or functional group manipulations are necessary (Scheme 3).



Scheme 3 Synthesis of the parent [5]helquat.

So far, racemic derivatives of different helquats were synthesised and, of course, in case of configurationally stable enantiomers non-racemic derivatives need to be prepared. That it is possible has been recently shown in case of a [5]helquat derivative which was resolved using inexpensive enantiopure dibenzoyltartrate anions[6] (Scheme 4). Moreover, the

enantiocomposition was easily monitored by capillary electrophoresis using sulfated β-cyclodextrin chiral selector highly suitable for charged helicene-like molecules. Other examples from our laboratory have shown that this method is a very practical and straightforward tool for enantiocomposition analysis of various helquats.



Scheme 4 Resolution of [5]helquat derivative.

Applications of N-heteroaromatic cations

In molecular biology fluorescent dyes, such as a basic representative ethidium, often possess cationic character and are used for DNA staining. Fluorescent techniques have been utilised in a wide range of biological application capitalising on the high sensitivity and specificity and the ability to monitor events with high temporal resolution. Except ethidium, other commonly used cationic alternatives include SYBR Green I or cyanines Cy3 and Cy5. Recent novel examples include selective nucleic acid binders diazonia or tetraazoniapolycyclic derivatives investigated for their affinity towards topoisomerase I, duplex, triplex or quadruplex DNA.

In organocatalysis[7] cationic species have been used extensively. From the many reactions, pyridiniums were utilised in promoting acetalisation, pyridiniums and viologens were also studied as organocatalysts for aziridine synthesis. Biginelli reaction used to construct hydropyrimidines directly from aldehydes, β-ketoesters and urea appearred to proceed also in the presence of catalytic amount of a piperidinium triflate.

Asymmetric epoxidation is a well-examined reaction for the preparation of epoxides, which serve as building blocks and intermediates in organic synthesis. Organocatalysts such as iminium, dihydrocinchonidinium or azoniaspiro catalyst were shown to be successful.

In case of nucleophilic substitution chiral phase-transfer catalysts (PTC) have been used largely. Maruoka's PTC reaction is of broad generality with selectivities of 91-99% ee in the synthesis of non-proteinogenic α,α-dialkylated amino acids important for the design of pharmaceutically interesting peptides.

PTC asymmetric Michael addition was investigated by Maruoka's group in case of 2-carboxypentanones reacting with enone or enals using only 2 mol % of a binaphthyl-derived catalyst. The tartaric acid-derived PTCs being the most effective and selective were utilised in the asymmetric addition of glycine enolates to acrylates.

4. The aim of the work

The aim of the work was to prepare novel kinds of helquats in racemic form, specifically:

- To prepare novel helquats with two *n*-butyl substituents to test if lipophilic side chains are compatible with the straightforward helquat skeleton build-up. The key question to answer was also if the purification protocols used for the parent structures lacking *n*-butyl groups are applicable for *n*-butyl analogs (Figure 3).

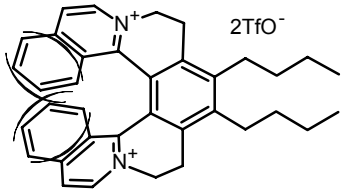


Figure 3.

- To synthesise a set of new helquats based on an unsymmetrical substrate containing quinoline and pyridine moiety. The aim was to test the concept of differential quaternisation with an unsymmetric quaternisation precursor (Figure 4).

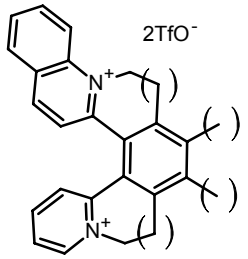


Figure 4.

- To prepare new helquats with phenanthridine moiety and determine their photophysical characteristics (Figure 5).

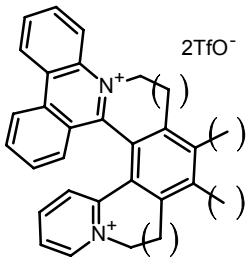
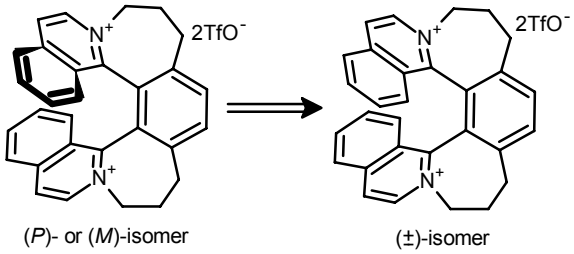


Figure 5.

- To resolve into enantiomers the already prepared racemic [7]helquat (Scheme 5).

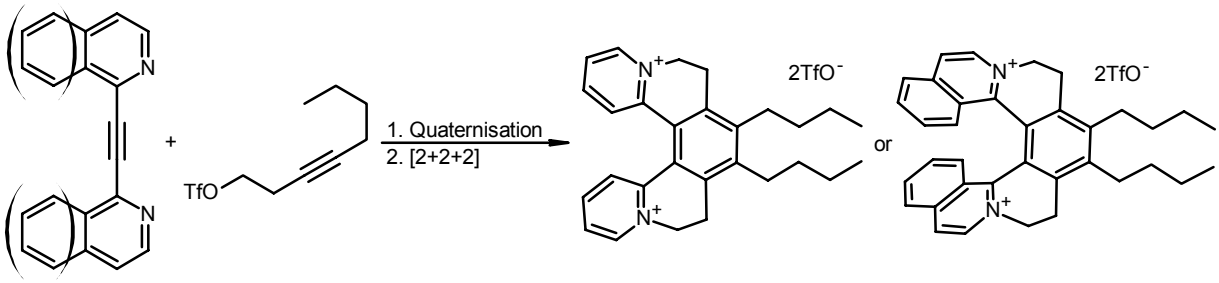


Scheme 5.

6. Results and discussion

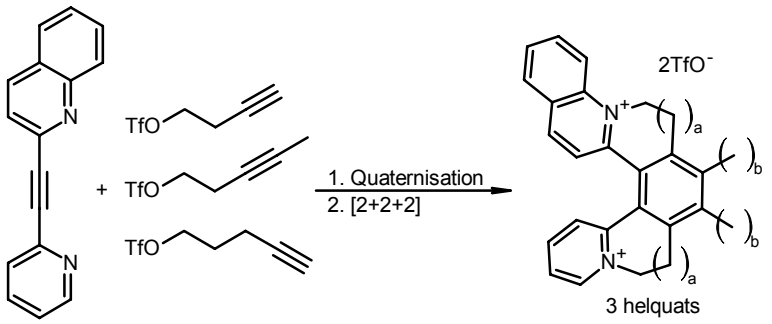
The synthesis of helquats used in this work follows conceptually the general route described in the first publication about helquats[73]. The alkyne precursors were prepared by Sonogashira coupling of heteroarylhalides either with gaseous acetylene or with 2-ethynylpyridine. A significant modification lies in the preparation of triflates performed in CH_2Cl_2 instead of carcinogenic CCl_4. The relative inaccessibility of hindered nitrogens in quinoline or phenanthridine moieties required slightly elevated temperatures for the quaternising reactions to proceed. The [2+2+2] cyclisations were performed satisfactorily in DMF or EtOH as solvents.

For the preparation of butylsubstituted helquats oct-3-ynyl trifluoromethanesulfonate was prepared and purified by distillation. Subsequent double quaternisation of 1,2-di(pyridin-2-yl)ethyne was performed at room temperature and an easy purification gave the triyne of excellent purity as white solid. The [2+2+2] cyclotrimerisation of the triyne furnished the helquat again as white solid after similar purification in good yield. Lesser yields in both reactions were obtained with 1,2-di(isoquinolin-1-yl)ethyne as the substrate (Scheme 6).



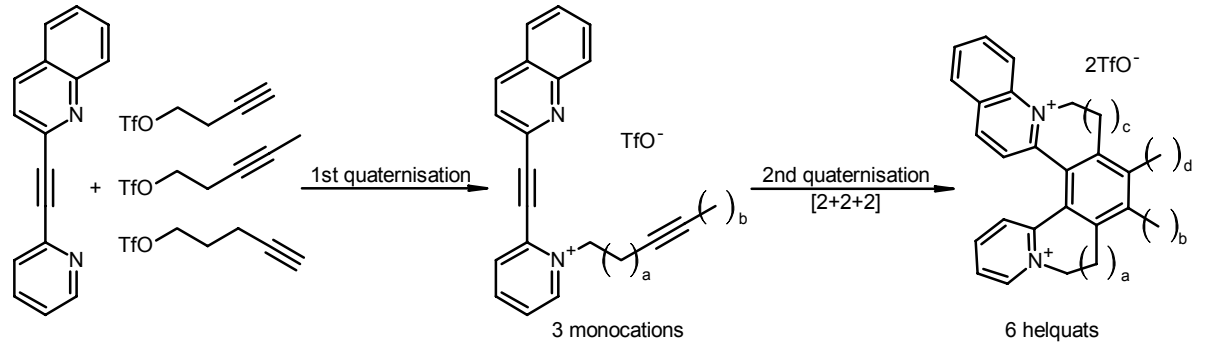
Scheme 6 Prepared butylated helquats.

Next, a series of nine helquats based on one asymmetric pyridine-quinoline unit was prepared using three different alkynyl triflates. The series consisted of three helquats with a build-in single triflate utilised in their preparation and six helquats made of a couple of different triflates. The trio of helquats with one type of triflates was easily synthesised, however, because of the sterically and electronically disfavoured quinoline a slightly elevated temperature was required in the quaternisation step (Scheme 7).



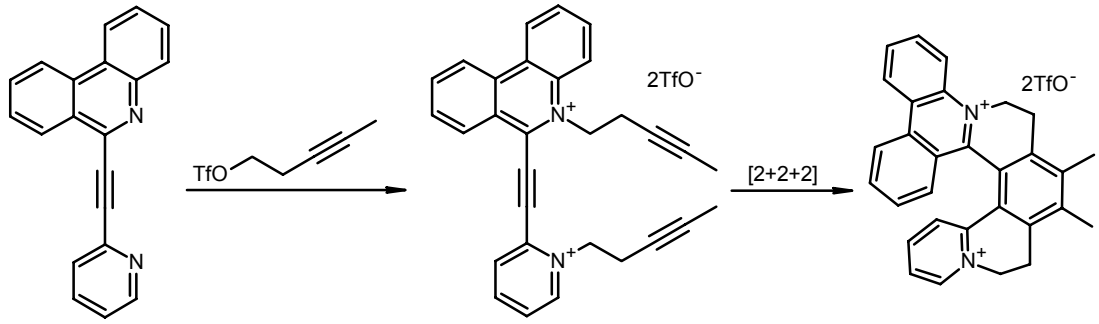
Scheme 7.

For the distinctly quaternised triynes, the first quaternisation required a less polar solvent to cause precipitation of the preferentially formed monocation. The second quaternisation was performed again under elevated temperature. The cyclotrimerisation proceeded without difficulties (Scheme 8).



Scheme 8.

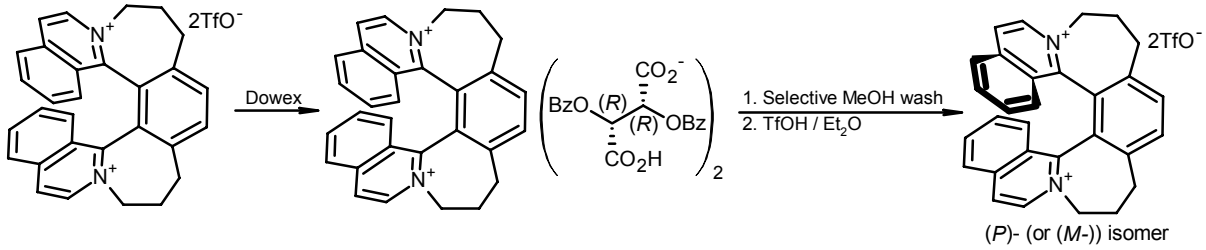
Being inspired by the structure and photophysical properties of ethidium bromide, we set off to synthesise helquats with phenanthridinium substructure. Having found a suitable approach to the substrate, quaternisation with the basic triflate was accomplished reaching only 17% yield of the triyne. Although low in yield, the triyne was pure enough to continue to the final step of cyclotrimerisation. The reaction proceeded according to TLC and NMR check, however all attempts to isolate the product in pure form failed. Finally, we succeeded in completing the preparation sequence using the methylated triflate (Scheme 9).



Scheme 9.

Our final aim was to isolate enantiomers of a [7]helquat expected to be stable at ordinary conditions. The racemic helquat was prepared according to a published procedure. The resolution procedure was based on changing the triflate anion to a nonracemic substitute followed by attempted separation of the formed diastereomers. The exchange proceeded without difficulty on a common ion-exchanger column. Starting with (1*S*)-camphorsulfonate as an anion it was found that the resulting [7]helquat bis((1*S*)-camphorsulfonate) being soluble in chloroform can be discriminated as to its diastereomeric ratio in ^{1}H NMR. Various attempts at separating a single diastereomer by preferential dissolution were not successful.

The second anion to try was (*R*,*R*)-dibenzoyltartrate. This derivative could not be discriminated in NMR, however a suitable method to resolve both diastereomers appeared to be capillary electrophoresis on sulfated γ-cyclodextrin. With dibenzoyltartrate being exchanged similarly to the (1*S*)-camphorsulfonate, it was found that the two resulting diastereomers differ significantly in their solubility in methanol. Thus, single diastereomers in purities of 1:99 and 90:10 were obtained. The absolute configuration was ascertained by x-ray crystal structure measurement. The reverse exchange from dibenzoyltartrate to triflate anion was performed simply by sonicating the solid dibenzoyltartrate in ethereal solution of triflic acid (Scheme 10).



Scheme 10.

In the end with a single enantiomer of the [7]helquat at hand a thermal racemisation was performed in order to find the racemisation barrier between (*P*)- and (*M*)-isomers. This was obtained by monitoring the decreasing specific rotation during the process. Moreover, the changing ratio of both enantiomers was followed by capillary electrophoresis. From both data sets the racemisation barrier (Gibbs energy of activation) was calculated as 148 kJ/mol corresponding to half-life of around 3 hours at 170 °C.

8. Conclusion

In summary, a series of helquats with various structural patterns was prepared based on common or successive pyridine-type nitrogen quaternisations and subsequent [2+2+2] cyclotrimerisation. The synthetic route is exclusively skeleton-building and therefore step-economic and the products are thus rapidly accessible. All nine helquats prepared from one unsymmetric quinoline-pyridine-type alkyne precursor and three different alkynyl triflates in only 21 steps overall demonstrate the modular advantage of this approach and subsequently, the possibility of straightforward molecular editing of cationic scaffolds. In addition, a successful synthesis of a helquat containing phenathridinium moiety was accomplished and finally, a configurationally stable racemic [7]helquat was synthesised, converted to a mixture of two diastereomeric (*R*,*R*)-dibenzoyltartrate salts and resolved into enantiomers by preferred wash of one diastereomer and a facile backward transformation to the ditriflate. The absolute configuration of the obtained enantiomer was confirmed by X-ray structure analysis. Moreover, the racemisation barrier of this [7]helquat was determined. In the end, optical properties including quantum yield were measured for selected series of prepared helquats.

In the near future, a separation of enantiomers of various configurationally stable helquats by entrainment, *i.e.* without any chiral auxiliary, will be pursued. This will reduce the cost of enantiopure helquats. The already prepared species will be investigated as to their potential for organocatalysis, material science and bioapplication, and other research areas.