

# Hack Your Chemistry

Michal Juriček\*

Dedicated to the past and present members of the JuricekLab

**Abstract:** Chemistry has a habit of surprising us. As we dig deeper, sometimes what we find will change the course of our research.

**Keywords:** Open-shell graphene fragments · Phenalenyl ·  $\pi$ -Radical reactivity · Triangulene



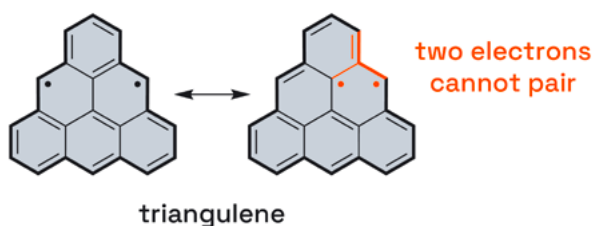
**Prof. Michal Juriček** was born and raised in Slovakia. He graduated from the Comenius University in Bratislava and received his PhD from the Radboud University Nijmegen under the supervision of Prof. Alan E. Rowan. In 2011, he was awarded the Dutch fellowship Rubicon that sponsored his postdoctoral research at Northwestern University in the laboratory of Prof. Sir J. Fraser Stoddart. In 2013, he

returned to Europe to start his independent research at the University of Basel, supported by the SNSF Ambizione fellowship and hosted by Prof. Marcel Mayor. In April 2017, he moved to the University of Zurich as an SNSF Assistant Professor. In April 2024, he was promoted to Associate Professor *ad personam* for Organic Materials. Beyond his passion for chemistry, he loves spending time in nature, ice cream, clean figures, and the rare sight of his empty work desk.

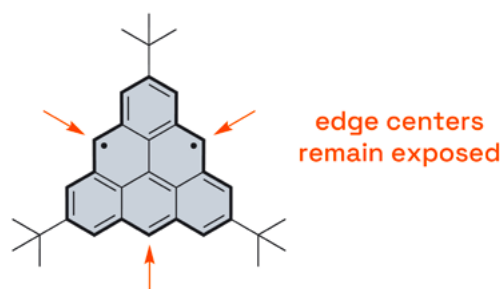
## The Chemistry

*It was love at first sight. The first time we drew the structure of cethrene, we knew we had to give its synthesis a try.*<sup>[1]</sup>

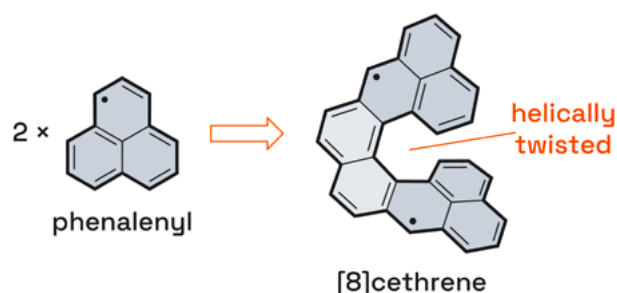
It was October 2014, and we were on the lookout for a new synthetic target. Our group expanded from one to three members, which put us in a good position for the start of a new project. For the past year, we had been working on triangulene and we were beginning to realize the extent of the challenge we had undertaken. Triangulene was the first enterprise of the newly launched JuricekLab, when back in 2013, we set out to explore magnetism of carbon-based materials. Often referred to as Clar's hydrocarbon,<sup>[2,3]</sup> this iconic molecule is a molecular fragment of graphene, which is composed of six benzenoid rings fused to form a triangle with zigzag edges. The signature characteristic of this conjugated hydrocarbon is that it cannot be assigned a classical Kekulé structure, since each of its resonance forms contains two carbon atoms that are not  $\pi$ -bonded.<sup>[4]</sup> In other words, it is a diradical.



Formally, triangulene belongs to the family of non-Kekulé hydrocarbons,<sup>[4–7]</sup> being an archetype of this class of compounds. Like dioxygen,<sup>[8]</sup> it possesses a triplet ground state, conforming to Hund's rule, but is far less stable. First attempted by Erich Clar in the 1950s,<sup>[9,10]</sup> the synthesis of triangulene has posed a challenge for chemists due to its high reactivity.<sup>[3]</sup> In 2013, when our group set out to pursue an isolable derivative, only one neutral derivative of triangulene had been reported by Kubo and coworkers.<sup>[2]</sup> Equipped with tri-*tert*-butyl groups at the vertices, this short-lived species could only be observed at cryogenic temperatures, as the substituents were too distant from the edge centers to provide adequate protection. Isolable derivatives of triangulene had not been reported.

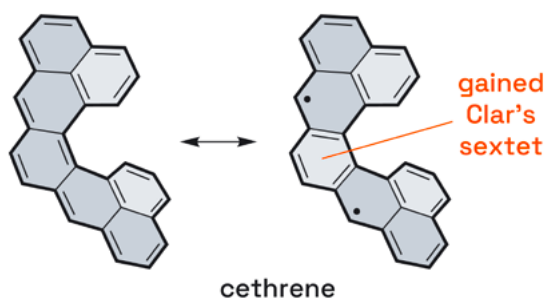


At that time, known hydrocarbons with diradical character were limited to planar structures. Thus, as a parallel project, we thought it would be interesting to construct a non-Kekulé diradical with a non-planar geometry. We considered different ring fusions, varied the number of rings, and ultimately conceived a structure we would later call [8]cethrene. This compound consists of eight fused benzenoid rings arranged to form a twisted [6]helicene backbone and two phenalenyl subunits. Phenalenyl is a smaller, three-ring version of triangulene with one unpaired electron and the first homolog of the open-shell triangular graphene fragment series.<sup>[11]</sup> The merging of the triplet ground state electronic structure with helical geometry is intriguing for investigating the interplay of spin and chirality.<sup>[12]</sup> At that moment, however, it was the molecule's aesthetic appeal that captivated us.

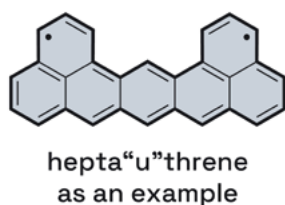


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During the synthesis design, we realized it might be easier to prepare the shorter [5]helicene analog,<sup>[13]</sup> a compound we now refer to as parent cethrene. What was not immediately obvious to us is that cethrene is no longer non-Kekulé, and all electrons can be paired in a quinoidal resonance structure. In fact, the homologs in the cethrene series alternate between Kekulé and non-Kekulé structures depending on the number of rings in the helicene backbone.<sup>[14]</sup> Despite this, cethrene is still a peculiar molecule. When a diradical resonance structure is drawn, an extra Clar's sextet is obtained. As a result, cethrene possesses a certain degree of diradical character in its singlet ground state and a low-energy triplet excited state, which makes it magnetically active at room temperature.<sup>[15]</sup>

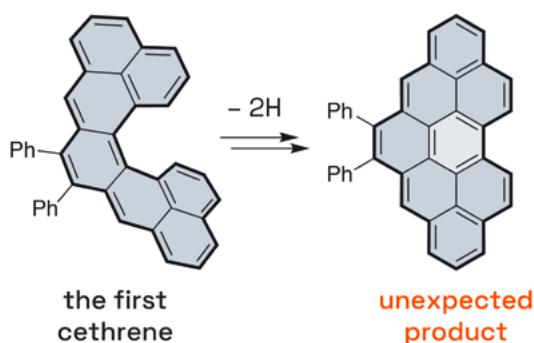


The origin of the name cethrene follows a naming convention tied to the shapes of its isomers.<sup>[16]</sup> There are five isomers in total that feature two phenalenyl units. When cethrene was reported in 2016, two other isomers were already known and named after the letters their shapes resemble: hepta“z”ethrene (Kekulé)<sup>[17]</sup> and hepta“u”threne (non-Kekulé).<sup>[18]</sup> Following this principle, cethrene<sup>[19]</sup> was a natural choice. Later, in 2020, Kubo and coworkers reported the fourth isomer, sigmarene (Kekulé).<sup>[20]</sup>

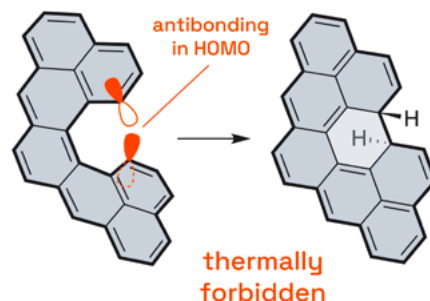


### The Unexpected

The first cethrene derivative that we synthesized was diphenylcethrene.<sup>[21]</sup> The inclusion of two phenyl groups on the central ring of the [5]helicene subunit was a strategic choice to facilitate the synthesis. We initially obtained a dihydroprecursor, which was subsequently oxidized to the final product by using *p*-chloranil. While monitoring the oxidation process with proton NMR spectroscopy, we observed not only the formation of our target product but also detected an unexpected species, which were later identified as diphenylbenzoperopyrene.



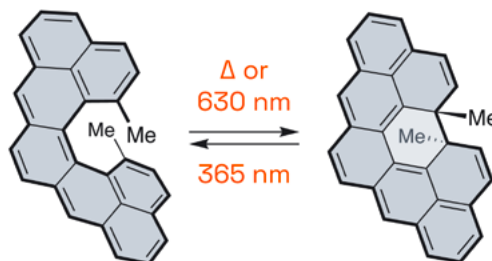
To explain the formation of this product, we hypothesized that cethrene undergoes a conrotatory electrocyclic ring closure followed by oxidation.<sup>[21]</sup> The only *catch* was that this thermal process formally violated the Woodward–Hoffmann rules,<sup>[22]</sup> which indicated that it would be thermally forbidden.



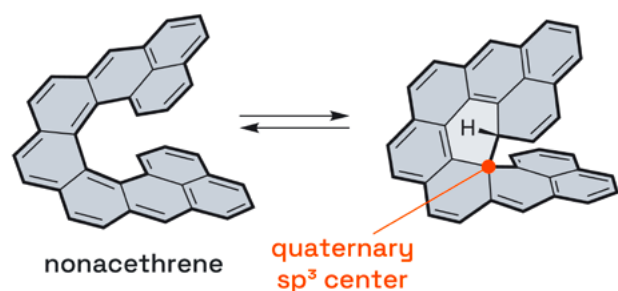
Despite being formally forbidden, the ring closure does proceed, and with an activation energy of just 14 kcal/mol, as determined through kinetic measurements.<sup>[23]</sup> This value is surprisingly low but consistent with a study published shortly before, in which Kubo and coworkers reported an activation energy of 16 kcal/mol for a structurally similar biphenalenylidene system.<sup>[24]</sup> The insights into these processes and the reasons behind the low barriers are not covered here as they have been discussed in other accounts.<sup>[16,23–26]</sup> Interested readers can refer to those works for further information.

### Digging Deeper

Cethrene's electrocyclization inspired the idea to translate its reactivity into a function, leading us to conceptualize the working principle of a metal-free, all-organic magnetic photoswitch.<sup>[27]</sup> To prevent oxidation of the flat compound, we installed two methyl substituents in the fjord region, while omitting the phenyl groups present in the first derivative. The closed form of the dimethyl derivative was stable and could be isolated. Its solid-state structure validated the *anti*-orientation of the methyl groups and thus the conrotatory ring closure. Upon irradiation, the open form could be generated and underwent both thermal and photochemical electrocyclization back to the closed form. We had a photoswitch,<sup>[28]</sup> however, it was not a magnetic switch.<sup>[29]</sup> The methyl groups increased the singlet–triplet gap due to a combination of steric and electronic effects, rendering the compound EPR silent (EPR = electron paramagnetic resonance).<sup>[30,31]</sup>



Hence, we turned our attention to the third cethrene homolog, a Kekulé system known as [9]cethrene or nonacethrene. With two additional rings compared to cethrene and a more pronounced overlap of the terminal rings, a significantly lower singlet–triplet gap was anticipated. Moreover, the electrocyclic ring closure would result in the formation of one quaternary  $sp^3$  center, preventing full fusion. It seemed that we had found the perfect candidate for the magnetic photoswitch.



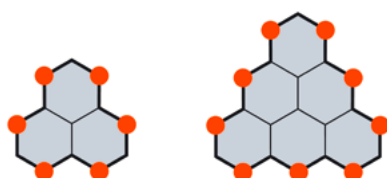
But not quite.

### The Turning Point

As we were to discover, nonacethrene undergoes a complex oxidative dimerization sequence.<sup>[32]</sup> Despite its complexity, the reaction yields a single product. It features two configurationally locked [7]helicene units, a peropyrene unit, and two sp<sup>3</sup> centers, a compound for which a synthetic route employing traditional methods is hard to imagine.

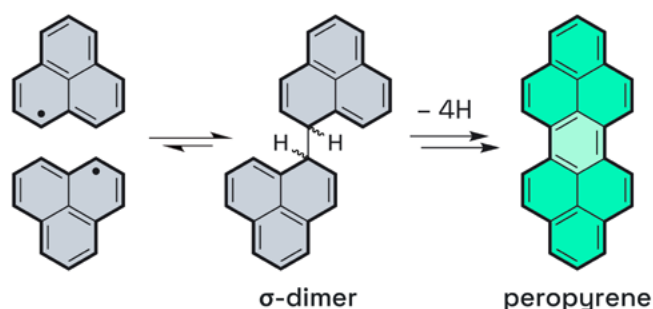


This nine-step process, in which four  $\sigma$ -bonds, one  $\pi$ -bond, and three rings are formed, inspired us to revisit and rethink the reactivity of  $\pi$ -radicals like phenalenyl and triangulene. Their characteristic feature is the delocalization of unpaired electrons over multiple peripheral  $\alpha$ -positions—six in the case of phenalenyl and nine in the case of triangulene.<sup>[33]</sup>

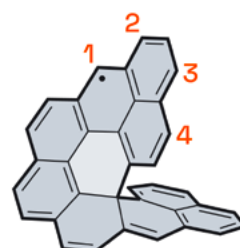


### Rethinking

The reaction cascade of nonacethrene involves an oxidative dimerization process analogous to that of the phenalenyl radical, which undergoes a five-step cascade to peropyrene.<sup>[24]</sup> The first step of this sequence is the formation of a  $\sigma$ -dimer between two phenalenyl radicals, and it is the selectivity of this step that determines the reaction outcome.



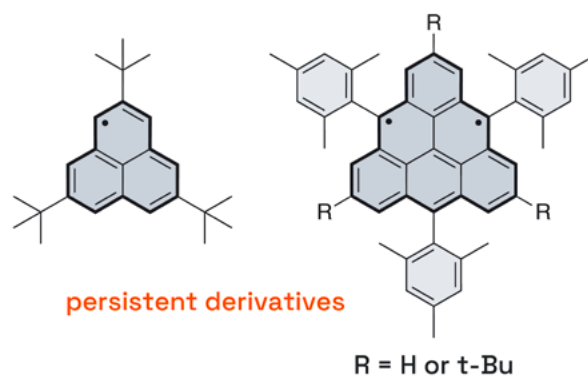
Unsubstituted phenalenyl can react at any of the six  $\alpha$ -positions, but every scenario gives the same product. Adding just one substituent changes the outcome, and reactions at different positions give different products. Our dimerization of nonacethrene is a good example of this concept. The phenalenyl unit of the mono-radical intermediate could potentially react at one of the four non-equivalent positions, but only one combination gives the observed product, meaning the process is highly selective.<sup>[32]</sup>



one radical reacts at position 1  
and the other at position 2  
to give the observed  
product

Yet,  $\pi$ -radical reactivity remains an underexplored territory, often overshadowed by its perceived undesirability. An example is Kubo's biphenalenylidene mentioned above, which was the subject of a study focused on identifying reactive intermediates in the decomposition pathway of the phenalenyl radical.<sup>[34]</sup> This is likely due to the fact that open-shell graphene fragments like phenalenyl and triangulene have primarily been investigated for their magnetic properties arising from the presence of unpaired electrons.<sup>[35,36]</sup> Consequently, processes leading to the loss of the unpaired electrons are not desirable and must be mitigated by using bulky substituents that sterically protect all reactive positions.<sup>[37–39]</sup>

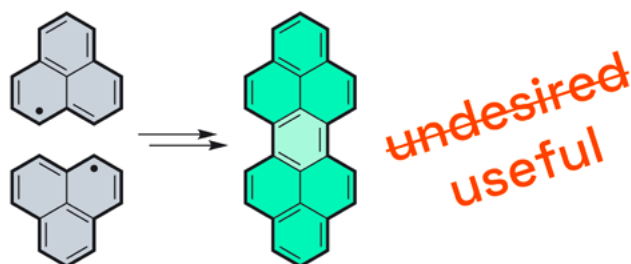
In the case of phenalenyl, three *tert*-butyl groups installed at the vertices are sufficient to fully suppress  $\sigma$ -dimerization.<sup>[40]</sup>



The same substitution pattern is insufficient to protect all of triangulene's reactive positions,<sup>[2]</sup> necessitating a different functionalization. We demonstrated this in 2021, when we achieved our very first goal of synthesizing a persistent derivative of triangulene. To fully suppress its reactivity in solution, we installed three mesityl substituents in the center of its edges, sterically shielding all nine reactive positions.<sup>[41]</sup> Simultaneously, an isolable derivative bearing six substituents was reported by Shintani and coworkers.<sup>[42]</sup>

## The Hack

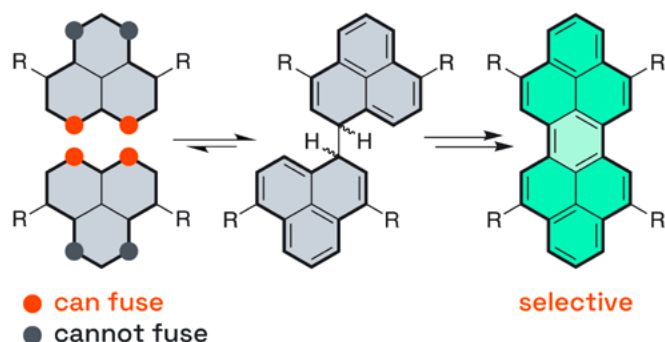
But what if we hack<sup>[43]</sup> our chemistry and explore  $\pi$ -radical reactivity through the lens of methodology with the aim to realize its hidden potential as a useful synthetic tool?



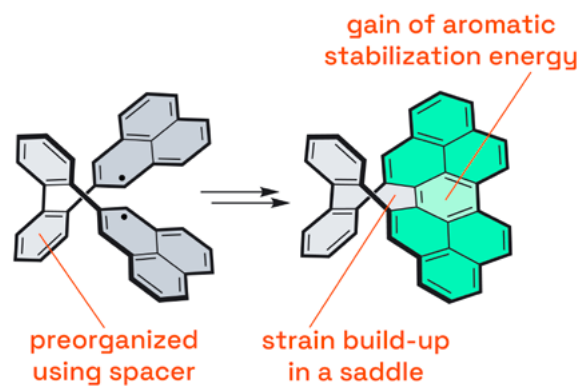
While significant advances have been made in the kinetic stabilization of these radicals, the challenge of controlling the reactivity of graphene-based  $\pi$ -radicals persists. This is partly because  $\pi$ -radical reactivity is often viewed as an undesirable trait, leading to infrequent study of the side reactions that do occur. Consequently, these ‘decomposition’ reactions are often considered undefined and difficult to control. Nevertheless, cases like phenalenyl,<sup>[24]</sup> nonacethrene,<sup>[32]</sup> and other recent reports<sup>[44–52]</sup> demonstrate that the reactivity of  $\pi$ -radicals can be well-defined.

Hence, from the perspective of a methodologist, the reactivity of graphene-based  $\pi$ -radicals represents an *opportunity*. Radical reactions are among the most efficient, and radical cascades are an ideal synthetic tool for constructing complex molecular structures by forming multiple bonds and rings in a single step. Yet, high reactivity also impedes the general use of radical cascades in synthesis, as it further increases the grand challenge of reaction control.<sup>[53]</sup>

Fortunately, the same tools used to suppress reactivity can be employed to control it. This is the advantage of systems in which unpaired electrons are delocalized. By blocking certain positions from reacting while leaving others exposed, we can achieve selectivity and control the reaction outcome. Recently, we employed this principle to direct a selective dimerization of phenalenyl: by sterically blocking two of the three edges, leaving only one available for fusion, we achieved the selective formation of a tetrasubstituted peropyrene.<sup>[54,55]</sup>



To demonstrate the transformative potential of  $\pi$ -radical reaction cascades in synthesis, we showcased that oxidative dimerization of phenalenyl can be used to build up strain. The rationale for this approach lies in the gain of aromatic stabilization energy in the final step. By preorganizing two phenalenyl units using a biphenylene linker, they had no choice but to form an eight-membered ring. The result was a saddle-shaped hydrocarbon with a strain energy of 12 kcal/mol.<sup>[56]</sup>



## Future Pathways

Chemistry has a habit of surprising us, often steering research in unexpected directions. The recent examples<sup>[24,32,44–52,54–56]</sup> illustrate that  $\pi$ -radical reactivity is one such case, holding exciting potential in synthetic chemistry. By leveraging our insights into kinetic stabilization and harnessing the selective reactivity of  $\pi$ -radicals, new pathways for complex molecule synthesis can be unlocked. Let’s keep refining our methods and expand our toolkit, and transform radical cascades into powerful tools for constructing intricate carbon nanostructures.

## Acknowledgements

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**JuricekLab**

## Author Contributions

This manuscript was written by M.J.

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