IMPROVING MEDICINES WITH CARBON PROPELLERS

Introduction

Welcome to the University of Oxford's Department of Chemistry's resource on carbon propellers!

Throughout this document we are going to learn about the structure of these carbon propellers, how researchers at the University of Oxford are using the power of light to create new reactions using these molecules, and how they can be incorporated into drugs to improve how well medicines work in our bodies.

The blue boxes contain questions you should aim to answer as you go through the document.

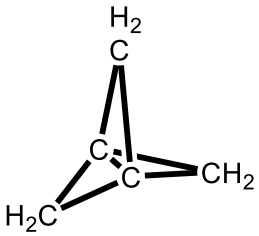
The green boxes give you more information about the Chemistry and sometimes include extra reading for those interested!

The orange boxes contain optional activities you can do to help further your understanding.

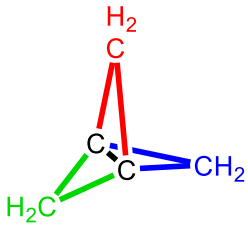
Introduction to carbon propellers

[1.1.1]Propellane

[1.1.1]Propellane is a small hydrocarbon with an unusual structure. It consists of a central C–C bond with three CH_2 bridges attached to both of these central carbons. These bridges look a bit like the blades of a propeller, which is where [1.1.1]propellane gets its name from!



The [1.1.1] before its name refers to the number of carbon atoms in each of its bridges.



[1.1.1]Propellane

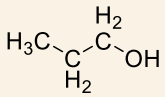
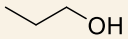
Q1. What is the chemical formula for [1.1.1]propellane?

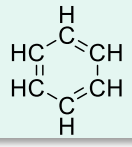
Q2. What would [3.1.1]propellane look like?

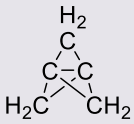
Q3. What is the geometry of each of the carbons in propellane? How might this affect its reactivity?

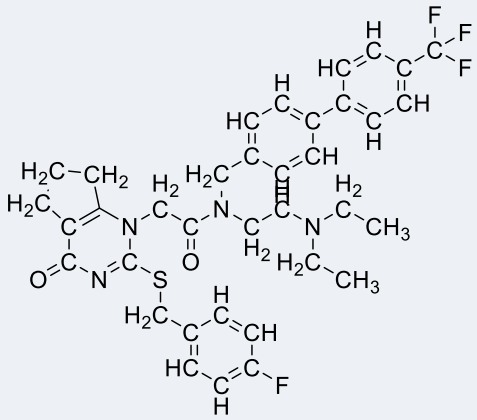
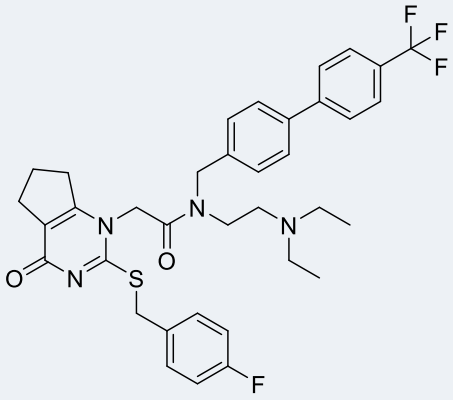
Try to make [1.1.1]propellane out of molymods. What do you notice?

Skeletal Formula

Propan-1-ol  

Benzene  

[1.1.1]Propellane  

Darapladib  

Drawing organic compounds as their skeletal formula can be very useful to chemists as it simplifies a lot of information into a much clearer structure. For simple molecules such as propan-1-ol and benzene it might not make too much difference, but when we look at complicated drug compounds such as darapladib, if every atom is drawn out it looks very confusing! Drawing the skeletal structure instead allows us to see the overall structure and the functional groups much more clearly. Structures from this point will be drawn using their skeletal formula.

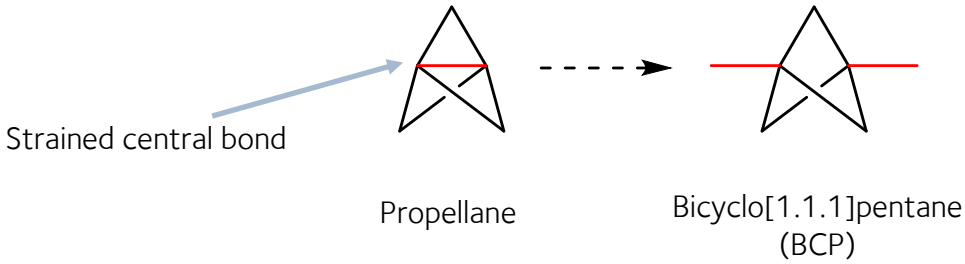
Reactivity of propellane

To make the central C–C bond in propellane, these two carbon atoms have to adopt a geometry that is very unfavourable.

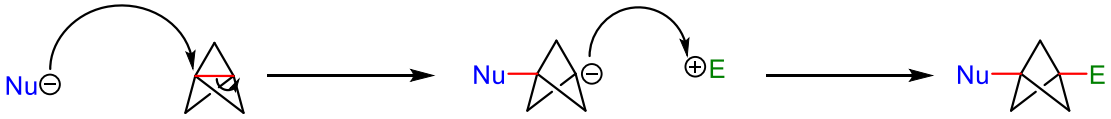
Q1. What is the normal geometry and bond angles of a carbon atom with four single bonds?

Q2. Why is it unfavourable for propellane to have this geometry?

This makes the central bond unstable and therefore reactive to a wide range of reactants including nucleophiles and radicals. When we perform a reaction that breaks this central bond, the two carbon atoms that made up this central C–C bond are now able to form new bonds to an atom or molecule. The products of these reactions are called a bicyclo[1.1.1]pentanes, or BCPs for short.

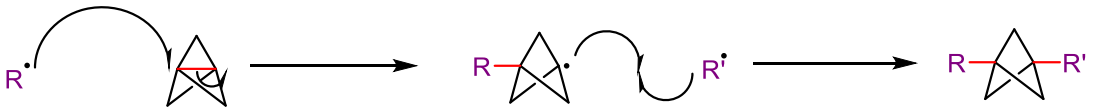


A nucleophile (Nu) can donate a pair of electrons to one of the central C–C bond carbon atoms. In doing so, Nu forms a covalent bond with this carbon atom and at the same time, the central bond breaks. The pair of electrons from the central bond become localised on the other carbon atom. This pair of electrons can now be donated to an electrophile (E) to form a new covalent bond. We can show this movement of electrons using curly arrows.



Radicals can react with propellane in a similar way. We show the movement of a single, unpaired electron using an arrow with half an arrow head, this is called a fish hook arrow.

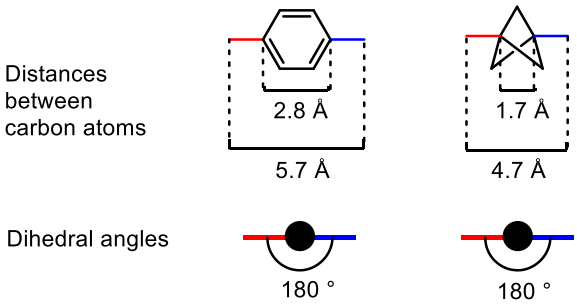
A species with an unpaired electron (R) can donate this electron to one of the carbons that make up the central C–C bond. The central bond then breaks homolytically – one electron goes to form the new covalent bond between the carbon atom and R and one electron goes to the other carbon atom. This unpaired electron can then recombine with another radical species R' to form another new covalent bond.



Learn more about radical chemistry and mechanism by watching this YouTube video from Khan Academy

Why are BCPs useful?

We have seen that we can turn [1.1.1]propellane into BCPs by breaking the central bond as a result of adding a nucleophile or radical to it. But why do we want to? A BCP is a 'bioisostere' for a *para*-substituted benzene ring. This means if we take a drug molecule that contains a benzene ring, and we remove the benzene ring and replace it with a BCP, the drug maintains its overall biological activity. In other words, by making this swap, the drug still works in the way it's supposed to, for example, a painkiller such as ibuprofen still works as a painkiller. A BCP is a good bioisostere for a para-benzene ring because they both hold their substituents at 180° from each other (this is the dihedral angle).



Learn about nomenclature of aromatic rings including para and meta benzenes

Q1. What is the dihedral angle in a *meta*-substituted benzene ring?

Q2. Find the chemical structure of ibuprofen, now draw BCP-ibuprofen where the benzene ring has been substituted for a BCP.

Make a BCP out of molymods. By adding CH_2 groups to the bridges can you find a good bioisostere for a *meta*-substituted benzene ring?

Why are bioisosteres useful?

Developing new drugs is surprisingly difficult! For every 100 drugs that begin development, 96 of them never get to the point where they're approved for public use. That's a 96% failure rate!

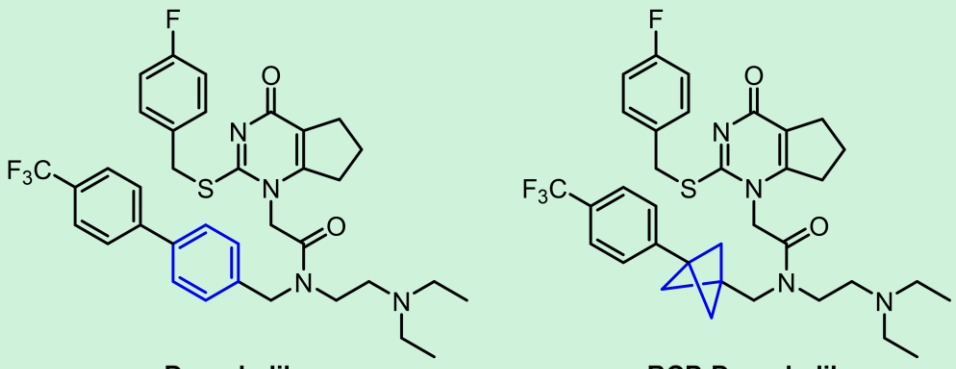
Some of the major problems that drugs in development have are:

- They are not soluble enough in water.
- They are metabolised too fast.
- The level of lipophilicity (solubility in fats, oils and non-polar solvents) is either too high or too low.

Q1. Why does a drug need to be soluble in water? What about oil?

Q2. Why is it a problem if a drug is metabolized by the body too fast? What about if it's metabolized too slowly?

Darapladib was a drug developed to treat atherosclerosis, but it suffered from poor solubility and fast metabolism. In 2017, GSK synthesized BCP-darapladib and found that it had improved aqueous solubility and was metabolized more slowly – demonstrating the benefits of the use of BCPs as bioisosteres.



Darapladib **BCP-Darapladib**

Read about the role of medicinal chemists.

Making BCPs from [1.1.1]propellane

Now we've seen how BCPs can be useful in medicine, and that we can make them by reacting nucleophiles or radicals with [1.1.1]propellane. As it turns out radical species react very efficiently with [1.1.1]propellane and so this is a very useful method of making BCPs. But how are we going to generate these radicals in the first place? We can draw inspiration from what we already know about the depletion of ozone in the atmosphere catalysed by chlorofluorocarbons (CFCs). UV radiation can homolytically cleave a C–Cl in CFCs to form radical species that start the propagation of the decomposition of ozone to oxygen.

Q1. Why does the C–Cl bond break rather than the C–F bond in a CFC?

Q2. Write out equations for the initiation, propagation, and termination steps for the decomposition of ozone to molecular oxygen.

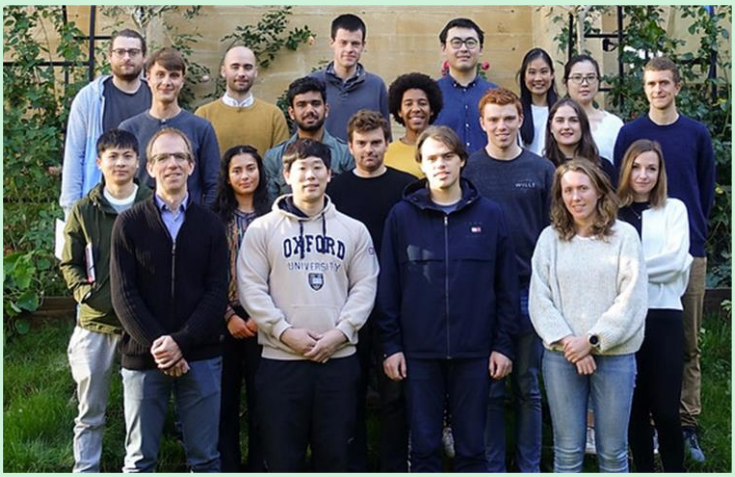
Find out more about ozone decomposition.

This gives inspiration of how we can form the radical species we need to add across [1.1.1]propellane – by breaking carbon-halogen bonds! UV radiation is hazardous however so it would be preferable to use safer, lower energy forms of radiation like visible light. As it is lower energy however, C–Cl bonds are now too strong to break, so using compounds with weaker carbon-iodide bonds is a better option.

Photoredox catalysis

At the University of Oxford, Professor Ed and Anderson along with his research group are creating new chemical reactions to turn [1.1.1]propellane into BCPs. One of the ways in which they do this uses a technique called **photoredox catalysis**.

Find out more about the Ed Anderson group



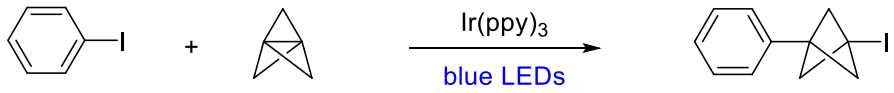
Photoredox catalysis is a technique that uses the energy in light (photo) along with a catalyst to perform reactions that involve both reduction and oxidations (redox). You will have come across redox processes for transition metal complexes, but redox reactions are incredibly important for organic chemistry reactions too.

Q1. Can you think of a chemical process that occurs in nature that uses the energy from visible light?

Q2. What defines an oxidation process? What about reduction?

Q3. Write half equations and then a balanced overall equation for the processes of $Al \rightarrow Al^{3+}$ and $Cu^{2+} \rightarrow Cu$.

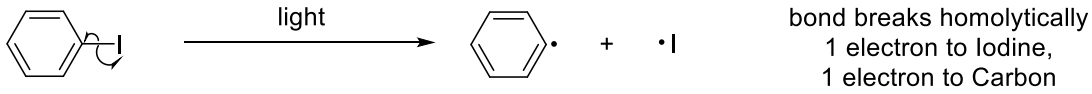
The Anderson group uses photoredox catalyst to catalyse the overall radical addition of a variety of iodobenzenes (also substituted with other functional groups) across [1.1.1]propellane to make BCPs substituted with a benzene ring on bonded to one side, and an iodine atom bonded to the other. The overall transformation is shown below:



$Ir(ppy)_3$ is a common photoredox catalyst used by chemists. It consists of an Ir^{3+} metal cation with 3 phenylpyridine (ppy) ligands surrounding it. Before we look at how this catalyst works, let's consider how this reaction would proceed in the absence of the catalyst.

This is a radical reaction so we need to think about an initiation step, one or more propagation steps, and a termination step. The initiation step is shown below.

Without a catalyst:



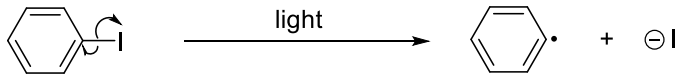
Q1. Suggest propagation and termination steps for this reaction form the overall product shown at the top of the page. Check page 6 if needed for a hint of how radicals add to [1.1.1]propellane.

As it turns out, the reaction discussed on the previous page in the absence of catalyst is very inefficient. The C–I bond is from an sp^2 hybridised carbon atom, and this bond is strong enough that it is still hard to cleave homolytically when just shining light on it.

Read about hybridisation

This is where photoredox catalysis can be very useful. Using a catalyst allows the mechanism of the reaction to go via a different pathway with a lower activation energy. In this case, instead of trying to break the C–I bond of the starting material homolytically using the energy from light, the photoredox catalyst **reduces** the C–I bond instead by donating an electron into it. The catalyst has therefore lost and electron and has been **oxidised**.

With a photoredox catalyst:



catalyst donates an electron to C-I bond
2 electrons to Iodine
1 electron to Carbon

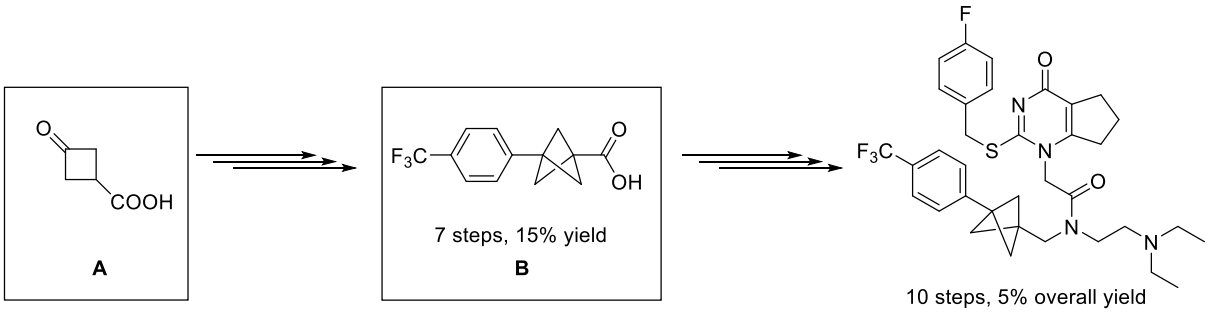
When blue light is shone on the $Ir(ppy)_3$ catalyst, it absorbs some of the energy from the light, which excites one of the electrons in its highest energy molecular orbital to an even higher energy level. This electron is therefore held less tightly by the nucleus and therefore makes it easier for it to donate an electron to the iodobenzene starting material.

Q1. Suggest propagation and termination steps for this reaction.

Q2. Write half equations and the overall equation for the initiation step when the photoredox catalyst $Ir(ppy)_3$ is used. *Hint – The Ir starts in a +3 oxidation state.*

Using photoredox to improve drug synthesis

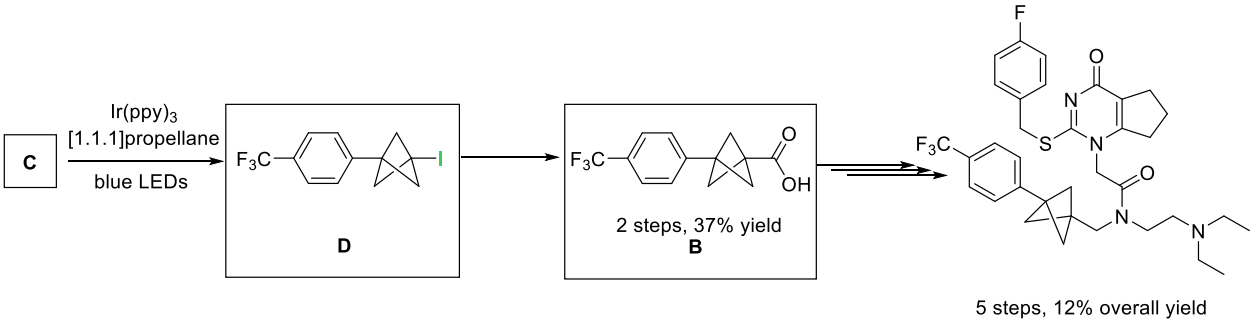
The Anderson group were able to demonstrate the use of this reaction in improving the synthesis of BCP-darapladib. The previous synthesis was done in 2017 and took 10 steps to make the target. A key intermediate made was the compound labelled **B** in the scheme below. It consists of a BCP with a benzene ring on one side (also substituted with a CF_3 group) and a carboxylic acid on the other.



Q1. Identify the functional groups in starting material **A**.

Q2. What is the average yield for all of the steps to make **B** from starting material **A**.

However, if we use photoredox catalysis we can make the same intermediate **B** far more efficiently:



In one step we can make BCP intermediate **D** using our photoredox reaction with starting material **C**. It then only takes one more reaction to

transform the iodide into carboxylic acid and there the same intermediate **B** is made in only two steps.

Q1. Identify starting material **C**.

Q2. What is the average yield for all of the steps to make **B** from starting material **C**.

This method allows us to make BCP-darapladib in only five steps – half the number of steps – and with over twice the overall yield. This means it is quicker, cheaper and easier to make BCP-darapladib.

Research into the synthesis and uses of propellanes and BCPs has only gained significant interest relatively recently and the number of ways to make BCPs is limited. The are currently a number of research groups around the world who are performing chemical research to try and expand our 'toolkit' of possible reactions to make these interesting molecules.

The hope is that as more new chemical reactions are developed to turn [1.1.1]propellanes into BCPs, the easier it will be to include them when developing brand new medicines. Given their clear benefits when it comes to issues like solubility and metabolism in certain drugs, one day we may see a BCP containing medicine make its way to the public!

Find out more about the work of the Department of Chemistry at:
www.chem.ox.ac.uk

About the authors

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Bethany recently finished her PhD in Organic Chemistry at the University of Oxford as part of the synthesis for biology and medicine centre for doctoral training (SBM CDT). She works on new catalytic methods for the synthesis of BCPs with Professor Ed Anderson. Before moving colleges to Lady Margaret Hall to undertake her PhD, Bethany was an undergraduate at Pembroke College, Oxford, graduating with a master's degree in Chemistry.

Saskia O'Sullivan

Saskia is the Educational Outreach Officer for the Department of Chemistry at the University of Oxford. Previous to this role, Saskia taught Chemistry in secondary schools, having moved into school teaching from youth work. Saskia is a Natural Sciences graduate of the University of Cambridge and holds a master's degree in Science and Education from the University of Bristol.

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Answers to all the questions in this booklet can be found **here**.