Improving medicines with carbon propellers

Answer Booklet

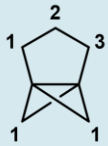
Introduction to carbon propellers

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

C_5H_6

Q2. What would [3.1.1]propellane look like?

It has a central bond with three bridges, one bridge contains 3 carbons, the other two bridges contain 1 carbon each.



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

Bridging carbons are roughly tetrahedral but bridgehead carbons (that make up the central bond) are not and forced to adopt an unusual inverted tetrahedral geometry. This is very unfavourable meaning the molecule is unstable and therefore it is very reactive.

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

If molymods are available, if students try to make [1.1.1]propellane they will find that they are unable to. They can make all of it (using bendy bonds) other than the central bond which they will not be able to form as molmods force carbon atoms to take a tetrahedral arrangement of bonds. This should help demonstrate the strained/unfavourable nature of the bond.

Reactivity of propellane

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

Tetrahedral, 109.5°

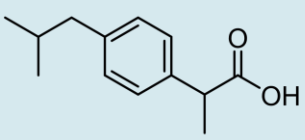
Q2. Why is it unfavourable for propellane to have this geometry?

Electrons repel each other so atoms like to arrange pairs of electrons e.g. bonding pairs as far away from each other as possible. In order to form the central bond of propellane, many bonding pairs of electrons are forced to be in very close proximity to each other so there is alarge amount of repulsion between these pairs of electrons. This causes this structure to be very strained.

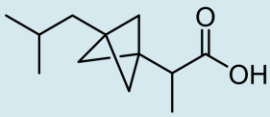
Q1. What is the dihedral angle in a *meta*-substituted benzene ring?

120°

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



ibuprofen



BCP-ibuprofen

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?

[3.1.1]propellane should be a good match but there are proabably others too.

Why are bioisosteres useful?

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

Soluble in water – to be absorbed and dissolve in blood and be carried around the body to wherever it needs to be.

Oil – needs to be lipophilic enough to pass through phospholipid bilayer in cell membranes.

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

Too fast – drug is broken down and excreted before it has time to take effect, would have to be constantly taking more of the drug.

Too slow – the drug isn't broken down and can build up in the system and lead to toxicity.

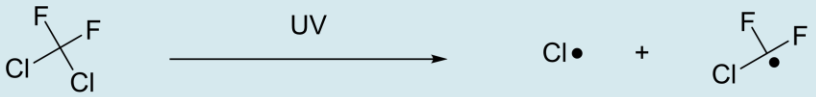
BCPs from [1.1.1]propellane

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

It is weaker (lower bond enthalpy).

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

CFCs catalyses ozone breakdown: $2O_3 \longrightarrow 3O_2$

Initiation: 

Propagation: $Cl\bullet + O_3 \longrightarrow ClO\bullet + O_2$

$ClO\bullet + O_3 \longrightarrow Cl\bullet + 2O_2$

Any reasonable termination step is fine.

Photoredox catalysis

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

Photosynthesis

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

Oxidation is loss of electrons. Reduction is gain of electrons.

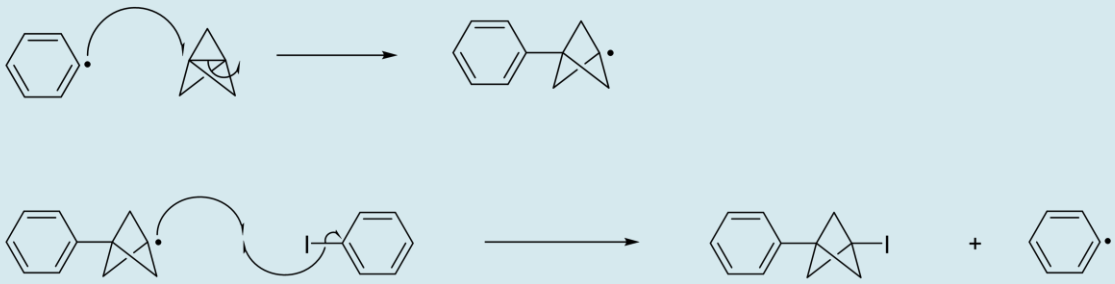
Q3. Write half equations and then a balanced overall equation for the processes of $Al \rightarrow Al^{3+}$ and $Cu^{2+} \rightarrow$ Cu.

$Al \rightarrow Al^{3+} + 3e^-$, $Cu^{2+} + 2e^- \rightarrow Cu$

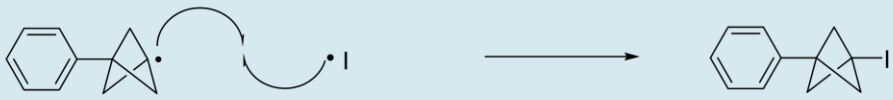
Overall: $2Al + 3Cu^{2+} \rightarrow 2Al^{3+} + 3Cu$

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.

Propagation



Termination



Q1. Suggest propagation and termination steps for this reaction.

Propagation steps are the same as above, termination could also be the same. Any reasonable termination steps should be ok. A question that might be how is the catalyst reformed? Something needs to be oxidized in order to reduce the catalyst from Ir(IV) back to Ir(III). This could be done by reducing the BCP radical to a BCP cation or iodide anions to iodine radical.

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.*

$Ar{-}I + e^- \rightarrow Ar\bullet + I^-$, $Ir^{3+}(ppy)_3 \rightarrow Ir^{4+}(ppy)_3 + e^-$

Overall: $Ar{-}I + Ir^{3+}(ppy)_3 \rightarrow Ar\bullet + I^- + Ir^{4+}(ppy)_3$

Using photoredox to improve drug synthesis

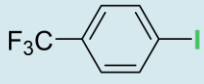
Q1. Identify the functional groups in starting material A.

Ketone and carboxylic acid.

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

76%

Q1. Identify starting material C.



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

61%