

9.2: Background

Introduction

While often unreactive, aliphatic C–H bonds can be functionalized via a radical halogenation reaction. Radical halogenation reactions are sensitive to the type of C–H bond being halogenated and the identity of the halogen being used in the reaction. Weaker 3° C–H bonds are typically more reactive than stronger 1° C–H bonds. This reactivity is relatively predictable, leading to reactivity charts that allow you to estimate the relative ratio of products in a radical halogenation reaction. For example, as shown in Figure 1, a secondary C–H bond is, on average, 3.9 x more likely to be chlorinated than a primary C–H bond.

Radical	Decreasing C-H Bond Strength		
	1 C-H	2 C-H	3 C-H
F•	1	1.2	1.4
Cl•	1	3.9	5.2
Br•	1	82	1600

Figure 1. The relative reactivity of halogen radicals towards differing C–H bonds. These values represent average reactivity and will change due to the specific electronic and steric nature of a molecule. Darker colors in this scheme represent greater selectivity for the indicated C–H bond type by the indicated radical.

These values, however, are for average C–H bonds and can be influenced by the local environment of the bonds undergoing halogenation. For example, a primary C–H bond adjacent to the oxygen atom in an ether is often more reactive than would be predicted in Figure 2. Moreover, C–H bonds on a carbon adjacent to a π bond are more reactive than predicted because the radical formed upon hydrogen atom abstraction is resonance stabilized. For this exercise, we will be examining the radical chlorination of norbornane, a bicyclic hydrocarbon molecule. When chlorinated, the hydrocarbon norbornane does not yield the expected distribution of products. As shown in Figure 3, radical chlorination of norbornane yields exo-2-chloronorbornane (**1**) and endo-2-chloronorbornane (**2**) as the majority products, while 1-chloronorbornane (**3**) is only found in a trace amount. No 7-chloronorbornane (**4**) was detected.⁶ In this case, some secondary C–H bonds would appear to be more reactive than a tertiary C–H bond; this is the opposite selectivity that we would expect.

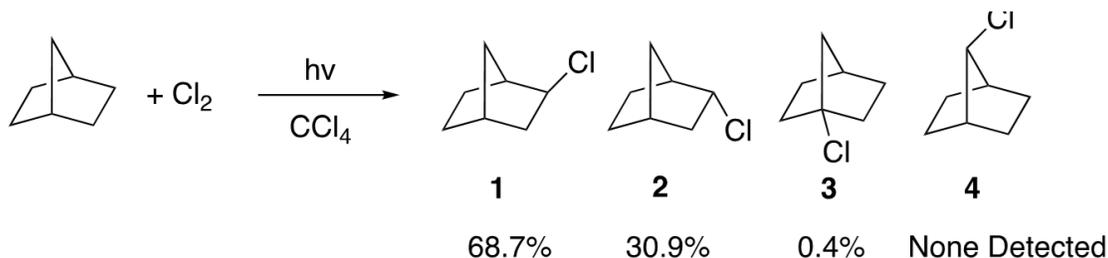


Figure 2. The radical chlorination of norbornane. The yields reported represent the relative percent of the monochlorinated product.

The goal of our exercise today is to use computation to gain understanding as to why the halogenation of norbornane yields results different than those that would be predicted by the relative reactivity table in Figure 1.

Background

A C–H halogenation reaction occurs via a radical, or single electron, process. This reaction first involves a radical initiation where high-energy, unpaired-electron species known as radicals are produced from even electron precursors. As shown in Figure 4, the reaction begins when light promotes the homolytic cleavage of an X–X bond, yielding halogen radicals (X•). The halogen radical (X•) will then abstract a hydrogen atom from the hydrocarbon substrate, yielding a carbon-based radical (R•) and an equivalent of H–X. This hydrogen atom abstraction is typically the slow or rate-determining step of this reaction. The carbon-based radical will then abstract a halogen atom from an equivalent of molecular halogen (X–X), yielding halogenated product and another equivalent of halogen radical. The process whereby a halogen radical is both consumed and regenerated yielding product and H–X is known as the propagation phase of the reaction. This is where most alkyl halide product is produced in a radical halogenation reaction. Finally, in the termination phase of the reaction, radical species dimerize to yield even electron compounds.

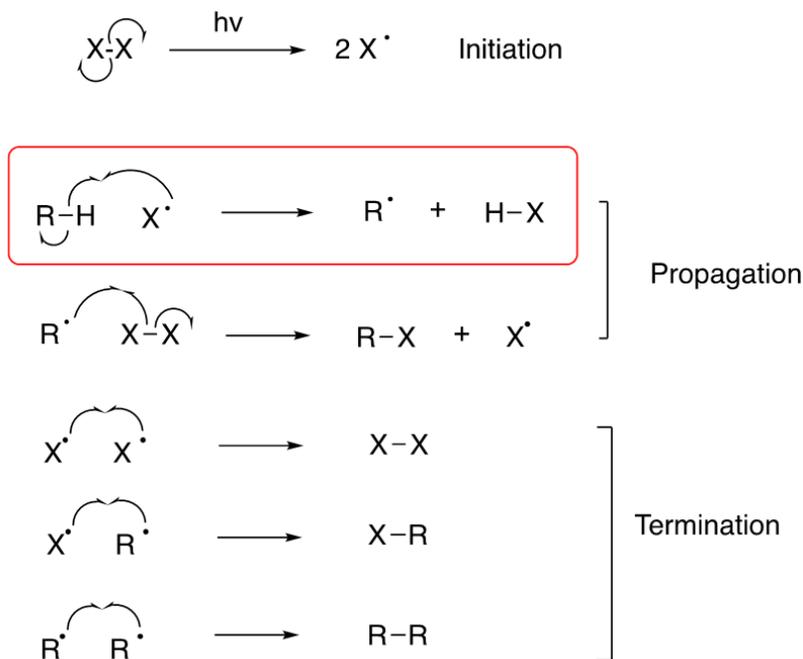


Figure 3. Mechanism of radical halogenation. The rate determining, or slow step, of this reaction is the hydrogen abstraction step. This is indicated in the figure above by a red box.

The substitution of a carbon-based radical, such as those formed in a radical halogenation reaction, dramatically influences its stability. Radicals can be stabilized via hyperconjugation if an adjacent bond is oriented parallel to the orbital where the radical resides. If the orientation is right, electrons from the filled bonding orbital can be shared with the half-filled p -orbital of the carbon-based radical. Primary radicals are less stable than secondary radicals or tertiary radicals because they have fewer C–C and C–H bonds available with the correct orientation to engage in **hyperconjugation** (Figure 4).

The greater the opportunity for hyperconjugation, the more stable the radical is because the other parts of the molecule help stabilize the unpaired electron.

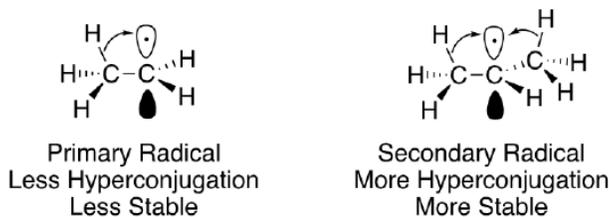


Figure 4. Increased opportunity for hyperconjugation leads to greater stability in a carbon-based radical.

The dominant product of a radical halogenation is determined by the reactivity of the halogen radical, and the carbon-centered radicals formed upon removal of a hydrogen atom ($\text{H}\cdot$). The selectivity of the overall halogenation reaction is determined by the rate of the most difficult step, the so-called rate determining step. Because it is difficult to make a carbon-centered radical, removal of a hydrogen atom from a C–H bond is the rate determining step of this reaction. The stability of the formed radical influences the energy of the transition state and by extension ΔG^\ddagger . According to Hammond's postulate, the transition state of a reaction resembles the structure of the reactant, or product to which it is closer in energy. Because chlorine radicals are more reactive than most carbon-centered radicals, the transition states of the reactions studied today are more reactant-like. Thus, the ΔG^\ddagger for this process varies based upon the stability of the carbon based radical. A similar reaction with less reactive bromine radicals ($\text{Br}\cdot$) more strongly depends upon the stability of the carbon-based radical because the abstraction step is endergonic (Figure 5).

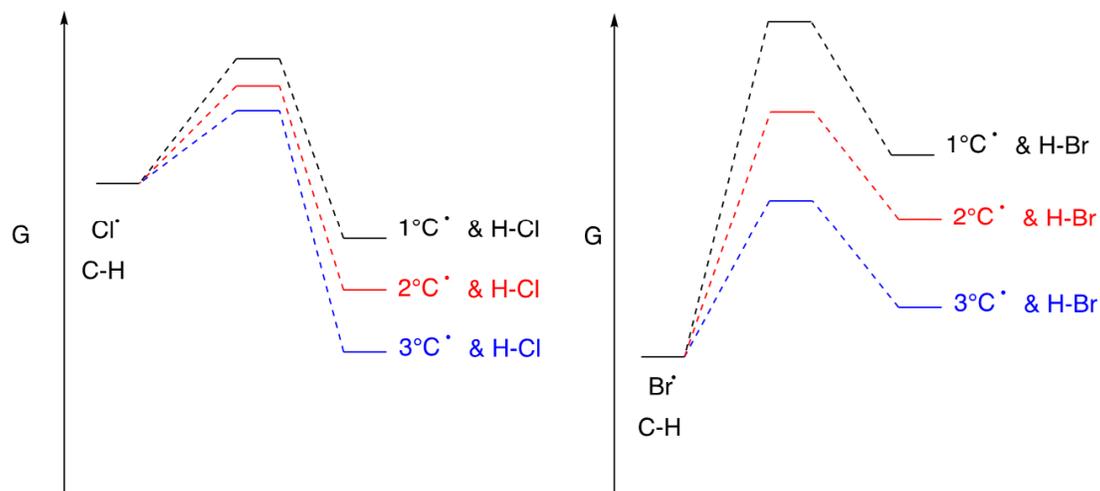


Figure 5. Reaction coordinate diagrams of the hydrogen atom abstraction step of radical halogenation. Please note that the ΔG^\ddagger energy value decreases as the formed radical becomes more stable (lower in energy).

The concept of bond dissociation enthalpy, known as BDE, is a measure of the stability of radicals. As shown in Figure 6, the bond dissociation enthalpy is simply the difference in enthalpy between products and reactants of a reaction where a bond is broken homolytically (each atom keeps one electron from the bond). Because the enthalpy of forming a hydrogen radical will be the same for each reaction, differences in the value of BDE reflect the stability of the carbon-centered radical. The higher the BDE of a C – H bond, the less stable a radical formed at that position will be.



Figure 6. The definition of bond dissociation enthalpy (BDE) for a C – H bond.

In this way, we can use DFT to estimate the bond dissociation enthalpy of C – H bonds in an organic molecule to determine the relative reactivity of each bond toward a radical halogenation reaction. To understand the math involved, let's work through the simple example of methane. As shown in Figure 7, the methane C – H BDE represents the enthalpy change in the homolytic cleavage of a C – H bond yielding a methyl radical and a hydrogen atom (H^\cdot). The absolute enthalpy (H) of methane and the methyl radical were calculated in Orca (B3LYP, DEF2-SVP) and the enthalpy of the hydrogen atom was reported in the chemical literature.⁷ The BDE of methane's C – H bond can then be calculated by finding the difference between the enthalpies of the products (H^\cdot and methyl radical) and the reactant (methane). As shown below, we calculate a value of 101.8 kcal/mol. This value is consistent with experimental values of the methane C – H bond strength of 104.9 kcal/mol, indicating that this method is yielding a reasonable answer for our purposes.⁸

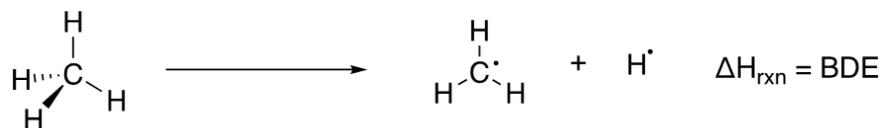


Figure 9.2.1: Copy and Paste Caption here. (Copyright; author via source)

Species	Enthalpy (EH)	Enthalpy (kcal/mol)
Hydrogen Atom	-0.49764	-312.119808
Methane	-40.40362394	-25341.15294
Methyl Radical	-39.74373799	-24927.27247

The calculation of the BDE of the C – H bond of methane:

$$\begin{aligned} \text{BDE} &= \sum (H_{\text{Products}}) - \sum (H_{\text{Reactants}}) \\ &= (-312.119808 \text{ kcal/mol} + -24927.27247 \text{ kcal/mol}) - (-25341.15294 \text{ kcal/mol}) \\ &= 101.8 \text{ kcal/mol} \end{aligned}$$

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