Preparation of Alkyl Halides, R-X

Reaction of alkanes with Cl_2 & Br_2
(F_2 is too reactive, I_2 is unreactive):

$$\mathrm{R{-}H} \;+\; \mathrm{X_2} \xrightarrow[\text{or heat}]{\text{UV}} \mathrm{R{-}X} \;+\; \mathrm{HX}$$

As we have seen previously, the mechanism involves a *chain reaction*. A chain reaction involves a series of steps *in which a product formed in a later step is a reactant in an earlier step*.

Initiation-

$$\mathrm{X{-}X} \xrightarrow[\text{or UV}]{\text{heat}} 2\ \mathrm{X}\bullet$$

Propagation-

$$\mathrm{X}\bullet \;+\; \mathrm{H{-}R} \xrightarrow{\Delta H_1} \mathrm{X{-}H} \;+\; \bullet\mathrm{R}$$

$$\mathrm{R}\bullet \;+\; \mathrm{X{-}X} \xrightarrow{\Delta H_2} \mathrm{R{-}X} \;+\; \bullet\mathrm{X}$$

Termination-

$$2\ \mathrm{X}\bullet \longrightarrow \mathrm{X{-}X}$$

$$\mathrm{X}\bullet \;+\; \bullet\mathrm{R} \longrightarrow \mathrm{R{-}X}$$

$$2\ \mathrm{R}\bullet \longrightarrow \mathrm{R{-}R}$$

ΔH^o in kJ/mole

R =	CH_3	1^o R	2^o R	3^o R
ΔH_1, Cl_2	+6	-12	-31	-42
ΔH_1, Br_2	+72	+54	+35	+24
ΔH_2, Cl_2	-108	-95	-96	-87
ΔH_2, Br_2	-100	-92	-87	-70

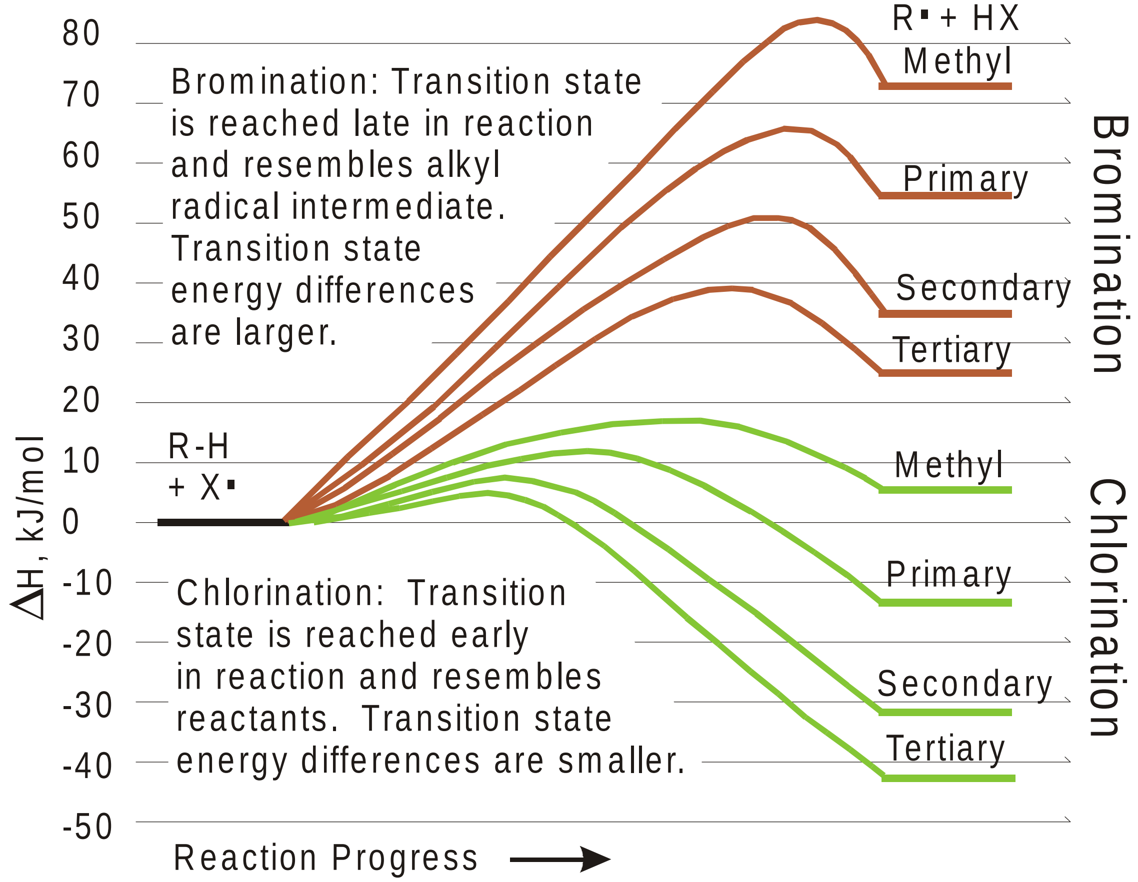
Note that the second propagation step (ΔH_2) is quite exothermic in all cases. The first step (ΔH_1) is less exothermic or endothermic. It is reasonable to conclude that the first step would have the larger $\Delta G^\ddagger$ and is rate limiting. It also follows that the rate of reaction for substitution of hydrogens by halogens would be
$3^o > 2^o > 1^o >$ methane. This is also the order of stability of the alkyl free radicals that are formed: the more stable intermediate radical is formed faster.

At room temperature, the relative rate of replacement of hydrogen atoms in alkanes by chlorine is
$3^o : 2^o : 1^o = 5.0 : 3.5 : 1.0$ (per hydrogen).

At 125^o C, the relative rate of replacement of hydrogen atoms in alkanes by bromine is

$3^o : 2^o : 1^o = 1600 : 80 : 1$ (per hydrogen).

Bromination is more selective because the rate limiting step for bromination is more endothermic. This causes the transition state to be reached later in the reaction compared to chlorination. With a later transition state the transition state energies more closely reflect the radical intermediate energies.

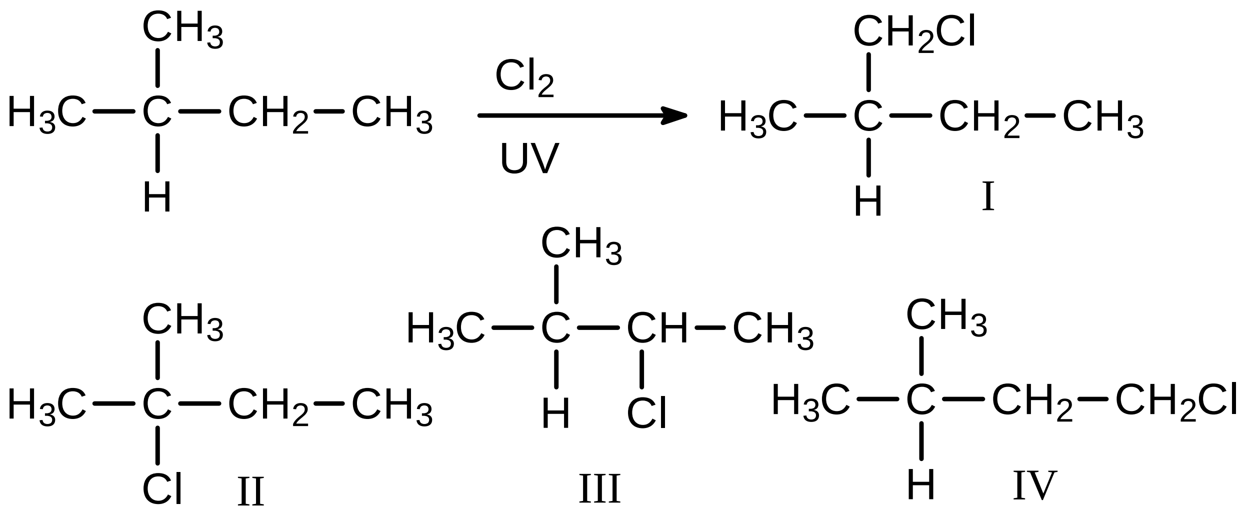


Bromination: Transition state is reached late in reaction and resembles alkyl radical intermediate. Transition state energy differences are larger.

Chlorination: Transition state is reached early in reaction and resembles reactants. Transition state energy differences are smaller.

ΔH for Radical Chlorination and Bromination

Problem: Calculate the amounts of monochloro isomers formed by chlorination of 2-methylbutane.



$$\mathrm{H_3C{-}C(CH_3)(H){-}CH_2{-}CH_3} \xrightarrow[\mathrm{UV}]{\mathrm{Cl_2}} \mathrm{H_3C{-}C(CH_2Cl)(H){-}CH_2{-}CH_3}\ \text{I}$$

$$\mathrm{H_3C{-}C(CH_3)(Cl){-}CH_2{-}CH_3}\ \text{II} \qquad \mathrm{H_3C{-}C(CH_3)(H){-}CH(Cl){-}CH_3}\ \text{III} \qquad \mathrm{H_3C{-}C(CH_3)(H){-}CH_2{-}CH_2Cl}\ \text{IV}$$

Partial rates of formation of products –

I: 6H x 1.0 = 6. II: 1H x 5.0 = 5. III: 2H x 3.5 = 7.

IV: 3H x 1.0 = 3.

Total rate = 6+5+7+3 = 21

% of I: (6/21)x100 = 28.6%, % of II: (5/21)x100 = 23.8%

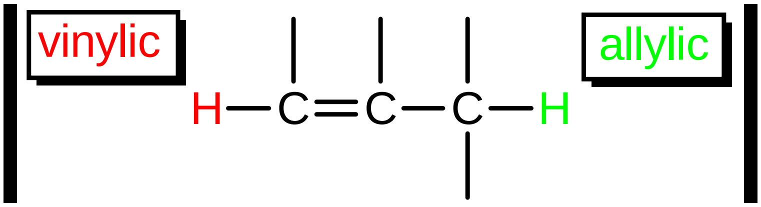
% of III: (7/21)x100 = 33.3%, % of IV: (3/21)x100 = 14.3%

Owing to its lack of selectivity, free radical chlorination is of limited usefulness in synthesis.

Another problem with free radical chlorination in synthesis is polychlorination.

Bromination is more selective than chlorination but polybromination can be a problem.

Allylic and Vinylic Hydrogens



$$\mathrm{H{-}C{=}C{-}C{-}H}$$

Vinylic hydrogens are hard to remove: the vinylic free radical which is formed is more unstable than methyl free radical.

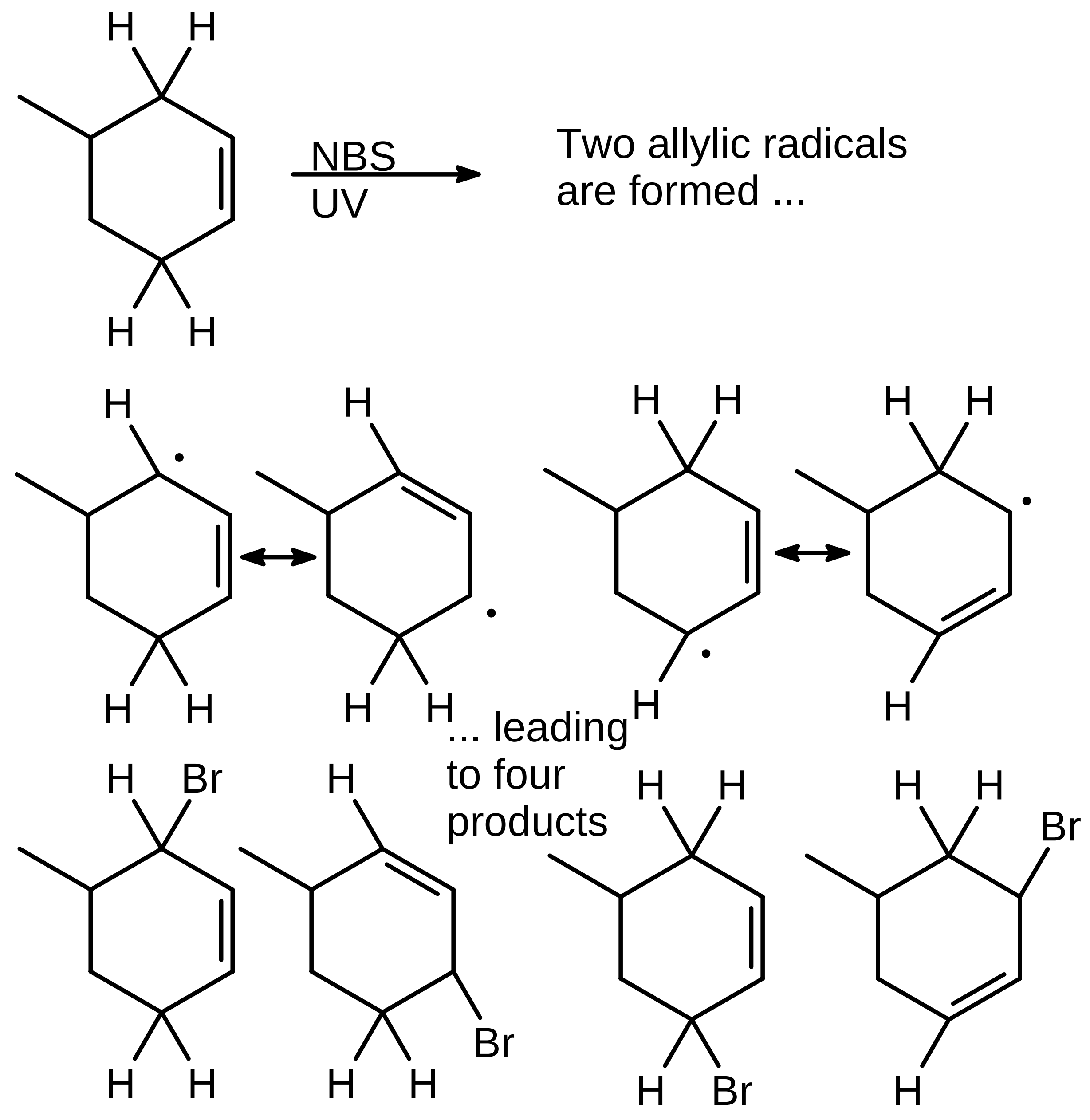
Allylic hydrogens are easy to remove: the allylic free radical which is formed is more stable than *t*-butyl free radical, owing to resonance stabilization. Thus, allylic hydrogens can be selectively removed. This is usually done using NBS, which provides a low concentration of bromine.

Complications of allylic bromination in terms of synthesis–

1. There may be different allylic hydrogens in the same compound.

2. Since the allylic radical is resonance stabilized it has more than one reactive site that can be brominated.

An example –



Two allylic radicals are formed ...

... leading to four products

Alkyl Halides from Alcohols

$$\mathrm{R{-}OH} + \mathrm{HX} \longrightarrow \mathrm{R{-}X} + \mathrm{H_2O}$$

X = Cl, Br, I

Reactivity of ROH: $3^o > 2^o > 1^o$

Rearrangement of 2^o R possible; rearrangement of 1^o occasionally occurs.

Reactivity of HX: HI > HBr > HCl

Other reagents that are used:

thionyl chloride, $SOCl_2$,

phosphorous tribromide, PBr_3,

phosphorous + iodine, $P + I_2$

Rearrangements are less likely with these reagents.

Formation of Grignard Reagents

$$\mathrm{R{-}X} + \mathrm{Mg} \xrightarrow[\text{or THF}]{\text{ether}} \text{"}\mathrm{R{-}Mg{-}X}\text{"}$$

R = 1^o, 2^o, or 3^o alkyl, vinylic, aromatic;

vinylic and aromatic are less reactive.

X = Cl, Br, I; usually not F; reactivity: I > Br > Cl.

Structure in solution – complex mixture – partly:

$$2\ \mathrm{R{-}Mg{-}X} \rightleftharpoons \mathrm{R_2Mg} + \mathrm{MgX_2} \rightleftharpoons \mathrm{R_2Mg{*}MgX_2}$$

but acts like $\overset{\delta-}{\mathrm{R}}{-}\overset{\delta+}{\mathrm{Mg}}{-}\overset{\delta-}{\mathrm{X}}$; thus the R-group has both nucleophilic and basic character.

Base – If the R-group is alkyl, R-Mg-X will react with any material that is more acidic than an alkane, *eg*

$$\mathrm{R{-}Mg{-}X} + \mathrm{H_2O} \longrightarrow \mathrm{R{-}H} + \mathrm{Mg(OH)X}$$

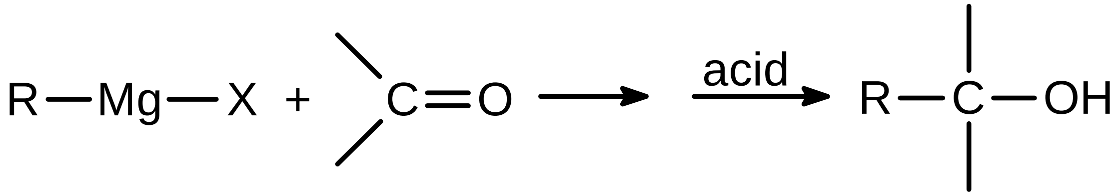
Thus, R-Mg-X cannot be prepared in the presence of any material that is slightly acidic, including compounds with H attached to O or N.

R-Mg-X can react with alkyl or aryl halides –

$$\mathrm{R{-}Mg{-}X} + \mathrm{R'{-}X'} \longrightarrow \mathrm{R{-}R'} + \mathrm{MgXX'}$$

Order of reactivity of R’-X’: I > Br > Cl.

A major reason for making Grignard reagents is to synthesize alcohols by reacting the Grignard with carbonyl compounds:



Alkyllithium Reagents

$$R{-}X + Li \longrightarrow R{-}Li + LiX$$

R-Li is chemically similar to a Grignard reagent.

Gilman Reagents – Lithium Diorganocopper Reagents

Preparation –

$$2\ R{-}Li + Cu{-}I \longrightarrow R_2Cu^- Li^+ + Li^+ I^-$$

Coupling reaction –

$$R_2Cu^- Li^+ + R'{-}X \longrightarrow R{-}R' + Li^+ X^- + RCu$$

Works best if R & R’ are 1^{o} alkyl, aryl, or vinyl.