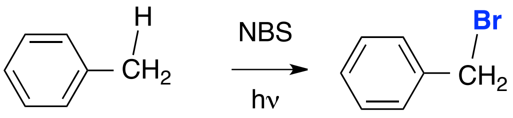
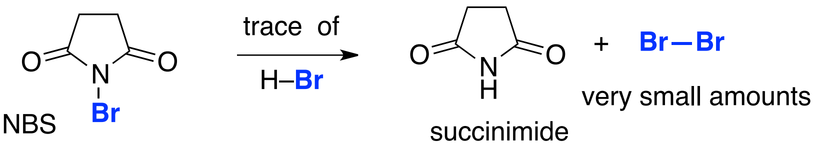
CHEM 203

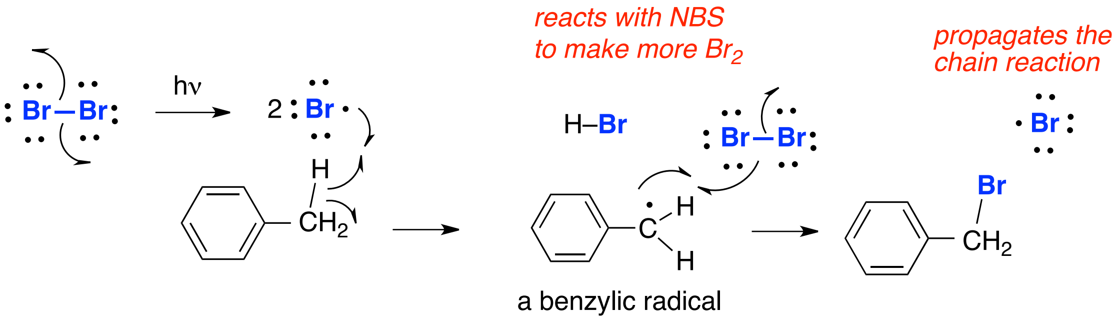
Topics Discussed on Oct. 28

Radical bromination of benzylic positions as a favorable process that is also widely employed in contemporary organic chemistry, and that works particularly well with NBS:



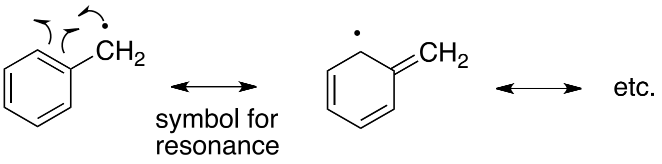
via :



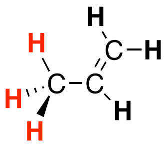


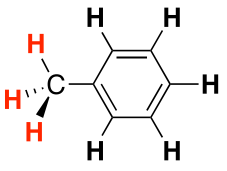
reminder: the "olefinic" bonds in a benzene ring are unusually unreactive toward Br_2, HBr, BH_3, OsO_4, radicals, etc, due to "aromaticity" (a set of properties, to be discussed in detail in CHEM 213, that cause the π bonds of benzene to behave differently from those of ordinary alkenes).

High degree of stabilization of benzylic radicals through resonance interactions:



Elevated strength of sp^2-C–H bonds: $\Delta H_{diss} \approx$ 110-120 kcal/mol:

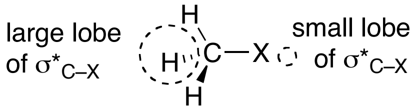




bold: C–H bonds connecting to an sp^2 carbon: unusually strong ($\Delta H_{diss} \approx$ 110 kcal/mol)

Radical bromination of tertiary C–H bonds as a feasible, but not particularly useful, reaction

Principle: the chemistry of alkyl halides is largely controlled by a low-lying carbon-halogen sigma antibonding orbital:



Principle: alkyl halides tend to interact with electron-rich species, **A**, which introduce electrons into the above σ^*_{C-X} orbital and promote **substitution reactions** according to the following general scheme:

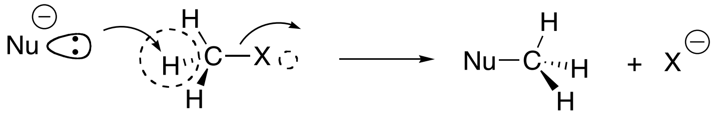
$$\text{C–X} \quad + \quad \text{A} \quad \longrightarrow \quad \text{C–A} \quad + \quad \text{X}^{\ominus}$$

Principle: substitution reactions of alkyl halides require the introduction of two electrons into the σ^*_{C-X} orbital. These electrons may be introduced either simultaneously ("nucleophilic" or "ionic" mechanisms) or one at a time ("SET" mechanisms – notes of Oct. 23)

Nucleophilic substitution reactions: processes in which a nucleophilic Lewis base functions as the A reagent in the following equation above

$$\text{C–X} \quad + \quad \text{A} \quad \longrightarrow \quad \text{C–A} \quad + \quad \text{X}^{\ominus}$$

Interaction of an electron pair from the nucleophile, Nu**:** , with the σ^*_{C-X} orbital during a nucleophilic substitution reaction:



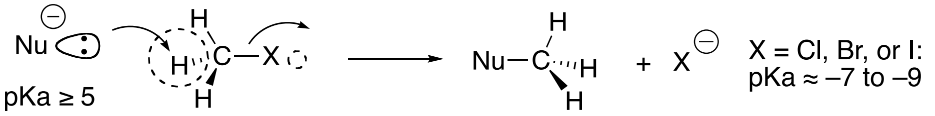
Rupture of the C–X bond as the Nu**:** introduces electron density into the σ^*_{C-X} orbital

Leaving group or nucleofuge: that fragment of the substrate that is expelled by the incoming nucleophile in the course of a nucleophilic substitution reaction

> The halide ion X^{-} (chloride, bromide, iodide) in the above diagram functions as a leaving group (= nucleofuge) in the depicted substitution reaction

Thermodynamic driving force for the above substitution reaction: the decrease in the basicity of the system — as gauged from changes in pKa's — as a more Bronsted basic agent (Nu**:**) is consumed and a less Bronsted basic one (X^{-}) is released:

> changes in the basicity of the system (ΔpKa's) incurred during a nucleophilic substitution process can be correlated with approximate equilibrium constants, Keq, for the reaction, which in turn can be used to estimate the driving force (ΔG) for the reaction:



$\Delta pKa < -12 \Longrightarrow Keq > 10^{12} \Longrightarrow \Delta G° = - nRT \ln Keq << 0 \Longrightarrow$ **very** favorable

Principle: most nucleophiles that successfully engage alkyl halides in nucleophilic substitution processes are conjugate bases of weak acids (pKa ≥ 5)

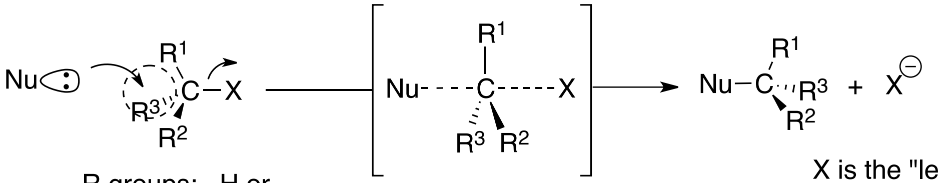
Correlation between the pKa of the conjugate acid of X^- and the ability of X^- to function as a leaving group in a substitution reaction of the above type:

H–X	H–F	H–Cl	H–Br	H–I
approx. pKa	+ 4	− 7	− 8	− 9
comments	F^- does not behave as a leaving group in the above rxs.	Cl^- is substituted fairly easily by nucleophiles in the above rxs.	Br^- is an even more rapidly substituted in the above rxs.	I^- is substituted the fastest in the above reactions

the ability of "X" to function as a leaving group in nucleophilic substitution reactions increases with decreasing Bronsted basicity (=weaker bases are better leaving groups)

Principle: the leaving group in a nucleophilic substitution reaction of the above type must be the conjugate base of a strong Bronsted acid with pKa < 0. Conjugated bases of weak Bronsted acids, e.g. F^-, cannot function as leaving groups in such reactions, regardless of how favorable (negative) ΔG_{react} may be, i.e., regardless of how strong the driving force for the reaction is.

Stereochemical aspects of nucleophilic substitution reactions of alkyl halides proceeding through the interaction of an electron pair from the nucleophile with the σ^*_{C-X} orbital:



R groups: H or alkyl substituents

transition state: the Nu–C bond not fully formed; the C–X bond is not fully broken. For an instant, the C atom is trigonal bipyramidal

X is the "leaving group" in this rx.

Note: the nucleophile, Nu, has become connected to the C atom with a spatial orientation that is *opposite* that of the original X: the reaction has occurred with **inversion of configuration**

"Backside" attack of the nucleophile onto the alkyl halide and consequent inversion of configuration during the substitution process