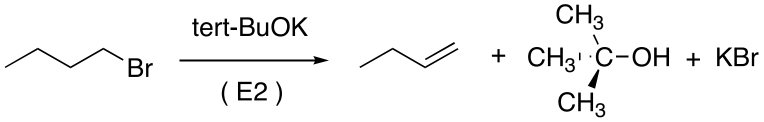
CHEM 203

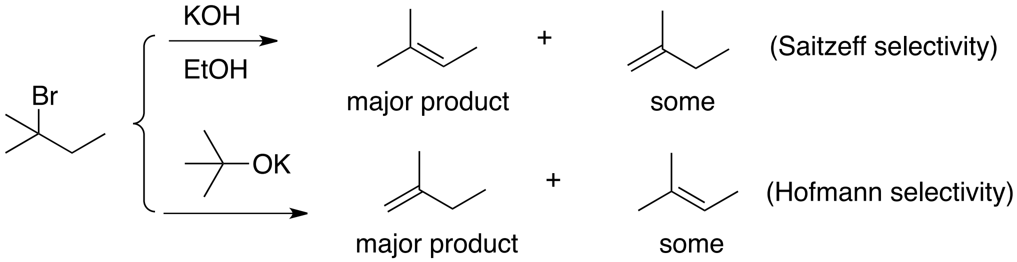
Topics Discussed on Nov. 6

Sterically hindered alkoxides such as potassium tert-butoxide as effective bases for E2 reactions of alkyl halides, even primary ones:



the tert-butoxide ion is too hindered to function as a nucleophile: it only expresses basic reactivity (=proton affinity) toward the halide

Steric effects in the E2 reaction: Saitzeff vs. Hofmann Selectivity:



Principle: hindered alkyl halides, such as tertiary ones, cannot undergo substitution by the S_N2 mechanism, but they can do so by alternative mechanisms

Principle: hindered alkyl halides, such as tertiary ones, may undergo substitution reactions, but typically with **non-basic nucleophiles** (i.e., nucleophiles that are the conjugate bases of acids with pKa's < 0; such as H_2O, CH_3OH, etc.) and **in media of high dielectric constant** ($\varepsilon > 20$)

Obviously, basic nucleophiles (pKa > 5) would promote E2 reaction of tertiary halides

Dielectric constant: a measurable property of bulk matter (solid, liquid or gas) that indicates the extent of weakening of the electrostatic force between two charges embedded in that matter, relative to the force between the same charges in a vacuum

reminder: the electrostatic force between two charges, q_1 and q_2, separated by a distance *d* and embedded in a medium (gas, liquid, or solid), is given by the **Coulomb equation**:

$$F = \frac{1}{4 \pi \varepsilon_0 \varepsilon_r} \frac{q_1 \cdot q_2}{d^2}$$

where:

ε_0 = dielectric permittivity of vacuum

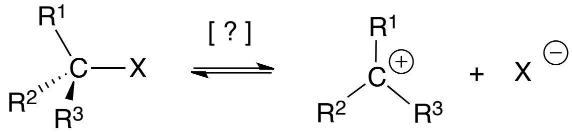
ε_r = dielectric constant of the medium

High dielectric constants of solvents such as CH_3OH ($\varepsilon_r \approx 30$), water ($\varepsilon_r \approx 80$), etc.

Polar solvent (medium): one of high dielectric constant, e.g. H_2O ($\varepsilon_r \approx 80$), CH_3OH ($\varepsilon_r \approx 30$), etc.

Nonpolar solvent (medium): one of low dielectric constant

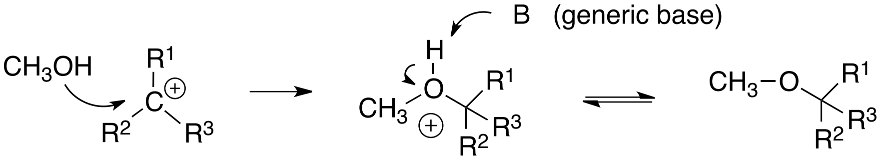
Possible dissociation of alkyl halides to give a carbocation plus a halide ion (analogous to the dissociation of H–X):



X = Cl, Br, I

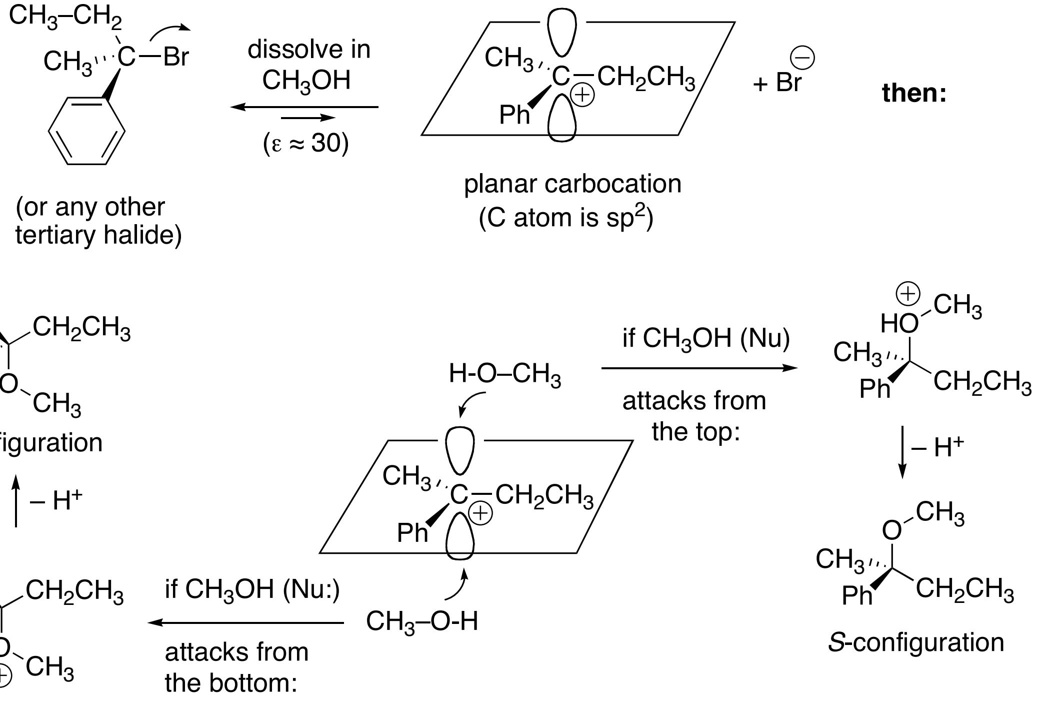
The above dissociative process as an energetically unfavorable one (one must separate a + charge from a – charge), which will be facilitated in a medium of high dielectric constant, such as an aqueous, methanolic, etc., solution

Principle: if the above dissociation reaction were to take place at all in a medium containing H_2O, CH_3OH, etc., the resultant carbocation would be intercepted by H_2O, CH_3OH, etc., to give an alcohol, an ether, etc.; e.g.:



Principle: the above dissociation reaction is likely to be easiest with tertiary alkyl halides, much less so with secondary halides, very difficult with primary halides, and virtually impossible with methyl halides, due to the relative degree of hyperconjugative stabilization of tertiary (most highly stabilized), secondary, primary and methyl (not at all stabilized) carbocations

Stereochemical aspects of the above reaction: loss of configuration:



there is no reason why CH_3OH (in general, the nucleophile) should favor attack from one side or the other (top or bottom) of the carbocation. Therefore, top- and bottom-face attack will occur with equal probability, leading to a 1:1 mixture of (*S*)- and (*R*)-products, i.e., to a racemic mixture.

Kinetic aspects of the above reaction: unlike the S_N2 reaction, which proceeds in a single kinetic event (the Walden inversion), the substitution process outlined above involves two distinct and independent steps: ionization of the starting halide and nucleophilic capture of the resulting carbocation

Endothermic nature of the dissociative process leading to formation of the carbocation (slow, difficult)

Exothermic nature of the capture of the carbocation by the nucleophile (fast, facile)

The dissociation of the starting alkyl halide (slow, difficult) as the rate-limiting step of the above substitution reaction (= the rate of the substitution reaction depends only on the rate of formation of the carbocation, i.e., the rate of dissociation of the alkyl halide)

The rate of formation of the carbocation (= the rate of the overall substitution process) as a function of the instant concentration of alkyl halide *only*; i.e., the substitution reaction proceeds with first order kinetics

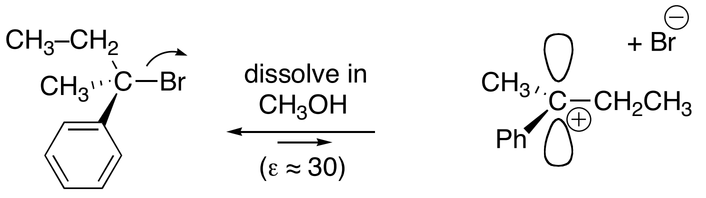
$$\text{rate} = \frac{d\,[\text{substitution product}\,]}{dt} = k\,[\text{alkyl halide}]$$

S_N1 reactions: those nucleophilic substitutions (i) typical of tertiary (in general, hindered) alkyl halides reacting with non-basic nucleophiles in media of high dielectric constants, (ii) characterized by first-order kinetics, and (iii) proceeding with loss of configuration.

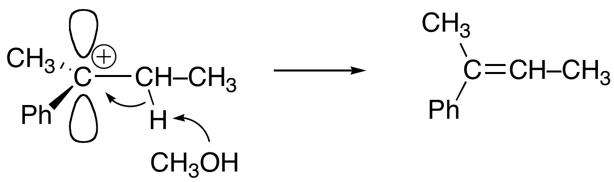
Strong Bronsted acidity of carbocations ($pKa < 10^{-11}$) and consequent possibility that the carbocation generated through dissociation of, e.g., a tertiary halide in a medium of high dielectric constant may release a proton and form an olefin

Exothermic nature of the deprotonation of the carbocation by CH_3OH, H_2O, etc. (fast, facile)

Preferential formation of the more highly substituted olefin isomer (Seytzeff rule) during deprotonation of carbocations; e.g.:



then:



formation of the olefin as per the Seytzeff rule

The above process as a special type of β-elimination reaction

The dissociation of the starting alkyl halide (slow, difficult) as the rate-limiting step of the above elimination reaction (= the rate of the elimination reaction depends only on the rate of formation of the carbocation, i.e., the rate of dissociation of the alkyl halide)

The rate of formation of the carbocation (= the rate of the overall elimination process) as a function of the instant concentration of alkyl halide *only*; i.e., the elimination reaction proceeds with first order kinetics

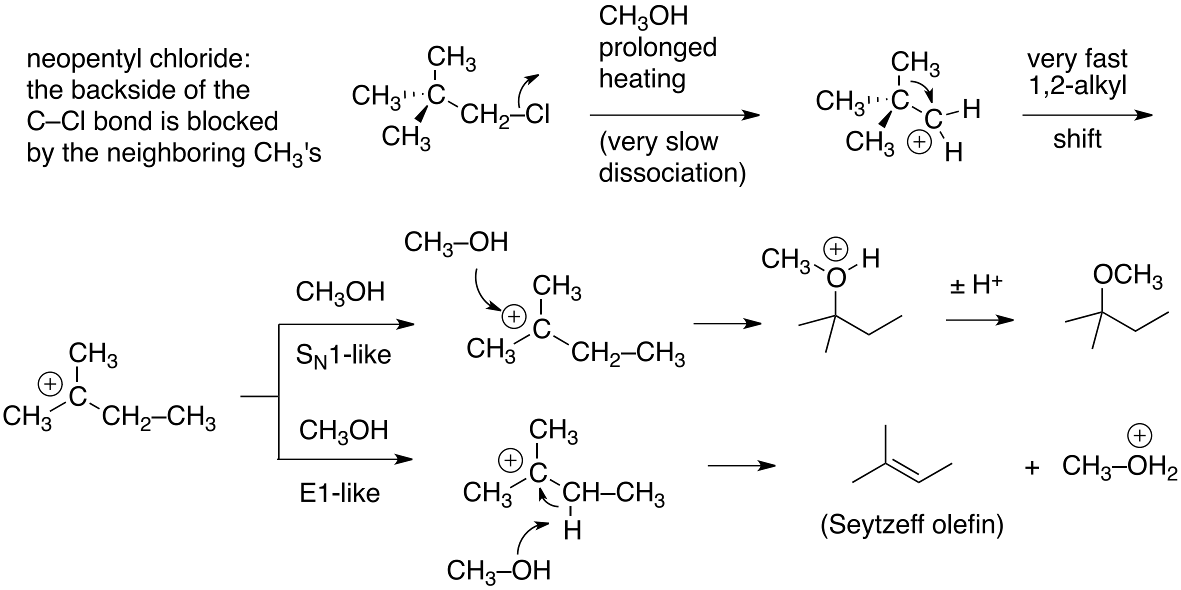
$$\text{rate} = \frac{d\,[\text{elimination product}]}{dt} = k\,[\text{alkyl halide}]$$

E1 reactions of alkyl halides: those elimination reactions that occur as a consequence of dissociation of, e.g., tertiary alkyl halides in media of high dielectric constants, and that proceed with first-order kinetics

Principle: just as in the case of S_N2 and E2 reactions, S_N1 and E1 reactions always occur in competition with each other

Possible rearrangement of carbocations formed by ionization of alkyl halides

Example: the case of neopentyl chloride:



neopentyl chloride: the backside of the C–Cl bond is blocked by the neighboring CH_3's

(Seytzeff olefin)