Haloalkanes, Alcohols and Amines. Year 1

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Aims of course: To introduce the chemistry of haloalkanes, alcohols and amines via consideration of the unifying mechanistic framework of nucleophilic aliphatic substitution (S_N2 and S_N1) and 1,2-elimination (E2 and E1).

Course objectives: At the end of this course you should be able to:

- Identify correctly the various functional groups introduced on this course;
- Identify the product of a given nucleophilic aliphatic substitution or elimination product when presented with the substrate and reagent;
- Select reagents to achieve a given nucleophilic aliphatic substitution or 1,2-elimination reaction when presented with the starting material and desired product;
- Predict whether a given nucleophilic aliphatic substitution occurs via an S_N2 or S_N1 mechanism, and the consequences for any stereochemistry at the reacting centre;
- Predict whether a given 1,2-elimination reaction occurs via an E2 or E1 mechanism, and the regioselectivity of the elimination;
- Explain, with arrow-pushing, the mechanistic rationale underpinning the above.

Recommended Texts

Clayden, Greeves, Warren and Wothers *Organic Chemistry* OUP, Oxford 2001;
Sykes *A Primer to Mechanism in Organic Chemistry* Longman, Harlow, 1995.

Course Content

1. General

A. Structure, nomenclature and physical properties; 1˚, 2˚, 3˚, hydrogen bonding.

B. General reactivity considerations; haloalkanes as electrophiles, (deprotonated) alcohols and (neutral) amines as nucleophiles.

2. Reactivity of Haloalkanes, Alcohols and Amines

A. Nucleophilic Aliphatic Substitution: S_N1 & S_N2

(i) Mechanisms;

(ii) Kinetics and reactivity; *rate laws, 1˚ vs 2˚ vs 3˚, steric effects, carbocation stability - hyperconjugation, allylic and benzylic substrates.*

(iii) Stereochemical consequences; *complete inversion in S_N2, racemisation in S_N1*

(iv) Solvent effects; *S_N1 in protic solvent, S_N2 in dipolar aprotic solvent*

(v) Electrophiles; *Comparison of leaving group ability of halides – bond strengths and pKa of HX; converting an alcohol to a halide; activation of alcohols as tosylates, cleavage of aryl methyl ethers.*

(vi) Nucleophiles; *Halide based: Finkelstein reaction. Oxygen based: hydroxide, alkoxide, carboxylate - Williamson ether synthesis, ether formation with diazomethane. Nitrogen based: Amines – overalkylation, Gabriel synthesis, azides. Carbon based: nitriles.*

B. 1,2-Elimination (β-elimination): E1 & E2

(i) Mechanisms;

(ii) Regioselectivity (Orientation) & Reactivity; *stability of alkenes, Saytzeff orientation, 3˚ vs 2˚ vs 1˚*

(iii) Stereochemistry of E2 elimination; *anti-periplanar stereospecific elimination*

(iv) E1 vs E2; *conc strong base favours E2*

(v) Elimination vs Substitution; *steric factors*

(vi) Elimination of $HOCr(O)_2OH$ from chromate esters: *oxidation of alcohols.*