CH271-15 Mechanistic and Biological Chemistry

23/24

Department
Chemistry
Level
Undergraduate Level 2
Module leader
Andrew Marsh
Credit value
15
Module duration
10 weeks
Assessment
20% coursework, 80% exam
Study location
University of Warwick main campus, Coventry

Description

Introductory description

N/A

Module web page

Module aims

Conformation and stereochemistry are crucial in understanding how molecules interact. Initially, compounds containing a stereogenic carbon, (or another element) will be reviewed as an introduction to axial and helical chirality. A discussion of the effect of strain on the conformational preferences in acyclic molecules will lead onto the boat and chair forms of cyclohexane. Elimination reactions in these ring systems will be used to illustrate the requirement of orbital overlap in syn/anti elimination mechanisms. Guidance on elucidating reaction mechanisms using rate data, substituent effects and isotopic labeling will be illustrated with examples of hydrolysis, additions, eliminations and ring closure reactions. Factors that favour the chair conformation of cyclohexanes will inform the conformational preferences of monosaccharides but an additional stereoelectronic factor (the alpha effect) that influences conformational preference in the glycoside bond will also be introduced. The principles of general acid/base and specific acid/base catalysis

will be explained and the importance of these factors in hydrolysis and enzyme catalysis.
The second half of the module will be an introduction to biological and medicinal chemistry. The principles of carbohydrate chemistry will be discussed, including stereoelectronic effects and synthetic methods. A more detailed discussion of enzyme catalysis will cover transition state theory and Michaelis-Menten kinetics and the use of enzymes for biocatalysis and enantiomer resolution. An introduction to medicinal chemistry will cover enzyme inhibitors, the role of receptors, and examples of receptor agonists and antagonists for adrenaline, acetylcholine and histamine receptors.

Outline syllabus

This is an indicative module outline only to give an indication of the sort of topics that may be covered. Actual sessions held may differ.

Chirality
Chirality in systems lacking a stereogenic carbon atom. Point chirality: tertiary amines, sulfoxides, phosphines. Axial chirality: allenes and hindered biphenyls. Assignment of stereochemistry in these systems. Helical structures: helicenes, other examples. Prochirality and facial chirality Si, Re.

Conformational analysis
Revision ethane and butane. Newman projections and energy - plots. Terms used include staggered, eclipsed, gauche, anti-conformations. Heats of combustion – comparison of cyclic and acyclic systems leading to concepts of strain (torsion and syn-pentane). Strain in acyclic molecules: 1 consequences on conformations e.g. 1,5-pentane interactions.

6-Membered rings (how to draw). Axial and equatorial hydrogens. Chair (GS), half chair (TS), twist chair (GS), boat (TS). 6-Rings. A-values - gauche and syn-pentane interactions (1,3-diaxial); experimental evidence and linkage to computation (see also workshop on using PC Model).

Ring size strain for cyclopropane, cyclobutane, cyclopentane. Medium rings and transannular strain. Stabilising electronic effects upon conformation. Simple orbital view of organic molecules and orbital overlap. Look at consequences of best donor – best acceptor interactions upon conformation e.g. FCH2CH2F ‘gauche effect’. Sugars and the anomeric effect. Esters and amides; peptide bond; phosphodiesters in DNA.

Introduction to reactivity
Rate determining steps and reaction profiles. Exothermic and endothermic reactions. Early and late transition states. Stereoselectivity and stereospecificity definitions Kinetic and thermodynamic control.

Elimination reactions. Basicity and nucleophilicity: hard and soft; E2 vs SN2. 4pKa vs. nucleophilicity. alpha effect E1 and E2 elimination reactions: mechanism. a) kinetics and stereochem 4-tBu-cychex-OTs cis eliminates with EtO- in EtOH , trans does not react. b) orbital alignment c) reaction profiles. Single step reaction. Enthalpy and entropy of activation d) solvent dependence of selectivity.

Syn vs anti-eliminations. E1cb reactions: mechanisms a) kinetics and stereochem b) electron withdrawing groups and acidity c) Two step reaction RDS vs slow step (two extreme cases). Changes in rate determining step. Reactions in six-membered rings.

More reactions in 6 membered rings. Rates of ring closure. Ring contractions and fragmentations, Anchimeric assistance.

Carbonyl reactions
Carbonyl reactions. Additions and additions/eliminations. General trends in reactivity. Sterics and electronics. Kinetics of hydrolysis and esters and amides: data analysis and mechanistic elucidation. Imine formation and hydrolysis. Rates and mechanistic interpretation. AAc1 isotopic labelling.

Acid and base catalysis
From rate data to a inferring a mechanistic hypothesis. Mechanisms and catalysis – looking at ester hydrolysis and inferring mechanism. Specific acid catalysis, General acid catalysis. Specific base catalysis, General base catalysis. Precise meanings of each term arising from rate data. Enzymatic catalysis – chymotrypsin. Termolecular base amide hydrolysis

Linear free energy relationships
Mechanistic investigations. Substituent effects. Hammett equation. Sigma (substituents), Rho (reactions). Similarity parameters. Swain-Scott nucleophilicity scales. Brønsted plots.General base catalysed eliminations. general acid catalysed reactions.

Diastereoselective reactions.
Definitions; measuring diastereoselection. Examples for carbonyl additions. Development of models for understanding experimental results: Felkin-Anh model. Aldol reaction and cyclic 6-membered transition states.

Isotope Effects in Elucidation of Mechanism
Primary kinetic isotope effects. Secondary isotope effects. Equilibrium isotope effects. What they tell us about the reaction mechanisms.

Applying stereoelectronic principles.
Non-classical carbocations. Examples of stereoelectronic effects in synthesis. Stereoelectronics of non-first row elements.

Carbohydrates
Cellular energy and glucose; the structure of D-glucose, anomers and the anomeric effect; the structures and functions of monosaccharides; the glycosidic bond; oligosaccharides – structures and functions of disaccharides and polysaccharides; biosynthesis of oligosaccharides

Proteins & Enzymes
Protein structure, information flow from DNA to RNA to proteins; Enzyme catalysis, transition state theory, Michaelis-Menten kinetics, selected examples of enzyme catalytic mechanisms; use of enzymes for biocatalysis, resolution of enantiomers

Introduction to Medicinal Chemistry
Introduction to drug discovery process; enzyme inhibition, examples of enzyme inhibitors; receptors, introduction, structure/function of receptors; selected examples of receptor agonists/antagonists

Learning outcomes

By the end of the module, students should be able to:

- Understanding of the concept of kinetic isotope effects and its use to determine energetic and geometrical changes.
- Appreciate importance of enantio- and diastereotopism.
- Understanding of the mechanistic concept to describe chemical reactions and awareness of some of the tools to derive mechanistic insight
- Construction of a reaction profile based on kinetic and thermochemical properties of a chemical reaction.
- Confident design of labelling experiments to obtain mechanistic insight into the reaction.
- Understand and explain the structures, reactivity and synthesis of monosaccharides, disaccharides, and polysaccharides; answer problem-based questions on these topics.
- Understand and explain the molecular basis for enzyme catalysis, enzyme structure, and Michaelis-Menten enzyme kinetics; answer problem-based questions on these topics.
- Understand the principles and practices of introductory medicinal chemistry, examples of drug action through enzyme inhibition and receptor binding; assess structure-activity data and answer problem-based questions on these topics.
- Assign C-I-P (R/S) nomenclature to a range of stereogenic centres including non-carbon centres.
- Be able to competently draw a range of three-dimensional molecules in two dimensions and appreciate key stereochemical conventions.
- Appreciate that stereochemistry is not necessarily associated with a stereogenic centre. Give examples of helically and axially chiral molecules.
- Be able to carry out conformational analysis of simple acyclic and cyclic molecules using appropriate diagrams (Newman projections, chair / boat structures).
- Explain the effect of ring size on energy and conformation of small and medium sized rings.
- Explain in mechanistic terms how conformation in cyclic systems directly affects reactions such as base catalysed (E2) eliminations in cyclic systems.
- Understand and demonstrate the use of simple protecting groups in the synthesis of sugars
- Give examples of the development of therapeutics involving the beta adrenergic receptor and demonstrate understanding of measures of inhibition
- Demonstrate the use of simple non-linear curve fitting using Microsoft Excel Solver in the context of physical organic chemistry based on minimising standard error

Indicative reading list

1. Organic Chemistry J. Clayden, N. Greeves, S. Warren, OUP, 2012 2nd Edn [CGWW].
2. Modern Physical Organic Chemistry E. V. Anslyn, D. A. Dougherty University Science Books, 2005
3. Stereochemistry David G. Morris, RSC Books, 2001.
4. Stereoelectronic Effects A. J. Kirby, Oxford Chemistry Primers, 1996.
5. A Guidebook to Mechanism in Organic Chemistry, P. Sykes, 6th Edn., Longman.
6. Chemtube3D.com

Further Reading

1. Mechanism in Organic Chemistry R. W. Alder, R. Baker, J. M. Brown Wiley, 1971. QD 1722.A5.
2. The search for organic reaction pathways P. Sykes Longman, 1972.

3. Stereochemistry at a Glance J. Eames and J. M. Peach, Blackwell, 2003.
4. Guide to Organic Stereochemistry S. R. Buxton, S. M. Roberts, Longman, 1996, QD1858.B8.
5. Mechanism and Theory in Organic Chemistry, T.H. Lowry, K. S. Richardson, 2nd Edn., Harper & Row, 1981, QD 1722.L6.
6. Advanced Organic Chemistry, J. March, 4th Edn., Wiley, 1992, QD 1722.M2.
7. Alicyclic Chemistry, F. J. McQuillan, 2nd Edn., Cambridge, 1983, QD 2310.M2.
8. Physical Organic Chemistry N. S. Isaacs, 2nd Edn., Longman, 1995, QD 1611.I8.
9. Stereochemistry of Organic Compounds E. L. Eliel, S. H. Wilen, L. N. Mander Wiley, 1994, QD1858.E5.
10. Introduction to Enzyme and Coenzyme Chemistry, T.D.H. Bugg, 2nd edition, Blackwells Science, 2004
11. An Introduction to Medicinal Chemistry, G.L. Patrick, 3rd edition, OUP, 2005
12. Biochemistry, L. Stryer, 5th edition, W.H. Freeman and Company, New York, 2001

View reading list on Talis Aspire

Subject specific skills

Numeracy
Problem solving
Written communication

Transferable skills

Numeracy
Problem solving
Written communication

Study

Study time

Type	Required
Lectures	30 sessions of 1 hour (19%)
Tutorials	4 sessions of 1 hour (3%)
Demonstrations	(0%)
Practical classes	2 sessions of 1 hour (1%)
Other activity	2 hours (1%)
Private study	112 hours (71%)
Assessment	8 hours (5%)
Total	158 hours

Private study description

Self-study., including practice with structure building using molecular model kits and simple molecular model building with a freely available computing package such as Avogadro or Chem3D.

Other activity description

Revision sessions.

Costs

No further costs have been identified for this module.

Assessment

You do not need to pass all assessment components to pass the module.

Assessment group D4

	Weighting	Study time
Assessed work report	20%	8 hours
A single report based on set tasks in the area of non-linear data fitting by standard error calculation using MS Excel.		
In-person Examination	80%	

- Students may use a calculator
- Graph paper
- Answerbook Green (8 page)
- Periodic Tables

Feedback on assessment

Oral and written feedback on assessed work and tutorials from module leader/ tutors. Cohort level examination feedback provided via Moodle.

Past exam papers for CH271

Availability

Pre-requisites

To take this module, you must have passed:

- All of
  - CH161-30 Introduction to Organic Chemistry

Post-requisite modules

If you pass this module, you can take:

- CH3G3-30 Advanced Chemistry (Organic, Inorganic and Physical) Industrial Placement
- CH3F5-15 Bioorganic Chemistry
- CH3F3-30 Advanced Chemistry (Organic, Inorganic and Physical)
- CH3E9-15 Advanced Organic Chemistry and Laboratory

Courses

This module is Core for:

- UCHA-4 Undergraduate Chemistry (with Intercalated Year) Variants
  - Year 2 of F101 Chemistry (with Intercalated Year)
  - Year 2 of F122 Chemistry with Medicinal Chemistry (with Intercalated Year)
- UCHA-3 Undergraduate Chemistry 3 Year Variants
  - Year 2 of F100 Chemistry
  - Year 2 of F100 Chemistry
  - Year 2 of F121 Chemistry with Medicinal Chemistry
- UCHA-F110 Undergraduate Master of Chemistry (with Industrial Placement)
  - Year 2 of F100 Chemistry
  - Year 2 of F110 MChem Chemistry (with Industrial Placement)
  - Year 2 of F112 MChem Chemistry with Medicinal Chemistry with Industrial Placement
- Year 2 of UCHA-F107 Undergraduate Master of Chemistry (with Intercalated Year)
- UCHA-F109 Undergraduate Master of Chemistry (with International Placement)
  - Year 2 of F109 MChem Chemistry (with International Placement)
  - Year 2 of F111 MChem Chemistry with Medicinal Chemistry (with International Placement)
- UCHA-4M Undergraduate Master of Chemistry Variants
  - Year 2 of F100 Chemistry
  - Year 2 of F105 Chemistry
  - Year 2 of F110 MChem Chemistry (with Industrial Placement)
  - Year 2 of F109 MChem Chemistry (with International Placement)
  - Year 2 of F125 MChem Chemistry with Medicinal Chemistry
- Year 2 of UCHA-F127 Undergraduate Master of Chemistry with Medicinal Chemistry(with Intercalated Year)