Good morning!

Please build a model of cyclohexane

including ALL H atoms....

Exam 1:

Historical mean 84

Your mean 88 ☺

Exam 2: Watch out
Don't get complacent.

≈ Below 70 ⟶ at best ≈ C

Exams back in section

Stereoisomers as Reactants

- We are often interested in the differences in *reactivity* of various chemical compounds. Usually, we express the differences in reactivity in terms of the *rates* of the reactions. How is the rate of a reaction related to the energies of the reactant, the transition state, and the product?

Enantiomers have same energy.

Diastereomers often have different energies.

Rate ≈ $\frac{1}{\text{activation energy } E_a}$

Equilib ≈ ΔG diff react. and products

- We can make several generalizations about rates of reactions involving various stereoisomers. Can you explain why each of these generalizations is true?

Compounds that are diastereomers may react at different rates with any reagents.

A and B diastereomers ⟹ diff energies reactants, T.S. ⟹ diff E_a's.

Compounds that are enantiomers must react at the same rate with *achiral* reagents.

A and B enantiomers | react with achiral C | same E_a | A, B same E → $[AC]^{\ddagger}$ vs $[BC]^{\ddagger}$ enantiomers.

Compounds that are enantiomers may react at different rates with *chiral* reagents.

(R) (S) A and B enantiomers ⟹ chiral C (R) | A, B same E → $[AC]^{\ddagger}$ vs $[BC]^{\ddagger}$ RR SR diastereomers | different E_a

Reading: Section 7.7

Can't create optical activity from nothing!

achiral reactant

Stereoisomers as Products

- Determine the product of the following reaction:

benzene not affected.

enantiomers

- Is the product chiral or achiral? Are the reactants and reagents chiral or achiral?

Achiral S.M. → chiral product will be racemic mixture.

(+/−) notation

- We can make several generalizations about reactions that form stereoisomeric products. Can you explain why each of these generalizations is true?

Achiral starting materials that give enantiomeric products will yield a racemic mixture.

Same E Same E identical TS and prod. energies ⇒ racemic

Achiral starting materials that react in a *chiral* environment (e.g. a chiral catalyst or chiral solvent) may yield different amounts of each enantiomer.

now TS can have diff. E's. TS are diastereomers ⇒ diff amounts of each enant.

$H_2O + CO_2 \rightarrow$ glucose $+ O_2$

Achiral starting materials that give diastereomeric products may yield different amounts of each diastereomer.

→ plant has chiral enzymes

get diastereomers

generally diff. E's, diff. amounts.

Reading: Section 7.8

Introduction to Cyclic Compounds: Cyclohexanes

- The most common ring in natural compounds is a **6-membered ring**. Take out your model kits and make a model of cyclohexane:

cyclohexane - **chair conformation** is most stable...

means

there are 2 "different types of H atoms"

3 H's "up"

Axial

3 H's "down"

all at an angle
a little up/down

- How should you *draw* the chair conformation of cyclohexane?

same length and parallel

Avoid: bowtie

lightning bolt

cow

Reading: Section 7.2

Cyclohexanes: Interconversion of Chair Conformations

chair 1

chair 2

move • up

move • down

boat (unstable!!)

high energy! eclipsed H's and

Effectively the 2 chairs are in rapid equilibrium

equatorial H's...

become axial H's...

this equilibrium is very important for substituted cyclohexanes

- Can you accomplish this "ring flip" with your models?

swap axial / equatorial

Reading: Section 7.2

Monosubstituted Cyclohexanes: Axial vs. Equatorial

methylcyclohexane:

chair 1 **chair 2**

1,3-diaxial interactions (van der Waals repulsions)

1.8 kcal/mol ***less stable***

...which is 2 x the "cost" the CH_3 repulsion in gauche butane

gauche butane - "cost" 0.9 kcal/mol

= 1 gauche butane interaction

Axial less stable by 1.8 kcal/mol

Reading: Section 7.3

Energies of Axial vs. Equatorial Substitution

- The relative energy of axial vs. equatorial substitution is called the "*A value*" for that substituent. Generally, bulky substituents have larger A values:

Ax $\Delta G^o = -RT\ln K$ **Eq**

"A value"

percent equatorial

"flat"

"A Value" = $-\Delta G^o$

Group	A Value	K (25 °C)	% Eq
CH_3	1.8 kcal/mol	21	95%
$CH(CH_3)_2$	2.2 kcal/mol	42	98%
$C(CH_3)_3$	4.8 kcal/mol	3316	99.9%
$CH{=}CH_2$	1.6 kcal/mol	15	94
Cl	0.5 kcal/mol	2.3	70

methyl
isopropyl
tert-butyl
vinyl

long C–Cl bond

Notice: A *tert*-butyl group effectively "locks" the chair conformation

Eq

often written as...

...or...

t-butyl

"locks" chair in conformation with t-butyl equatorial

Reading: Section 7.3

axial / eq
up / down
alternate on ring

Disubstituted Cyclohexanes

Example: 1-chloro-2-methylcyclohexane

there are 2 possible diastereoisomers

***cis*-1-chloro-2-methylcyclohexane**

***trans*-1-chloro-2-methylcyclohexane**

same face of ring

...so what about their conformations??

opposite faces.

CH_3 and Cl equatorial strongly favored

CH_3 and Cl axial strongly disfavored

cis

CH_3 has larger A value than Cl - so it will "prefer" to be equatorial

CH_3 prefers eq.

Cl smaller A value so it prefers axial.

Reading: Section 7.4

Stereochemistry of Alkene Addition Reactions

- Predict the product(s) of each of the following reactions. Be sure to indicate stereochemistry when relevant!

Br_2

anti

Br's axial, CH_3 eq.

1. BH_3

2. H_2O_2 , OH^-

syn

(racemic)

both eq.

1. BH_3

2. H_2O_2 , OH^-

+

enantiomers → both equatorial

Reading: Section 7.9

Other Cyclic and Bicyclic Compounds

angle strain

Other Cyclic Compounds

angles

Examples:

60°

cyclopropane

planar ring
highly strained
v. reactive

higher energy

≈ 90°

cyclobutane

puckered ring
pretty strained
reactive

cyclopentane

puckered ring
not strained

109.5°
tetrahedral

Bicyclic compounds

Examples:

bicyclo[4,3,0]nonane

a **fused bicyclic compound:** bridgehead atoms (*) adjacent

share an edge

bicyclo[2,2,1]heptane

a **bridged bicyclic compound:** bridgehead atoms (*) not adjacent

spiro[4,4]nonane

a **spirocyclic compound:** one common atom (*)

share a vertex

Reading: Sections 7.5 and 7.6

Bicyclic Compounds and Bredt's Rule

two fused 6-mem. rings

Decalins

Decalin... ..the common name for bicyclo[4,4,0]decane...

...exists as 2 diastereoisomers...

two 6-mem rings

***cis*-decalin**

***trans*-decalin**

locked with Hs axial.

conformations:

able to undergo ring flip

***not** able to undergo ring flip*

...take out your models and prove this!!

...and while those models are out, prove that *trans*-cyclohexene is likely to be very unstable...

***cis*-cyclohexene**

***trans*-cyclohexene**

Can't have trans alkene in "small" ring.

...as is a "bridgehead alkene" such as **bicyclo[2,2,1]hept -1(2) -ene** (Bredt's rule)

Cannot have sp^2 carbon (alkene) at bridgehead in "small" ring.

- Why is this "bridgehead alkene" so unstable?

No way for π-bond to be planar

same plane.

Reading: Section 7.6

Test Yourself Now!

- For each of the following molecules, identify whether the molecule is chiral or achiral. For molecules that are chiral, assign *R* or *S* configurations to each stereocenter, and draw the enantiomer of the molecule.

(in purple book)

S

chiral

(S) (S)

chiral

(R)(S)

(meso)

achiral

(R)

(R)

(R)

(R)

chiral

R–X R–OH R–O–R R–SH R–S–R

Alkyl Halides, Alcohols, Ethers, Thiols, and Sulfides

Alkyl halides:

# of subst. on C with –X or –OH

methyl bromide

a primary alkyl bromide

a secondary alkyl bromide

a tertiary alkyl bromide

Alcohols:

methyl alcohol

a primary alcohol

a secondary alcohol

a tertiary alcohol

Common nomenclature & substitutive nomenclature:

ethyl chloride
chloroethane

methylene chloride
dichloromethane

allyl chloride
3-chloropropene

chloroform
trichloromethane

ethyl alcohol
ethanol

ethyl mercaptan
ethanethiol

allyl alcohol
propen-3-ol

***tert*-butanol**
2-methyl-2-propanol

diethyl ether

ethyl methyl sulfide

furan

tetrahydrofuran (THF)

ethylene oxide
oxirane

styrene oxide
2-phenyloxirane

cyclic ether

epoxide

Reading: Section 8.1

Vacuum $\varepsilon = 1$

$H_2O \rightarrow \varepsilon \approx 80$

Solvents in Organic Chemistry

dielectric const

- The vast majority of organic reactions are carried out in a **solvent**, a liquid that is used to dissolve the reactants, reagents, and products. Each solvent can be characterized based on three properties: whether it is **polar**, whether it is **protic**, and whether it is a **donor**:

1 • ***polar*** or ***nonpolar***:

polar - dielectric constant greater than 15

nonpolar - dielectric constant less than 15

Coulomb's Law

Force $\propto \frac{q_1 q_2}{\varepsilon r^2}$

2 • ***protic*** or ***aprotic***: dissolves anions

protic - solvent acts as hydrogen bond donor → contains FH, OH, NH

aprotic - solvent cannot act as hydrogen bond donor

H—O—H ····: $X^{\ominus}$

3 • ***donor*** or ***nondonor***: dissolves metal ions

donor - solvent can share (donate) lone pair

nondonor - solvent cannot share (donate) lone pair

a few examples:

hexane: aprotic, apolar, nondonor

diethyl ether: aprotic, apolar, donor

CH_2Cl_2

methylene chloride: aprotic, apolar, nondonor

Cl lone pairs not good donors

acetone: aprotic, polar, donor

ethanol: protic, polar, donor

dimethylsulfoxide (DMSO): aprotic, polar, donor

Reading: Sections 8.3 and 8.4

Acidity and Basicity of Alcohols and Thiols

($pK_a > 45$)

Alcohols and thiols are weakly acidic: $Na^{\oplus}\ H^{\ominus}$

- What bases could you use to deprotonate the following compounds? Why?

pK_a: 16

$(+\ B^{\ominus})$ $\xrightarrow{NaH}$ + $H_2(g)$

alkoxide

pK_a: 12

+ NaOH (16) $\longrightarrow$ + H_2O

thiolate

Alcohols and thiols are also weakly basic (as are ethers and sulfides):

- What acids could you use to protonate the following compounds?

$\xrightarrow{HX}$ (HCl, H_2SO_4, ..) strong acid

protonated alcohol

-2 pK_a

$\xrightarrow{HX}$

protonated thiol

$pK_a < -2$

$\xrightarrow{HX}$

protonated ether

Reading: Sections 8.6 and 8.7

$pK_a \approx -2$

Making "Carbanion" Bases from Alkyl Halides: Grignard and Organolithium Reagents

- Do you recall what the pKa of methane is? CH_4 = 48
- What is the conjugate base of methane? Why might we call this a "carbanion"?

$H_3C:^{\ominus}$ carbanion very strong base.

- Carbanions are just about the strongest bases we know. Why might that make it difficult to form a carbanion?

$$CH_4 + B:^{\ominus} \longrightarrow CH_3^{\ominus} + BH$$

need $pK_a \gg 48$

- In that case, how can we form a "carbanion"?

$$\underset{\text{alkyl halide}}{R-Br} \xrightarrow[\underset{\text{diethyl ether}}{Et_2O}]{Mg} R-MgBr$$

acts like $R:^{\ominus}\ {}^{\oplus}MgBr$

Grignard reagent

$$R-Br \xrightarrow[Et_2O]{2\,Li} R-Li + LiBr$$

Organolithium acts like $R:^{\ominus}\ Li^{\oplus}$

- What are some uses for these "carbanions"?

Act like carbanions → strong bases!!!

alkane.

Reading: Section 8.8