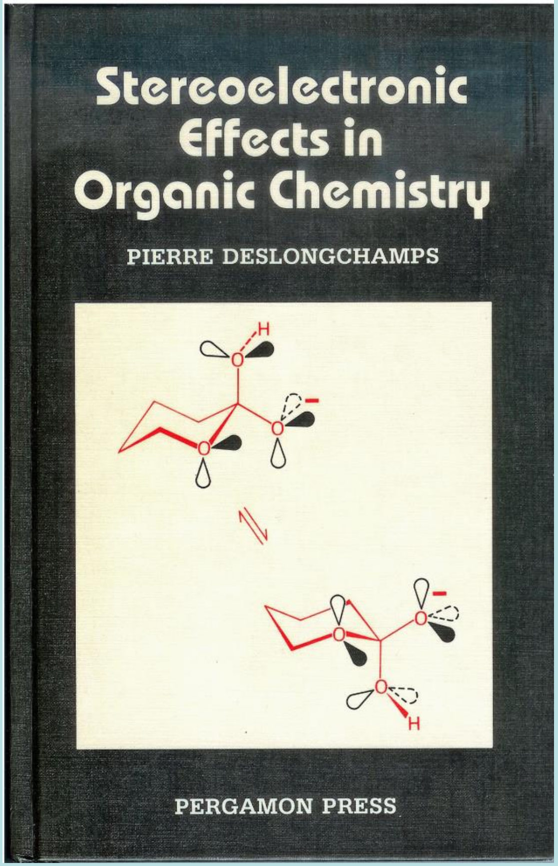
STEREOELECTRONIC EFFECTS (S.E.)

IN ORGANIC CHEMISTRY

SECTION 1:
Fundamental Concepts

INTRODUCTION

(2018)



Stereoelectronic Effects in Organic Chemistry

PIERRE DESLONGCHAMPS

PERGAMON PRESS

Free pdf file:

http://www.chm.ulaval.ca/prof_deslongchampsp.html

STEREOELECTRONIC EFFECTS (S.E.) IN ORGANIC CHEMISTRY

PIERRE DESLONGCHAMPS

SECTION 1: Fundamental Concepts

SECTION 2: Antiperiplanar Hypothesis and Reactions at Saturated Carbons

SECTION 3: Antiperiplanar Hypothesis and Reactions at Unsaturated Systems

SECTION 4: Stereoelectronic Effects (S.E.) and Reactivity of Acetals and Related Functions

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SECTION 7: Stereoelectronic Effects and Reactivity of Amides and Related Functions

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SECTION 12: «Pot-pourri» in Organic Synthesis

GENERAL REFERENCES ON STEREOELECTRONIC EFFECTS

1. ***Stereoelectronic Effects in Organic Chemistry***
   P. Deslongchamps
   Pergamon Press, Oxford, England, 1983

2. ***The Anomeric Effect and Related Stereoelectronic Effects at Oxygen***
   A. J. Kirby
   Springer-Verlag, Berlin, Heidelberg, New-York, 1983

3. ***Carbohydrates, Synthesis, Mechanisms and Stereoelectronic Effects***
   M. Miljkovic
   Springer, NY, 2010

4. ***Electostatic and Stereoelectronic Effects in Carbohydrate Chemistry***
   M. Miljkovic
   Springer, NY, 2014

5. ***Stereoelectronic Effects. A Bridge Between Structure and Reactivity***
   I. V. Alabugin
   Wiley, 2016

6. ***The Nature of the Chemical Bond and the Structure of Molecules and Crystals; An Introduction to Modern Structural Chemistry, 3rd Edn.***
   L. Pauling
   Cornell University Press, Ithaca, 1960

7. ***Pauling's Defence of Bent-Equivalent Bonds: A View of Evolving Explanatory Demands in Modern Chemistry***
   J. R. Bursten
   Annals of Science 2012, 69 (1), 69-90

PUBLICATIONS ON *TAU* (τ) BONDS

G. Deslongchamps, P. Deslongchamps.
Bent Bonds, the Antiperiplanar Hypothesis and the Theory of Resonance. A Simple Model to Understand Reactivity in Organic Chemistry.
Org. Biomol. Chem. **2011**, *9*, 5321 (2011); ChemInform 42 (47), Nov. 22nd, 2011.

G. Deslongchamps, P. Deslongchamps.
Bent Bonds and the Antiperiplanar Hypothesis as a Simple Model to Predict Diels-Alder Reactivity: Retrospective or Perspective?
Tetrahedron **2013**, *63*, 6022.

G. Deslongchamps, P. Deslongchamps.
Bent Bonds and the Antiperiplanar Hypothesis – A Simple Model to Rationalize [1,3]-Sigmatropic Alkyl Shifts.
Org. Biomol. Chem. **2016**, *14*, 7754.

J.-F. Parent, P. Deslongchamps.
Bent Bonds and the Antiperiplanar Hypothesis and the Reactivity at the Anomeric Center in Pyranosides.
Org. Biomol. Chem. **2016**, *14, 11183.*

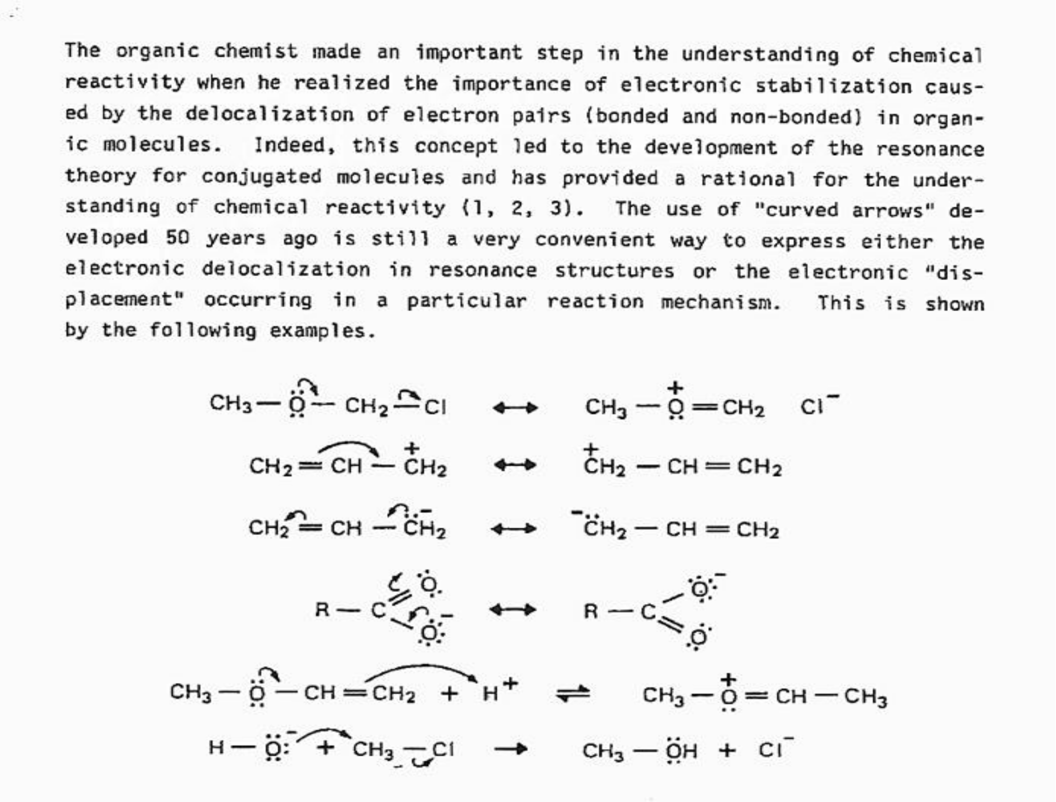
J.-F. Parent, P. Deslongchamps.
High Temperature Isomerization of Benzenoid Polycyclic Aromatic Hydrocarbons.
An Analysis Through the Bent Bond and Antiperiplanar Hypothesis Orbital Model.
J. Org. Chem. **2018**, *83, 3299.*

G. Deslongchamps, P. Deslongchamps.
Bent Bonds (τ) and the Antiperiplanar Hypothesis – the Chemistry of Cyclooctatetraene and other C_8H_8 *Isomers.*
J. Org. Chem. **2018**, *83, 5751.*

G. Deslongchamps, P. Deslongchamps.
Bent Bonds and the Antiperiplanar Hypothesis. A Model to Account for Sigmatropic [1,n]-Hydrogen Shifts.
J. Org. Chem. **2018**, *83, 10383.*

VIDEO: https://youtu.be/h1biL-1o394

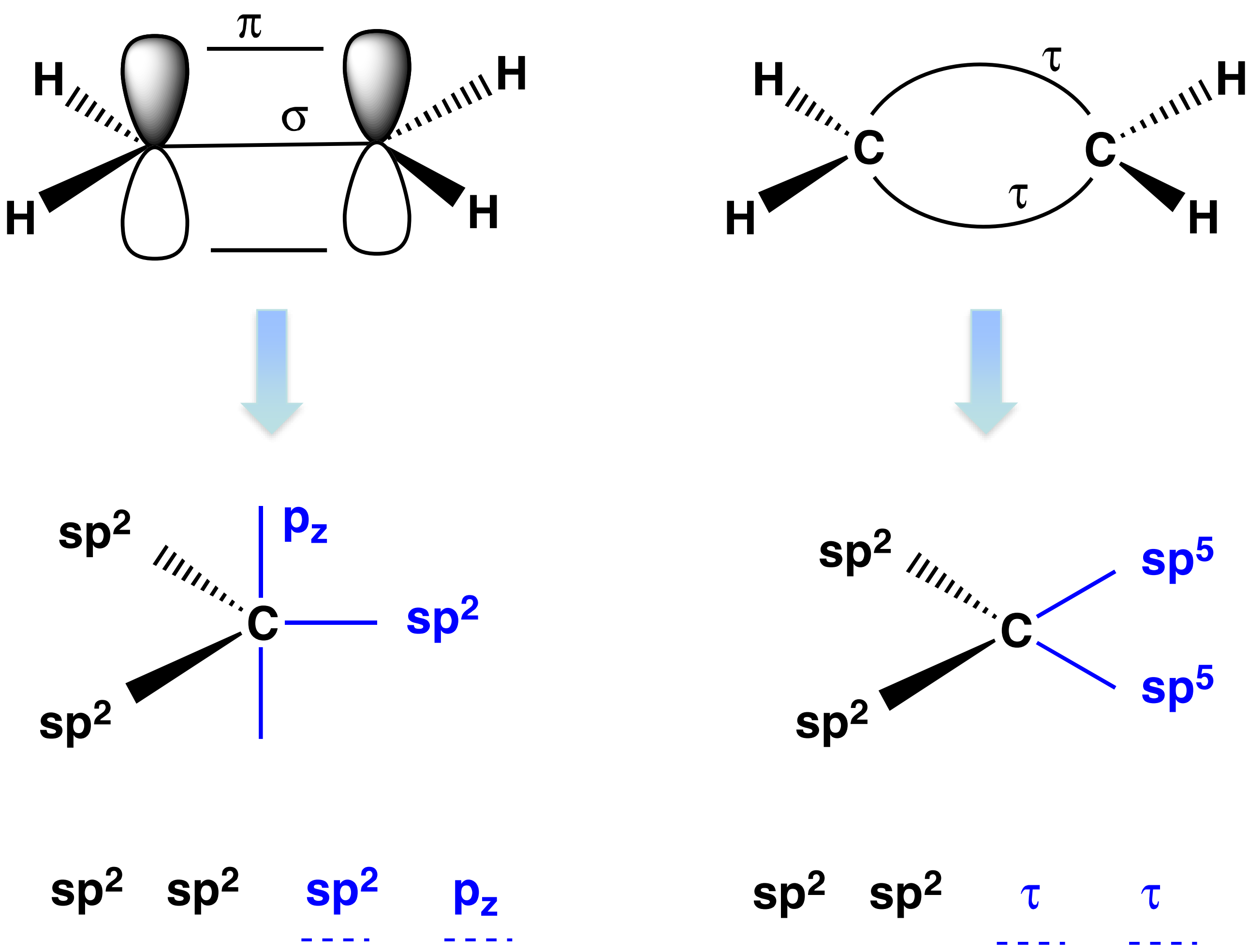
STEREOELECTRONIC EFFECTS IN ORGANIC CHEMISTRY



The organic chemist made an important step in the understanding of chemical reactivity when he realized the importance of electronic stabilization caused by the delocalization of electron pairs (bonded and non-bonded) in organic molecules. Indeed, this concept led to the development of the resonance theory for conjugated molecules and has provided a rational for the understanding of chemical reactivity (1, 2, 3). The use of "curved arrows" developed 50 years ago is still a very convenient way to express either the electronic delocalization in resonance structures or the electronic "displacement" occurring in a particular reaction mechanism. This is shown by the following examples.

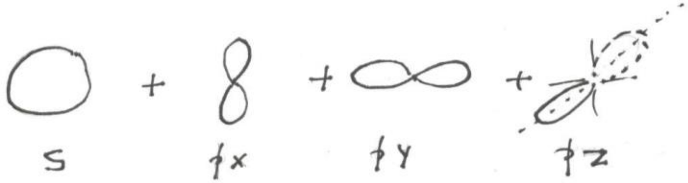
Stereoelectrochemistry being an important factor in organic molecules,
it means that the electronic delocalization must be taken into account in three-dimension.
This leads to what is called « **stereoelectronic effects** ».
In other words, electron delocalization can take place only
when there is proper alignment of orbital.

Foundational Concept: Hückel Model *vs* Pauling-Slater Model

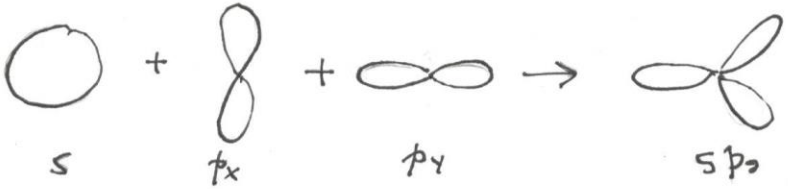


J.C. Slater, *Phys. Rev.*, 1931, *37*, 481.
L. Pauling, *J. Am. Chem. Soc.*, 1931, *53*, 1367.
W.A. Bernett, *J. Chem. Educ.*, 1967, *44*, 17.

Hybridization.

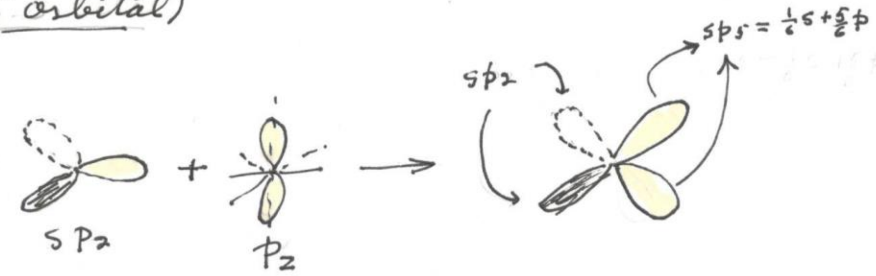


sp2



each lobe: $\frac{sp_2}{3} = \frac{1}{3} s \frac{2}{3} p$

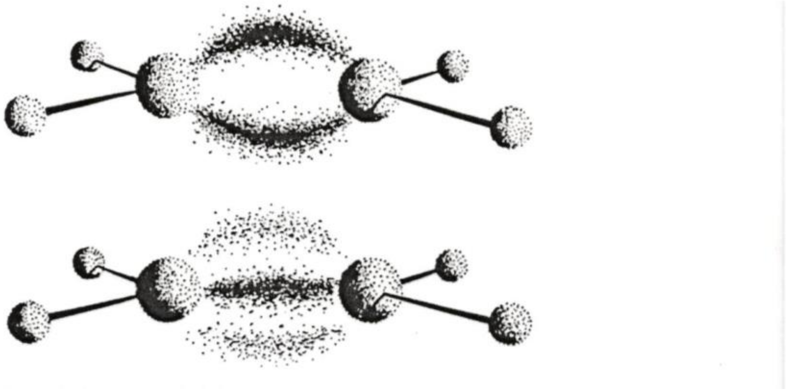
Tau (τ orbital)



Pauling’s Defence of Bent-Equivalent Bonds: A View of Evolving Explanatory Demands in Modern Chemistry

Julia R. Bursten

Annals of Science **2012**, *69 (1)*, 69-90



VALENCE BOND (VB) AND MOLECULAR ORBITAL (MO)

(1) Both models predict the behavior of electrons in bonds by using quantum-mechanical results about the nature of electrons obtained from the “Schrödinger equation”.

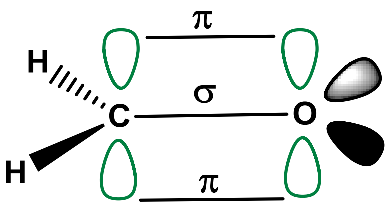
(2) MO was born out of <u>primarily physical interest</u> and considers the electron as spread out over the entire system of atomic centres in a molecule.

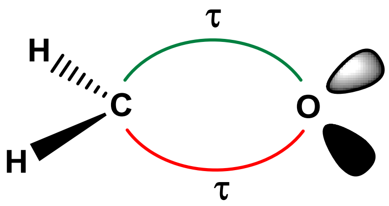
(3) VB was born out of <u>primarily chemical interest</u> and considers the electron as localized to a definite range of atomic centres.

VB is associated with Lewis’ classical valence theory of chemical bonding, i.e., one electron from each atomic centre forms the electron pair in a covalent bond. Such restriction is absent in MO theory.

(4) Both models refer to atomic orbitals, s, p, d, f, which by hybridization leads to σ, π and τ hybridized atomic orbitals which by association can form bonding in molecules.

(5) Thus, olefins (C=C) can either be σ–π or τ (Bent-equivalent Bond).



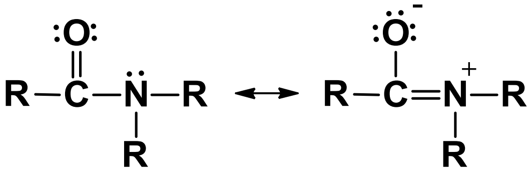


There was however a problem.

How to explain electronic conjugation in organic molecules?

Valence Bond method (VB)

Pauling introduced the “theory of resonance”



Cf. G.W. Wheland, Resonance in Organic Chemistry, Wiley, NY, 1955

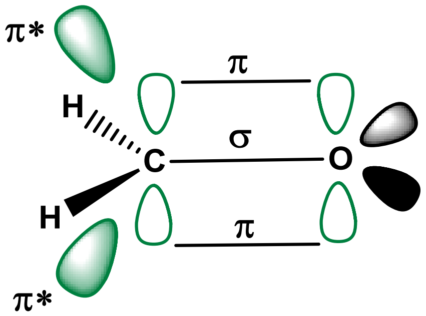
Molecular Orbital theory (MO)

Introduced by Mulliken, Coulson, Longuet-Higgins and Lennard-Jones.
“MO based method known as a “generalized perturbation model”
is used to describe bonds in difficult-to-model conjugated bonds in aromatic compounds.

N.B. Methods (MO) were accurate and the maths were simpler than the VB model. MO became much more popular, but experimental organic chemists continued to use the theory of resonance!

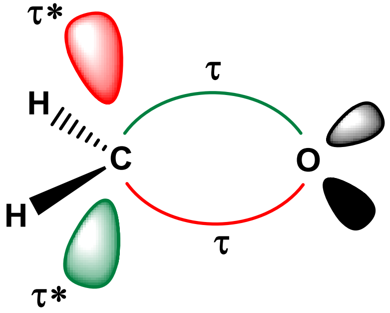
α-π vs τ Bonds in Carbonyl Group and Antibonding Orbitals

σ–π



The two antibonding orbitals π* correspond to a single orbital

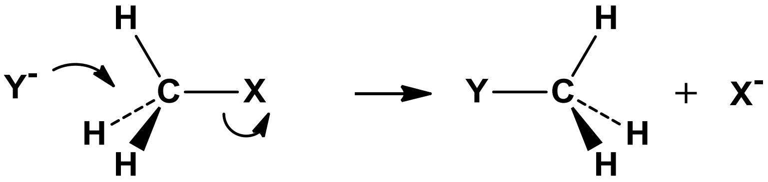
τ



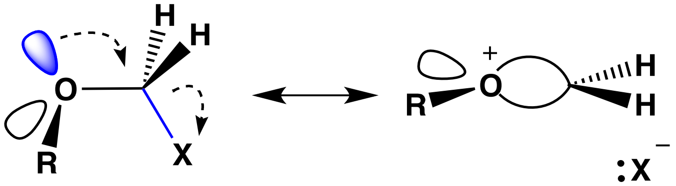
The two antibondiding orbitals τ* correspond to two different orbitals and confer tetrahedral character to carbonyl group

The Antiperiplanar Hypothesis, a Traditional Stereoelectronic Concept is Based on

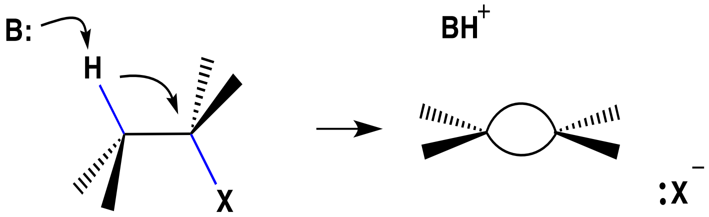
S_N2 Reaction



Anomeric Effect

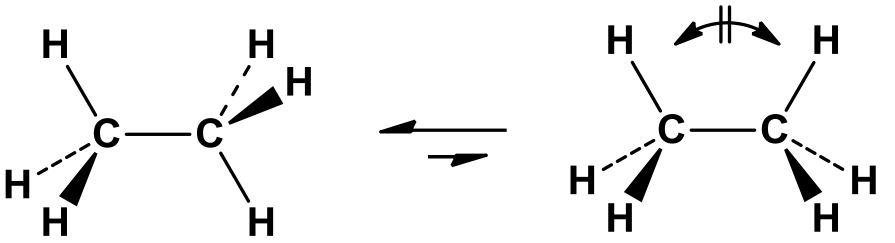


E_2 Elimination



Staggered *vs* Eclipsed Conformation

Ethane



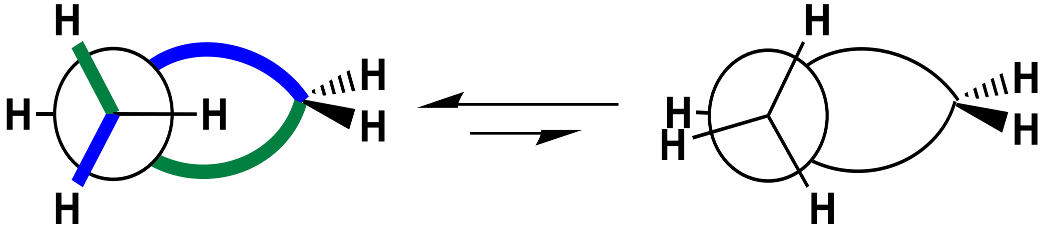
staggered

eclipsed

(3 kcal/mol)

Propene

(CH_3-CH=CH_2)



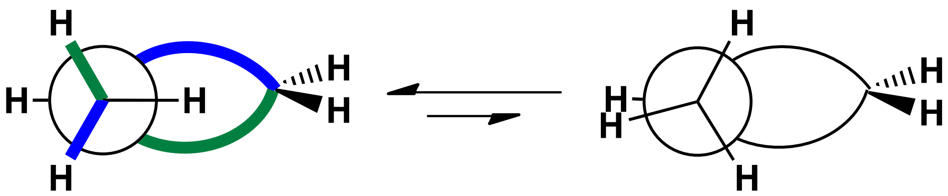
staggered

eclipsed

(2 kcal/mol)

Hyperconjugation Affecting Conformational Stability

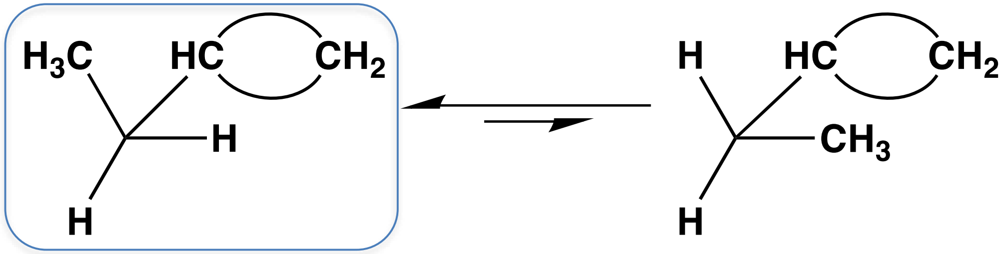
Propene

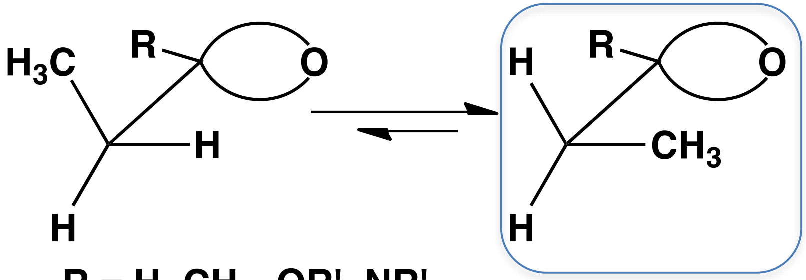


staggered

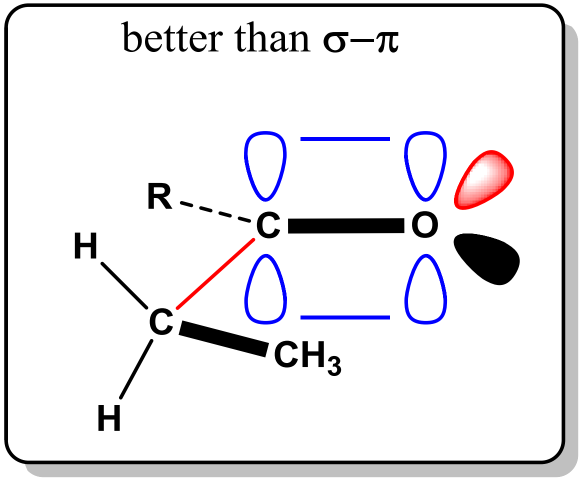
eclipsed

Butene



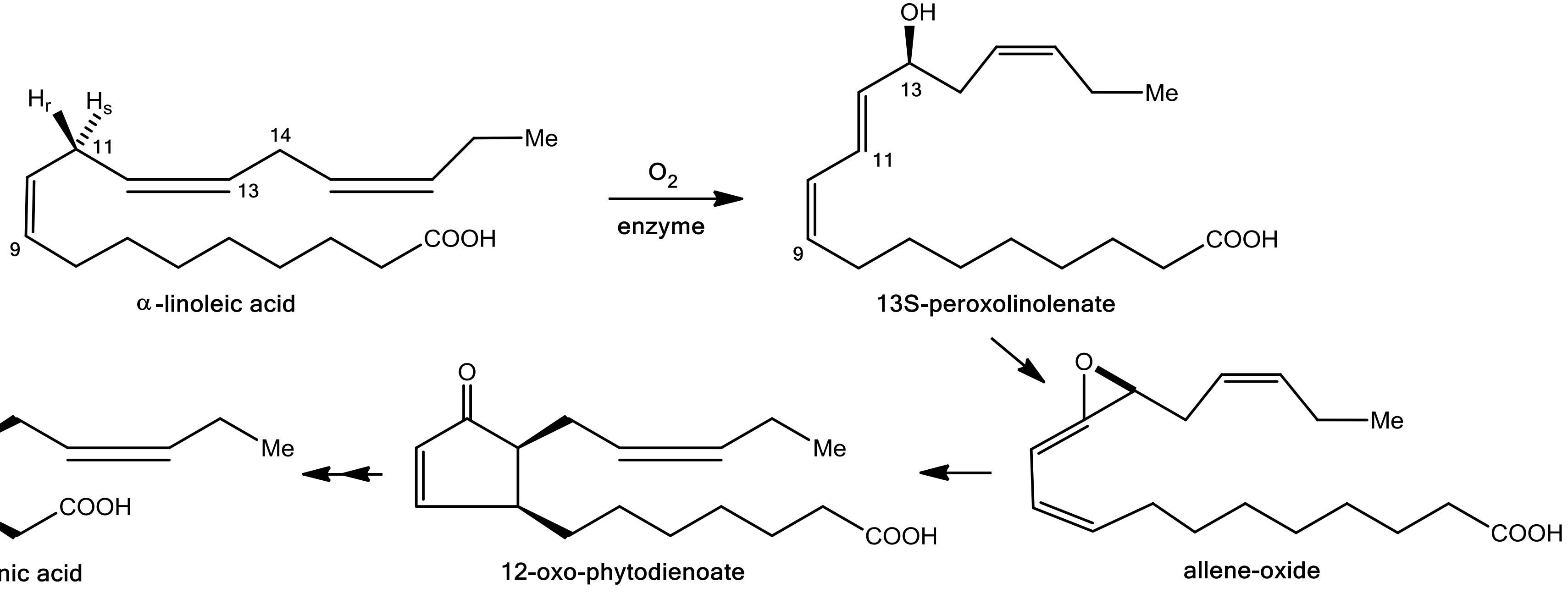


R = H, CH_3, OR', NR'_2

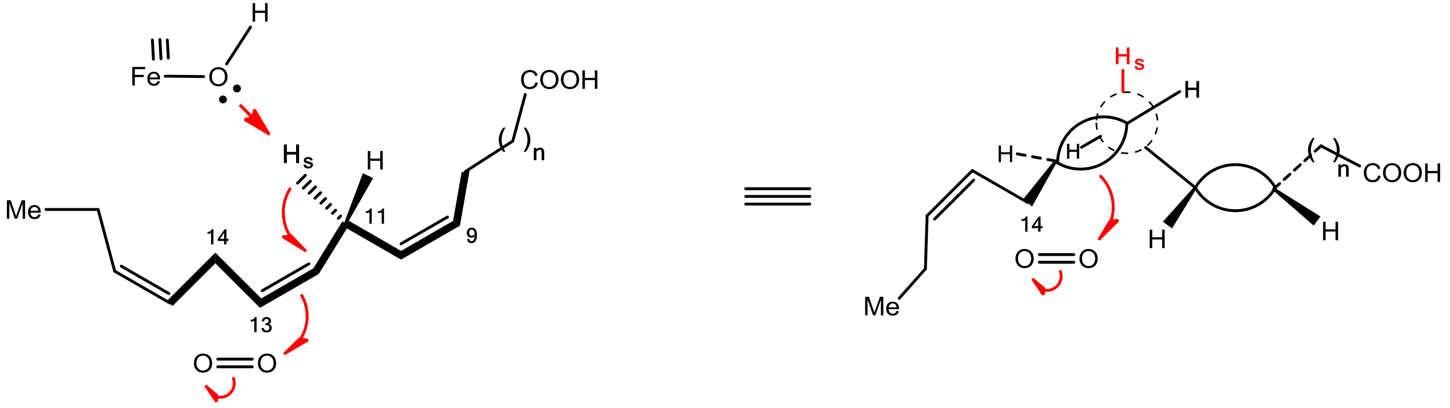


K. Inomata, *J. Synth. Org. Chem. Jpn*, 2009, *67*, 1172.

Biosynthesis of cyclopentenones from unsaturated fatty acids

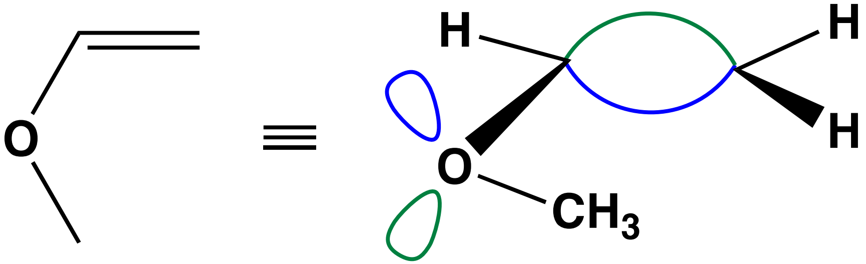


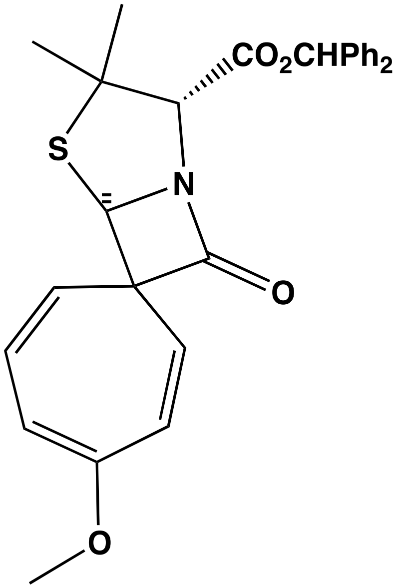
Conformation of α-linolenic acid

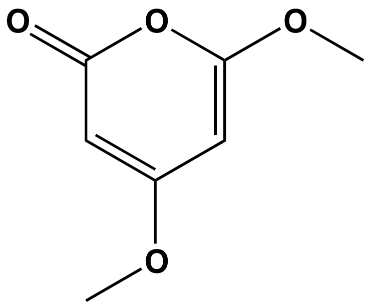


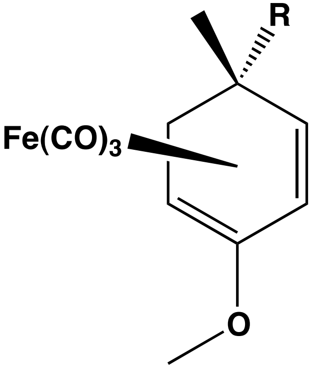
Audran, G.; Brémond, P.; Marque, S.R.A.; Siri, D.; Santelli, M. Tetrahedron **2014**, *70*, 8606-8613.

Conformational Analysis: Enol Ethers



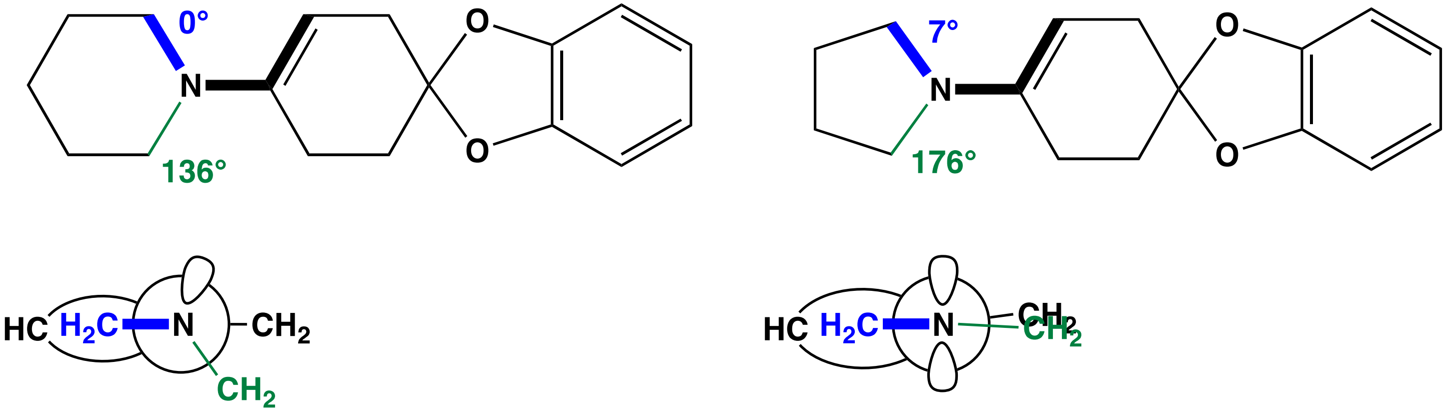


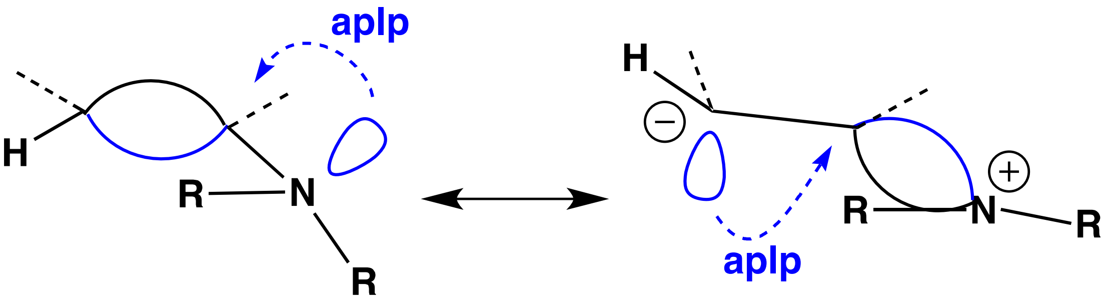




J. D. Mersh, J. K. M. Sanders, *Tetrahedron Lett.,* 1981, *22*, 4029.

Enamine Conformation and Reactivity





N.B. Pyrrolidine enamines are more nucleophilic than piperidine enamines.

K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi, C. Kratky,
***Helv. Chim. Acta* 1978, *61*, 3108.**

Stereoelectronic Effects (S.E.) and Conformation of Acetals and Related Functions

Anomeric Effect

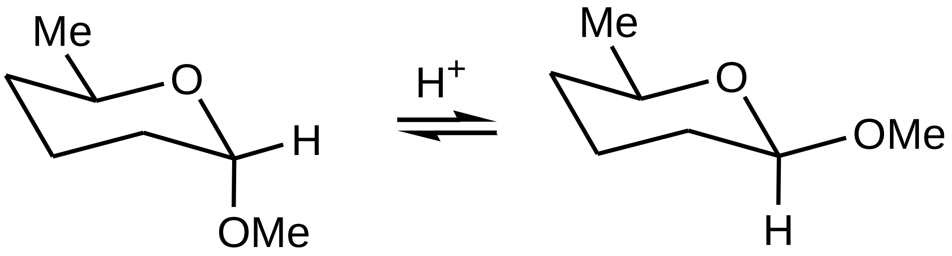
Axial Isomer is More Stable than the Equatorial One in Glycosides !

Lemieux

One example:

Relative Stability (exp.)

Eliel



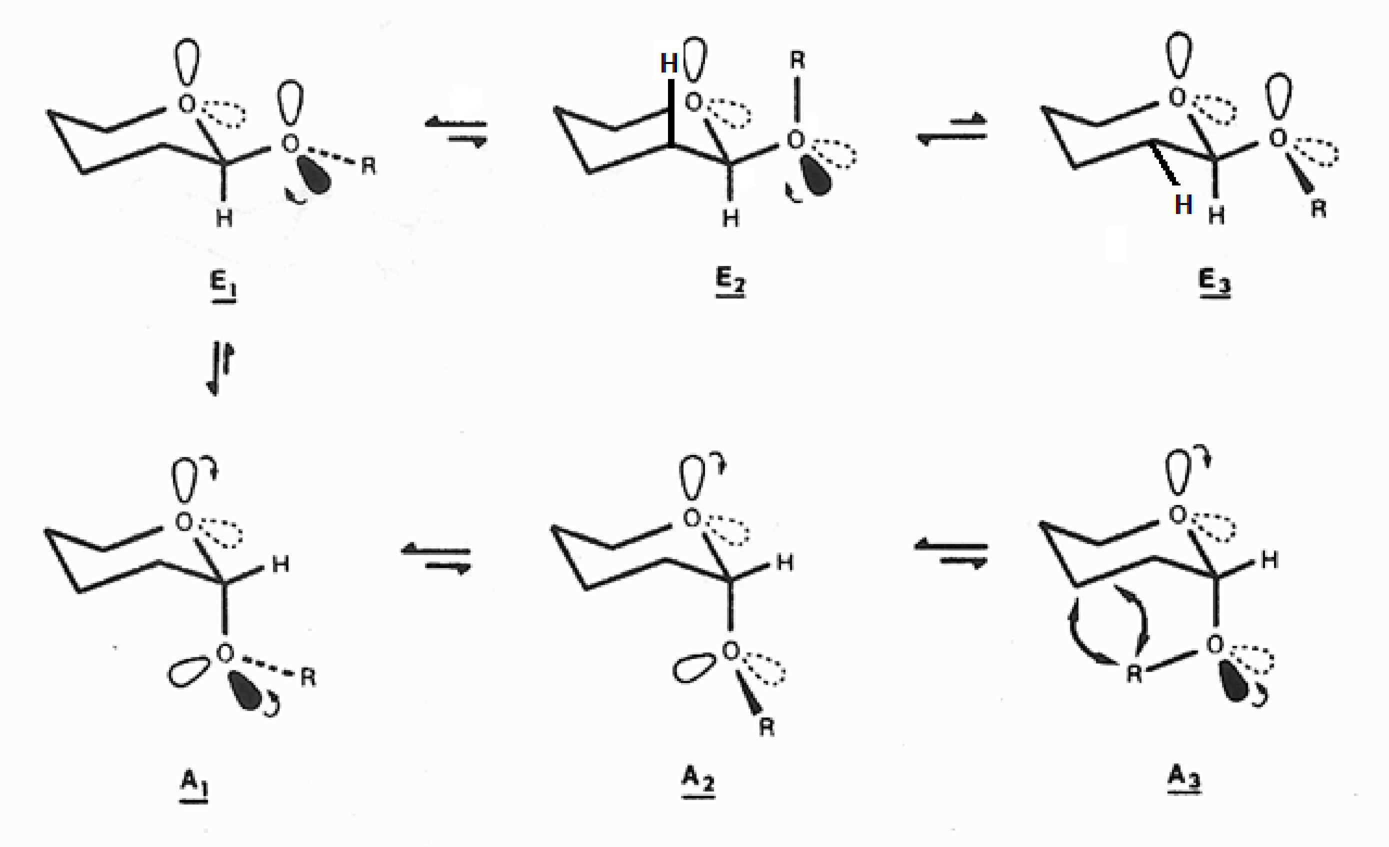
0 kcal/mol

(80%)

0.8 kcal/mol

(20%)

Conformation of Glycosides:
Exo and *Endo* Anomeric Effects and Relative Stability



α and β Glycosides exist exclusively in A_1 and E_1

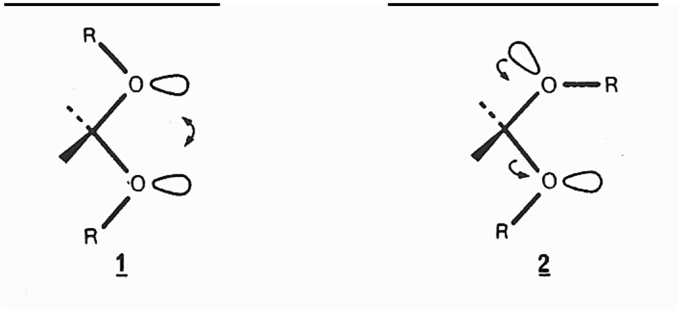
Evidence by NMR and Rx

ANOMERIC EFFECT (explanation)

Electronic

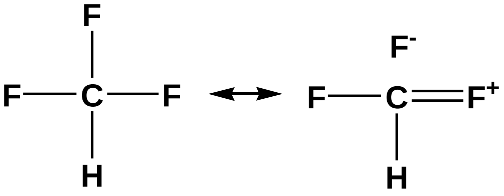
REPULSION — STABILIZATION

Edward Eliel



Altona Lemieux

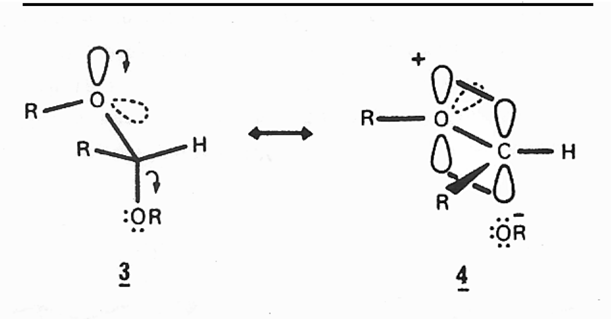
HYPERCONJUGATION



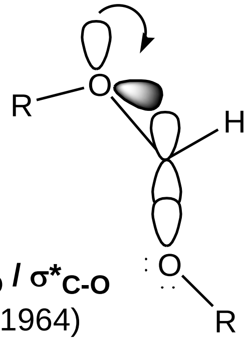
$F{-}\overset{F}{\underset{H}{C}}{-}F \longleftrightarrow F{-}\overset{F^-}{\underset{H}{C}}{=}F^+$

L. Brockway. J.Phys.Chem. 41, 185 (1937)
L. Pauling. Nature of Chemical Bond, 314 (1960)

BOND – NO BOND RESONANCE



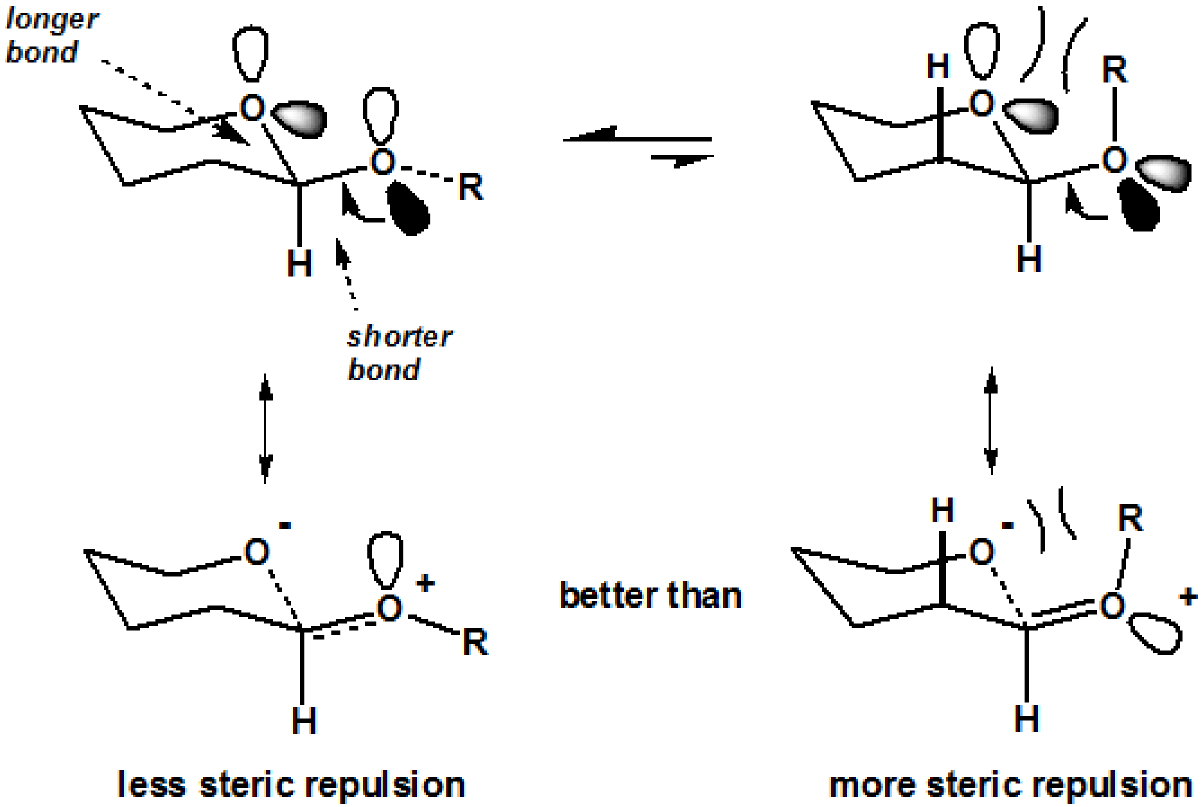
Altona



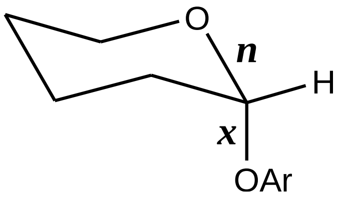
n_O / $\sigma^*_{C\text{-}O}$
(1964)

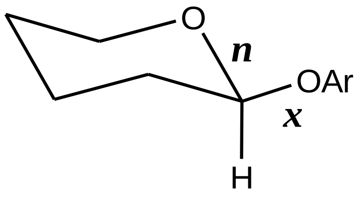
Influence on bond length and oxygen basicity

Exo-Anomeric Effect and Steric Repulsion



Bond Length Changes in the Ground State of Axial and Equatorial Aryloxytetrahydropyrans (X-rays analysis)





axial OAr

x : exocyclic bond increases

n: endocyclic bond decreases
with a greater pKA

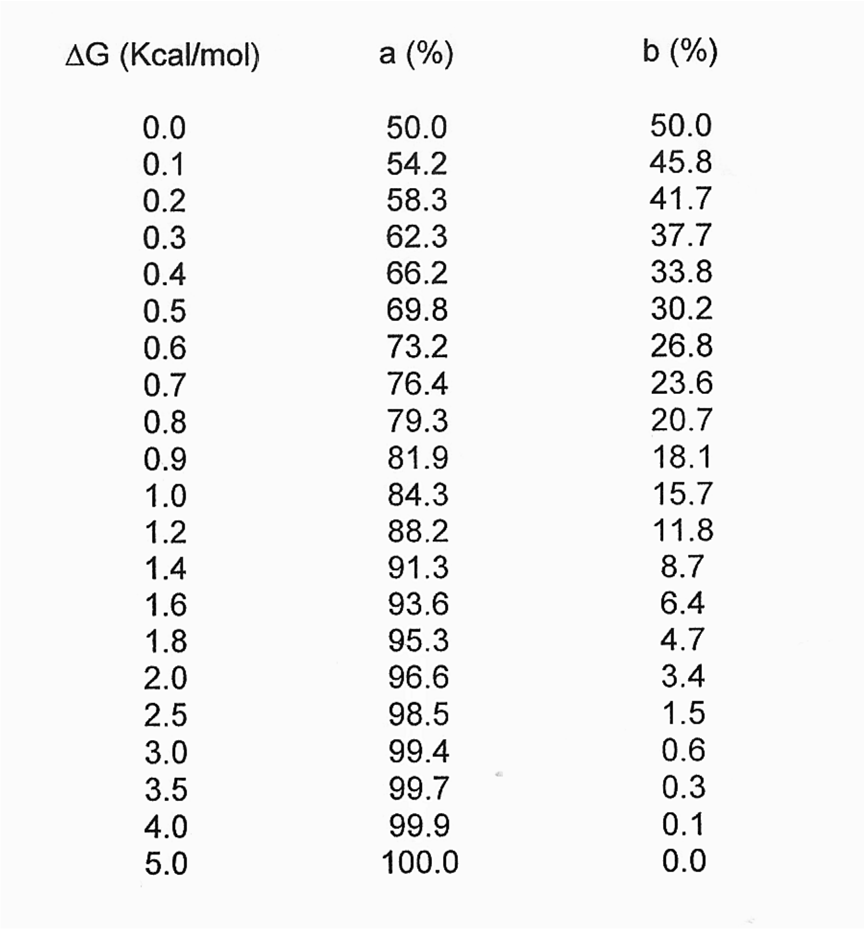
equatorial OAr

x : exocyclic bond increases
to a less extent

n: endocyclic bond does not change

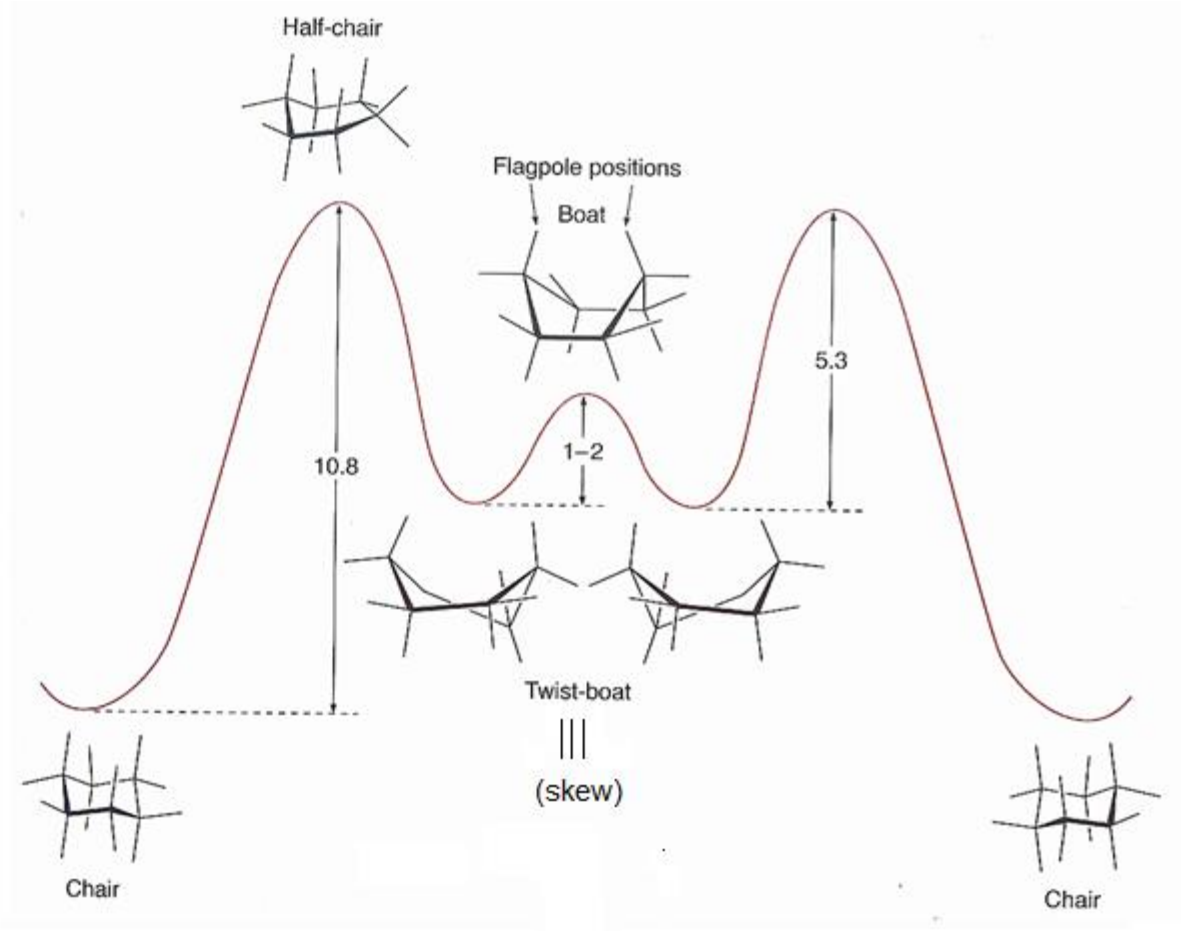
Kirby

Relative Population of Two Species a and b at Equilibrium (25°C)

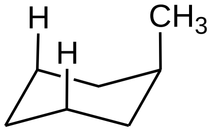


ΔG (Kcal/mol)	a (%)	b (%)
0.0	50.0	50.0
0.1	54.2	45.8
0.2	58.3	41.7
0.3	62.3	37.7
0.4	66.2	33.8
0.5	69.8	30.2
0.6	73.2	26.8
0.7	76.4	23.6
0.8	79.3	20.7
0.9	81.9	18.1
1.0	84.3	15.7
1.2	88.2	11.8
1.4	91.3	8.7
1.6	93.6	6.4
1.8	95.3	4.7
2.0	96.6	3.4
2.5	98.5	1.5
3.0	99.4	0.6
3.5	99.7	0.3
4.0	99.9	0.1
5.0	100.0	0.0

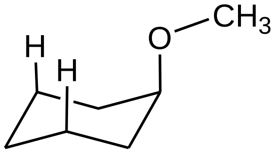
Cyclohexane Conformation



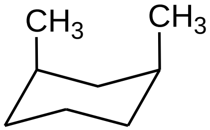
Steric Effects in *n*-Butane and $CH_3{-}CH_2{-}CH_3{-}OCH_3$



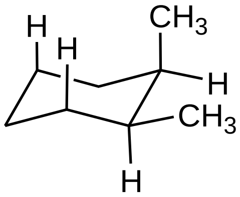
2 x 0.85 = 1.7



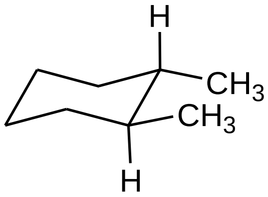
2 x 0.4 = 0.8



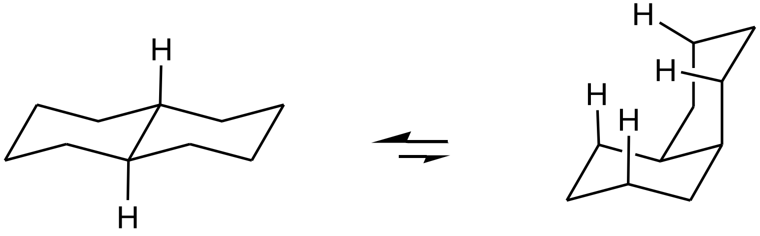
> 4.0 kcal/mol



1.7 + 0.85 = 2.55



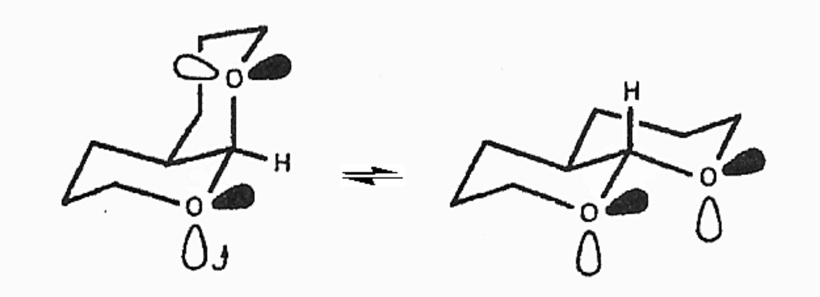
0.85



0

3 x 0.85 = 2.55 kcal/mol

Evaluation of the Anomeric Effect

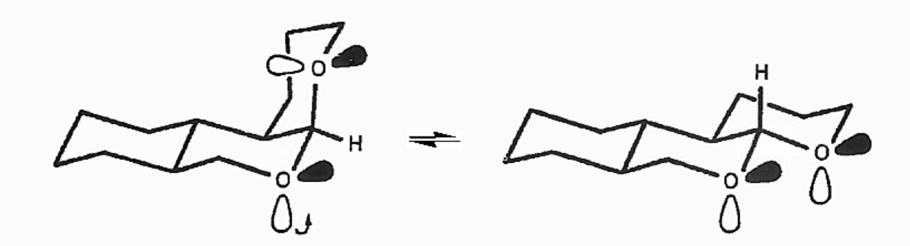


5 6

57% (0) 43% (0.17 kcal/mol)

Descotes

1 gauche form of *n*-butane = +0.85
1 OR axial to cyclohexane = +0.8
entropy factor = -0.42 (favor 5)
1 anomeric effect (A.E.) = -1.4
energy difference = -0.17 kcal/mol (favor 5)



7 8

45% (0.25) 55% (0)

Deslongchamps

steric effect = +1.65 (favor 8)
1 anomeric effect (A.E.) = -1.4 (favor 7)
energy difference = -0.25 kcal/mol

1,7-Dioxaspiro[5.5]undecane (Spiroketal)
Anomeric Effect and Relative Stability)

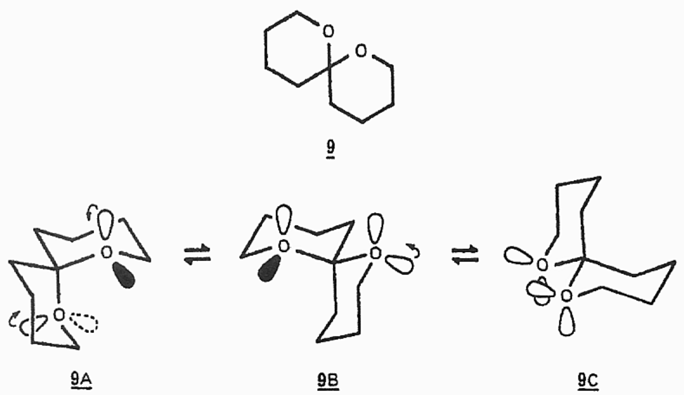


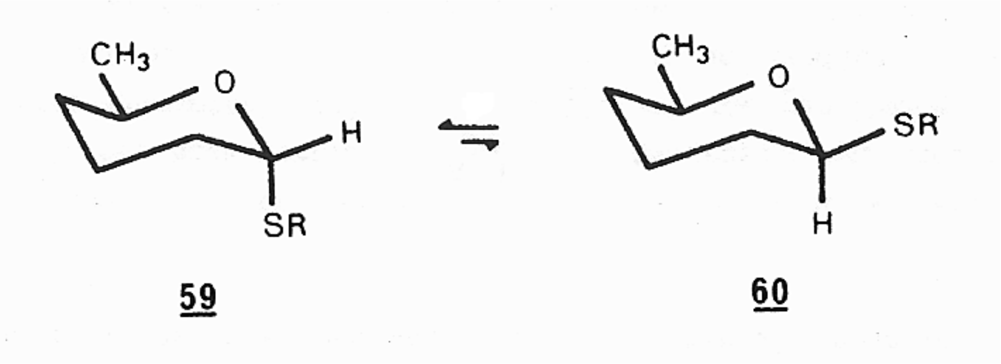
Fig. 2

	9A	9B	9C
Steric Effects	+1.6	+2.6	+3.6
A.E.	-2.8	-1.4	0
	-1.2 (0)	+1.2 (2.4)	3.6 (4.8 kcal/mol)

Gauche form of *n*-propyl ether ($OCH_2CH_2CH_3$) = 0.4
Gauche form of *n*-butane = 0.9

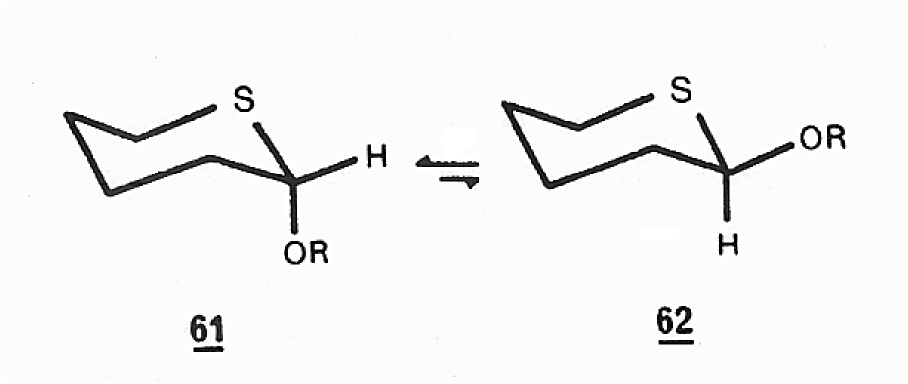
Deslongchamps

Conformation of Mono and Dithioacetals



59 **60**

65% 35%

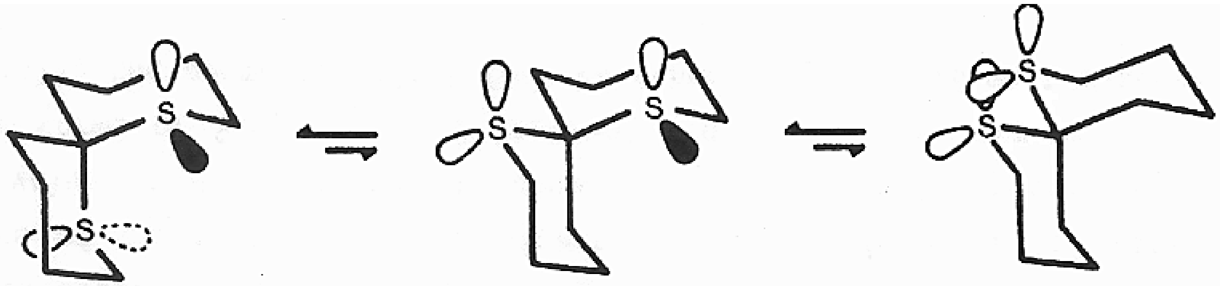


61 **62**

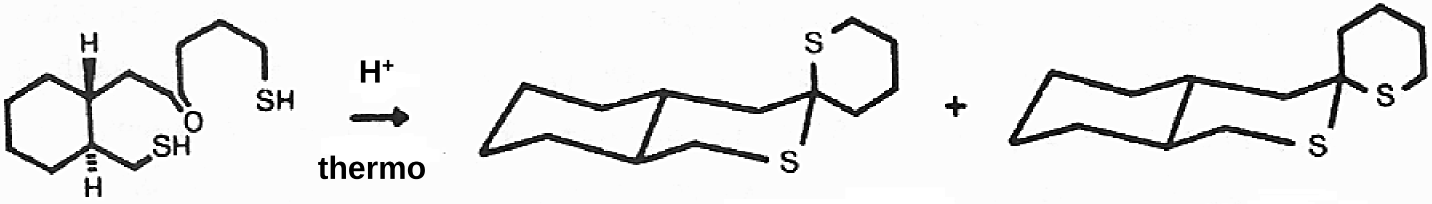
90% 10%

Eliel

Dithio Spiroketal



64A **64B** **64C**

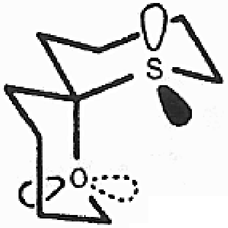


65 **66** **67**

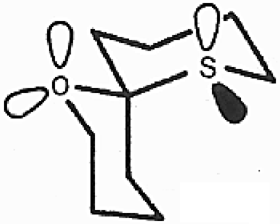
(98%) (2%)

Deslongchamps

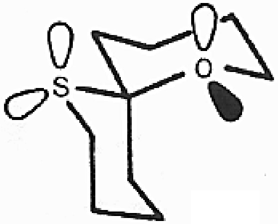
Monothio Spiroketal



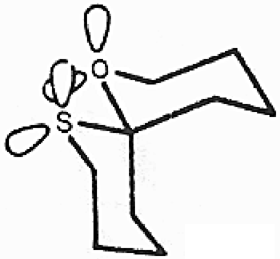
68A



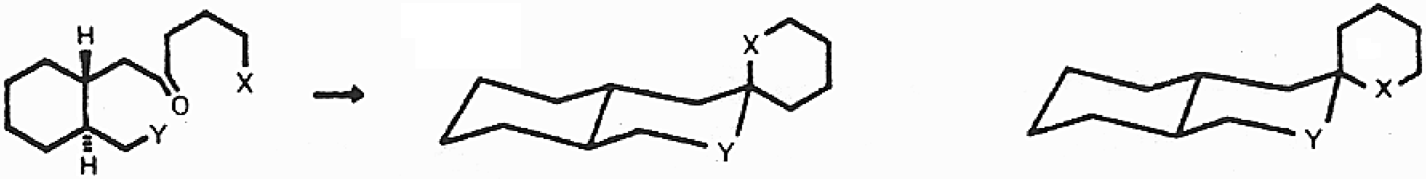
68B



68C



68D



69 X = OH, Y = SH

72 X = SH, Y = OH

70 (100%)

73 (100%)

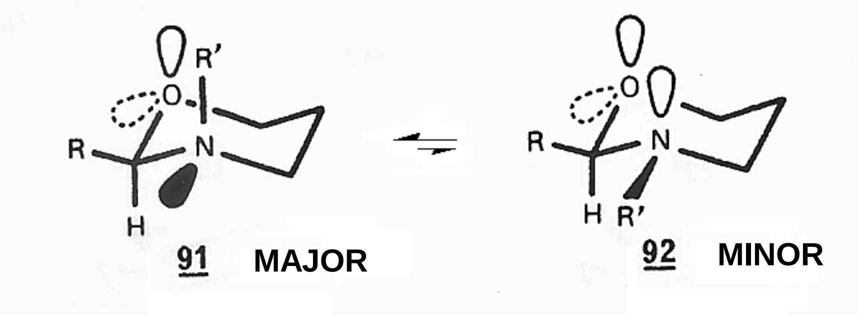
71

74

Deslongchamps

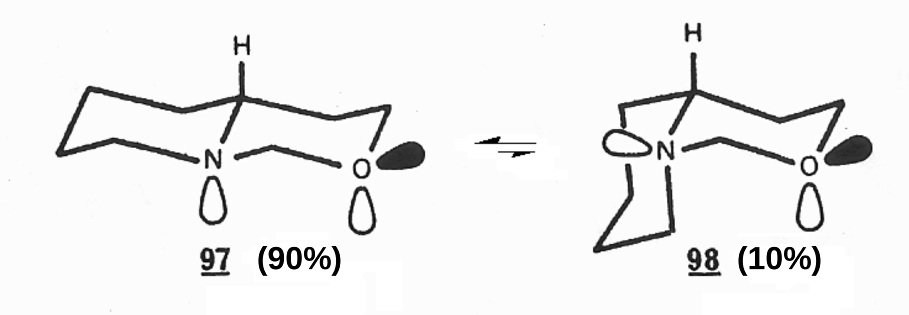
Conformation of 1,3-Oxazine and 1,3-Diazane

Lemieux



91 MAJOR

92 MINOR



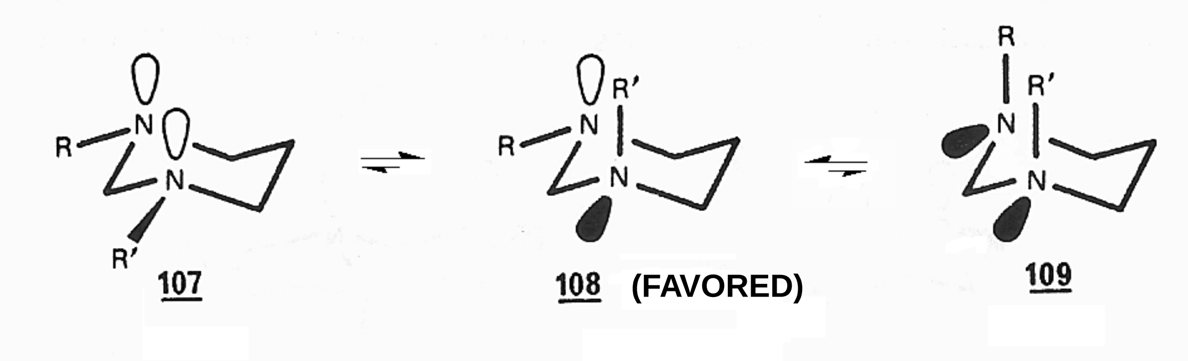
97 (90%)

98 (10%)

Newton

1 A.E. = -1.4	2 A.E.	= -2.8
	2 gauche butane	= +1.8
	1 gauche *n*-propylether	= +0.4
-1.4		-0.6
0		+0.8 kcal/mol

Lemieux
Eliel

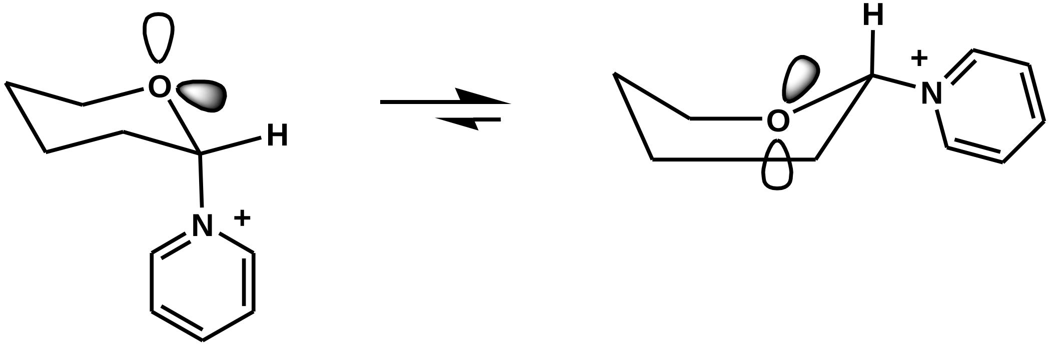


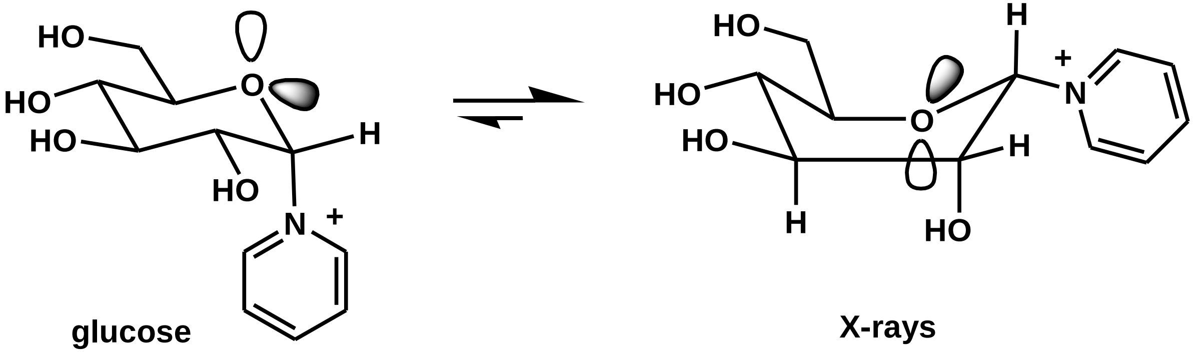
107

108 (FAVORED)

109

Reverse Anomeric EFfect

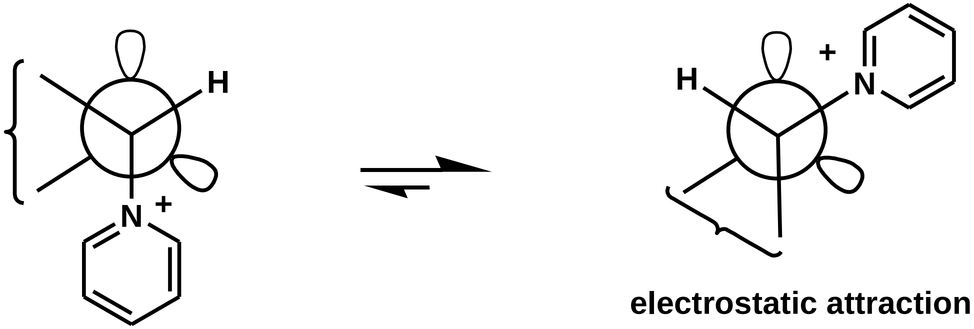




glucose

X-rays

Lemieux



electrostatic attraction

Deslongchamps

THE ANOMERIC EFFECT

by R.U. Lemieux

- **Unequivocal evidence for the conformational preferences of sugars and their derivatives became available in 1958 [1, 2].**
- **Thus, it became possible to assign a stereoelectronic contribution to the relative thermodynamic stabilities of the α- and β-forms of sugar derivatives since this contribution, by favoring the axial orientation, was opposite to that expected from a consideration of non-bonded interactions [3].**

[1] R.U. Lemieux, R.K. Kulling, H.J. Bernstein and W.G. Schneider.
***J. Am. Chem. Soc*. 80, 6098 (1958).**

[2] R.U. Lemieux.
***Current Contents* (Citation Classic), 26 10 (1980).**

[3] R.U. Lemieux and N.J. (Paul) Chü.
***Abstracts of Papers, Am. Chem. Soc.* 133, 31N (1958).**

THE ANOMERIC EFFECT (cont'd)

by R.U. Lemieux

- **Riiber and Sørensen [4], in 1933, had introduced the term "anomeric" as a class name for the α- and β-forms of sugars and their glycosides. Accordingly, the term "anomeric effect" was introduced in 1959 [5] to describe this stereoelectronic feature which appeared to be a general property of acetal linkages. It was recognized [5] that the anomeric effect should have an important influence on the orientation of the aglycon of α glycoside.**

[4] C.N. Riiber and N.A. Sørensen.
***Kgl. Norske Videnskat. Selskabs. Skrifter* 7, 50 (1933).**
[5] R.U. Lemieux.
***Abstracts of Papers, Am. Chem. Soc.* 135, 5E (1959).**

THE ANOMERIC EFFECT (cont’d)

by R.U. Lemieux

- **The term “*exo*-anomeric effect” was introduced in 1969 [6] to specify this component of the overall anomeric effect in the case of glycosides wherein the pyranose ring is anchored in a specific chair conformation.**
- **The term “reverse-anomeric effect” was introduced in 1965 [7] in view of the observation that pyridinium α-glycopyranosides possessed abnormal high-energy conformations.**

[6] **R.U. Lemieux, A.A. Pavia, J.C. Martin and K.A. Watanabe.**
***Can. J. Chem.* 47, 4427 (1969).**

[7] **R.U. Lemieux and A.R. Morgan.**
***Can. J. Chem.* 43, 2205 (1965).**