The Anomeric Effect

Baran Group Meeting

Further Reading: G.R.J. Thatcher (ed.), The Anomeric Effect and Related Stereolectronic Effects. ACS Symposium Series #539, 1993.

Review: Juaristi, E., Cuevas, G., Tetrahedron, 1992, 48(24), 5019-5087.

Historical Aspects of the Anomeric Effect

First observed in 1955 by J.T. Edward and in 1958 by R.U. Lemieux.

Both were studying carbohydrate chemistry and noticed a preference for alkoxy and acetyl groups to reside in the axial position. Edward proposed that the lone pairs on the ring oxygen were contributing to the effect.

alkyl substituted cyclohexanes prefer equitorial orientation over axial

alkyl substituted tetrahydropyrans show this same preference

the anomeric carbon of the most abundant natural sugar, D-glucopyranose, also prefers an equtorial orientation.

ratio of preference gives us some insight that something is different

conversion into a methyl ether at the anomeric carbon produces a different result from the above

different from reigning cyclohexane conformational analysis model

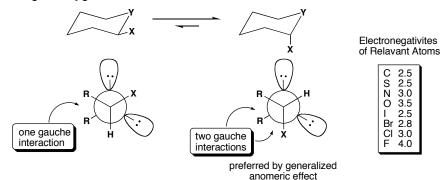
substitution with more electronegative groups changes the observed ratio to a greater extent

Anomeric Effect Defined (IUPAC):

Originally defined as the thermodynamic preference for polar groups bonded to C-1 (the anomeric carbon of a glycopyranosyl derivative) to take up an axial position.

-OR has an axial preferecne in a C1 substituted tetrahydropyran

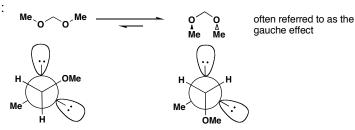
This effect is now considered to be a special case of a general preference (the **generalized anomeric effect**) for gauche conformations about the bond C–Y in the system X–C–Y–C where X and Y are heteroatoms having nonbonding electron pairs, commonly at least one of which is nitrogen, oxygen, sulfur or fluorine.



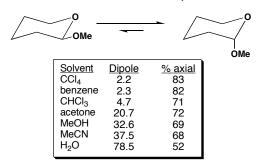
$$\Delta\Delta G^{o}$$
 anomeric effect (stabilization) = $\sum \Delta G^{o}$ (heterocycle) - $\sum \Delta G^{o}$ (steric) Franck, R.W., *Tetrahedron*, **1983**, 39, 3251.

For the anomeric stabilization to effect the conformation at all it must be more stabalizing then the sum of all of the steric factors

Linear Example:

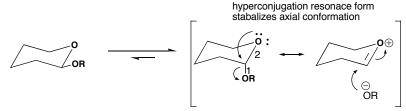


Sovent also plays a role: Increase in anomeric stabilization associated with low solvent dipole



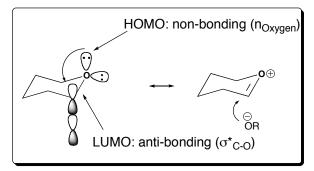
Lemieux, R.U., et al. Can. J. Chem. 1969, 47, 4427.

Most widely accepted explanation for the anomeric effect:



observed bond length for bond 2 is shorter then typical O-C bond and longer for bond 1

Closer Examination of Orbitals:



stabalizing 2 electron interaction



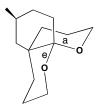
antiperiplanar representation

This model is referd to as Antiperiplanar Lone Pair Hypothesis or **ALPH**

Further Evidence:

bond lenght: increased in the axial C-Cl bond (1.819Å) versus the equatorial C-Cl bond (1.7181Å)

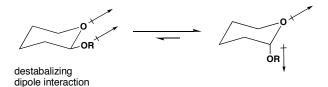
Romers, C., et al. Topics Stereochem., 1969, 4, 39.



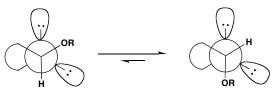
axial bond also observed to be longer then equitorial bond in this constrained case

Other Explanations:

Dipole Stabilization: Opposing dipoles are stabalizing relative to aligned dipoles



Electrostatic Repulsion: Decreased electrostatic interactions are favored



destabalizing interaction of electronegative atom gauche with two lone pairs

destabalizing interaction of electronegative atom gauche with only one lone pair favored

Net Anomeric Effect probably due to a combination of factors

The Exo-Anomeric Effect:

same orbital overlap with exocyclic oxygen observed as stabalizing resonance form

minor contribution to overall resonance relative to *endo* anomeric effect

also can be stabalizing with equitorial substituents

endo anomeric effect is the dominant stabalizing interaction with axial substituents, the exo anomeric effect is stronger with equitorial substitutents

Anomeric Effect=(exo-AE_{eq})-(exo-AE_{ax}+endo-AE_{ax})

endo anomeric effect is absent in the equitorial conform so this term is zero

Praly, J. P., Lemieux, R.U., Can. J. Chem. 1987, 65, 213.

Anomeric Effect of Radicals:

Giese, B., Dupuis, J., Tetrahedron Lett., 1983, 25, 1349.

Effect is observed in tetrahydrothiopyran:



Less significant contribution of anomeric effect with tetrahydrothiopyran. However, since C-S bonds are longer then C-C bonds 1,3-diaxial interactions are decreased and as a result more axial isomer is seen then in the oxygen analogs

Effect is observed in dioxanes and dithianes:



simple extention of the tetrahydropyran case however now there are two oxygens that take part in the resonance structure



dithianes show an even greater preference for axial substituents due to greater relaxation of 1,3-diaxial interactions

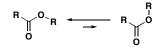
Effect is very minimal with amine nitrogens:

O NH₂

amine nitrogen not electronegative enough to produce a NH₂ significant anomeric effect on tetrahydropyran

Structures with N-C-X bonds where X is a strongly electronegative substitutent on piperadine are not stable so the effect cannot be studied on these systems

Effects at sp₂ centers:

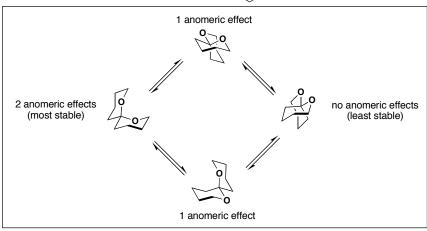


increased barrier of rotation due to stabalizing interaction

Spiroketals: found in many natural products

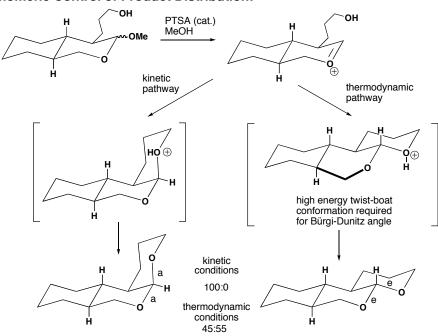
reviews: Perron, F., Albizati, K.F. Chem.Rev. 1989, 89, 1617-1661 Brimble, M.A., Furkert, D.P. Current Organic Chemistry, 2003, 7, 1461-1484.

structural conformations that depend on the anomeric effect



General considerations for spiroketal ring systems. Actual outcome will also be dependent on substituents

Anomeric Control of Product Distribution:



G.R.J. Thatcher (ed.), The Anomeric Effect and Related Stereolectronic Effects. ACS Symposium Series #539, 1993.

The Reverse Anomeric Effect: Fact or Fiction?

Preference for equatorial position with positively charged-electronegative substituents C. L. Perrin, Tetrahedron, 1995, 51, 11901.

highly debated in the literature

- -often the charged species studied are bulky and sterics have a greater contributioin
- -dipole interactions in equitorial state are not stabalizing (evidence for this model)
- -no lone pair on axial subsituent to contribute to the exo-anomeric effect
- -the axial structure is weak (favored by elimination) and unlikely to exist, only the equitorial isomer is preferred as a result

interesting exception:

H CH₂OH H CH₂OH CH₂OH

Brief Sampling of Simple Spiroketal Natural Products:

SCHEME 7. Spiro[5.5] Insect Pheromones



1.7-Dioxaspirol 5.5 lundecane Dacus oleae (racemic) D. cacuminatus (racemic)

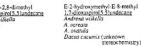


E.Z-2,8-dimethyl-1,7-dioxaspiro 15.5 undecane Dacus cucumis Dacus halfordiae

Megarhyssa norton



4-hydroxy-2,8-dimethyl 1,7-dioxaspirol5,5lundecane Andrena wilkella



E-2-propyl-1,7-dioxaspiro (5.5)undecane Andrena wilkella A. ocreata A. ovatula A. haemorrhoa





E-8-methyl-E-2-propyl-1,7-dioxaspiro 15.5lundecane Andrena wilkella A. ocreata A. ovatula A. haemorrhoa Dacus dorsalis

E-2-ethyl-1,7-dioxaspirol 5,5 lundecane Coelioxys quadridentata C mondibutoris

E.E-2,8-dimethyl-1,7-dioxaspiro 15,5 lundecane Epeolus cruciger E. variegatus

Andrena wilkella A. ocreata A. ovatula Dacus dorsalis

D. cucumis
D. kalfordiae
Megarkyssa nortoni
Ontholestes murinus

D. cucurbitae

Z,Z-2,8-dimethyl 1,7-dioxaspiro [5,5]undecane

2-butyl-1,7-dioxaspiro[5,5]undecane
Dacus latifrons (unknown stereochemistry



2-ethyl-8-methyl 1.7-dioxaspiroi5.5lundecane Dacus occupitalis



Z-4-hydroxyl-1,7-dioxaspiro [5.5]undecane Dacus oleae

Z-3-hydroxyl-1,7-dioxaspiro [5.5]undecane Dacus oleae

SCHEME 8. Spiro[4.4] Insect Pheromones



2.7-diethy)-1,6-dioxespix [4.4]nonane (3 isomers) Andrena wilkella A. ocreata A. ovumla



Z-2 Ethyl-1.6-dioxaspiro [4.4]nonane (Chalcogran) Pityogenes chalcographus



2-methyl-7-propyl-1.6-dioxaspiro[4.4]nonane Andrena haemorrhoa (all 4 diustereopers)

2-(2-hydroxyethyj)-7-methyl 1.6 dioxaspiro(4.5)decane

SCHEME 9. Spiro[4.5] Insect Pheromones







Z-2-ethyl-E-7-propyl-1.6-dioxaspirol 4.5 Idecane Andrena wilkella



E-7-ethyl-E-2-methyl1-6-dioxaspiol-4-5ldecane
Coclioxys quadridensas
C. mandbularis
A. oranda
A. ovanula
A. hoemorthoa
Parawespula vulgaris
P. germanica
Dolichovespula saxonica





1.6-dioxaspiro[4.5]decane Paravespuda vulgaris



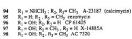
Dacus cucumis Paravespula vulgaris P. germanica Dolichovespula saxonica



E-7-ethyl-Z-2-methyl-16-dioxsepirol 5. Sidecane Coeloxys quadridentata C mandibulisis Andrena wilkelia A ocreata A ocreata A vanula A haemorrhoa Paravespula vulgaris P. germanica Dolichovespula saxonica











105 grindelistrictic acid (chrysothame)



Z-2-methyl-1.6-dioxaspirol 4.5 lde Paravespula vulgaris



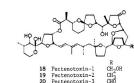




E-2-ethyl-E-7-propyl-1.6-dioxaspiro[4.5]der Andrena wilkella



Non-Anomeric spiroketal:



Agric. Biol. Chem., 1986. 50, 2693

Org. Lett., 2004, 6(21), 3849-3852.















117 A 204A



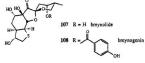






















125 oligomycin B

123 hippurin-1 mono

124 calcimycin

| 25a + 25b | acid promote | ferent Acid Promoters ^a 12 + 26 (anomeric) | | |
|-------------------------|--------------------------------------|---|-----|--|
| | CH ₂ Cl ₂ , rt | 11 (+ 27) (nonanomer | ic) | |
| thermodynamic, anomeric | | Ainetic, nonenomeric | | |
| TBDPSO 12 TBDPSO 1 H | OPW | TBDPSO 1 0 0 10 H | OPi | |

PPTS (20 mol %) TsOH (20 mol %) 5.21 (3.4) -1.3 -1.3 10 min CICH2CO2H (80 mol %) 4 h 4 h 6 h 21 h 2.86 3.77 4.76 (12.3) 4.76 (12.3)

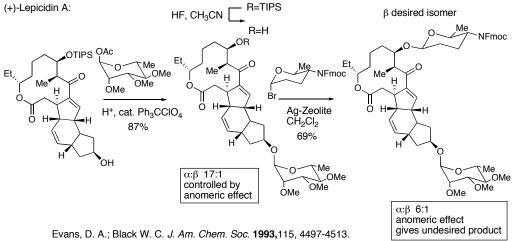


SCHEME 10. Spiro[n.6] Insect Pheromones

2.7-dimethyl-1.6-dioxaspiro[4.6] undecane

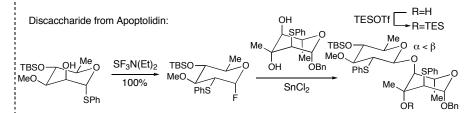
E-2-methyl-1.7-dioxaspiro[5.6]dodecane Andrena haemorrhoa Dacus cucumis (unknown stereochemistry) How can we use the anomeric effect?

Danishefsky, S. Langer, M. J. Org. Chem. 1985, 50, 3674-3676.



$$\begin{array}{c} \textbf{O} \\ \textbf{OH} \\$$

Ratcliffe, A.J. Fraser-Reid, B. J. Chem. Soc. Perkin Trans. 1 1990 747-750.



bulky SPh groups used to discourage anomeric control of product

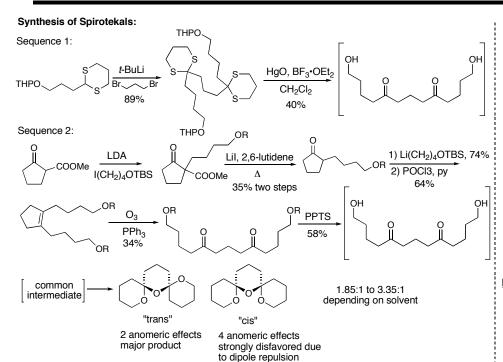
Nicolaou, K.C. et. al. J. Am. Chem. Soc. 2001, 125, 15433-15442.



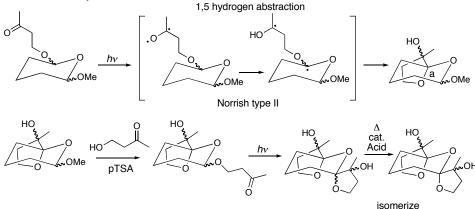
whereas:

Semmelhack, M.F., et al. Pure & Appl. Chem., 1990, 62(10), 2035-2040.

Photochemical Cyclization:

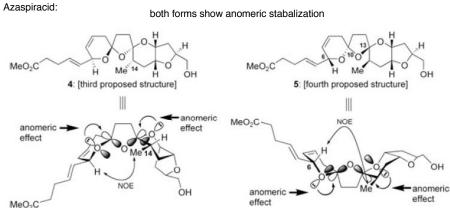


McGarvey, G.J., Stepanian, M.W. Tet. Lett., 1996, 37(31), 5461-5466.



Cottier, L.; Descotes, G. Tetrahedron 1985, 41(2), 409.

isomerize to anomerically stabalized isomer



incorrect structure originally targeted and synthesized correct structure as compared to natural product key spiroketal step:

Nicolaou, K.C., et al. Angew. Chem. Int. Ed. 2004, 43, 4318-4324.

Iodine(III) mediated radical cyclization to Spiroacetals:

TBDPSO OH Phl(OAc)₂

$$I_2$$
, hv
 90%

TBDPSO Phl(OAc)₂
 I_2 , hv
 I_3 , hv
 I_4 , hv

TBDPSO Phl(OAc)₂
 I_5 , hv
 I_4 , hv

TBDPSO Phl(OAc)₂
 I_5 , hv
 I_5 , hv

TBDPSO Phl(OAc)₂
 I_5 , hv

Brimble, M. A. Molecules. 2004, 9, 394-404

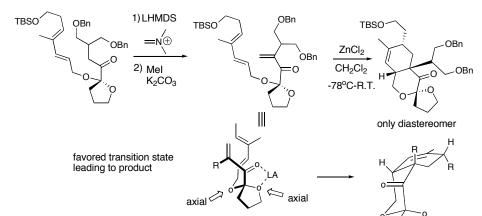
Examples of Spiroketal Tethering:

Olefin Metathesis

will be applied to the synthesis of spirastrellolide A

Liu, J., Hsung, R. P., Org. Lett. 2005, 7(11), 2273-3376.

Diels Alder

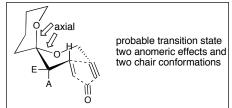


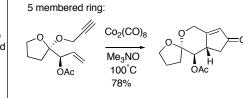
Wang, J., Hsung, R. P., Ghosh, S.K. Org. Lett. 2005, 6(12), 1939-1942.

endo-boat-boat w/ two anomeric effects

Pauson-Khand

[cis:trans] [< 5:95]





anomeric control dominates stereochemical outcome even if substituent is forced into axial position

finally able to force selectivity with bulky silyl group - sterics beat anomeric effect

Ghosh, S.K., Hsung, R.P., Liu, J. J. Am. Chem. Soc. 2005, 127, 8260-8261.