Veejendra K. Yadav

# Steric and Stereoelectronic Effects in Organic Chemistry

*Second Edition*

Springer

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*To Arpita, Dhananjay, and Dhruv with love*

# Preface to the Second Edition

After the publication of the first edition of the book in 2016, some incorrect structures and lack of emphasis, here and there, were noticed by the MSc and PhD students whom I recently taught a course (Physical Organic Chemistry) and myself. All such structures have been corrected and requisite emphasis laid to make the reading enjoyable. The presentation has been toned up to prevent distractions.

The contents of the erstwhile Chap. 6 now appear in Chap. 10. However, torquoselectivity and Hammett Substituent Constants are now dealt with separately in Chaps. 7 and 8, respectively. The discussion on torquoselectivity has been expanded to include recent developments in depth to give the reader a broader perspective. Hammett Substituent Constants are relevant to theoretical chemists involved with Quantitative Structure–Activity relationships. Now, Chap. 10 also includes a description of the captodative effect, an area that is significant for specific materials research.

The relative aromaticity of pyrrole, furan, and thiophene has been a subject of intense research for quite some time. Several new approaches have been designed with the sole aim to prove that thiophene has the most aromatic character because it undergoes Diels–Alder reactions with comparatively great difficulty. The designed approaches are not consistent among themselves because the relative aromaticity index changes with the approach used. It was therefore felt necessary to address this issue from the viewpoint of non-experts in theory. The author has carried out intensive computational research and arrived at pyrrole > furan > thiophene aromaticity order by emphasizing *R*-factor and allylic interactions in the diene. *R* is the distance between the reacting termini of the diene. Chapter 9 deals with this subject in detail. The author is confident that the reader will find the arguments convincing.

This book aims to facilitate teaching the concepts to undergraduate and graduate students, and also encourage research in areas such as torquoselectivity and relative aromaticity index.

I dare not say that the script is completely error-free now. I would gratefully acknowledge criticism and suggestions from the readers for further improvement.

Kanpur, India — Veejendra K. Yadav

# Summary of Second Revised Edition

This edition of the book has been modified with the aim of making the reading enjoyable by laying emphasis and elaborating on topics relevant to the stereochemistry of important organic reactions. While modifying, all errors noticed in structures and text have been corrected.

The contents of the erstwhile Chap. 7 now appear in Chap. 10. Chapter 10 includes a description of captodative effect, a subject of great significance for specific materials research. Two topics, namely Torquoselectivity and Hammett Substituent Constants, have been taken out and dealt with separately in Chaps. 7 and 8, respectively. The discussion on torquoselectivity has been expanded to include recent developments in depth to give the reader a broader perspective.

The relative aromaticity of pyrrole, furan and thiophene has been a subject of intense research for quite some time. Different new approaches have been designed with the sole aim to prove that thiophene has the most aromatic character because it undergoes Diels-Alder reactions with comparatively great difficulty. The designed approaches are not consistent among themselves because the relative aromaticity index changes with the approach used. It was, therefore, felt necessary to address this issue from the view-point of non-experts-in-theory.

This book aims to facilitate teaching the concepts to undergraduate and graduate students, and encourage research in areas such as torquoselectivity and relative aromaticity index. Hammett substituent constants are relevant to the theoretical chemistry audience involved with Quantitative Structure-Activity Relationships.

Veejendra K. Yadav

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# About the Author

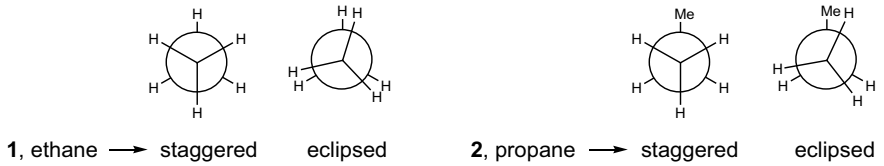
**Veejendra K. Yadav** earned his Ph.D. under the mentorship of Dr. Sukh Dev in 1982. He has carried out his postdoctoral research at University of Calgary, Memorial University of Newfoundland, University of Ottawa, and University of Southern California over the years 1983–1990 before joining Indian Institute of Technology Kanpur (IITK) as Assistant Professor in late 1990. Over the years, he rose through ranks and became full professor in 2001. He has taught undergraduate- and postgraduate-level courses at IITK over the past 30 years, and has remained a popular teacher among the students throughout. His research focuses on the development of new reactions with emphasis on the construction of pharmacophores, synthesis of biologically active molecules, computational-cum-experimental investigation of facial selectivity, and computational investigation of reaction mechanisms. He has three international patents and over 100 research papers to his credit. More details may be found on the link http://home.iitk.ac.in/~vijendra or by visiting: veejendrakyadav.com.

# Chapter 1
# Steric and Stereoelectronic Control of Molecular Structures and Organic Reactions

**Abstract** This chapter emphasizes the important aspects of steric and stereoelectronic effects and their control on conformational and reactivity profiles. The conformational effects in ethane, butane, cyclohexane, variously substituted cyclohexanes, and *cis*- and *trans*-decalins allow a good understanding of the discussions that follow. The application of these effects to E2 and E1cB reactions followed by the anomeric effect and mutarotation is discussed. The conformational effects in acetal formation and the reactivity profile, carbonyl oxygen exchange in esters, and hydrolysis of orthoester have been discussed. The application of the anomeric effect in 1,4-elimination reactions, including preservation of geometry of the newly created double bond, has been presented in detail. Brief discussions of the conformational profiles of thioacetals and azaacetals, and rate acceleration on account of $\sigma_{C–Si}$, $\sigma_{C–Ge}$, $\sigma_{C–Sn}$, and $\sigma_{C–Hg}$ bonds have also been explained.

## 1 Influence of Steric Effects on Structures

Consider the staggered and eclipsed conformers of ethane **1** as shown below. The staggered conformer is more stable than the eclipsed conformer by 3.0 kcal/mol. The electron pairs of the eclipsed bonds repel each other to raise the energy of the system by 1.0 kcal/mol. Three such interactions make up to 3.0 kcal/mol.




On replacing one hydrogen with methyl, we arrive at the staggered and eclipsed conformers of propane **2**. Other than the three repulsive electron pair−electron pair interactions, each contributing 1.0 kcal/mol, there is also methyl-hydrogen steric interaction (or van der Waals repulsion) that contributes 0.4 kcal/mol in the eclipsed conformer. Thus, the eclipsed conformer is less stable by $(3 \times 1.0) + 0.4 =$



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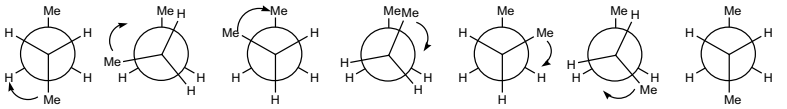
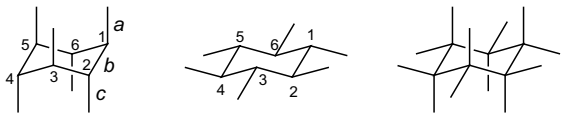
https://doi.org/10.1007/978-3-030-75622-2_1

3.4 kcal/mol than staggered conformer. On either side of the methyl group in the staggered conformer, there is hydrogen on the front carbon with a dihedral (torsion) angle of 60°. The methyl and hydrogen are said to be gauche to each other with no repulsive interaction between them. However, a gauche methyl−methyl interaction contributes 0.9 kcal/mol. The eclipsing methyl−methyl repulsion is 2.5 kcal/mol (bond pair−bond pair repulsion = 1.0 kcal/mol; van der Waals repulsion between the two methyl groups = 1.5 kcal/mol). We encounter the last two interactions in the conformations of butane.



| **3**, butane ⟶ | **a** | **b** | **c** | **d** | **e** | **f** | **a** |
|---|---|---|---|---|---|---|---|
| kcal mol$^{-1}$ ⟶ | 0.0 | 3.8 | 0.9 | 4.5 | 0.9 | 3.8 | 0.0 |

Butane **3** can exist in different conformations **3a–f** across the central $\sigma_{C-C}$ bond as shown. Beginning from the staggered conformer **3a** that has both methyl groups at a torsion angle of 180°, we can write other conformers by clockwise 60° rotation each time about the central $\sigma_{C2-C3}$ bond, as shown. Note that the conformers **3b** and **3f**, and **3c** and **3e** are one and the same. There are no issues related to either the eclipsing electron pair−electron pair repulsion or van der Waals repulsion in **3a**. Hence, **3a** is the most stable conformer and lets us arbitrarily place its energy at 0.0 kcal/mol. Now, we can calculate the energies of other conformers as follows: **3b** and **3f**: 3.8 kcal/mol; **3c** and **3e**: 0.9 kcal/mol; **3d**: 4.5 kcal/mol. All these values are, in fact, so small that butane exists as an equilibrium mixture of all the conformers at Standard Temperature and Pressure (STP). The equilibrium distribution is a function of the relative energies; the more stable a conformer, the more is its contribution.



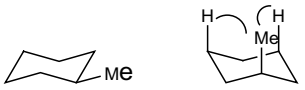
**4a** **4b** **4**

Consider the structure **4a** for the cyclohexane chair. The axial bonds on any two adjacent ring positions are parallel and also anti to each other. The three bonds involved in this relationship are *a*, *b*, and *c*, and they could also be viewed to be in the same plane geometrically. The ‘anti’, ‘parallel’, and ‘same plane’ put together is ‘antiperiplanar’. Thus, the axial bonds on two adjacent cyclohexane positions are antiperiplanar.

The equatorial bonds on any two adjacent ring positions, such as C1 and C2, are gauche to each other with a torsion angle of 60°, as shown in **4b**. With these substituents as methyl, the situation is exactly the same as in the gauche butane

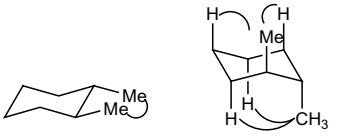
conformers **3c** and **3e**. This will raise the energy by 0.9 kcal/mol. Another important structural feature stems from the observation that an equatorial bond is antiperiplanar to two ring bonds. For instance, the equatorial bond on C1 is antiperiplanar to $\sigma_{C2–C3}$ and $\sigma_{C5–C6}$. Likewise, the bond on C2 is antiperiplanar to $\sigma_{C3–C4}$ and $\sigma_{C1–C6}$. A special note should be taken of the orientations of equatorial bonds on C3 and C6. Other than being antiperiplanar to each other across a hypothetical $\sigma_{C3–C6}$ bond, both the bonds are also antiperiplanar to $\sigma_{C1–C2}$ and $\sigma_{C4–C5}$ bonds.

A good knowledge of the structural relationship of the axial and equatorial bonds on the cyclohexane ring will help us understand the underlying stereoelectronic and conformational effects on reactivity. Methylcyclohexane can adopt the two chair conformations **5a** and **5b**. The conformer **5b** is obtained from **5a** on ring flip. The conformer **5a** is fully devoid of van der Waals interactions. However, one discovers two butane gauche interactions in conformer **5b**, as shown, each raising the energy by 0.9 kcal/mol. Thus, **5b** is less stable than **5a** by $2 \times 0.9 = 1.8$ kcal/mol. In other words, mono-substituted cyclohexane should prefer the conformer with the substituent occupying the equatorial position.



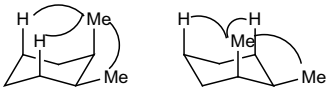

**5a** **5b**

Consider *trans*-1,2-dimethylcyclohexane **6**. In conformer **6a**, the two equatorial methyl groups are gauche to each other to raise the energy by 0.9 kcal/mol. In conformer **6b**, the product of ring flip in **6a**, each axial methyl group is engaged in two butane gauche interactions. This will raise the energy by $2 \times (2 \times 0.9) = 3.6$ kcal/mol. The conformer **6a**, therefore, is more stable than **6b** by $3.6 - 0.9 = 2.7$ kcal/mol. Thus, *trans*-1,2-disubstituted cyclohexane prefers the conformer in which both the substituents occupy equatorial positions.



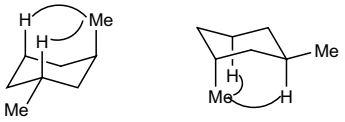

**6a** **6b**

In either of the two conformations **7a** and **7b** of *cis*-1,2-dimethylcyclohexane **7**, one methyl is axial and the other equatorial. The two methyl groups are mutually gauche to each other and the axial methyl is further gauche to two axial hydrogen atoms, as shown. Both the conformers are one and the same. In the event that one substituent is different from the other, the molecule will largely adopt the conformer in which the larger substituent occupies an equatorial position.



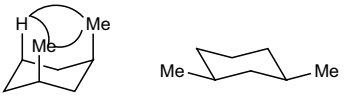

**7a** **7b**

*Trans*-1,3-dimethylcyclohexane can adopt the conformations **8a** and **8b**. In both, one methyl is axial and the other equatorial. Both the conformers, therefore, are one and the same. While the equatorial methyl is not involved in any van der Waals interaction, the axial methyl is engaged in two butane gauche interactions, as indicated. Thus, compared to methylcyclohexane, *trans*-1,3-dimethylcyclohexane is higher on the energy scale by $2 \times 0.9 = 1.8$ kcal/mol.



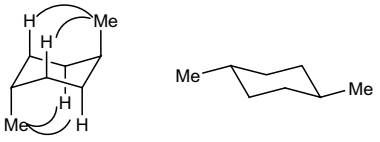

**8a** **8b**

*Cis*-1,3-dimethylcyclohexane can adopt two conformations. In conformer **9a**, both the methyl groups are axial and, hence, gauche to each other. Each methyl is additionally gauche to an axial hydrogen, as shown. The total increase in energy of this conformer will, therefore, be $2.5 + 0.9 + 0.9 = 4.3$ kcal/mol. In **9b**, both the methyl substituents are equatorial and there are no issues arising from gauche interactions. Thus, **9b** is more stable than **9a** by 4.3 kcal/mol. Also, the more stable conformer **9b** of *cis*-1,3-dimethylcyclohexane is more stable than *trans*-1,3-dimethylcyclohexane **8a**/**8b** by 1.8 kcal/mol.



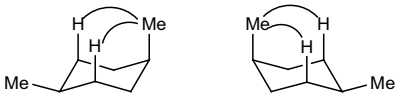

**9a** **9b**

The two conformers of *trans*-1,4-dimethylcyclohexane are **10a** and **10b**. In view of the foregoing discussions, the conformer **10b** is more stable than **10a** by $2 \times (2 \times 0.9) = 3.6$ kcal/mol. In **10a**, each axial methyl is engaged in two butane gauche interactions, as shown.



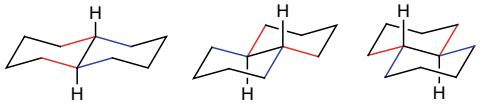

**10a** **10b**

Each conformer of *cis*-1,4-dimethylcyclohexane, **11a** or **11b**, has one methyl axial and the other equatorial. The axial methyl is engaged in two butane gauche interactions as shown, raising the energy of the system by $2 \times 0.9 = 1.8$ kcal/mol. In comparison, the more stable conformer of *trans*-1,4-dimethylcyclohexane, **10b**, is more stable than *cis*-1,4-dimethylcyclohexane **11** by 1.8 kcal/mol.



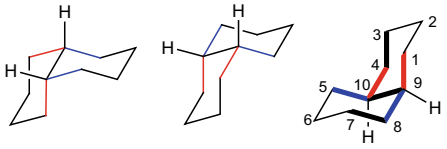

**11a** **11b**

Three different representations of *trans*-decalin are **12a**–**c**. The bonds in both red and blue colors are equatorial to the other ring, leaving the hydrogens on ring junctions axial. We know that the 1,2-diequatorial substituents are gauche to each other and two such interactions will raise the energy of the system by 1.8 kcal/mol. These interactions are present in *cis*-decalin as well, but between axial and equatorial substituents (vide infra). For the purpose of relative energy calculations of *trans*-decalin and *cis*-decalin, these gauche interactions are, therefore, ignored. The ring flip in *trans*-decalin is not permitted for the reason that it requires two current equatorial bonds to turn axial and still remain connected by a two-carbon chain without subjecting the ring to strain, which is geometrically not possible.




**12a** **12b** **12c**

The three different representations of *cis*-decalin are **13a**–**c**. Of the two red bonds, one is axial and the other equatorial to the ring. The same is true of the two blue bonds in the other ring. Consequently, one of the two hydrogen atoms on the ring junction is axial and the other equatorial to any one of the two rings. Note the three distinct gauche interactions present in the representation **13c**. These are the interactions across C1–C9–C10–C5, C1–C9–C8–C7, and C5–C10–C4–C3 for having the C1- and C5-methylene groups axial to the other ring system. These gauche interactions may be traced in other representations as well. Unlike *trans*-decalin, ring flip in *cis*-decalin is allowed and it reduces the energy of the system by 0.4 kcal/mol. This lowering of energy is called entropy gain. Thus, *trans*-decalin is more stable than *cis*-decalin by $(3 \times 0.9) - 0.4 = 2.3$ kcal/mol. The conformational mobility in *cis*-decalin is only slightly below that of cyclohexane.




**13a** **13b** **13c**

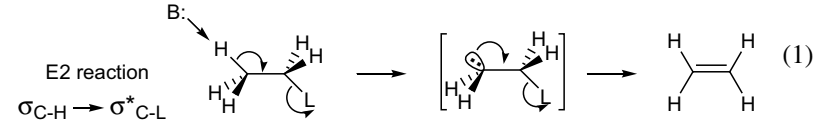
## 2 Influence of Stereoelectronic Effects on Reactions

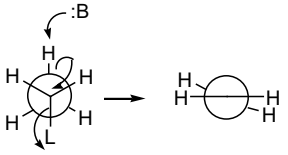
We will first define the stereoelectronic effect by following the progress of the E2 (elimination bimolecular) reaction shown in Eq. 1. The following points are to be noted:

(a) The axis of electron pair orbital on base B is collinear with $\sigma_{C–H}$ to allow the abstraction of H as $H^+$. It is a typical $S_N2$ reaction, wherein a base attacks H from one side and the $\sigma_{C–H}$ electron pair is released from the other side.

(b) The resultant carbanion has transient life as it undergoes another $S_N2$ reaction, wherein the above electron pair orbital attacks the carbon bearing the leaving group L, as shown, and an olefin is formed.

(c) It must be noted that the axes of the carbanion electron pair orbital (*n*) and the electron-deficient $\sigma_{C–L}$ bond in the transient species are antiperiplanar, leading to strong $n \rightarrow \sigma^*_{C–L}$ interaction. An interaction of this sort is termed an *anomeric effect* in the study of sugars and *stereoelectronic effects* elsewhere. It may also be called the *antiperiplanar effect* for the antiperiplanar disposition of the electron pair orbital (or electron-rich bond) and the electron-deficient bond.



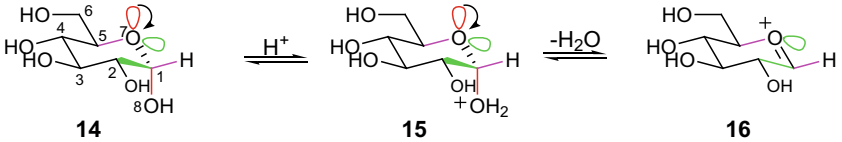



(d) For the E2 reaction to succeed, $\sigma_{C-H}$ and $\sigma_{C-L}$ bonds must be antiperiplanar to each other, as shown in Eq. 1. This structural feature allows $\sigma_{C-H} \rightarrow \sigma^*_{C-L}$ interaction, which is responsible for the enhanced acidity of the hydrogen to allow its abstraction as $H^+$ by the base in the rate-determining step. The rate of E2 reaction is, therefore, dependent on the concentrations of both the substrate and the base. The E2 reaction using the Newman projection is shown in Eq. 3.

(e) In contrast to the E2 reaction, the rate of the E1cB reaction (elimination unimolecular through the conjugate base) is dependent only on the concentration of the carbanion formed from deprotonation of the substrate; see Eq. 2. To begin with, the $\sigma_{C-H}$ bond is not required to be antiperiplanar to the $\sigma_{C-L}$ bond. The resultant carbanion (conjugate base of the substrate) survives until its collapse to olefin by ejecting the leaving group through a transition state (TS) similar to that for the E2 reaction. The attainment of the TS requires rotation around the $\sigma_{C-C}$ bond.

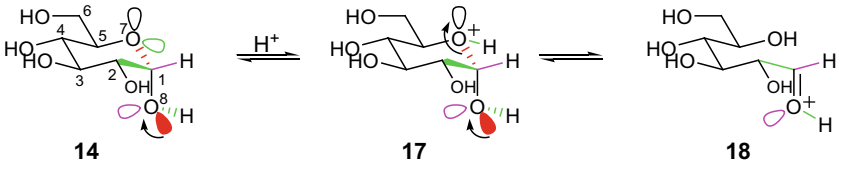
From the above discussions of E2 and E1cB reactions, it is clear that an electron-rich bond such as $\sigma_{C-H}$ or an electron pair orbital antiperiplanar to an electron-deficient bond such as $\sigma_{C-L}$ constitutes an energy-lowering prospect. This is necessarily because of the partial electron donation from the electron-rich bond or electron pair orbital to the anti-bonding orbital corresponding to the electron-deficient bond $\sigma_{C-L}$. It lowers the anti-bonding orbital and raises the corresponding bonding orbital on the energy scale. Consequently, the bonding orbital is weakened and its cleavage takes place with enhanced ease. We shall now exploit this information to understand the reactivity profiles of a select class of molecules to strengthen our knowledge base.

Note the antiperiplanar relationship of the axial electron pair orbital on the ring oxygen O7 and $\sigma_{C1-O8}$ bond in (α)-D-glucopyranose **14**. This relationship leads to $n \rightarrow \sigma^*_{C1-OH}$ interaction, also called the *anomeric effect*. The consequence of this interaction is the facile cleavage of the $\sigma_{C1-OH}$ bond after protonation, leading to the transformation **15** → **16**, as shown in Eq. 4. Likewise, we notice an electron pair orbital on O8, which is antiperiplanar to the $\sigma_{C1-O7}$ bond. This relationship results in yet another anomeric effect, called the *exo-anomeric effect* in distinction from the above *anomeric effect* that originates from the ring oxygen. The consequence of the exo-anomeric effect is smooth cleavage of the $\sigma_{C1-O7}$ bond on the protonation of ring oxygen and the transformation **17** → **18** is achieved, as shown in Eq. 5. However, this cleavage will be less facile than the cleavage in Eq. 4 for additional energy requirements for ring-cleavage.

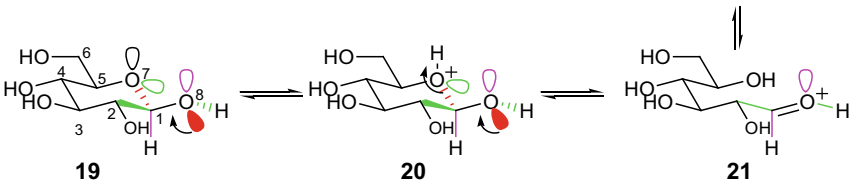



**14** **15** **16**

(4)




(5)




(6)

An electron pair orbital that is not engaged in an anomeric effect is more electron-rich than the one which is and, hence, vulnerable to faster protonation. This translates into the understanding that two electron pair orbitals on the same heteroatom are likely to be different from each other on account of whether or not they are engaged in an anomeric effects.

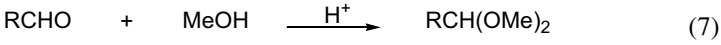
We now consider β-(D)-glucose **19**. It turns out from the given color coding that neither of the two electron pair orbitals on ring oxygen is antiperiplanar to the $\sigma_{C1-O8}$ bond. The cleavage of the $\sigma_{C1-OH}$ bond after protonation will, therefore, occur without anomeric assistance. In other words, this cleavage will be slower than the cleavage **15** → **16** shown in Eq. 4. Alternatively, O8 consists of an electron pair orbital antiperiplanar to the $\sigma_{C1-O7}$ bond. Therefore, the $\sigma_{C1-O7}$ bond can cleave after protonation of O7 with anomeric assistance and lead to the transformation **20** → **21**, as shown in Eq. 6. The oxonium ion **21** is a rotamer of **18**.

The species **18** is in equilibrium with α-(D)-glucose **14** and β-(D)-glucose **19** via **21**. Thus, under slightly acidic conditions, α-(D)-glucose and β-(D)-glucose will be predicted to equilibrate with each other and lead to what we popularly call *mutarotation*. The specific optical rotation of α-D-glucose is different from that of β-D-glucose. Thus, commencing from α-(D)-glucose in an aqueous solution, the optical rotation will change with time and become static at equilibrium. Of course, the equilibrium will be established fast when one begins with α-(D)-glucose because the changes **14** → **17** → **18** → **21** lead to relief from the steric strain arising from the axial OH group on the anomeric carbon C1.

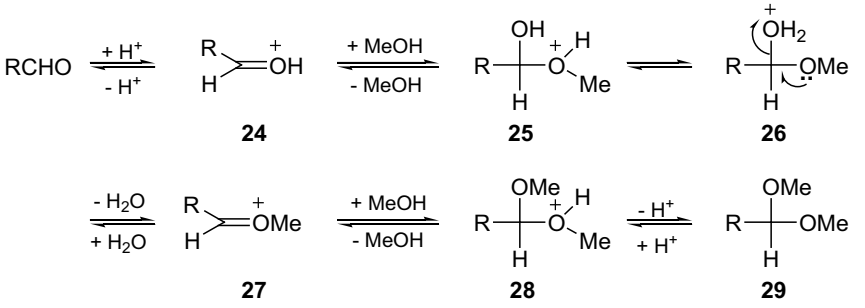
Alternatively, the oxonium ion **16** could be attacked by water from both axial and equatorial sites to generate, respectively, α-D-glucose and β-D-glucose. Of course, the axial attack will be favored over the equatorial attack due to the stabilizing nature of the resultant anomeric effect. In the transformation **16** → **14**, water attacks the oxonium ion on the axial face and the electron pair of the cleaved π bond ends up axial on the ring oxygen to exert an anomeric effect on the very $\sigma_{C-O}$ bond that is formed in the process. An attack from the equatorial site will generate **19**, where the formed $\sigma_{C-O}$ bond is not under the anomeric effect of any of the electron pair orbitals

on ring oxygen. Both the formation and cleavage of a bond under anomeric control are more facile than when the anomeric effect is absent. We shall continue to learn this aspect through the discussions below.

We know that the acid-catalyzed reaction of an aldehyde with an alcohol under dehydrating conditions generates an acetal, as shown in Eq. 7. The progress of the reaction is shown below in Eq. 7. One water molecule is released in the step **26** → **27** for every molecule of the acetal formed. Since the proton used at the beginning of the reaction is released in the end, the reaction is catalytic in the proton source. It must also be noted that each step leading to the acetal is reversible, which necessitates the removal of water from the reaction mixture to drive it to completion. The proton transfer from one oxygen to the other in the species **25**, leading to **26**, is very facile for the geometrical closeness of the two oxygen atoms for being located on a tetrahedral carbon.

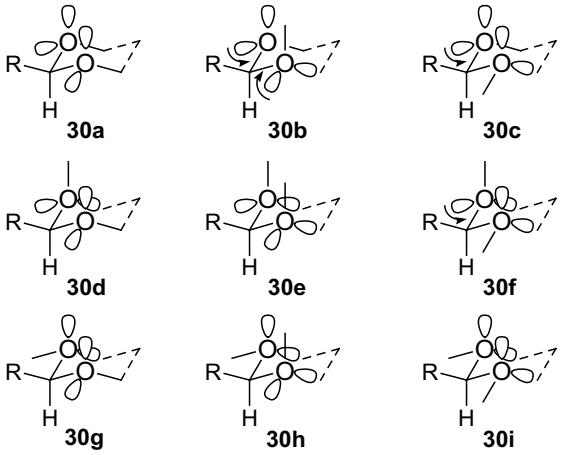



**22** **23** (7)




**24** **25** **26** **27** **28** **29**

The true joy is in considering the reverse of acetal formation, i.e., acid hydrolysis of an acetal within the ambit of stereoelectronic effects to explore the reactivity characteristics. We begin by understanding the conformational profile and the associated conformational effects by representing the acetal in such a way that it appears to be part of the cyclohexane chair. We have already understood the geometrical relationships of various cyclohexane ring bonds and also the bonds on the ring.

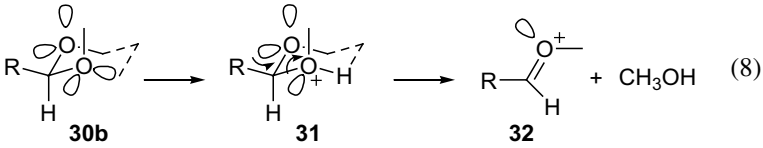



The acetal $RCH(OMe)_2$ can adopt nine conformers **30a–i**. Ignore the broken bonds that are used to allow the reader a quick conformational match with that of the cyclohexane chair to ascertain the geometrical relationships rather conveniently. The following points must be noted:

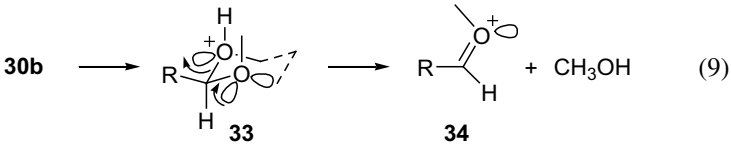
(a) The conformers **30a** and **30e** have two methyl groups within the van der Waals distance and, hence, their contributions to the overall equilibrium will be small, if not zero. We can, therefore, eliminate these conformers from further discussion.
(b) The conformers **30b** and **30d**, **30c** and **30g**, and **30f** and **30h** are mirror images and, thus, we consider only one from each pair.
(c) We are left with four distinct conformers, **30b**, **30c**, **30f** and **30i**, to take forward to consider acid hydrolysis. The relative contributions of these conformers may be estimated from the realization that they are laced with two, one, one, and zero stereoelectronic effects, respectively. The conformers **30b** and **30i** are, respectively, the most and least contributing. The conformers **30c** and **30f** contribute at the medium level.

The acid hydrolysis of the conformer **30b** is presented in Eqs. 8 and 9. The following specific points are to be noted:

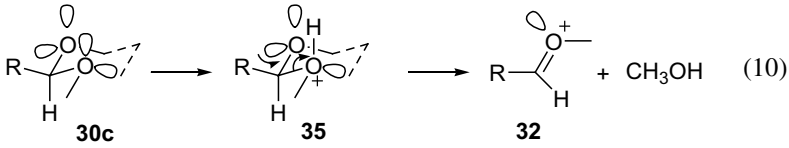
(a) Of the two oxygen atoms in **30b**, each has one electron pair orbital that does not participate in any stereoelectronic effect. Protonation of such an electron pair on the front oxygen leads to **31** that can undergo $\sigma_{C–O}$ bond cleavage under the anomeric effect arising from the other oxygen, as shown, to generate methanol and the oxonium ion **32**.
(b) Likewise, protonation of the rear oxygen followed by cleavage of the $\sigma_{C–O}$ bond, as in Eq. 9, will generate the oxonium ion **34** and methanol. The oxonium ions **32** and **34** are of *E*- and *Z*-configurations, respectively.



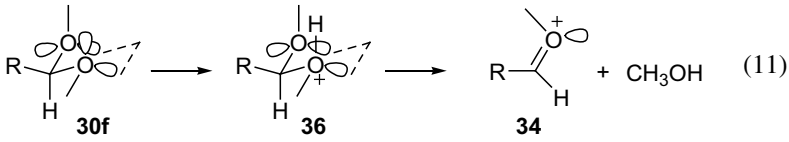

(8)




(9)




(10)

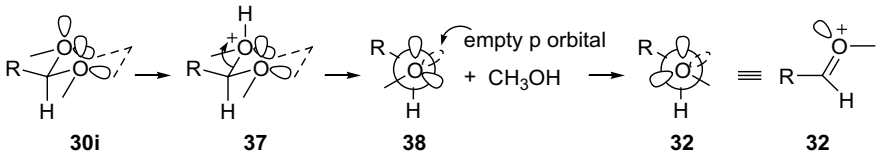



(11)

(c) With R that is small in size and, thus, marginally contributing to van der Waals repulsion with *O*-methyl in **34**, both the cleavage pathways will be expected to be, more or less, equally facile. However, with a large R, the pathway shown in Eq. 8 will predominate.

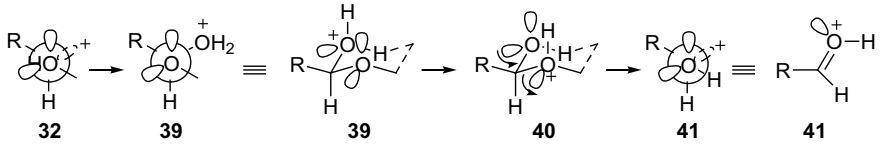
The acid hydrolyses of the conformer **30c** and **30f** are shown in Eqs. 10 and 11, respectively. Protonation of the front oxygen in **30c** followed by cleavage of the $\sigma_{C-O}$ bond under stereoelectronic control of the rear oxygen will generate **32**. Cleavage of the rear $\sigma_{C-O}$ bond after protonation will be relatively inefficient because it is not supported by any stereoelectronic effect arising from the front oxygen. Likewise, **30f** can be argued to generate **34**.

Finally, we discuss the cleavage of the conformer **30i** that lacks a stereoelectronic effect. The molecule has mirror plane symmetry and, hence, either $\sigma_{C-O}$ bond can cleave after protonation. However, this cleavage will take place without stereoelectronic assistance and the species **38** formed, as shown in Eq. 12. The most notable feature of **38** is the axis of the empty orbital which is antiperiplanar to the $\sigma_{O-C}$ bond and not to an electron pair orbital on the oxygen. The species **38** is, therefore, a high-energy species. Conformational change, while keeping methyl as far from R as possible (anticlockwise rotation) will allow the formation of the stable species **32** as it has an oxygen electron pair orbital antiperiplanar to the empty orbital required for oxonium ion formation. Since the formation of a high-energy species is involved, the conformer **30i** may be safely predicted to be a neutral conformer or a conformer that is resistant to hydrolysis.

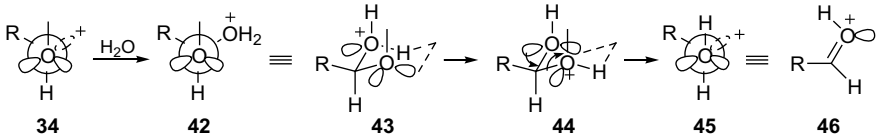



(12)

We have learnt so far that protonation of one of the two oxygen atoms followed by its cleavage in the reacting acetal conformers generates the oxonium ion **32** and/or **34**, depending upon the size of R. We will now consider reactions of these oxonium ions with water. The reaction of **32** is outlined in Eq. 13. The capture of the empty orbital, of course under the stereoelectronic effect of an oxygen electron pair, generates **39**, wherein the antiperiplanar relationship of R with methyl is firmly retained. Proton transfer from one oxygen to the other, by taking advantage of 1,3-diaxial proximity, will generate **40**. Now, cleavage of the $\sigma_{C-O}$ bond under the stereoelectronic effect, as shown, will generate **41** which is actually the protonated aldehyde. Loss of proton from **41** to another acetal molecule or even water, which is present in large excess, will generate RCHO, the product of hydrolysis. Considering a similar pathway, the reaction of **34** with water is shown in Eq. 14.




(13)



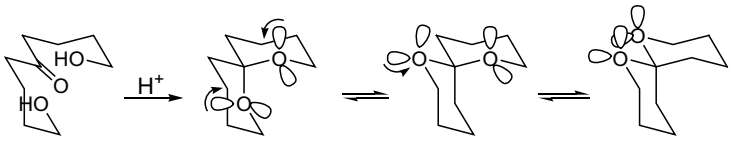

(14)

We have noted above that one of the two electron pair orbitals on the same oxygen is engaged in stereoelectronic effect and the other is not. The electron density in the latter orbital is, therefore, less than the former. Consequently, the latter orbital is more basic and, thus, its protonation will be kinetically favored.

The stereoelectronic effect is a stabilizing effect as it lowers the energy of the system by 1.4 kcal/mol. This effect originates from the interaction between oxygen electron pair orbital and the $\sigma_{C-O}$ bond. The following interaction energies must be noted to begin calculating the relative energies of the conformers **48a**, **48b**, and **48c**, Eq. 15, to enable us to predict the predominant conformer at the equilibrium.

(a) An axial methylene group on the cyclohexane ring contributes equivalent to two butane gauche interactions, i.e., $2 \times 0.9 = 1.8$ kcal/mol. The energy of the system is raised.

(b) An axial oxygen atom on the cyclohexane ring contributes $2 \times 0.4 = 0.8$ kcal/mol (1,3-diaxial steric interaction between oxygen and hydrogen = 0.4 kcal/mol) and the energy of the system is raised.




**47** **48a** **48b** **48c** (15)

$\mathbf{E_{48a}}$: -(2 × 1.4) + (2 × 0.4) + (2 × 0.4) = -1.2 kcal/mol

$\mathbf{E_{48b}}$: -1.4 + (2 × 0.9) + (2 × 0.4) = 1.2 kcal/mol

$\mathbf{E_{48c}}$: (2 × 0.9) + (2 × 0.9) = 3.6 kcal/mol

Now, we can analyze the relative energetics of the above conformers as follows:

(a) The conformer **48a** benefits from two stereoelectronic effects that contribute $-(1.4 \times 2) = -2.8$ kcal/mol. Each ring in this conformer also has an oxygen atom axial to the other ring and it contributes $2 \times (2 \times 0.4) = 1.6$ kcal/mol. The net change in the relative energy, therefore, is $-2.8 + 1.6 = -1.2$ kcal/mol.

(b) The conformer **48b** has only one stereoelectronic effect to contribute $-1.4$ kcal/mol. One ring has an oxygen atom axial to the other ring and this will contribute $2 \times 0.4 = 0.8$ kcal/mol. This conformer also has one methylene group axial to the other ring to contribute $2 \times 0.9 = 1.8$ kcal/mol. Thus, the net change in the relative energy is $-1.4 + 0.8 + 1.8 = 1.2$ kcal/mol.

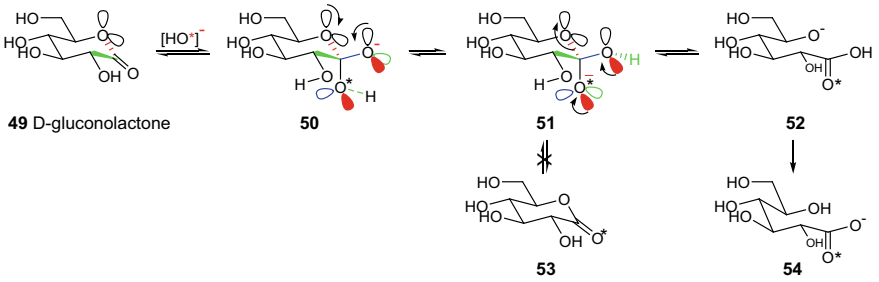
(c) The number of stereoelectronic effects in conformer **48c** is nil. However, each ring has one methylene group axial to the other ring to collectively contribute $2 \times (2 \times 0.9) = +3.6$ kcal/mol. Thus, the net change in relative energy is 3.6 kcal/mol.

It is clear that the conformer **48a** will predominate and **48c** contribute insignificantly to the equilibrium mixture. In other words, 1,9-dihydroxy-5-nonanone **47** will generate, when subjected to intramolecular acetal formation reaction under acidic conditions, an equilibrium mixture of three spiroacetals, wherein **48a** predominates.

In the discussion of acid hydrolysis of acetals, cleavage of a $\sigma_{C-O}$ bond with the assistance of a single stereoelectronic effect was considered facile. However, the leaving species was positively charged, which rendered the σ bond weak. Must the leaving species be neutral, two stereoelectronic effects are required for cleavage. We will demonstrate the essentiality of this requirement by considering the reaction hydroxide ion with D-gluconolactone. *To a good approximation, the weakness rendered to a $\sigma_{C-O}$ bond by a positive charge on the oxygen is equal to the weakness rendered by one stereoelectronic effect.*

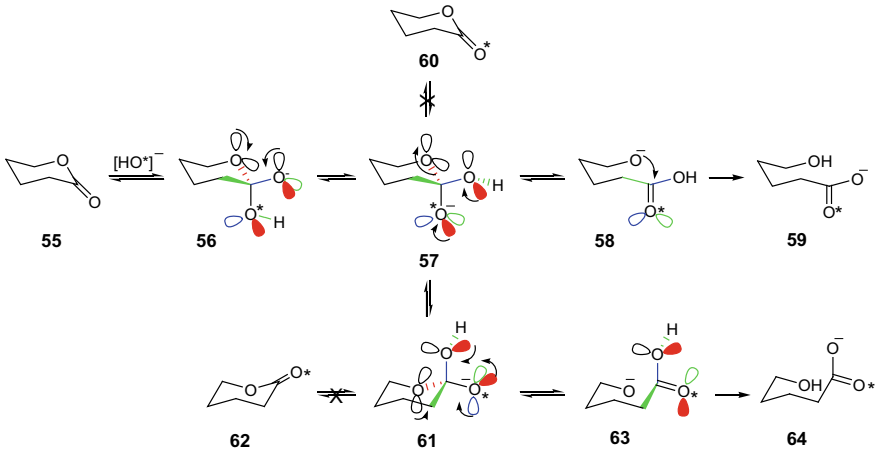
The reaction of D-gluconolactone **49** with $O^{18}$-labeled hydroxide ion under stereoelectronic control (axial attack) will furnish **50**. The new $\sigma_{C-O^*H}$ bond is antiperiplanar

not only to an electron pair orbital on the resultant oxy anion but also to the axial electron pair orbital on the ring oxygen. This reaction is reversible because $\sigma_{C-O^*H}$ can cleave with the same ease as it was formed in the first place, being antiperiplanar to two electron pair orbitals. Intramolecular proton transfer **50** → **51** is also reversible. The $\sigma_{C-OH}$ bond in **51** cannot cleave because it is antiperiplanar to only one electron pair orbital of oxy ion $[O^*]^-$ and, thus, **53** that retains the labeled oxygen will not form. In other words, if the hydrolysis reaction is interrupted (quenched before completion by an aqueous acid) and the unreacted D-gluconolactone is examined for the presence of $O^{18}$, it will be found absent.




However, the ring $\sigma_{C-O}$ bond in **51** is under stereoelectronic control of two electron pair orbitals (solid red) and, hence, it can cleave to generate **52**. The transformation **51** → **52** is also reversible because the intramolecular attack of oxy ion on the carbonyl group to result in **52** → **51** conversion is just about as efficient as the conversion **51** → **52** for exactly the same reasons. Intramolecular proton transfer from carboxylic acid to the oxy ion in **52** will generate **54**. The reversal **54** → **52** is difficult because the carboxylate ion is resonance-stabilized and, hence, its electrophilic character is considerably compromised.

D-Gluconolactone is an example of *E*-ester wherein the carbonyl oxygen and the substituent on ethereal oxygen are anti to each other across the intervening $\sigma_{C-O}$ bond. In the hydrolysis of D-gluconolactone, we did not consider the ring flip from one chair to the other because all the equatorial bonds will turn axial to cause large steric interactions. To allow for such a conformational flip for the consideration of carbonyl oxygen exchange during *E*-ester hydrolysis, we discuss below the simplest instance of δ-lactone **55**.




An argument similar to the one for the hydrolysis of D-gluconolactone leads us to **59** as the final product, wherein the label $O^{18}$ is incorporated. The transformation **57** → **60** is not allowed for the lack of the requisite number of stereoelectronic effects. Assuming that the ring flip **57** → **61** competes with the cleavage **57** → **58** and, thus, **61** is indeed formed, we consider its fate as follows:

(a) The $\sigma_{C–OH}$ bond in **61** is antiperiplanar to two electron pair orbitals, one on each of the other two oxygen atoms. It renders the cleavage of the$\sigma_{C–OH}$ bond facile, and the $O^{18}$-containing δ-lactone **62** is formed.

(b) A close inspection of **61** reveals an alternate possibility. Like the $\sigma_{C–OH}$ bond, the ring $\sigma_{C–O}$ bond is also antiperiplanar to two electron pair orbitals. The ring $\sigma_{C–O}$ bond could, therefore, also cleave with as much ease as the $\sigma_{C–OH}$ bond.

(c) There is a characteristic difference between the two processes above. The cleavage of the ring $\sigma_{C–O}$ bond leads to the formation of **63**, wherein the carboxylic acid function is in the *Z*-configuration and a *Z*-carboxylic acid (or ester) benefits from two stereoelectronic effects unlike an *E*-ester such as **62** that benefits from only one such effect (vide infra). This allows the TS energy for the change **61** → **63** to be smaller than **61** → **62**. The pathway **61** → **63** → **64** predominates. The label is incorporated in the carboxylic acid product **64**, and the δ-lactone **62** with the $O^{18}$ label is not formed.

(d) Overall, even if the ring flip **57** → **61** competes with the cleavage **57** → **58**, carbonyl oxygen exchange is not likely to occur. *The E-esters indeed do not undergo carbonyl oxygen exchange during base hydrolysis.*

Acyclic esters such as **65** necessarily exist in *Z*-configuration and undergo carbonyl oxygen exchange. The $\sigma_{C–OH}$ bond in the tetrahedral conformer **67**, obtained on proton exchange in **66**, is antiperiplanar to two electron pair orbitals, one on each of the other two oxygen atoms, to allow its facile cleavage and $O^{18}$-incorporated *Z*-ester **68** is formed, as shown in Eq. 16. Of course, cleavage of the $\sigma_{C–OMe}$ bond under the assistance of two stereoelectronic effects can also take place and lead to $O^{18}$-containing carboxylic acid.