Veejendra K. Yadav

Steric and Stereoelectronic Effects in Organic Chemistry

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To Arpita, Dhananjay and Dhruv with love

Preface

The aim of this book is to offer a decent understanding of the principles of steric and stereoelectronic effects in organic chemistry and their consequences on product selectivity and reaction rates. This book differs from most other books of the same level. In this book, strong emphasis is placed on logical evolution of the subject in a streamlined manner to aid structured comprehension of the intricacies. This book is intended for the honors undergraduate and graduate students, and the teachers.

The discussion is spread over seven chapters. Chapter 1 lays the stress on the important aspects of steric and stereoelectronic effects and their control on the conformational profile and reactivity features of the molecules. Chapter 2 describes the geometrical requirements for reactions at saturated and unsaturated carbons, and the resultant stereochemical features. Application of the said geometrical requirements to intramolecular instances results in remarkable control on diastereoselectivity. Chapter 3 deals with the facial selectivity of nucleophilic additions to acyclic and cyclic carbonyl compounds, and it explains how the steric and stereoelectronic effects control the same through elaborate discussions. The selectivity profile is explained using models such as Cram's model, Anh–Felkin modification of Cram's model, Houk's transition structure and electrostatic models, Cieplak's $\sigma \rightarrow \sigma^{*}$# model, and cation coordination model. Chapter 4 comments on allylic strain and its effect on the conformational profile and related stereochemical outcomes of reactions. The high diastereoselectivity observed in the reactions of Evans enolatesis solely on account of allylic strain. The conservation of orbital symmetry rules is presented in Chap. 5. After defining the bonding and antibonding orbitals of different types, reactions such as $\pi^2 + \pi^2, \pi^4 + \pi^2$, and electrocyclic processes have been used to demonstrate the application of the rules. Chapter 6 is an amalgamation of the conservation of orbital symmetry rules and orbital overlap effect, which serves as a very powerful tool to reliably predict the stereochemical course of pericyclic reactions. It is demonstrated by examples how the orbital overlap factor allows one of the otherwise two symmetry-controlled pathways to predominate. Chapter 7 is a must read to understand some of those control elements that did not find mention in the earlier chapters. The prominent among these elements are

spiroconjugation, periselectivity, torquoselectivity, α-effect, Hammett constants, Hammond postulate, and Curtin–Hammett principle. A set of questions are provided at the end to challenge the reader by allowing an evaluation of the comprehension level.

The book is based mainly on the lecture notes prepared for the classes at IIT Kanpur. I am grateful to the authors of many books that I have used in preparing the notes. Important among these books are: (a) Stereoelectronic Effects in Organic Chemistry by Pierre Deslongchamps, (b) Molecular Orbitals and Organic Chemical Reactions by Ian Fleming, (c) Modern Physical Organic Chemistry by Eric V. Anslyn and Dennis A. Dougherty, (d) Mechanism and Theory in Organic Chemistry by Thomas H. Lowry and Kathleen S. Richardson, and (e) The Physical Basis of Organic Chemistry by Howard Maskill. I thank Prof. J.N. Moorthy for reading the chapters critically and suggesting changes to improve the quality of presentation. I thank Prof. M.L.N. Rao for his pleasant company and stimulating discussions over numerous coffee sessions. Last but not least, I thank Dr. Arpita Yadav, my better half, and Dhananjay and Dhruv, our sons, for bearing with me while I have been busy with drawing the structures and also for their never-ending enthusiasm and support.

I would appreciate and gratefully acknowledge criticism, suggestion for improvement, and detection of errors from the readers. I thank the Publishers, Springer (India) Pvt. Ltd., for bringing out the book in the present form.

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 the late 1990. Over the years, he rose through ranks and became full professor in 2001. He has taught both undergraduate and postgraduate students at IITK over the past 25 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, and computational-cum-experimental investigation of facial selectivity. He has two international patents and 80 research papers in peer-reviewed journals to his credit. More details may be found on the link: http://home.iitk.ac.in/∼vijendra.

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

Abstract This chapter emphasises on the important aspects of steric and stereoelectronic effects and their control on the conformational and reactivity profiles. The conformational effects in ethane, butane, cyclohexane, variously substituted cyclohexanes, and *cis*- and *trans*-decalin systems allow a thorough understanding. Application of these effects to E2 and E1cB reactions followed by anomeric effect and mutarotation is discussed. The conformational effects in acetal-forming processes and their reactivity profile, carbonyl oxygen exchange in esters, and hydrolysis of orthoesters have been discussed. The application of anomeric effect in 1,4-elimination reactions, including the preservation of the geometry of the newly created double bond, is elaborated. Finally, a brief discussion on the conformational profile of thioacetals and azaacetals is presented.

Keywords Conformational profile · Steric effect · E2 reaction · E1cb reaction · Anomeric effect · Mutarotation · Acetal hydrolysis · Acetal formation · Carbonyl oxygen exchange in esters · Ozonation of acetals · Orthoester and hydrolysis · Numerical value of anomeric effect · Relative energy of acetals · 1,4-elimination · Mono and dithoacetals · Mono and diazaacetals

1 Influence of Steric Effects on Structures

With all the substituents as hydrogen, consider the staggered and eclipsed conformations of ethane **1** as shown below. The staggered conformation is more stable than the eclipsed conformer by 3.0 kcal mol^{-1}. The electron pairs of the eclipsed bonds repel each other to raise the energy of the system by 1.0 kcal mol^{-1}. Three such interactions make up to 3.0 kcal mol^{-1}.

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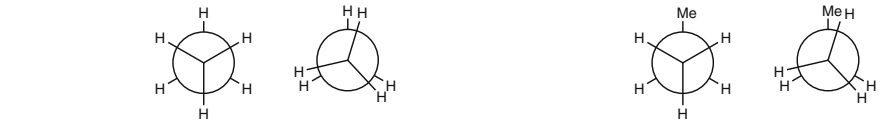
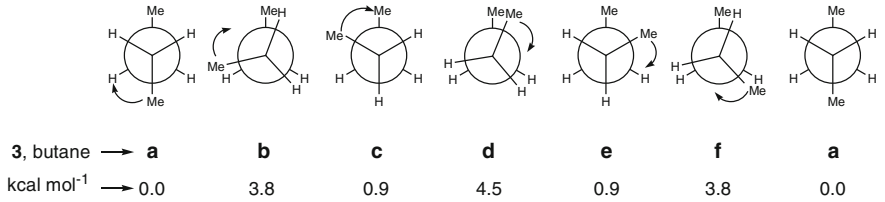
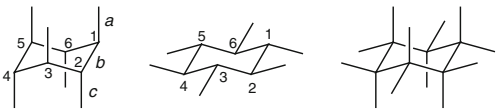


With one of the hydrogen atoms replaced by methyl, we arrive at the staggered and eclipsed conformations of propane **2**. Other than the three repulsive electron pair–electron pair interactions, each contributing 1.0 kcal mol^{-1}, there is also the methyl-hydrogen van der Waals repulsion (steric interaction) that contributes 0.4 kcal mol^{-1} in the eclipsed conformer. Thus, the eclipsed conformer is less stable by (3 × 1.0) + 0.4 = 3.4 kcal mol^{-1} than the staggered conformer. On either side of the methyl group in the staggered conformer, there is a hydrogen atom on the front carbon with a dihedral (torsion) angle of 60°. Methyl and hydrogen are said to be gauche to each other with no repulsive interaction between them. However, the gauche methyl–methyl interaction contributes by 0.9 kcal mol^{-1}. Also, the eclipsing methyl–methyl van der Waals repulsion is estimated to be 1.5 kcal mol^{-1}. One encounters the last two interactions below in the discussion of conformations of butane.



Different conformers **3a**–**f** of butane **3** across the central σ_{C-C} bond are shown above. Beginning from the staggered conformer **3a** that has two methyl groups with torsion angle of 180°, one can write the other important conformers by rotation about the central σ_{C-C} bond by 60° each time in the clockwise manner as shown. Note that the conformers **3b** and **3f**, and **3c** and **3e** are one and the same as far as their energies are concerned. There are no issues related to either eclipsing electron pair–electron pair repulsion or van der Waals repulsion in **3a**. Hence, **3a** is the most stable conformer and let us assume its energy as 0.0 kcal mol^{-1}. Now, we can calculate the energies of other conformers as follows: **3b** and **3f**: 3.8 kcal mol^{-1}; **3c** and **3e**: 0.9 kcal mol^{-1}; **3d**: 4.5 kcal mol^{-1}. All these values are, in fact, so small that butane exists as an equilibrium mixture of all the conformers at STP (standard temperature and pressure). The equilibrium distribution, as expected, is a function of the relative energies; the more stable a conformer, the more is its contribution.

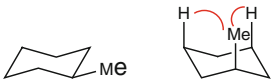


4a **4b** **4**

Consider the structure **4a** for cyclohexane. The axial bonds on any two adjacent ring positions, such as C1 and C2, 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', the 'parallel', and the 'same plane' are put together is termed 'antiperiplanar'. So, the axial bonds on two adjacent cyclohexane ring positions are antiperiplanar.

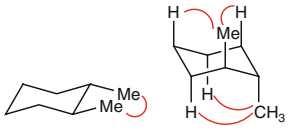
The equatorial bonds on any two consecutive ring positions, such as C1 and C2, are gauche to each other with a torsion angle of 60° as shown in **4b**. With these substituents as methyl, the situation is exactly the same as in the gauche butane conformers **3c** and **3e**. Therefore, this will raise the energy by 0.9 kcal mol^{-1}. Another important structural feature stems from the observation that an equatorial bond is antiperiplanar to two ring bonds. For instance, the 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 made of the orientations of the bonds on C3 and C6; other than being antiperiplanar to each other across a hypothetical $\sigma_{C3–C6}$ bond, both the bonds are antiperiplanar to $\sigma_{C1–C2}$ and $\sigma_{C4–C5}$ as well.

A good knowledge of the structural relationship of axial and equatorial bonds on cyclohexane ring will help us understand the underlying stereoelectronic and conformational effects on reactivity issues. Methylcyclohexane can adopt, in principle, the two chair conformations **5a** and **5b**. The conformer **5b** is obtained from **5a** after ring flip. The conformer **5a** is fully devoid of van der Waals interactions. However, one discovers two butane gauche interactions in the conformer **5b** as shown, each raising the energy by 0.9 kcal mol^{-1}. Thus, **5b** is less stable than **5a** by $2 \times 0.9 = 1.8$ kcal mol^{-1}. In other words, mono-substituted cyclohexane ring should prefer the conformer that allows the substituent to occupy equatorial position.



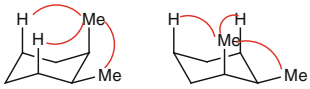
5a **5b**

Consider *trans*-1,2-dimethylcyclohexane **6**. In the conformer **6a**, the two equatorial methyl groups are gauche to each other, which will raise the energy by 0.9 kcal mol^{-1}. In the conformer **6b**, the product of chair inversion of **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^{-1}. The conformer **6a**, therefore, is more stable than **6b** by $3.6 - 0.9 = 2.7$ kcal mol^{-1}. Thus, *trans*-1,2-disubstituted cyclohexane must prefer the conformer in which both the substituents occupy equatorial positions.



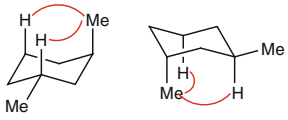
6a **6b**

Consider *cis*-1,2-dimethylcyclohexane. In either of the two conformers **7a** and **7b**, one methyl is axial and the other equatorial. The two methyl groups are mutually gauche to each other and the ax-methyl is further gauche to two axial H 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 the equatorial position.



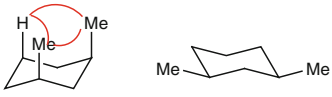
7a **7b**

Trans-1,3-dimethylcyclohexane can adopt either of the conformers **8a** and **8b**. In both, one methyl is axial and the other equatorial. Both the conformers, therefore, are one and the same. The equatorial methyl does not involve in any van der Waals interaction. However, 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^{-1}.



8a **8b**

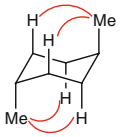
Cis-1,3-dimethylcyclohexane can adopt two conformers. In the conformer **9a**, both the methyl groups are axial and gauche to each other. Further, each methyl group is gauche to an axial hydrogen atom as shown. The total increase in the energy of this conformer will therefore be $2.5 + 0.9 + 0.9 = 4.3$ kcal mol^{-1}. In **9b**, the two 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^{-1}. Also, the more stable *cis*-1,3-dimethylcyclohexane conformer **9b** is more stable than *trans*-1,3-dimethylcyclohexane **8a/8b** by 1.8 kcal mol^{-1}.



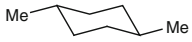
9a **9b**

The two possible conformers of *trans*-1,4-dimethylcyclohexane are **10a** and **10b**. From the foregoing discussions, it is obvious that the conformer **10b** is more

stable than the conformer **10a** by $2 \times (2 \times 0.9) = 3.6$ kcal mol^{-1}. In **10a**, each axial methyl group is engaged in two gauche interactions as shown.

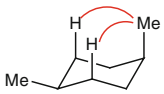


10a

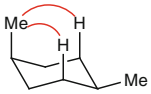


10b

Each conformer of *cis*-1,4-dimethylcyclohexane, **11a** or **11b**, has one methyl group axial and the other equatorial. The axial methyl group is engaged in two gauche interactions as shown, raising the energy of the system by $2 \times 0.9 = 1.8$ kcal mol^{-1}. 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^{-1}.

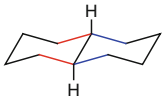


11a

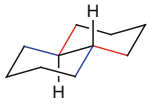


11b

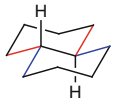
There are three different representations of *trans*-decalin, **12a–c**. Note that the bonds in both red and blue colors are equatorial to the other ring, leaving the hydrogen atoms on the ring-junctions axial. We have previously understood that the 1,2-diequatorial substituents are gauche to each other. Two such interactions raise the energy of the system by 1.8 kcal mol^{-1}. These interactions are present in *cis*-decalin as well, but now between one axial and one equatorial substituent (see below). For the purpose of relative energy calculation, these gauche interactions are therefore not counted. The ring flip in *trans*-decalin is not permitted for the reason that it requires two current equatorial bonds to turn axial and then get connected by a two carbon chain without subjecting the ring to strain. This is just not possible.



12a



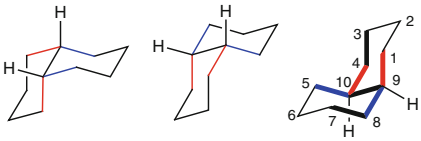
12b



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 other 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 one of the two rings. One may note that the three gauche interactions present in *cis*-decalin are distinct from those present in *trans*-decalin. 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 also. Unlike in *trans*-decalin, ring flip in *cis*-decalin, which reduces

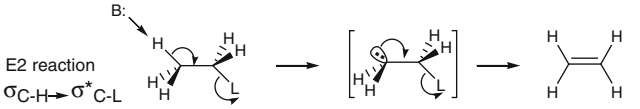
the energy of the system by 0.4 kcal mol^{-1}, is allowed. This energy corresponds to entropy. Thus, *trans*-decalin turns out to be more stable than *cis*-decalin by $(3 \times 0.9) - 0.4 = 2.3$ kcal mol^{-1}. The conformational mobility in *cis*-decalin is only slightly below that of cyclohexane.



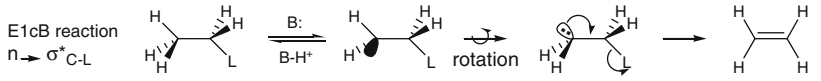
13a **13b** **13c**

2 Influence of Stereoelectronic Effects on Reactions

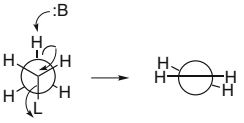
Let us first define stereoelectronic effect. In Eq. 1, we note the progress of an E2 (elimination bimolecular) reaction. The axis of the electron pair orbital of the base B is collinear with σ_{C-H} to allow abstraction of H as H^+. It is like S_N2 reaction, wherein a base attacks H from one side and the electron pair of σ_{C-H} bond leaves from the other side. The resultant carbanion has only a transient life, if at all, as it undergoes yet 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. It may be noted that the axes of the carbanion electron pair orbital and the electron-deficient σ_{C-L} bond in the transient species are antiperiplanar, leading to the possibility of a strong $n \rightarrow \sigma^*_{C-L}$ interaction. An interaction of this sort is termed *anomeric effect* in the study of sugars and *stereoelectronic effect* elsewhere. One may choose to call it *antiperiplanar effect* as well just because the said stereoelectronic effect is in place necessarily because of the antiperiplanar disposition of the electron pair orbital or electron-rich bond and the electron-deficient bond.



(1)



(2)



(3)

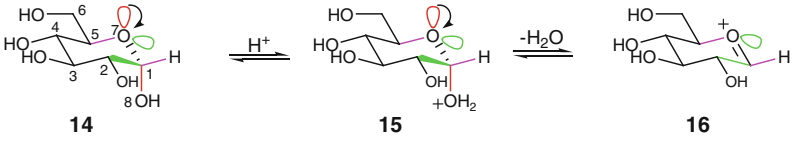
For the E2 reaction to succeed, σ_{C-H} and σ_{C-L} bonds must be antiperiplanar to each other as shown. This structural feature allows for $\sigma_{C-H} \rightarrow \sigma^*_{C-L}$ interaction which is responsible for the enhanced acidic character of the hydrogen to allow its

abstraction as H^+ by the base in the rate determining step. The rate of the E2 reaction is therefore dependent on the concentrations of both the substrate and the base. The E2 reaction using Newman projection is shown in Eq. 3.

In contrast to the E2 reaction, the rate of the E1cB reaction (elimination unimolecular through conjugate base) is dependent only on the concentration of the carbanion formed on deprotonation of the substrate by the base, see Eq. 2. However, to begin with, the σ_{C-H} bond is not required to be antiperiplanar to the σ_{C-L} bond. The resultant carbanion (conjugate base of the substrate) survives until it collapses to an olefin by ejecting the leaving group through a transition state similar to that for the E2 reaction. The attainment of the TS may require rotation around the σ_{C-C} bond to orient the electron pair orbital antiperiplanar to the σ_{C-L} bond.

From the above discussions of E2 and E1cB reactions, we learn one very important point: an electron-rich bond such as σ_{C-H} or an electron pair orbital antiperiplanar to an electron-deficient bond such as σ_{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 antibonding orbital corresponding to the electron-deficient bond (σ^*_{C-L}). This lowers the antibonding orbital and, thus, raises the corresponding bonding orbital on the energy scale. As a result, the bonding orbital is weakened and its cleavage takes place with increased ease. We shall now exploit this information to understand the reactivity profiles of select class of molecules to strengthen our knowledge base.

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



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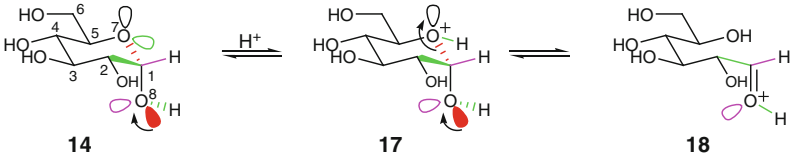

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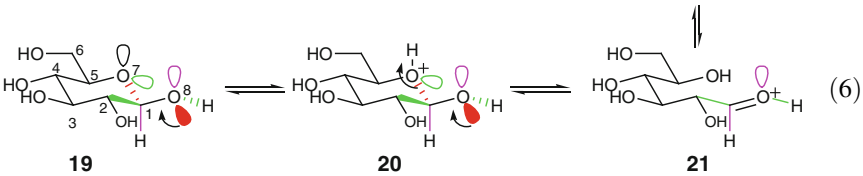


(6)

An electron pair orbital that is not engaged in anomeric effect is more electron rich and, hence, more vulnerable to protonation than an electron pair orbital that is involved in anomeric effect. 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 the electron pair is engaged in anomeric effect.

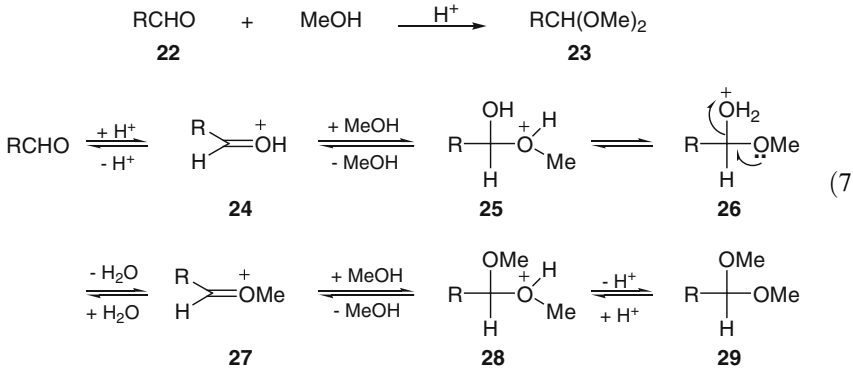
Let us now consider β-(D)-glucose **19**. It turns out from the given color codes that neither of the two electron pair orbitals on the ring oxygen is antiperiplanar to the σ_{C1-O8} bond. The cleavage of σ_{C1-OH} bond after protonation will therefore occur without assistance from any anomeric effect, i.e., the cleavage will be slower than the cleavage shown in Eq. 4. Alternatively, O8 has an electron pair orbital antiperiplanar to the σ_{C1-O7} bond. Therefore, σ_{C1-O7} bond can cleave after protonation of O7 with assistance from anomeric effect arising from O8, as shown in Eq. 6, and generate the oxonium ion **21**, which is essentially a rotamer of the oxonium ion **18**.

It should be noted from Eq. 5 that the species **18** is in equilibrium with α-(D)-glucose **14**. 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 know as *mutarotation*. The specific optical rotation of α-D-glucose is different from that of β-D-glucose. Thus, commencing from α-(D)-glucose (aqueous solution), the optical rotation will change with time and become static at the equilibrium. Of course, the equilibrium will be established fast if one begins with α-(D)-glucose because the changes **14** → **17** → **18** → **21** lead to relief from steric strain arising from the axial OH group in **14**. 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. The electron pair of the cleaved π bond ends up in the axial orbital on the ring oxygen that exerts anomeric effect on the σ_{C-O} bond that is just formed. An attack from the equatorial site will generate **19**, where the new σ_{C-O} bond formed is not in anomeric effect with any of the electron pair orbitals of the ring oxygen. Both the formation and the 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 as well.

We know that the reaction of an aldehyde with an alcohol under dehydrating conditions generates an acetal as shown in Eq. 7. The details regarding the progress

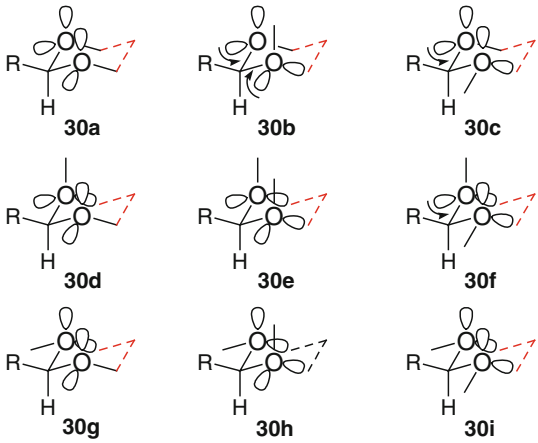
of the reaction are shown below Eq. 7. As can be seen, one molecule of water is released for every molecule of the acetal formed in the step **26** → **27** and that the proton used in the very beginning of the reaction is released in the end, making the reaction therefore catalytic in the proton source. It should be noted that each step leading to the acetal is reversible, which necessitates removal of the water formed from the reaction mixture to drive it to completion. The proton transfer from one oxygen to the other oxygen in the species **25**, leading to **26**, is very facile given the geometrical closeness of the two oxygen atoms on a tetrahedral carbon.



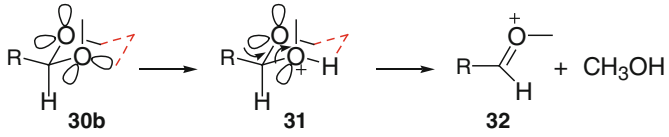
(7)

Let us consider the reverse of acetal formation, i.e., acid hydrolysis of an acetal within the ambit of stereoelectronic effects and explore the underlying features. 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 a cyclohexane chair. In doing so, we understand the geometrical relationship of various bonds on this ring system much better.

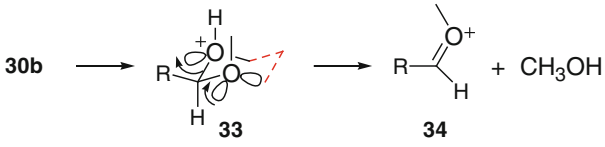
The acetal $RCH(OMe)_2$ can have a total of nine conformers, **30a–30i**. We may ignore the broken red bonds, which are included to allow a quick conformational match with that of the cyclohexane chair and, thus, ascertain the geometrical relationships rather easily. The conformers **30a** and **30e** have two methyl groups within van der Waals distance and, hence, their contributions to the overall conformational equilibrium will be small, if not zero. We can therefore eliminate these conformers from further discussion. The conformers **30b** and **30d**, **30c** and **30 g**, and **30f** and **30 h** are mirror images and, thus, we need to consider only one conformer of each pair. Thus, we are left with four distinct conformers, namely **30b**, **30c**, **30f,** and **30i**, to consider for acid hydrolysis. The relative contributions of these conformers could be estimated from the understanding that they are laced with two, one, one and zero stereoelectronic effects, respectively. The conformers **30b** and **30i** are, respectively, the most contributing and the 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. Note that both the oxygen atoms in **30**b have 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 easily undergo σ_{C-O} bond cleavage under stereoelectronic control arising from the other oxygen, as shown, to generate methanol and the *O*-methylated aldehyde **32**. Likewise, protonation of the rear oxygen coupled with the σ_{C-O} bond cleavage, as shown in Eq. 9, will generate methanol and the *O*-methylated aldehyde **34**. The *O*-methylated aldehyde **32** is of *E*-configuration while **34** is of *Z*-configuration. With R being that is small in size and, contributing to marginal van der Waals interaction with the *O*-methyl in **34**, both the cleavage pathways will be expected to be, more or less, equally facile. However, with R that is large, the pathway shown in Eq. 8 must predominate.



(8)



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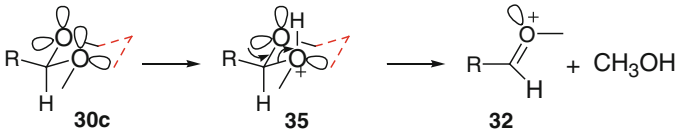

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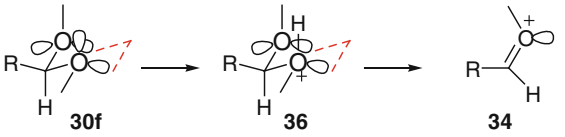
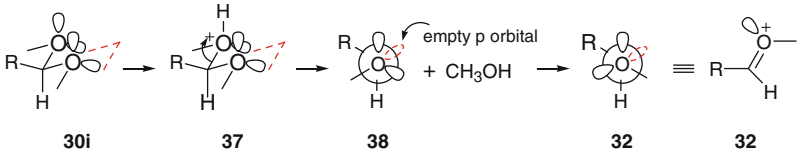


(11)

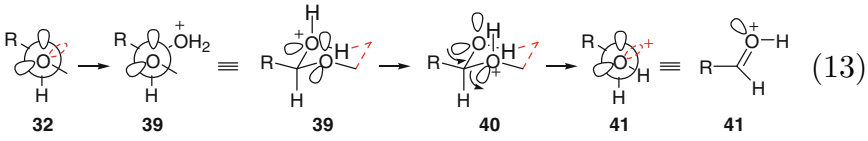
Protonation of the front oxygen in **30c** followed by cleavage of the σ_{C-O} bond under the stereoelectronic control of the rear oxygen, as shown in Eq. 10, generates **32**. Cleavage of the rear σ_{C-O} bond after protonation will be expected to be an inefficient process because it is not supported by any stereoelectronic effect arising from the front oxygen. Likewise, **30**f will generate **34** as shown in Eq. 11.

Finally, we discuss the conformer **30i** that lacks any stereoelectronic effects. The molecule is symmetrical and, hence, either of the two σ_{C-O} bonds can cleave after protonation. However, any such cleavage will take place without the assistance of stereoelectronic effect and, as shown in Eq. 12, the species **38** will be formed. The most notable characteristic of the species **38** is that the axis of the empty orbital (red) is antiperiplanar not to an electron pair orbital on the oxygen but to a σ_{O-C} bond. The species **38** will, therefore, be a high energy species. Conformational change, while keeping the methyl as far from R as possible (possible through anticlockwise rotation only), will allow 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 like **38** is involved, the conformer **30i** may be safely predicted to be a neutral conformer, *i.e.*, resistant to hydrolysis.

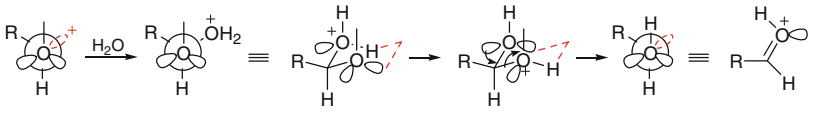


(12)

We have so far understood that protonation of one of the two oxygen atoms followed by cleavage of the σ_{C-O} bond in the important acetal conformers generates the oxonium ion **32** and/or **34**, depending upon the size of R. We will now consider the reactions of these oxonium ions with water. The reaction of **32** is outlined in Eq. 13. Capture of the empty orbital, of course under the stereoelectronic effect of an oxygen electron pair, generates **39**. Note the antiperiplanar relationship of R with the methyl in both **32** and **39**. Proton transfer from one oxygen to the other, taking advantage of the 1,3-diaxial proximity, will generate **40**. Now, cleavage of the σ_{C-O} bond with 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 end product of hydrolysis. Considering a similar pathway, the reaction of **34** with water is shown in Eq. 14.



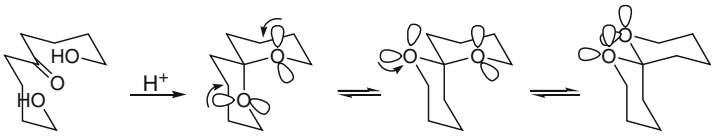
(13)



(14)

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

We have understood the stereoelectronic effect as a stabilizing effect that lowers the energy of a system by 1.4 kcal mol^{-1} and that it originates from the interaction of an oxygen electron pair orbital and a σ_{C-O} bond. Let us take notes of the following as well: (a) a methylene group axial to a cyclohexane ring contributes equivalent to two gauche butane interactions, i.e., $2 \times 0.9 = 1.8$ kcal mol^{-1}, and (b) an oxygen atom axial to a cyclohexane ring contributes $2 \times 0.4 = 0.8$ kcal mol^{-1}. With a knowledge of these values, we may now begin to calculate the relative energies of the three conformers **48a**, **48b,** and **48c**, Eq. 15, and predict the conformer that will predominate at equilibrium.



(15)

The conformer **48a** benefits from two stereoelectronic effects that will contribute $-(1.4 \times 2) = -2.8$ kcal mol^{-1}. Each ring in this conformer also has an oxygen atom axial to the other six-membered ring, which will contribute $+2 \times (2 \times 0.4) = +1.6$ kcal mol^{-1}. Therefore, the net change in the relative energy, is $-2.8 + 1.6 = -1.2$ kcal mol^{-1}. The conformer **48b** has only one stereoelectronic effect to contribute -1.4 kcal mol^{-1}. One ring has an oxygen atom axial to the other ring and this will contribute +0.8 kcal mol^{-1}. This conformer also has one methylene group axial to the other ring system and this will contribute 1.8 kcal mol^{-1}. Thus, the net change in the relative energy is $-1.4 + 0.8 + 1.8 = +1.2$ kcal mol^{-1}. The number of stereoelectronic effects in the conformer **48c** is nil. However, each ring has one methylene group axial to the other ring to contribute, collectively,