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Felkin-ahn model in organic chemistry

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The article reviews various research studies related to the topic of organic chemistry, focusing on the resonance in conjugated systems and hyperconjugation effects. The studies referenced date back from 1952 to 2007 and were conducted by numerous researchers. Some key findings from the reviewed articles include: * Research on the electronic structure and reactivity of conjugated molecules (Cram et al., 1952; Taft et al., 1959) * Studies on the mechanism of hyperconjugation effects in organic compounds (Baker, 1952; Cieplak et al., 1981) * Investigations into the electronic structure and reactivity of conjugated systems using quantum chemistry methods (Mehta et al., 1990; Paddon-Row et al., 1994) The article also references various computational studies that employed density functional theory (DFT) calculations to investigate hyperconjugation effects in organic compounds. Overall, the reviewed articles provide insights into the electronic structure and reactivity of conjugated systems and the importance of hyperconjugation effects in organic chemistry. In chemistry, asymmetric induction occurs when one chiral isomer (a molecule that can't be superimposed on its mirror image) is preferentially formed over another in a chemical reaction. This phenomenon was first described by Hermann Emil Fischer based on his work with carbohydrates. There are several types of asymmetric induction, including internal induction, where the chiral center is part of the starting material; relayed induction, where chiral information is introduced and then removed in separate reactions; and external induction, where a chiral catalyst or ligand influences the reaction. Asymmetric induction plays a crucial role in asymmetric synthesis, which involves creating molecules with specific three-dimensional structures. The Gibbs free energy plot of an enantioselective addition reaction shows how this process can lower the transition state energy for one enantiomer over the other. Several models have been proposed to explain chiral induction at carbonyl carbons during nucleophilic additions, including those developed by Cram, Cornforth, Felkin, and others. These models often rely on a combination of steric and electronic considerations, but may conflict with each other. Overall, asymmetric induction is an important concept in chemistry that allows chemists to selectively form one chiral isomer over another, which has significant implications for the development of new medicines, materials, and other products. The Cram's rule of asymmetric induction, named after Donald J. Cram, states that in certain non-catalytic reactions a diastereomer will predominate when the entering group approaches from the least hindered side due to steric hindrance. This rule suggests that the presence of an asymmetric center in a molecule induces the formation of another asymmetric center adjacent to it based on steric interactions. In experiments, the Cram's rule was tested by reacting 2-phenylpropionaldehyde with the Grignard reagent of bromobenzene, resulting in the formation of 1,2-diphenyl-1-propanol as a mixture of diastereomers, predominantly the threo isomer. The preference for the threo isomer can be explained by having the active nucleophile attacking from the least hindered side when the carbonyl group is positioned in a staggered formation with smaller substituents creating minimum steric hindrance. However, when a hydride anion attacks the same reaction product, the erythro isomer becomes more favored. This observation led to the development of the Felkin model by Hugh Felkin, which predicts the stereochemistry of nucleophilic addition reactions to carbonyl groups. The Felkin rules state that transition states are reactant-like and involve substantial torsional strain, with a staggered conformation instead of an eclipsed one. The main steric interactions in the transition state occur around the entering group and the nucleophile, rather than the carbonyl oxygen atom. Attack of the nucleophile occurs at a specific angle, known as the Dunitz angle, and is influenced by polar effects or electronic stabilizations that maximize separation between the nucleophile and electron-withdrawing groups. The Felkin rules offer an alternative explanation for the stereochemistry of these reactions, particularly in cases where Cram's rule does not apply, such as with haloketones. Replacing a phenyl group with cyclohexyl reduces stereoselectivity significantly. The Felkin–Anh model corrects two weaknesses in the Felkin model by incorporating suggestions from Nguyễn Trọng Anh and Odile Eisenstein. The first weakness addressed was the strong polar effect leading to complete stereochemical inversion, which was corrected by introducing the antiperiplanar effect. This effect aligns the best nucleophile acceptor σ* orbital with π and π* orbitals of the carbonyl, providing stabilization for the incoming anion. The second weakness was the assumption of substituent minimization around the carbonyl R, which is corrected by considering non-perpendicular attack by the nucleophile. The Felkin–Anh model predicts preferential addition of a nucleophile to the most sterically favored face of a carbonyl moiety. However, many reactions display stereoselectivity opposite of what is predicted, resulting in "anti-Felkin" products. One example of altered asymmetric induction selectivity occurs when an α-carbon is substituted with a Lewis base character component and a Lewis acid is introduced, causing bidentate chelation. This can result in an "anti-Felkin" product if the chelating R group is identified as the largest. The effect of an electron-withdrawing group on the addition of a nucleophile to an α-carbon is explained by various models. The Cornforth and Felkin models propose a polar effect, where the EWG substituent and incoming nucleophile are positioned anti to each other to minimize dipole moment. This model is supported by Newman projections illustrating the transition state with the EWG anti to the incoming nucleophile. The improved Felkin–Anh model considers molecular orbital interactions for a more accurate assessment of the polar effect. A typical reaction illustrates this anti-Felkin selectivity, with the proposed transition structure showing the EWG anti to the incoming nucleophile. Stereoelectronic environments at the β-carbon can also direct asymmetric induction, as observed in reactions involving β-alkoxy aldehydes and metals. The Cram-chelate model predicts the chelated complex of a β-alkoxy aldehyde and metal, with the nucleophile attacking from the less sterically hindered side and anti to the substituent Rβ. The reaction of β-alkoxy aldehyde with allyltrimethylsilane showed good selectivity for the anti-1,3-diol, explained by the Cram polar model. The Evans model presents a different approach for nonchelate 1,3-inductions, where the β-stereocenter is oriented anti to the incoming nucleophile and the X group at the β-stereocenter is placed anti to the carbonyl to reduce dipole interactions. Given article text here The stereochemistry of nucleophilic addition reactions plays a crucial role in determining the product's asymmetry. When dealing with large nucleophiles, the α-stereocenter dominates the interaction with the incoming nucleophile, leading to the Felkin product as the major outcome. In contrast, smaller nucleophiles result in 1,3 control, which influences the formation of diastereoisomers. Chiral alkenes exhibit similar behavior upon reactions like epoxidation and enolate alkylation, where substituents around the alkene favor the approach of the electrophile from one face over the other. This concept is rooted in Houk's model, which predicts stronger selectivity for cis double bonds. The Felkin-Ahn model further elucidates the factors influencing nucleophilic addition to chiral aldehydes, particularly through substrate control and asymmetric induction. By examining the molecular framework of an acyclic substrate, one can predict the chirality of subsequent chemical reactions and design synthetic strategies accordingly. Felkin-Anh model explains the stereochemistry of organometal additions to aldehydes. When X is an electronegative group, the polar Felkin-Anh model suggests hyperconjugative stabilization due to anti-periplanar interaction between C-X σ* orbital and forming bond. This model postulates that observed stereochemistry arises from hyperconjugative stabilization. To improve Felkin-Anh selectivity for organometal additions to aldehydes, organo-aluminum nucleophiles are used instead of Grignard or organolithium nucleophiles. Claude Spino's work demonstrates significant stereoselectivity improvements with vinylgrignard reagents and vinylalane reagents. Addition of achiral allylmetals to aldehydes forms a chiral alcohol, where stereochemical outcome is determined by α-carbon chirality on the aldehyde substrate. Cram's rule explains stereoselectivity considering transition state interaction between oxygen lone pair and boron centre. Strikin levels of stereo induction have been achievd usin substrates in reakcions such as kinetic enolate alkylation, dimethylcuprate addision, and catalytic hydrogenation. Even a single methyl group is often sufficent to bias the diastereomeric outcome of the reakcions. These studiis have helped challange the widely-held scientific belief that large rings are too floppy to provide any kind of stereochemical control. A number of total syntheses have made use of macrocyclic stereocontrol to achievd desired reaction produkts. In the synthesis of (−)-cladiella-6,11-dien-3-ol,[29] a strained trisubstituted olefin was dihydroxylated diasetereoselectively with N-methylmorpholine N-oxide (NMO) and osmium tetroxide, in the presence of an unstrained olefin. En route to (±)-periplanone B,[30] chemists achievd a facial selective epoxidation of an enone intermediate usin tert-butyl hydroperoxide in the presence of two other alkenes. Sodium borohydride reduction of a 10-membered ring enone intermediate en route to the sesquiterpene eucannabinolide[31] proceeded as predicted by molecular modelling calculations that accounted for the lowest energy macrocycle conformation. Substrate-controlled synthetic schemes have many advantages, since they do not requird the use of complex asymmetric reagents to achievd selective transformations. In organic synthesis, reagent control is an approach to selectively forming one stereoisomer out of many, the stereoselectivity is determined by the structure and chirality of the reagent used. When chiral allylmetals are used for nucleophilic addision reakcions to achiral aldehydes, the chirality of the newly generated alcohol carbon is determined by the chirality of the allymetal reagents (Figur 1). The chirality of the allymetals usually comes from the asymmetric ligands used. The metals in the allylmetal reagents include boron, tin, titanium, silicon, etc. Figur 1: Reagent control: addision of chiral allylmetals to achiral aldehydes Various chiral ligands have been developed to prepare chiral allylmetals for the reakcions with aldehydes. H. C. Brown was the first to report the chiral allylboron reagents for asymmetric allylation reakcions with aldehydes.[32] The chiral allylboron reagents were synthesized from the natural product (+)-a-pinene in two steps. The TADDOL ligands developed by Dieter Seebach has been used to prepare chiral allyltitanium compounds for asymmetric allylation with aldehydes.[33] Jim Leighton has developed chiral allysilicon compounds in which the release of ring strain facilitated the stereoselective allylation reakcions, 95% to 98% enantiomeric excess could be achievd for a range of achiral aldehydes.[34] Figur 2: Example of chiral allylmetals used: (a) allylboron, (b) allyltitanium, and (c) allyl silicon The Felkin-Nguyen Model is a concept in organic chemistry that describes the stereochemistry of lithium aluminium hydride reductions of simple ketones. First introduced by Marc Chérest, Hugh Felkin, and Nicole Prudent in 1968, the model has undergone significant development and refinement over the years. Researchers such as Nguyen Thai Hoc, Oskar Eisenstein, and Jean-Marie Lefour have contributed to the expansion of this concept. Studies have explored the stereochemical implications of these reactions, revealing intricate relationships between the reactants, catalysts, and product geometries. The model has been further supported by various chemical reactions, including those involving other reagents and conditions. Researchers like David Cram, M. T. Reetz, and Daniel Evans have employed different approaches to test the Felkin-Nguyen Model's predictions, validating its accuracy in predicting reaction outcomes. Recent studies have also applied the model to more complex systems, such as diterpenes and pheromones. The work of Still, Clark, and other researchers has demonstrated the versatility and reliability of this concept, paving the way for further applications in organic synthesis. The development of the Felkin-Nguyen Model highlights the importance of understanding stereochemistry in chemical reactions, enabling chemists to design more efficient and selective syntheses. The Evolution of Models for Carbonyl Addition: An Insight into the Work of the Evans Group This text discusses the development of models for carbonyl addition, a significant discovery made by the Evans group.