*International Research Journal of Pure and Applied Chemistry*

***Volume 24, Issue 5, Page 95-110, 2023; Article no.IRJPAC.106182***
***ISSN: 2231-3443, NLM ID: 101647669***

# Recent Advances Related to Anomeric and Exo-anomeric Effects in Carbohydrate Chemistry

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

***Article Information***

DOI: 10.9734/IRJPAC/2023/v24i5830

**Open Peer Review History:**
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/106182

***Review Article***

***Received: 11/07/2023***
***Accepted: 17/09/2023***
***Published: 22/09/2023***

## ABSTRACT

The anomeric effect in carbohydrate chemistry is known as the interaction between the OHd substituent at the anomeric position to favor an axial orientation rather than an equatorial one, despite the increased 1,3-diaxial interactions. In the anomeric effect, a sugar ring is stabilized by an

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electronegative substituent at the C1 carbon, also known as the anomeric carbon. The stabilization is thought to result from interactions between lone electron pairs on oxygen and a C1 antibonding orbital. On the other hand, the anomeric effect can be of two types: endo-anomeric and exo-anomeric. The effect is called endo-anomeric when the lone pair comes from the oxygen atom in the sugar ring and exo-anomeric when the lone pair comes from oxygen in a substituent on C1. Several factors influence the anomeric effect. In this way, this review aims to describe the recent advances in main theories, observations, and advances achieved in the last decades related to the anomeric effect.

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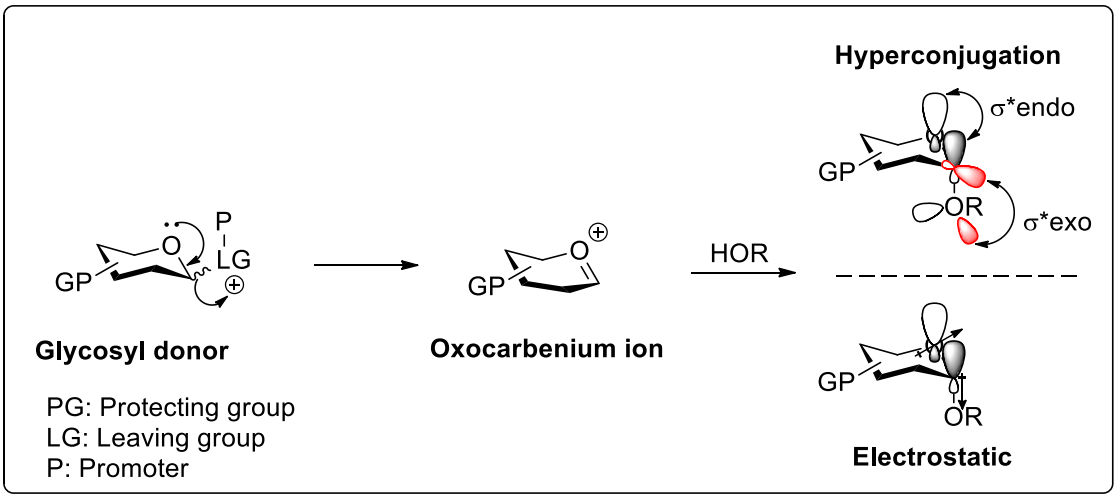
**GRAPHICAL ABSTRACT**




*Keywords: Carbohydrate chemistry; glycoside; anomeric effect; exo-anomeric.*

## 1. INTRODUCTION

Fisher's important advances in glycosylation drove new research perspectives in carbohydrate chemistry in understanding glycosidic anomers and their aspects. The formation of glycosidic bonds was highlighted in glycoscience by the particularities observed for glycosidic carbon that showed stereoselective tendencies caused by stereoelectronic and thermodynamic effects [1-4]. This makes the unique carbon, defined by anomeric the first stereogenic center of a monosaccharide, which is derived from the open chain of aldoses and ketoses, equivalent to C1 and C2, respectively [5].

The anomeric configuration is determined by the orientation of the substituent group at C5 relative to the hydroxyl of the anomeric carbon [6]; therefore, the same equatorial-equatorial plane has β-glycoside [7]; in opposite equatorial-axial planes, it is referred to as α-glycoside [8]. These compounds exhibited the majority formation of the α-anomer due to axial over the equatorial conformational preference of an electronegative substituent at the anomeric center. There are two widespread justifications for this conformational preference, the first is the stereoelectronic effect that arises with the electrostatic repulsive forces between the dipoles due to the lone oxygen pairs of the ring and the exocyclic oxygen [9,10]. The second rationalization is based on a stabilized gauche orientation that is attributed to the delocalization (or hyperconjugation) of the lone pair orbital on oxygen to the antibonding σ orbital [11,12]. The anomeric effect can undergo various influences, such as solvents that help in stabilization, substituents with a high capacity to hold electrons, and the exo-anomeric effect, which occurs when ligand X has non-bonding electron pairs, the exo-anomeric effect happens in the opposite direction to the endo-anomeric effect. Thus, glycoside synthesis becomes a challenge given the complexity of the factors surrounding the anomeric carbon.

The reaction process in the synthesis of carbohydrates involves specific aspects of the complexity of obtaining synthetic compounds. Since the 20th century, studies on the reactivity of anomeric carbon is highlighted in the chemistry of saccharides from concepts of

Pearson's hardness and softness with the anomeric tendency of attraction to species with similar characteristics [13-16]; theoretical calculations of thermodynamics and kinetics in the formation and anomeric stability [17]; influence [18] and absence[19] of solvent on the anomeric conformation [20,21] by hyperconjugation [22-25] and electrostatic [18]; isotopic labeling [26] in the determination of regio- and stereoselectivity to the development of stereoselective methods due to the challenges faced by sugar researchers [27-31]. Furthermore, the conditions of temperature, pressure, activator, catalyst, and anchimeric assistance contribute to the configuration of the anomeric carbon on oxocarbenium ion, determining the inclination of the nucleophilic attack achieving better hemiacetal selectivity [32]. Thus, it is seen that anomeric reactivity is complex due to the comprehensiveness of fundamentals that need constant deepening in the search for elucidation of the difficulties in the field of carbohydrate research (Fig. 1).

Given the structural complexity inherent in a large number of possible carbohydrate conformations, it is important to understand the aspects that drive the thermodynamically favored conformation. Computational and theoretical studies show that there are still conflicting ideas that need to be resolved [33,34]. For a long time, the real facts that influence the nature of the anomeric effect have intrigued chemists, not limited to carbohydrates, but extending to saturated heterocycles and acyclic systems containing heteroatoms [35]. According to statistical data from publications indexed in the Web of Science database from 2013 to 2023, using the keyword “anomeric effect”, around 578 publications were identified, while the number of citations has grown significantly in recent years, as shown in Fig. 2A. On the other hand, the keywords “exo-anomeric effect” and “endo-anomeric effect” identified 31 and 6 articles, respectively, in the same period Fig. 2B.

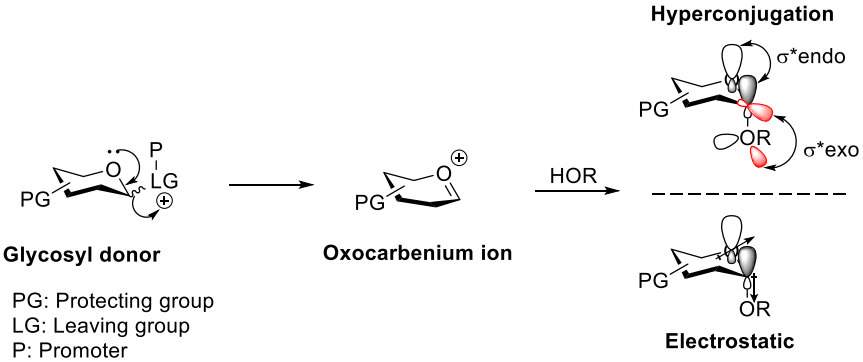



**Fig. 1. Anomeric effect by hyperconjugation and electrostatic.**

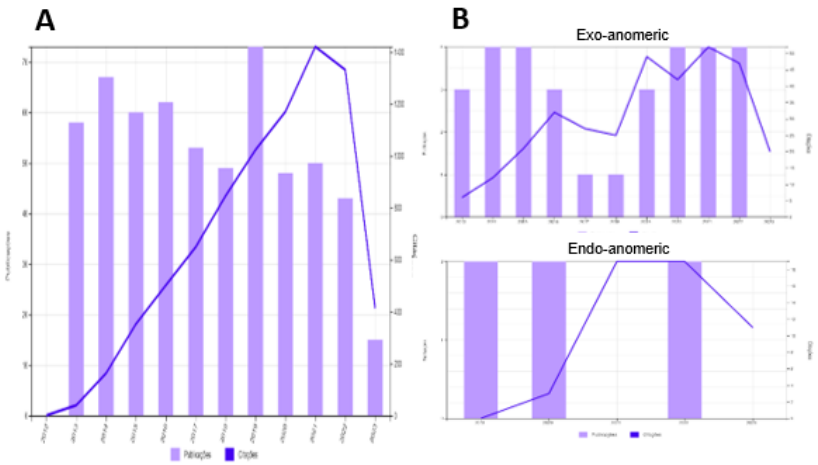



**Fig. 2. A) Number of articles and citations with the keyword “anomeric effect”; B) Number of articles and citations with keywords “exo-anomeric effect” and “endo-anomeric effect” in the last 10 years**

In this way, this review summarizes the recent advances in main theories, observations, and advances achieved in the last decades that seek to answer the questions that still intrigue researchers about aspects that need to be considered about the origin and nature of the anomeric effect for a consensus.

## 2. DEVELOPMENT

### 2.1. Understanding the Anomeric Effect

The preference for the axial conformation of electronegative substituents initially observed in carbohydrates that led to the discovery of the anomeric effect extends to any compound that has at least two heteroatoms with one or more pairs of free electrons attached to the same tetrahedral center. This discovery led to a fit between the standard Gibbs free energy difference for the carbohydrate and substituted cyclohexane conformers [36-39]. Therefore, in quantitative terms, thermodynamics describes the anomeric effect as:

$$\Delta G°_{298,15K}(\text{anomeric effect}) = [\Delta G° (C_E) - \Delta G°(C_A)] - [\Delta G°(cH_E) - \Delta G°cH_A)]$$

Where the observed relationship between the differences in standard Gibbs free energy (ΔG°298.15K) for the axial (A) and equatorial (E) conformers of carbohydrate (C), and of the substituted cyclohexane (cH), respectively at 298.15K.

Carbohydrates have a variety of conformations that are determined by the anomeric effect [40]. This effect is related to the tendency of an electronegative substituent attached to the anomeric carbon of a tetrahydropyran ring in chair conformation to assume the pseudo-axial orientation ($\alpha$-anomer) instead of the pseudo-equatorial form ($\beta$-anomer) [41]. Out another factor that is related to the anomeric effect is the significant shortening of the O5-C1 and C1-O1 bonds, when compared with the length of the C-O bonds commonly found in ethers, further evidencing that the O5-C1 bond is shorter in the $\alpha$ anomer than in the $\beta$ anomer, the latter being the shortest bond in the C1-O1 bond [42].

The anomeric effect can be substantiated using electrostatic theories, where the polar substituents attached to the anomeric center have an axial position, this is due to electrostatic repulsions between atoms. For example, in a heterocyclic the dipole moment is in the equatorial direction so that the charge associated with a polar substituent in the equatorial position will lead to a repulsive interaction, as opposed to if the substituent were in the axial position the repulsion would be smaller, therefore the axial position must have the lowest energy being the most stable [43].

The hyperconjugation, in a limited way, demonstrates the steric parameters by the trends in the axial substituent equilibrium by the interactions of the p orbitals from anomeric carbon and the heteroatom of the aglycone in the glycosidic bond, contributing a further explanation for the anomeric effect [44]. The model describes well the natural observations of C-O bond shortening and C-Subst bond elongation for most glycosides, as is seen in the dependence of hyperconjugative interactions in theoretical studies with sulfoxide α-glycosides influenced by high polarity solvents [45]. However the limitation comes from the fact that some aglycones prefer the equatorial position over the sugar used because of 1,3-diaxial interactions determined by the orientation of the protecting groups, developing an important bias of the employment of the protecting group in anomeric stereoselectivity [46]. Recent empirical investigations substantiate such evidence with methyl and acetyl *O*-glycosides having stereoselective favoritism in the anomeric ratio for β-glycosides by allocating better in the equatorial by dipolar stabilization, increasing the glycosidic bond length, thus eschewing the concepts of anomeric orbital interaction [47,48]. Anyway, the understanding of the anomeric effect is built by several important blocks that can be differentiated in each specific case, so the complexity in defining the term "anomeric effect" has become more in need of additions and elements that build a more solid and well-founded concept.

### 2.2 Experimental data of the Anomeric Effect

#### 2.2.1 Temperature and solvent

The effect of temperature is one of the factors that directly affects the stereoselectivity of carbohydrates, in general carbohydrates are synthesized at low temperatures, thus avoiding their degradation [49,50]. However, the anomeric effect is also influenced by temperature, allowing the formation of the $\alpha$-anomer as the major product at higher temperatures and the $\beta$-anomer at lower temperatures. Another very

relevant factor regarding stereoselectivity is the solvent that influences the anomeric effect, that is, during the synthesis of glycosides, polar solvents increase the formation of the $\beta$-glycoside isomer, thus reducing the anomeric effect, thus for the formation of $\alpha$-glycoside is used. If nonpolar solvents, moreover, it was observed that some solvents like 1,4-dioxane, tetrahydrofuran, and diethyl ether favor 1,2-*cis* ($\alpha$) type products while solvent like methyl cyanide provides 1,2-*trans* ($\beta$) type product. The solvent coordination network appears as a justification proposal. the first rationalization is that the solvent molecule coordinates with the anomeric carbon of the oxocarbenium cation preferentially on one side of the ring, as a result, the nucleophile has only one possible face to attack, the other rationalization is that acetonitrile preferentially binds to $\alpha$- face of the oxocarbenium ion giving rise to a $\alpha$-glucopyranosyl and acetonitrile ion blocks the incoming nucleophile from choosing the $\alpha$-face to attack the intermediate leaving only the $\beta$-face to attack, giving rise to 1,2-trans ($\beta$ -glycoside) [51,52].

### 2.2.2 Anchymeric assistance

Among the other factors that can influence regio- and stereochemical control much discussed in carbohydrate synthesis, anchymeric assistance, also known as Neighboring Group Participation (NGP), is responsible for a preference in the structure adopted by the molecule. Initially described by Lemieux in the 1950s, it is a frequently adopted strategy to obtain a carbohydrate with α-anomer as the major product, which consists of the interaction of available electrons from the group neighboring C-6 or C-3 of the carbohydrate molecule, given its structure Fig. 3 [53-55].

### 2.2.3 Promoter

Most glycosylation reactions involve some promoter to activate the leaving group, causing the formation of the oxocarbenium ion and the nucleophilic attack. The challenge in the search for activators that favor stereocontrol in the anomeric center is not trivial because of the need for chemical species that interact with the glycosyl donor to occur exclusively in the glycosidic bond from the underside face by the direct participation of the promoter to the exo-anomeric effect [56-58]. There is a strong emphasis on metals as promoters due to the availability of frontier orbitals, enabling new bonds as Lewis Acids [59]. The dipolar induction by metal coordination can be influenced by the nature of the ligands, directing the anomeric orbital in such a way that the attack by the lower interface is more kinetic [60].

From the classical example of the Ferrier rearrangement [61] advances have been made in the synthesis of glycosides using organometallic as a Lewis Acid of relative softness, making the sulfonate derivatives able to oxidize thioglycosyl donors to increase the anomeric capacity by forming the intermediate *O*-sulfonylglycoside, obtaining exclusively α-glycoside by NMR analysis [62]. However, the phosphate-derived promoter did not show as much efficiency in stereoselectivity by the steric effect of the ligands not being energetically favorable intermolecular arrangement, obtaining a diastereoisomeric mixture [63]. Lewis bases are less used as a promoter in glycosylation, but organic halides have played an important role in the synthesis of oligosaccharides by activating the anomeric center with high selectivity in the formation of the intermediate halonium ion by the upper face, exclusively allowing the nucleophilic entry in the alpha position [64].

Another type of activator widely used is the Brønsted-Lowry acids by rapid protonation and biomolecular nucleophilic substitution, but low stereocontrol on the anomeric carbon has led to the search for additives for stereoisomeric improvement, as studies report the combination with metallic salts that have low reactivity but make the reaction highly selective by chelation of the metal to the protective anomeric center, directing the attack of the nucleophile selectively by the formed chelate [65].

There are a range of promoters capable of performing glycosylation with high efficiency, yet most of them are not stereoselective due to the difficulties in the synthesis that favors the anomeric effect, mainly due to the high hardness in the anomeric carbon that does not facilitate the selectivity of the anomers. Thus, few promoters demonstrate be able to obtain exclusively the α-anomer under certain conditions by favoring the anomeric effect strategically.

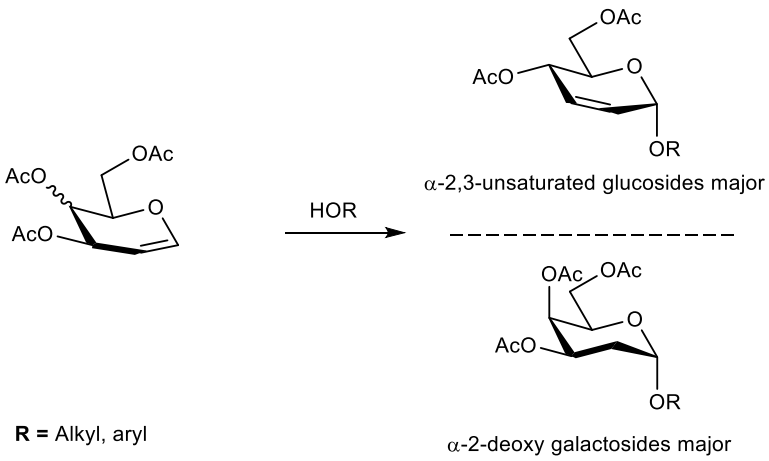



**Fig. 3. Formation of the α-anomer as a major product by anchymeric assistance.**

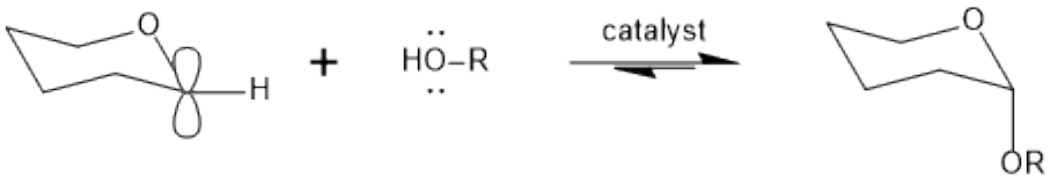



**Fig. 4. Example of the classical Lewis acid-catalyzed glycosylation.**

### 2.2.4 Catalysts

Donor and receiver groups that coexist in a proper molecule can make acceptor groups work the axial position of the anomeric carbon [66], it happens with catalyst reactions too, according to Fig. 4. The stereoelectronic effect decides the last step of the reaction Catalysts can be tested for preparing novel compounds [67].

A stoichiometric amount of a strong base or organotin reagent is a request for reactions of catalytic anomeric *O*-alkylation forming oligosaccharides. For example, effective catalysts for stereo or regioselective of 1,2- and 1,3-diols, and regioselective glycosylation, are boronic acids or borinic acids. The nucleophilicity of axial –OH groups is weaker than that of equatorial ones, it shows that few reports describe the predominant alkylation of the first ones, even though the functionalization of the last ones in hexoses has been achieved with high selectivity. Catalytic anomeric *O*-alkylation of 1,2-dihydroxyglucoses via borate complexes with borinic acids forming 1,2-cis-α-glucosides upon predominant activation of anomeric oxygens that were axially oriented was reported [68].

### 2.2.5 Pressure

Nigudkar and Demchenko described that the high pressure applied to the reactions with participating glycosyl donors further enhances 1,2-trans selectivity [69]. According to the same authors when the high-pressure conditions were applied for glycosylations with a non-participating glycosyl donor, a remarkable increase in the reaction yield was noted with only marginal changes in stereoselectivity.

According to Sasaki et al. [70] and Spijker and van Boeckel [71], unfavorable steric interactions that occur between glycosyl donor and acceptor in the transition state or other factors or conditions may unexpectedly govern the course and outcome of the glycosylation reaction. On the other hand, one of the most remarkable effects, so-called “double stereodifferentiation” takes place when stereochemical interactions between bulky substituents in glycosyl donor and glycosyl acceptor may outperform even the strong stereodirecting effect of a neighboring participating group.

## 2.3 The Application of *ab initio* Molecular Orbital Theory to the Anomeric Effect

For a long time, studies that relates the anomeric effect with calculations based on systematic

conformational data have helped to understand the behavior of various cues. In 2014, Szczepaniak and Moc [72] computationally investigated the cyclic (α- and β-pyranoses, α- and β-furanoses) and open-chain isomers of D-ribose and 2-deoxy-D-ribose using Møller-Plesset perturbation theory second order (MP2), M06-2X density function and multilevel G4 methods. It was possible to observe that β-pyranoses with chair conformations are the most stable isomers. The most favored ribofuranose is the α-anomer having the 2T1 twist ring conformation, with 10.4 kJ/mol higher in ΔG than the global minimum. The most stable 2-deoxy-D-ribose is α-pyranose, with the most stable 2-deoxy-D-furanose (the α-anomer) being only 6.2 kJ/mol higher in free energy. As for the pentoses, the more favored open-chain isomers are higher in energy than the cyclic isomers [72].

In 2016, Langenhan and collaborators [73] investigated the unprecedented magnitude of the anomeric effect in oxyamines and *N*-glycosylated hydrazides using functional density theory (DFT) calculations. The results showed that the greatest effect was observed on *N,O*-dimethyl-*N*-(tetrahydro-*2H*-pyran-2-yl)hydroxylamine 1 (AEcorr = 1.38 kcal/mol), and *N'*-(tetrahydro-*2H*-pyran-2-yl)acetohydrazide shows moderate (AEcorr = 0.54 kcal/mol). The results, in general, are compatible with the stereoelectronic and electrostatic explanations for the anomeric effect, considering that the $\sigma^*_{C1\text{-}N1}$ of 1 is a better acceptor orbital for $nO_5$ than the $\sigma^*_{C1\text{-}N1}$ of hydrazide 3, based on the higher electronegativity of O1 in hydroxylamine derivatives compared to N2 in hydrazide derivatives, which may lead to higher energy associated with dipole alignment in equatorial conformations of hydroxylamines compared to hydrazides. A suggests that the anomeric effect is not enough to nullify the influence of sterics in these derivatives [73].

In 2019, Ortega and collaborators [74] observed a series of pyranoside derivatives containing carbon, silicon, and germanium as anomeric centers using second-order Møller-Plesset (MP2)/aug-cc-pVDZ perturbation theory along with electronic structure calculations of bonding orbitals natural (NBO). Under these conditions, the conformational preference for the axial shape (α) can be explained in terms of the incidence of the endo-anomeric effect. A larger magnitude of the anomeric effect was observed for compounds with carbon as the anomeric center, which was explained by greater anomeric hyperconjugation in the α conformers. As for compounds containing Si and Ge, therefore, steric and electrostatic factors are responsible for the conformational α arrangement in the compounds, therefore the smaller magnitude observed in the anomeric effect was attributed to the availability of energetically accessible vacant d-type orbitals [74].

Recently, Alkhodier and coworkers [75] performed studies analyzing the comparative conformational properties of glycosidic bonds in *O-, C-* and *CF2-* glycosides using NMR spectroscopy and molecular dynamics (MD). In *O*-glycosides, the stabilization of the stereoelectronics is observed in the overlapping of the non-bonding orbital of the oxygen atom with the anti-bonding orbital of the C1″-O5″ bond through the sugar moiety, generating an antiperiplanar or gauche conformation attributed to the exo-anomeric effect. The replacement of the oxygen atom by a carbon atom in C-glycosides results in the absence of the anomeric effect and greater conformational flexibility. Different from the previously cited conformational behavior, *CF2* glycosides differ from O- or C-glycosides. This is due to the low-energy (σ*) antibonding sigma orbital of the C−F bond that can be an electron density acceptor in hyperconjugation interacting with the sigma (σ) bond orbital of the neighboring C-H bond or the C-C bond in the smaller scale. In addition, the π system or O5″ lone pairs can also act as a donor. All this can contribute to the stability of high-energy conformations, often leading to gauche conformers, as conformations that align the donor with the σ*$O$ $C{-}F$ bonding orbital will be preferable [75].

## 3. NATURE OF THE ANOMERIC EFFECTS IN CARBOHYDRATE CHEMISTRY

In the previous sections some evidence of the anomeric effect was presented, we can thus understand its influence on the formation of carbohydrates and other heterocyclics that have anomeric carbon. In this section, we will discuss a little about the nature of the anomeric effect.

The nature of the anomeric effect is the subject of much discussion by researchers, it can be rationalized according to electrostatic and hyperconjugation effects, although some researchers believe that this effect is the result of multiple influences, as reported in tetrahydro-2H-pyran and oxazinane rings where the origin of

the effect is complex, being attributed to a balance between non-covalent effects (weak van der Waals forces, dipole-dipole, electrostatic forces, hydrogen bonds) and hyperconjugative interactions that lead to the anomeric effect [76].

However, some researchers do not have a consensus on the origin of the anomeric effect, Bauerfrldt et al. [77] revealed using the Hartree-Fock expression that the exchange effect dominates the anomeric effect, concluding that this effect has no electrostatic origin. Percelin et al. [78] managed to demonstrate pseudo-anomeric effects by placing difluoromethylene groups adjacent to axial hydrogens at C-3 in methoxycyclohexane, and observed that the electrostatic effect outweighs hyperconjugation, although the delocalization effect is the most used rationalization to describe the anomeric effect.

Being the concept most discussed by researchers to try to rationalize the anomeric effect, hyperconjugation involves delocalization of the lone electron pair of oxygen, in the adjacent antibonding σ* orbital of the C(1)−X unit; when the X group is in the axial position this stabilizing interaction is more effective because the lone pair on oxygen and the axial C−X bond are antiperiplanar this interaction leads to an elongation of the axial C(1)−X bond and a shortening of the C(1)-O bond. A study by Changwei Wang et al. [79] reports the widespread anomeric effect and concluded that it exists ubiquitously in acyclic systems containing heteroatoms, with a gauche conformer preferred over an anti-conformer for an R-X-C-Y moiety.

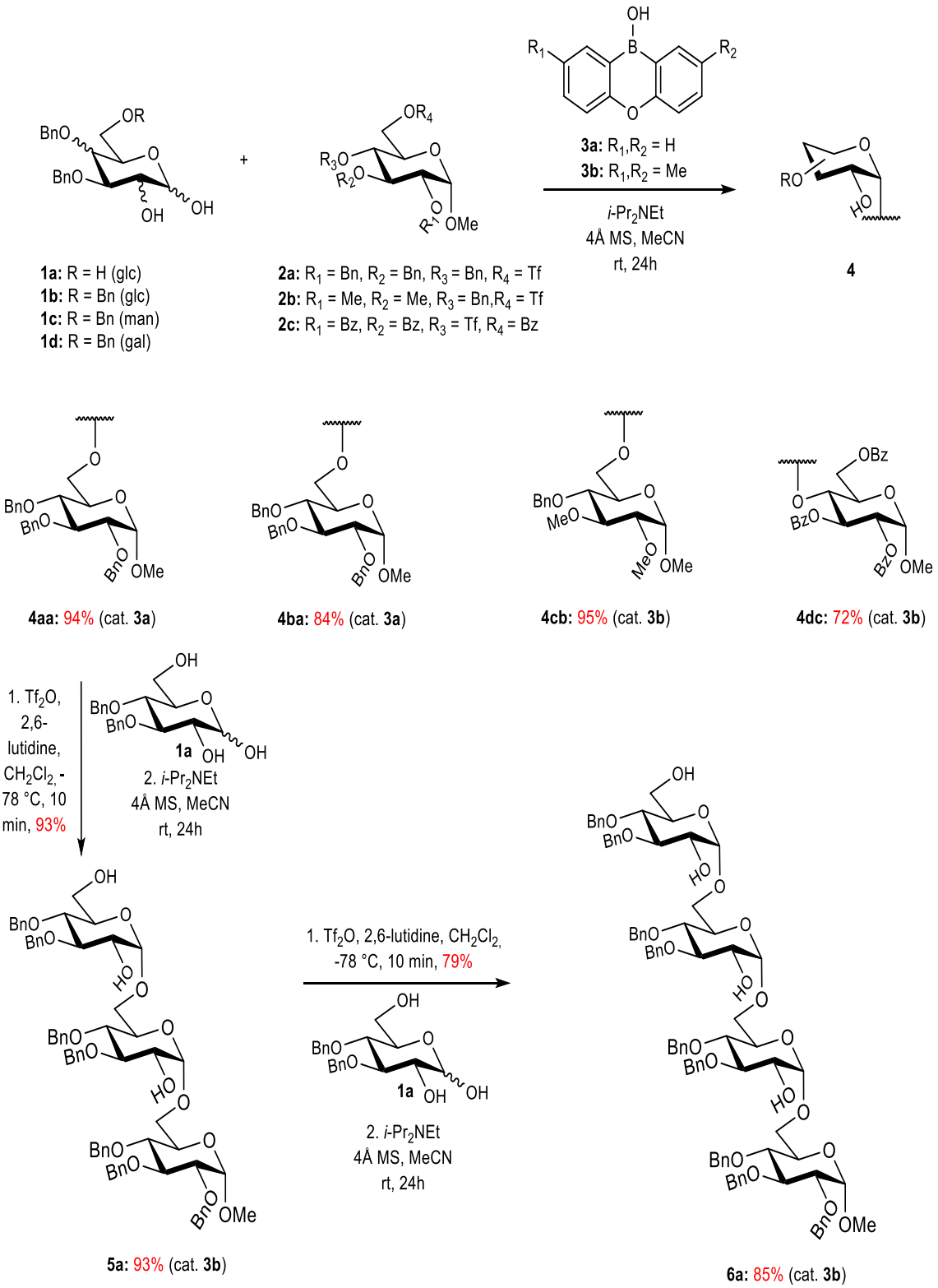
Freitas [80] observed that the orbitals of natural bonds may or may not contribute to the anomeric effect, this factor will depend on the substituent on the anomeric carbon, in addition to the medium to which the 2-CN-THP is inserted, the hyperconjugation effect has a very important contribution strong in the gas phase, but competitive for Lewis-type interactions using the implicit water model. Another very interesting observation was made by Nori-Shargh et al. [81] in which the exo- and endo hyperconjugative anomeric interactions in compounds such as 2-fluorotetrahydropian, selenopyrans and anoles, the most stable conformers were the equatorial ones in relation to the axial ones, configuring the anomeric effect rationalized by the hyperconjugation.

## 4. IMPORTANCE OF THE ANOMERIC EFFECT IN THE REACTIVITY OF CARBOHYDRATES

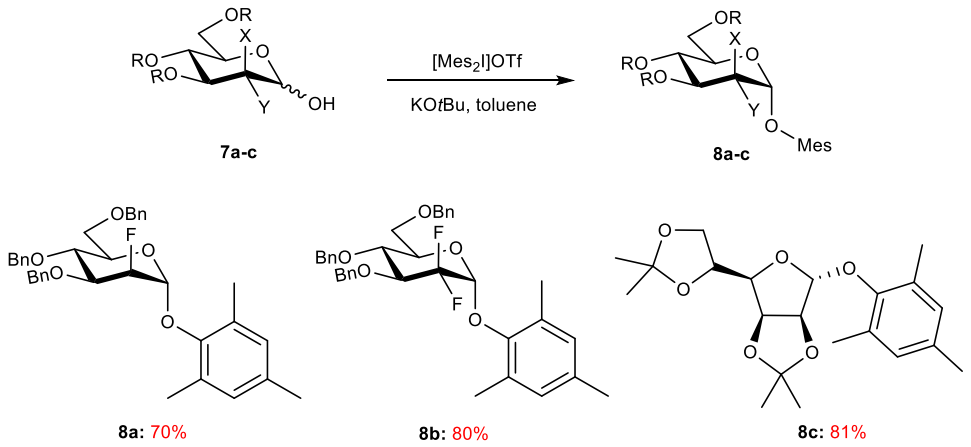
The diversity in glycosylation methods holds the possible ways to obtain stereoselective products. The small clipping in the last ten years contemplates a series of studies with quite satisfactory results in the face of the complexity and difficulty of reactions in glycosides chemistry. In the field of glycosides, the literature is vast by the anomeric reactivity providing to create new molecular designs, but the difficulty lies in the anomeric stereocontrol making attractive ideas that potentiate the anomeric effect, as was described by a series of regio- and stereoselective syntheses with modulation of the steric and electronic aspects of the manno-, galacto- and glycopyranosyl benzyl donors caused by the catalysis of cyclic borinic acid analogs with glycosyl and galactosyl receptors, producing exclusively 1,4- and 1,6-α-*O*-disaccharides and 1,6-α-*O*-oligosaccharides with excellent yields, presenting an efficient method for obtaining oligosaccharides with innovation in the orientation of the anomeric hydroxyl by the anchimeric assistance of the activator in the axial position, Scheme 1 [82].

New glycosylation methods are being developed all the time with easily accessible, low-cost, and highly stereoselective reagents. Reported a series of electrophilic iodine arylating reagents in the presence of pyranosyl and furanosyl derivatives in a basic medium promoting high efficiency by reductive elimination to alpha-glycoside with favoring the anomeric effect due to the stereoelectronic effect of electronegative substituents at C-2 without the need for activation of the anomeric carbon by the formation of the iodonic intermediate, achieving the preparation of stereoselective *O*-glycosides with a range of aglycones in excellent yields, Scheme 2 [83].

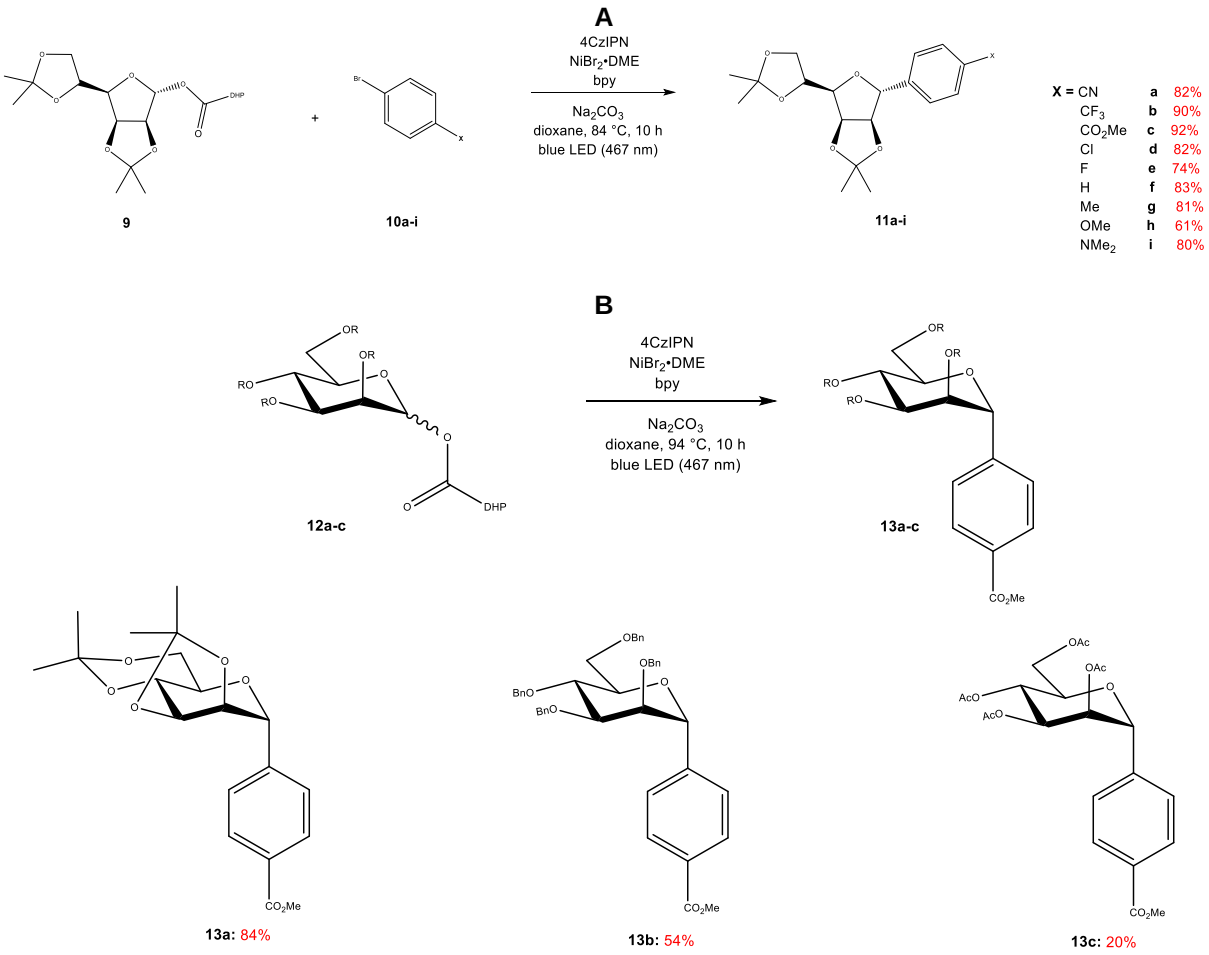
Recently, radical reactions were able to promote stereoanomeric control in the synthesis of *C*-glycosides in excellent yields from furanoside (**A**) and pyranoside (**B**) upon activation of nickel salts doped with electron-donating agents capable of inducing via redox-homolytic photochemical cleavage and coupling with varied aryl halides, finding efficient diastereoselective methods in *C*-glycosylation by the influence of the nickel complex in guiding the formation of the glycosidic bond, Scheme 3 [84].




**Scheme 1. Synthesis of oligosaccharides by tricyclic borinic acid**




**Scheme 2. *O*-glycosides with iodine arylating reagent**




**Scheme 3. *C*-glycosylation catalyzed by nickel complex**

The glycosylation protocol is a constant building block for the wide varieties of glycosyl donors that effectively contribute to the stereoisomeric control of the final product, requiring appropriate and specific reaction conditions to influence the anomeric behavior and contribute to the anomeric effect. Thus, it is a never-ending quest to achieve such goals by the varied factors governing the chemistry of glycosides [85].

## 5. CONCLUSION

The anomeric effect is a well-defined and much-studied example in carbohydrate chemistry. It involves a fundamental interaction between the lone pair electrons of oxygen and the antibonding orbitals of adjacent bonds, which can control not only conformation but also reactivity in suitable systems.

The anomeric effect can play the axial positions in carbohydrates because of the free Gibbs energy, the chair conformation, shortening of determined bonds C-O and electrostatic repulsions between atoms, interactions of the p orbitals from anomeric carbon, and the heteroatom of the aglycone in the glycosidic bond. It depends on the temperature, solvent, catalysis, and press, among other things. Studies over time could calculate the anomeric effect. Another point is about the determinants of this, which can be hyperconjugation, electrostatic effects, non-covalent forces, or other factors. For years, many studies have included reactions with anomeric effect, providing novel molecular designs of carbohydrates.

On the other hand, the anomeric effect in a pyranose sugar or derivative thereof is the term, also referred to as the Edward–Lemieux effect that denotes the tendency of a polar group at the anomeric carbon to favor the axial position. The anomeric effect has been assigned as being due to hyperconjugation, electrostatic/steric interactions, or exchange effects; thus, there is no general consensus about its actual origin.

## ACKNOWLEDGEMENTS

The authors are grateful to the Brazilian National Research Council (CNPq), FACEPE (APQ 1037-1.06/2021) and Coordination for the Improvement of Higher Education Staff (CAPES) for financial support.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Souza Neto PR, Guimarães BM, Freitas JJR, Oliveira RN, Freitas Filho JR. Development in glycosylation Methods: A key to accessing their applications in the synthesis of bioactive molecules. Quim. Nova. 2020;44(4):432–459. DOI:10.21577/0100-4042.20170676
2. Tursi A. A review on biomass: Importance, chemistry, classification, and conversion. Biofuel Res. J. 2019;6(2):962-979. DOI:10.18331/BRJ2019.6.2.3
3. Melo VN, Dantas WM, Camara CA, De Oliveira RN. Synthesis of 2,3-Unsaturated Alkynyl O-Glucosides from Tri-O-Acetyl-d-Glucal by Using Montmorillonite K-10/Iron(III) Chloride Hexahydrate with Subsequent Copper(I)-Catalyzed 1,3-Dipolar Cycloaddition. Synth. 2015;47(22): 3529–3541. DOI:10.1055/s-0034-1378829
4. Crucho CIC, Correia-Da-Silva P, Petrova KT, Barros MT. Recent progress in the field of glycoconjugates. carbohydr. Res. 2015;402:124–132. DOI:10.1016/j.carres.2014.10.005
5. Motta VT. Bioquímica Básica. 2.Ed. MedBook, 2023. ISBN-10: 8599977660, ISBN-13: 978-8599977668.
6. Miljkovic M. Carbohydrates: Synthesis, mechanisms, and stereoelectronic effects. Springer Science & Business Media; 2009. ISBN 978-0-387-92264-5. DOI: 10.1007/978-0-387-92265-2
7. Vetter ND, Jagdhane RC, Richter BJ, Palmer DRJ. Carbocyclic substrate analogues reveal kanosamine biosynthesis begins with the α-anomer of glucose 6-phosphate. ACS Chem. Biol. 2020;15(8): 2205–2211. DOI:10.1021/acschembio.0c00409
8. Haraguchi K, Kumamoto H, Tanaka H. 4-Thiofuranoid glycal: Versatile glycosyl donor for the selective synthesis of β-anomer of 4-thionucleoside and its Biological Activities. Curr. Med. Chem. 2022;29(21):3684-3731. DOI:10.2174/0929867328666211115121434
9. Gomes, GDP, Alabugin I. Chapter 15 stereoelectronic effects: Analysis by computational and theoretical methods. Book: Applied Theoretical Organic Chemistry. World Scientific. 2017;451-502. DOI:10.1142/9781786344090_0015
10. McMahon CM, Isabella CR, Windsor IW, Kosma P, Raines RT, Kiessling LL. Stereoelectronic Effects Impact Glycan Recognition. J Am Chem Soc. 2020; 142(5):2386-2395. DOI:10.1021/jacs.9b11699

11. Mo Y, Jiao H, Schleyer PVR. Hyperconjugation effect in substituted methyl boranes: An orbital deletion procedure analysis. J. Org. Chem. 2004; 69(10):3493–3499.
DOI:10.1021/jo035724i
12. Alabugin IV, Dos Passos Gomes G, Abdo MA. Hyperconjugation. WIREs Comput. Mol. Sci. 2019;9:e1389.
DOI:10.1002/wcms.1389
13. Ahrland S, Chatt J, Davies NR. The relative affinities of ligand atoms for acceptor molecules and ions. Q. Rev. Chem. Soc. 1958;12(3):265–276.
DOI:10.1039/QR9581200265
14. Pearson R, Songstad J. Application of the principle of hard and soft acids and bases to organic chemistry. J. Am. Chem. Soc. 1967;89(8):1827-1836.
DOI: 10.1021/ja00984a014
15. Ho TL. The Hard Soft Acids Bases (HSAB) principle and organic chemistry. Chem. Rev. 1975;75(1):1-20.
DOI:10.1021/cr60293a001
16. Hass K. Inoranic Chemistry. LibreTexts by UC davis library, the California State university affordable learning solutions program, and merlot. National Science Foundation: 1246120, 1525057, and 1413739; 2023.
17. Martins FA, Silla JM, Freitas MP. Theoretical study on the anomeric effect in α-substituted tetrahydropyrans and piperidines. Carbohydr. Res. 2017;451(8):29-35.
DOI:10.1016/j.carres.2017.09.007
18. Wang C, Ying F, Wu W, Mo Y. How solvent influences the anomeric effect: Roles of hyperconjugative versus steric interactions on the conformational preference. J. Org. Chem. 2014;79(4):1571–1581.
DOI:10.1021/jo402306e
19. Cocinero EJ, Carcabal P, Vaden TD, Simons JP, Davis BG. Sensing the anomeric effect in a solvent-free environment. Nature. 2011;469 (7328):76-79.
DOI:10.1038/nature09693
20. Ortega PGR, Montejo M, Valera MS, González JJL. Anomeric effect in pyranose-ring derivatives containing carbon, silicon, and germanium as anomeric centers: an ab initio systematic study. Struct. Chem. 2019; 30:2245-2255.
DOI:10.1007/s11224-019-01336-7
21. Buffington LA, Blackburn DW, Hamilton CL, Jarvis TC, Knowles JJ, Lodwick PA, McAllister LM, Neidhart DJ, Serumgard JL. Effects of Solvent and Anomeric Configuration upon the Circular Dichroism, Temperature Dependence of Amide Proton Chemical Shifts, Amide Proton Exchange Rates, and Infrared Absorption of Methyl 2-Acetamido-2-deoxy-D-glucopyranoside. J. Am. Chem. Soc. 1989;111 (7):2451-2454.
DOI:10.1021/ja00189a013
22. Praly JP, Lemieux RU. Influence of solvent on the magnitude of the anomeric effect. Can. J. Chem. 1987;65(1):213-223.
DOI:10.1139/v87-034
23. Piscelli BA, OHagan D, Cormanich RA. Contribution of hyperconjugation and inductive effects to the pseudo-anomeric effect in 4-substituted methoxycyclohexanes. J. Phys. Chem. A 2023;127(3): 724-728.
DOI:10.1021/acs.jpca.2c08090
24. Wiberg KB, Bailey WF, Lambert KM, Stempel ZD. The anomeric effect: Its Complicated. J. Org. Chem. 2018; 83(9):5242–5255.
DOI:10.1021/acs.joc.8b00707
25. Nori-Shargh D, Mousavi SN, Tale R, Yahyaei H. Hyperconjugative interactions are the main responsible for the anomeric effect: A direct relationship between the hyperconjugative anomeric effect, global hardness and zero-point energy. Struct. Chem. 2016;27(6):1753–1768.
DOI:10.1007/s11224-016-0791-0
26. Risley JM, Van Etten RL. Kinetics of oxygen exchange at the anomeric carbon atom of d-glucose and d-erythrose using the oxygen- 18 isotope effect in carbon- 13 nuclear magnetic resonance spectroscopy. Biochemistry. 1982;21(25):6360–6365.
DOI:10.1021/bi00268a007
27. Achilonu MC, Umesiobi DO. The formation of carbon–carbon and carbon–heteroatom bonds using silver tetrafluoroborate as a promoter. Arab. J. Chem. 2016; 9(2):S1984-S2003.
DOI:10.1016/j.arabjc.2015.06.038
28. Singh K, Tyagi R, Mishra VK, Tiwari G, Sagar R. Recent advances in the synthesis of bioactive glycohybrids via click-chemistry. SynOpen 2023;07(03):322-352.
DOI:10.1055/a-2130-7319
29. Downey AM, Hocek M. Strategies toward protecting group-free glycosylation through selective activation of the anomeric center. Beilstein J. Org. Chem. 2017;13: 1239-1279.
DOI:10.3762/bjoc.13.123

30. Park SS, Hsieh HW, Gervay-Hague J. Anomeric o-functionalization of carbohydrates for chemical conjugation to vaccine constructs. Molecules. 2018; 23(7):1742-1765.
DOI:10.3390/molecules23071742
31. Zhu F, Rodriguez J, Yang T, Kevlishvili I, Miller E, Yi D, ONeill S, Rourke MJ, Liu P, Walczak MA. Glycosyl cross-coupling of anomeric nucleophiles: scope, mechanism, and applications in the synthesis of aryl c-glycosides. J. Am. Chem. Soc. 2017;139(49):17908–17922.
DOI:10.1021/jacs.7b08707
32. Demchenko AV. Handbook of chemical glycosylation: advances in stereoselectivity and therapeutic relevance. Willey-VCH. 2008;1-27. ISBN:9783527317806 ISBN:9783527621644.
DOI:10.1002/9783527621644
33. Cao X, Liu S, Rong C, Lu T, Liu S. Is there a generalized anomeric effect? Analyses from energy components and information-theoretic quantities from density functional reactivity theory. Chem. Phys. Lett. 2017;687(1):131-137.
DOI:10.1016/j.cplett.2017.09.017.
34. Zhou X, Yu D, Rong C, Lu T, Liu S. Anomeric effect revisited: Perspective from information-theoretic approach in density functional reactivity theory. Chem. Phys. Lett. 2017;684(16):97-102.
DOI:10.1016/j.cplett.2017.06.048.
35. Juaristi E, Bandala Y. Chapter 2 - anomeric effect in saturated heterocyclic ring systems. Ad. in Het. Chem. 2012;105:189-222.
DOI:10.1016/B978-0-12-396530-1.00002-4
36. Wang C, Chen Z, Wu W, Mo Y. How the generalized anomeric effect influences the conformational preference. Chem. - A Eur. J. 2012; 19(4):1436–1444.
DOI:10.1002/chem.201203429.
37. Liu S. Origin and Nature of Bond Rotation Barriers: A Unified View. J. Phys. Chem. A 2013;117(5):962-965.
DOI:10.1021/jp312521z
38. Eliel EL, Reese MC. Conformational analysis. XV. Conformational enthalpy, entropy, and free energy of the carboxyl, carboxylate, carbomethoxy, carbonyl chloride, and methyl ketone groups. J. Am. Chem. Soc. 1968;90(6):1560-1566.
DOI:10.1021/ja01008a029
39. Booth H, Khedhair KA, Readshaw SA. Experimental studies of the anomeric effect: Part I. 2-substituted tetrahydropyrans. Tetrahedron 1987; 43(20):4699-4723.
DOI:10.1016/S0040-4020(01)86912-X
40. Lavecchia MJ, Rodríguez OM, Echeverría GA, Diez RP, Colinas PA. Conformational behavior of peracetylated β-d-mannopyranosyl methanesulfonamide: Implications for the mechanism of sulfonamidoglycosylation of carbohydrate derivatives. Carbohydr. Res. 2012; 361:182-188.
DOI:10.1016/j.carres.2012.08.016
41. Silva CODA. Anomeric effect in carbohydrates: Facts and hypothesis. Rev. Virt. Quím. 2011;3(4):235-246.
DOI:10.5935/1984-6835.20110031
42. Juaristi E, Cuevas G. Recent studies of the anomeric effect. Tetrahedron 1992;48(24):5019-5087.
DOI:10.1016/S0040-4020(01)90118-8
43. Wiberg KB, Bailey WF, Lambert KM, Stempel ZD. The anomeric effect: Its complicated. J. Org. Chem. 2018;83(9): 5242-5255.
DOI:10.1021/acs.joc.8b00707
44. Filloux CM. The problem of origins and origins of the problem: Influence of language on studies concerning the anomeric effect. Angew. Chemie Int. 2015;54(31):8880–8894.
DOI:10.1002/anie.201411185.
45. Freitas MP. The anomeric effect on the basis of natural bond orbital analysis. Org. Biomol. Chem. 2013;11(17):2885–2890.
DOI:10.1039/C3OB40187A
46. Alabugin IV, Kuhn L, Medvedev MG, Krivoshchapov NV, Vil VA, Yaremenko IA, Mehaffy P, Yarie M, TerentEv AO, Zolfigol MA. Stereoelectronic power of oxygen in control of chemical reactivity: The anomeric effect is not alone. Chem. Soc. Rev. 2021;50(18):10253–10345.
DOI:10.1039/D1CS00386K
47. Gubica T, Zimniak A, Szeleszczuk Ł, Dąbrowska K, Cyrański MK, Kańska M. Influence of Acetylation on Anomeric Effect in Methyl Glycosides. Mol. Phys. 2019; 117(3):349–358.
DOI:10.1080/00268976.2018.1512723
48. Alabugin IV, Kuhn L, Krivoshchapov NV, Mehaffy P, Medvedev MG. Anomeric Effect, Hyperconjugation and Electrostatics: Lessons from Complexity in a Classic Stereoelectronic Phenomenon. Chem. Soc. Rev. 2021;50(18):10212–10252.
DOI:10.1039/D1CS00564B

49. Ishiwata A, Munemura Y, Ito Y. Synergistic solvent effect in 1,2-cis-glycoside formation. Tetrahedron. 2008;64(1):92-102.
DOI:10.1016/j.tet.2007.10.087

50. Heuckendorff M, Pedersen CM, Bols M. Rhamnosylation: Diastereoselectivity of Conformationally Armed Donors. J. Org. Chem. 2012;77(13):5559–5568.
DOI:10.1021/jo300591k

51. Nigudkar SS, Demchenko AV. Stereocontrolled 1,2-cis glycosylation as the driving force of progress in synthetic carbohydrate chemistry. Chem Sci. 2015; 6:2687-2704.
DOI:10.1039/C5SC00280J

52. Kafle A, Liu J, Cui L. Controlling the stereoselectivity of glycosylation via solvent effects. Canad. J. Chem. 2016; 94(11):894-901.
DOI:10.1139/cjc-2016-0417

53. Zhang Y, He H, Chen Z, Huang Y, Xiang G, Li P, Yang X, Lu G, Xiao G. Merging reagent modulation and remote anchimeric assistance for glycosylation: Highly stereoselective synthesis of α-glycans up to a 30-mer. Angew. Chemie Int. Ed. 2021;25(60):12597-12606.
DOI:10.1002/anie.202103826

54. Komarova BS, Tsvetkov YE, Nifantiev NE. Design of α-selective glycopyranosyl donors relying on remote anchimeric assistance. Chem. Record 2016;16(1):488-506.
DOI:10.1002/tcr.201500245

55. Das R, Mukhopadhyay B. Chemical O-Glycosylations: An Overview. ChemistryOpen. 2016;5(5):401-433.
DOI:10.1002/open.201600043

56. Bennett CS, Galan MC. Methods for 2-Deoxyglycoside Synthesis. Chem. Rev. 2018;118(17):7931–7985.
DOI:10.1021/acs.chemrev.7b00731

57. Adero PO, Amarasekara H, Wen P, Bohé L, Crich D. The experimental evidence in support of glycosylation mechanisms at the SN1-SN2 Interface. Chem. Rev. 2018;118(17):8242–8284.
DOI:10.1021/acs.chemrev.8b00083

58. Yadav RN, Hossain F, Das A, Srivastava AK, Banik BK. Organocatalysis: A Recent Development on Stereoselective Synthesis of o-Glycosides. Catal. Rev. Sci. Eng. 2022;00(00):1–118.
DOI:10.1080/01614940.2022.2041303

59. Bauer EB. Transition metal catalyzed glycosylation reactions-an overview. Org. Biomol. Chem. 2020;18:9160-9180.
DOI:10.1039/D0OB01782E

60. Frihed TG, Bols M, Pedersen CM. Mechanisms of glycosylation reactions studied by low-temperature nuclear magnetic resonance. Chem. Rev. 2015; 115(11):4963–5013.
DOI:10.1021/cr500434x

61. Gõmez AM, Lobo F, Uriel C, Lõpez JC. Recent developments in the ferrier rearrangement. Eur. J. Org. Chem. 2013; 32:7221–7262.
DOI:10.1002/ejoc.201300798

62. Kitowski A, Jiménez-Moreno E, Salvadó M, Mestre J, Castillón S, Jiménez-Osés G, Boutureira O, Bernardes GJL. Oxidative activation of c-s bonds with an electropositive nitrogen promoter enables orthogonal glycosylation of alkyl over phenyl thioglycosides. Org. Lett. 2017;19 (19):5490–5493.
DOI:10.1021/acs.orglett.7b02886

63. Williams R, Galan MC. Recent advances in organocatalytic glycosylations. Eur. J. Org. Chem. 2017;42:6247–6264.
DOI:10.1002/ejoc.201700785

64. Pal R, Das A, Jayaraman N. One-pot oligosaccharide synthesis: Latent-active method of glycosylations and radical halogenation activation of allyl glycosides. Pure Appl. Chem. 2019;91(9):1451–1470. DOI:10.1515/pac-2019-0306

65. Sletten ET, Tu YJ, Schlegel HB, Nguyen HM. Are brønsted acids the true promoter of metal-triflate-catalyzed glycosylations? A Mechanistic Probe into 1,2- Cis-Aminoglycoside Formation by Nickel Triflate. ACS Catal. 2019;9(3):2110–2123.
DOI:10.1021/acscatal.8b04444

66. Yarie M. Catalytic vinylogous anomeric based oxidation (part I). Iran. J. Catal. 2020;10(1):79-83.
Available:https://journals.iau.ir/article_669880_9c50583cbb6c155d42cf668496df2977.pdf

67. Sepehrmansourie H, Zarei M, Zolfigol MA, Babaee S, Azizian S, Rostamnia S. Catalytic synthesis of new pyrazolo [3,4-b] pyridine via a cooperative vinylogous anomeric-based oxidation. Scient. Reports. 2022;12(1):14145-14160.
DOI:10.1038/s41598-022-17879-5.

68. Wang C, Chen Z, Wu W, Mo Y. How the generalized anomeric effect influences the conformational preference. Chem. 2013; 19(4):1436-1444.
DOI:10.1002/chem.201203429.

69. Nigudkar SS, Demchenko AV. Stereocontrolled 1,2-cis glycosylation as the driving force of progress in synthetic carbohydrate chemistry. Chem Sci. 2015;6(5):2687-2704.
DOI:10.1039/C5SC00280J

70. Sasaki M, Gama Y, Yasumoto M, Ishigami Y. Glycosylation reaction under high-pressure. Tetrahedron Lett. 1990, 31, 6549-6552.

71. Spijker NM, van Boeckel CAA. Double stereodifferentiation in carbohydrate coupling reactions: The mismatched interaction of donor and acceptor as an unprecedented factor governing the $\alpha/\beta$-ratio of glycoside formation. Angew. Chem. Int. Edit. Engl. 1991;30:180-183.
DOI:10.1002/ANIE.199101801

72. Szczepaniak M, Moc J. Conformational studies of gas-phase ribose and 2-deoxyribose by density functional, second order PT and multi-level method calculations: the pyranoses, furanoses, and open-chain structures. Carbohydr. Res. 2014;384:20–36.
DOI:10.1016/j.carres.2013.10.013
Langenhan JM, McLaughlin RP, Loskot SA, Rozal LM, Clay MS, Alaimo PJ. Using density functional theory to calculate the anomeric effect on hydroxylamine and tetrahydropyran hydrazide derivatives. J. Carbohydr. Chem. 2016;35(2):106–117.
DOI:10.1080/07328303.2016.1139122

73. Khan D, Duarte LJ, Popelier PLA. An interacting quantum atoms (iqa) and relative energy gradient (reg) analysis of the anomeric effect. Molecules. 2022; 27:5003.
Available:https://doi.org/10.3390/molecules 27155003.

74. Alkhodier RA, Mishra SK, Doerksen RJ, Colby DA. Comparison of conformational analyses of naturally occurring flavonoid-o-glycosides with unnatural flavonoid-cf2-glycosides using molecular modeling. J. Chem. Inf. Mod. 2023;63(1):375-386.
DOI:10.1021/acs.jcim.2c01147.

75. Tsipis CA, Bakalbassis EG, Zisopoulou SA, Gallos JK. Probing the anomeric effect and mechanism of isomerization of oxazinane rings by DFT methods. Org. Biomol. Chem. 2021;19(5):1066-1082.
DOI:10.1039/d0ob02453h

76. Bauerfeldt GF, Cardozo TM, Pereira MS, Silva, CODA. The anomeric effect: The dominance of exchange effects in closed-shell systems. Org. Biomol. Chem. 2013;11:299-308.
DOI:10.1039/C2OB26818C

77. Piscelli BA, Sanders W, Yu C, Al Maharik N, Lebl T, Cormanisch RA, OHagan D. Fluorine induced pseudo-anomeric effects in methoxycyclohexanes through electrostatic 1,3-diaxial interactions. Chem. Eur. J. 2020;26(52):11989-11994.
DOI:10.1002/chem.202003058

78. Wang C, Chen Z, Wu W, Mo Y. How the generalized anomeric effect Influences the conformational preference. Chem. 2013; 19(4):1436-1444.
DOI:10.1002/chem.201203429

79. Freitas MP. The anomeric effect on the basis of natural bond orbital analysis. Org Biomol Chem. 2013;11(17):2885-2890.
DOI:10.1039/C3OB40187A

80. Nori-Shargh D, Mousavi SN, Tale R, Yahyaei H. Hyperconjugative interactions are the main responsible for the anomeric effect: A direct relationship between the hyperconjugative anomeric effect, global hardness and zero-point energy. Struct Chem. 2016;27(6):1753-1768.
DOI:10.1007/s11224-016-0791-0

81. Izumi S, Kobayashi Y, Takemoto Y. Regio- and stereoselective synthesis of 1,2- cis-glycosides by anomeric o-alkylation with organoboron catalysis. Org. Lett. 2019;21(3):665–670.
DOI:10.1021/acs.orglett.8b03823

82. Lucchetti N, Gilmour R. Reengineering chemical glycosylation: Direct, metal-free anomeric o-arylation of unactivated carbohydrates. Chem. Eur. J. 2018; 24(61):16266–16270.
DOI:10.1002/chem.201804416

83. Wei Y, Ben-zvi B, Diao T. Diastereoselective synthesis of aryl c -glycosides from glycosyl esters via c−o bond homolysis. Angew. Chemie. 2021; 133(17):9519–9524.
DOI:10.1002/anie.202014991

84. Gaweda K, Plazinski W. The endo- and exo-anomeric effects in furanosides. A

Computational Study. Eur. J. Org. Chem. 2020;6:674-679.
DOI:10.1002/ejoc.201901473

85. Daneshpajuh M, Hasanzadeh N. Study of influence of anomeric effect on conformational preferences using hybrid density functional theory (dft) and natural bond orbital (nbo) interpretation. Rev. Roum. Chim. 2023;68(1–2):61–74.
DOI:10.33224/rrch.2023.68.1-2.06



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