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## ЭКСПЕРТНОЕ ЗАКЛЮЧЕНИЕ О ВОЗМОЖНОСТИ ОПУБЛИКОВАНИЯ

Руководитель-эксперт Федерального государственного бюджетного учреждения науки Института элементоорганических соединений им. А.Н.Несмеянова Российской академии наук, рассмотрев статью авторов I. V. Alabugin, L. Kuhn, M. G. Medvedev, N. V. Krivoshchapov, V.A. Vil', I. A. Yaremenko, P. Mehaffy, M. Yarie, A. O. Terent'ev & M. A. Zolfigol «Stereo-electronic power of oxygen in control of chemical reactivity: the anomeric effect is not alone», подготовленную для печати в журнале *ChemSocRev*, подтверждает, что в материале не содержатся сведения, предусмотренные Постановлением Правительства РФ №1233 от 30.11.1994г. и на публикацию материала не следует получать разрешение Минобрнауки и/или Президиума РАН

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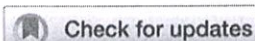
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## Stereoelectronic power of oxygen in control of chemical reactivity: the anomeric effect is not alone

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Although carbon is the central element of organic chemistry, oxygen is the central element of stereoelectronic control in organic chemistry. Generally, a molecule with a C–O bond has both a strong donor (a lone pair) and a strong acceptor (e.g., a  $\sigma^*_{C-O}$  orbital), a combination that provides opportunities to influence chemical transformations at both ends of the electron demand spectrum. Oxygen is a stereoelectronic chameleon that adapts to the varying situations in radical, cationic, anionic, and metal-mediated transformations. Arguably, the most historically important stereoelectronic effect is the anomeric effect (AE), *i.e.*, the axial preference of acceptor groups at the anomeric position of sugars. Although AE is generally attributed to hyperconjugative interactions of  $\sigma$ -acceptors with a lone pair at oxygen (negative hyperconjugation), recent literature reports suggested alternative explanations. In this context, it is timely to evaluate the fundamental connections between the AE and a broad variety of O-functional groups. Such connections illustrate the general role of hyperconjugation with oxygen lone pairs in reactivity. Lessons from the AE can be used as the conceptual framework for organizing disjointed observations into a logical body of knowledge. In contrast, neglect of hyperconjugation can be deeply misleading as it removes the stereoelectronic cornerstone on which, as we show in this review, the chemistry of organic oxygen functionalities is largely based. As negative hyperconjugation releases the “underutilized” stereoelectronic power of unshared electrons (the lone pairs) for the stabilization of a developing positive charge, the role of orbital interactions increases when the electronic demand is high and molecules distort from their equilibrium geometries. From this perspective, hyperconjugative anomeric interactions play a unique role in guiding reaction design. In this manuscript, we discuss the reactivity of organic O-functionalities, outline variations in the possible hyperconjugative patterns, and showcase the vast implications of AE for the structure and reactivity. On our journey through a variety of O-containing organic functional groups, from textbook to exotic, we will illustrate how this knowledge can predict chemical reactivity and unlock new useful synthetic transformations.

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### Organic chemistry of oxygen-containing functional groups through the prism of the anomeric effect

Oxygen is one of the key elements of the chemical universe with many important biological functions including respiration,

photosynthesis, and biosynthesis. Furthermore, in combination with carbon, oxygen is also an essential architectural component for the construction of organic molecules. Like a sprinkle of spice, incorporation of oxygen adds many useful properties including polarity, H-bond formation, hydrophilicity, Lewis basicity *etc.* that help to convert plain hydrocarbon molecules into medicinally active molecular entities. Not surprisingly, the O-containing functional groups, from ethers and alcohols to ketones and carboxylic acid derivatives, define much of undergraduate chemistry.

The role of oxygen in organic synthesis is equally profound. The reactivity patterns of O-functionalities are diverse with much of this diversity traceable to the chameleonic properties of this element, as oxygen combines high electronegativity with Lewis basicity. This combination is essential for creating controlled charge separation in nucleophilic and electrophilic

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fragmentations or an unexpected facilitating role of “bystander” substituents.

When needed, anomeric delocalization can be controlled. For example, H-bonding to oxygen can moderate its donor ability, while deprotonation of OH groups can dramatically activate negative hyperconjugation. Amplification of anomeric effects at anionic oxygen compounds is assisted by “stereoelectronic promiscuity” of negatively charged oxygen leading to cascade C–C fragmentations or unexpected roles of “bystander” substituents.

It is also important to say that, although our focus is on orbital interactions, one should not underestimate the importance of electrostatic, steric, dispersive interactions. They are also essential parts of the overall molecular puzzle. In particular, charges certainly matter. However, their influence generally comes, especially in neutral systems, from a combination of several components. In contrast, the predictive power of stereoelectronic analysis can often be traced down to a single dominant effect.

We hope that this review will be useful to a broad chemical audience – from theoretical physical chemists to industrial practitioners – because it can serve as the conceptual bridge between fundamental stereoelectronic interactions and the practical reactivity trends in omnipresent O-containing compounds. The stereoelectronic give-and-take of oxygen lone pairs and C–O orbitals with the neighboring functionalities can induce new reactivity features, define physical properties, and even serve as the main reason for certain oxygen-containing compounds to exist at the practical timescales.

## Conflicts of interest

There are no conflicts to declare.

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