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# A WEB AND SIMPLE CLICKS TO UNDERSTAND CHEMICAL CONCEPTS

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## Abstract

In the new era of machine learning and artificial intelligence, the project is designed to impart knowledge about ligands, substituents, and elements bonded to or surrounding a metal in a catalytic context. Leveraging successful web servers in the research field, the project enables researchers, irrespective of their computer chemistry expertise, to access pertinent information effortlessly. The methodology involves using a steric index, $\%V_{Bur}$, which gauges the occupancy in the metal's first sphere to reveal the catalytic performance of the corresponding catalyst. The web server, available at *https://www.aocdweb.com/OMtools/sambvca2.1/index.html*, facilitates the calculation of steric hindrance for any ligand (Poater et al., 2009; Falivene, 2016; Falivene et al., 2019; Liu, Montgomery, & Houk, 2011). For students in the Master in Advanced Catalysis and Molecular Modeling (MACMoM) program at the University of Girona, the project becomes an inspiring exercise. Through experimental and computational approaches, students correlate catalytic reaction pathway yields with the $\%V_{Bur}$ steric index. The exercise entails delving into past experimental results, manipulating xyz coordinates from X-Ray data, and employing linear and multilinear regressions. Importantly, each student in the class tackles a unique problem, fostering collaboration as solutions are shared within the group. This collaborative aspect not only aids in unraveling complex systems but also enhances the collective understanding of the intricacies involved. Emphasizing self-directed learning, the project encourages students to connect theory with results, promoting a deeper comprehension of the impact of specific groups.

***Keywords:*** *Chemistry, educational exercise, ligand, steric hindrance, project-based learning.*

## 1. Introduction

In the new era of machine learning and artificial intelligence, the project is tailored to impart knowledge about ligands, substituents, and elements bound to or surrounding a metal in a catalytic context. Leveraging successful web servers in the research field, the project aims to enable researchers, regardless of their expertise in computational chemistry, to effortlessly access relevant information.

A straightforward steric index like $\%V_{Bur}$ reveals how much space is occupied around the metal, indicating the effectiveness of the catalyst it belongs to (Poater et al., 2009). These web servers have been successful in research, where researchers, even those with limited knowledge of computational chemistry, can easily access relevant information with just a few clicks (Falivene, 2016; Falivene et al., 2019),

Choosing the best catalyst from a vast array of transition metal complexes is often done without a clear protocol (Liu et al., 2011). It is not due to negligence, but rather because there isn't a well-established understanding of what constitutes the best catalyst for each scenario. This decision is often based more on intuition than rationality. However, molecular descriptors offer a solution by organizing the catalyst space, similar to how enzymes work around their active sites (Wu et al., 2012). These descriptors quantitatively correlate the properties of the catalytic pocket with its experimental behavior. Understanding the interaction between the metal and the ligand is crucial in determining the stability, activity, and selectivity of the resulting catalyst (Poater et al., 2010).

Developing an effective catalyst involves shaping the catalytic pocket correctly. Achieving selectivity greater than 95% requires finding a catalyst that can differentiate between desired and undesired reactions by at least 2 kcal/mol. To increase certainty towards 100% selectivity, this difference should ideally be above 5 kcal/mol (Dehghani et al, 2019; Tabrizi et al., 2021). The challenge lies in developing descriptors capable of capturing subtle structural differences in the catalytic pocket, leading to more significant differences in energetic pathways. This strategy aims to pave the way for the in silico

design of new catalysts (Harper, Vilardi, & Sigman, 2013; Monreal-Corona, Pla-Quintana, & Poater, 2023; Fey, 2010).

The initial articles on $\%V_{Bur}$ and steric maps (Shams et al., 2022; Tomasini et al., 2021; Luque-Urrutia et al., 2017), along with their corresponding web servers, have garnered significant attention and citations since their publication, with thousands of citations worldwide (Escayola, Bahri-Laleh, & Poater, 2024). However, the lack of educational resources has motivated the redesign and simplification of discussions on organometallic reaction performance using web servers, with the aim of involving students in the process (Czerwinski et al., 2016).

The project focuses on indirectly teaching about ligands, substituents, and their interactions with metals. The selected reaction, the NHC–copper(I) halide-catalyzed direct alkynylation of trifluoromethyl ketones on water, was chosen not because it's perfect but because it provides ample data for analysis. In summary, the goal of this exercise is to use the SambVca 2.1 web application to calculate the $\%V_{Bur}$ index and steric maps of various complexes. By comparing different NHC complexes and others from the literature, the aim is to establish a linear relationship between $\%V_{Bur}$ and reaction yield or another relevant metric.

## 2. Methodology

The methodology involves the use of a steric index, $\%V_{Bur}$, which measures the occupancy in the metal's first coordination sphere to reveal the catalytic performance of the corresponding catalyst. The following website hosted the tool that allows anyone to calculate the steric hindrance of any ligand: https://www.molnac.unisa.it/OMtools/sambvca.php (Falivene et al., 2016; Falivene et al., 2019), that has been recently moved to https://www.aocdweb.com/OMtools/sambvca2.1/index.html. Changing the web server was not a whim, but rather to ensure that these servers are successful in their use, whether by researchers or undergraduate or master's students. It is necessary that they are not only easily accessible but also consistently accessible without suffering from connection interruptions from the institution they are associated with. In this sense, in 2023, the use of a professional web service that avoids such contingencies was considered.

The SambVca 2.1 web application was used to conduct calculations and obtain $\%V_{Bur}$ indexes and steric maps for the ligands under study. Essentially, $\%V_{Bur}$ serves as a descriptor to quantify the steric hindrance of ligands, particularly focusing on N-heterocyclic carbenes (NHCs), by considering the fraction of the first coordination sphere occupied by a ligand.

The use of a spherical section is because catalysis and substrate recognition typically occur within the first coordination sphere around the metal. However, the need for more comprehensive treatment of asymmetric ligands led to the development of steric maps. These maps depict the available surface area that ligands offer to substrates, defining the catalyst-substrate interaction and explaining the origin of enantioselectivity. Similar to physical maps depicting land and water features on Earth, steric maps use different colors and shading to represent elevations and differentiate between areas where ligands protrude towards reacting groups (brown areas) and areas where ligands withdraw from reacting groups (blue areas).

## 3. Results and discussion

For students in the Master's program in Advanced Catalysis and Molecular Modeling (MACMoM) at the University of Girona, the project serves as an inspiring exercise. Through experimental and computational approaches, students correlate the yields of catalytic reaction pathways with the $\%V_{Bur}$ steric index. The exercise involves delving into previous experimental results, manipulating xyz coordinates from X-ray data, and employing linear and multilinear regressions. It is noteworthy that each student in the class tackles a unique problem, fostering collaboration as solutions are shared within the group. This collaborative aspect not only aids in unraveling complex systems but also enhances the collective understanding of the involved intricacies. By emphasizing self-directed learning, the project encourages students to connect theory with results, promoting a deeper understanding of the impact of specific groups.

A comprehensive 4-hour laboratory exercise is proposed for, actually, any Master's program focusing on catalysis, tailored for classes comprising up to 20 students. The exercise aims to inspire students to grasp the intricate influence of 3D ligands on the metal's first coordination sphere. Moreover, it seeks to establish correlations between catalytic reaction yields and the $\%V_{Bur}$ steric index, calculated using the web server. So, it is not just about calculating the steric index; the goal is for students to find practical applications for it, making it a useful tool rather than just a calculation exercise. It is important for students to spend time thinking and reflecting on why a catalyst with ligands of varying steric hindrance might have a significant impact on a particular reaction (Bosson et al., 2009). This approach

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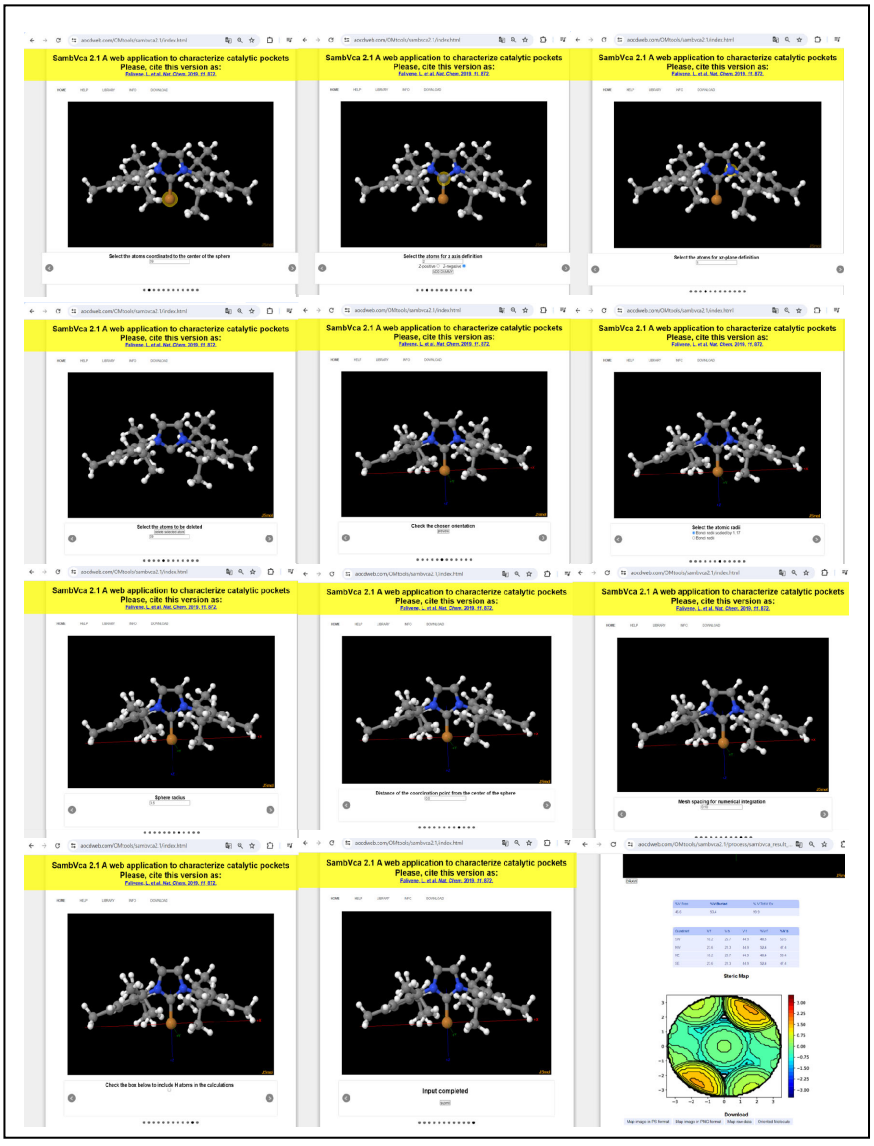
promotes a deeper understanding of key concepts in catalytic chemistry and encourages critical thinking skills.

Overall, this exercise encompasses various components, including searching for past experimental results, manipulating xyz coordinates primarily sourced from X-ray data, and conducting linear regressions. Before delving into the exercise, students are provided with a brief overview of the fundamentals and theoretical background, drawing from the introduction and methodology sections of relevant literature. The exercise is structured around three sections: 1) Calculate the $\%V_{Bur}$ index and corresponding steric maps of NHC ligands for catalysts of Michalak and coworkers' work ((Czerwinski et al., 2016), with the chance to exclude some catalysts for the sake of simplification. Utilize xyz coordinates extracted from the Supporting Information file, ensuring accessibility for all students. 2) Analyze and comment on the symmetry of the steric maps' four quadrants. Justify your selection criteria. 3) Establish a correlation between the yield of alkynylation of trifluoromethyl ketones and the $\%V_{Bur}$ index. Initially, students focus on assessing the NHC ligands of a selected list of 15 catalysts. The necessary xyz coordinates are retrieved from the Supporting Information file, ensuring students have the requisite data for analysis.

Take for instance, Figure 1 depicts the step-by-step process for utilizing the $\%V_{Bur}$ server.

*Figure 1. Sequence of screens to generate the $\%V_{Bur}$ and the steric map.*

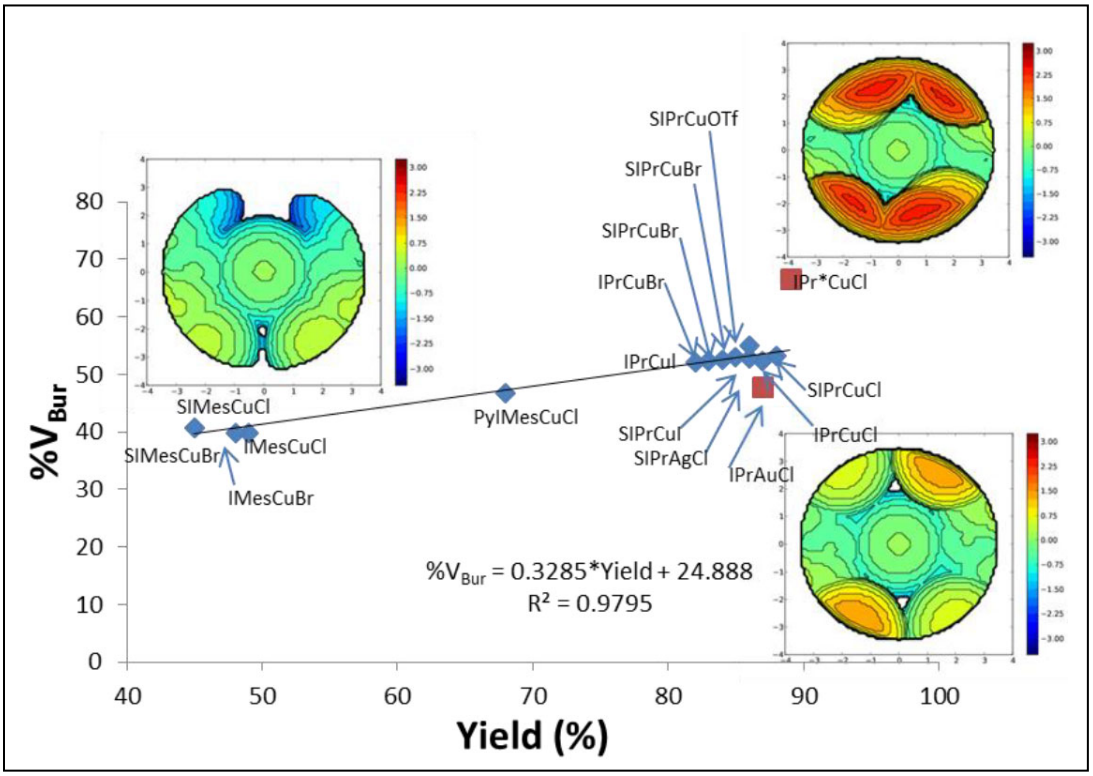



Initially, in Figure 1 the user selects the relevant section of the file and then designates the center, typically the metal atom. Subsequently, the z-axis is defined by the carbon atom of the N-heterocyclic carbene (NHC) ligand bonded to the metal, followed by the selection of the xz plane by clicking on either of the N atoms of the NHC ligand. Since the primary objective of this exercise is to

elucidate the influence of NHC ligands on the metal, the metal atom is then removed from the analysis. To ensure consistency and minimize errors, the orientation of the axes can be examined at this stage. Subsequent windows allow for the customization of various parameters. By default, Bondi Radii are used, and although the metal atom is removed, its contribution is still considered in the calculation of the plane. The level of integration is set to 0.1, and there is an option to include hydrogen atoms in the analysis, which is particularly relevant for experimentalists utilizing X-ray crystallography data, where hydrogen atoms are included through parametrization. The final output provides both total and quadrant-specific $\%V_{Bur}$ values, along with a steric map that can be saved in a high-quality format if desired.

Once the analysis of $\%V_{Bur}$ indices is complete, they are plotted against the experimental yield. Figure 2 illustrates that the most sterically hindered NHC ligands yield higher reaction yields, contrary to conventional expectations. In fact, the transition state defining the rate-determining step (rds) worsens as the steric hindrance of the NHC ligand increases. However, this is offset by the relative stability of the rate-determining intermediate (rdi), resulting in a lower overall energy barrier.

*Figure 2. Graph depicting the relationship between the yield of phenylacetylene addition to trifluoroacetophenone and the steric bulkiness of the N-heterocyclic carbene (NHC) represented by the percent of buried volume ($\%V_{Bur}$), including selected steric maps.*




The evaluation of the exercise is done on an individual level, with particular emphasis on the reasoning behind the results. Furthermore, the positive reception of this proposal by students, as indicated by surveys, highlights the integration of professors' basic research within the Master's teaching framework. This is seen not only by experimentalists but also by others, as a valuable tool that can be utilized without the need for computational calculations, simply by examining X-ray structures.

## 4. Conclusions

A web server is the tool that a group of students, who have so far been at the Master's level but could also be at the undergraduate level, can use to understand the steric effect of ligands linked to their role in catalysis, without needing to grasp the theory beforehand or be experts in computing. It can be accessed from any computer, including tablets or mobile devices, making education flow seamlessly, which can then be quantified in correlations and even linked to artificial intelligence.

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