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# Theoretical insights on the nucleophilicity and electrophilicity concepts

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**Internship from the European Master in Theoretical Chemistry and Computational Modelling**

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## Theoretical insights on the nucleophilicity and electrophilicity concepts: Modelling the chemical reactivity of some reagents used for hair coloration and hair bleaching

The work included in this report was done during a 6 months long internship that took place between February and July of 2015 in the “L’Oréal R&I center” in Aulnay-sous-Bois, and the “Institut national des sciences appliquées (INSA)” in Toulouse, under the supervision of Dr Jérôme Gomar and Pr Laurent Maron.

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## Abstract

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In this study, quantum chemical calculations at the DFT level of theory, over a set of benzhydrylium electrophiles and a diverse set of nucleophiles, were done to develop a method to rank different nucleophiles according to their predicted reactivity. Those predictions were compared with the results and the linear relationship of the free energy studied by the Pr H. Mayr, that only depends on 3 parameters:  $\log k_{20^\circ\text{C}} = s_N(N + E)$ .

In the first place, a study of affinities that takes into account the energy of reactants and products was used. In this study, several functionals were tested (B3LYP, B3PW91, M06-2X) and it was also taken into account the solvent effects, using the SMD model.

A second, more in depth, study was done connecting Pr. H. Mayr findings with Transition State Theory. In this second method it was also considered the effect of including empirical dispersion using the GD3BJ scheme. The method chosen was able to rank most of the nucleophiles according to the experimental data.

This method was applied to predict the reactivity of the complexes of urea and PVP with peroxide, reactants that are used for hair dyeing and hair bleaching and led to the proposal of a ranking of the reagents modeled. However, the method used and the results obtained couldn't have been validated because of the lack of the experimental data, that is going to be obtained soon.

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# 1. - Introduction

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## 1.1. - Introduction of L'Oréal

The origins of L'Oréal go back to the early 20th century. Eugène Schueller, a young chemist graduated in 1904 at “the Institut de Chimie Appliquée de Paris” developed in 1907 a hair color formula that he manufactured and sold to Parisian hairdressers. This was the first steps that would lead him to create on the 30<sup>th</sup> of July in 1909 “Société Française des Teintures Inoffensives pour Cheveux”, the company that will later become L'Oréal.

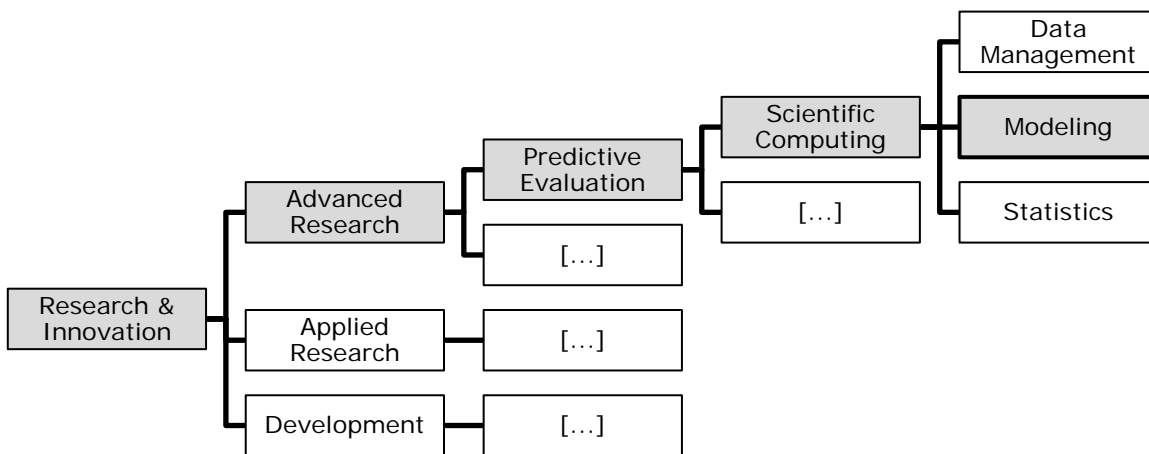
Over the following decade, he kept expanding the company selling products throughout France and expanding in other countries like Italy, United States, UK or Brazil. Its expansion and lines of products have been increasing ever since and, nowadays, L'Oreal is the world leader in cosmetics, with 32 international brands with representation in 130 countries and selling 50 products every second worldwide.

## 1.2. - Research in L'Oréal

To ensure its development, L'Oréal relies on global Research and Innovation, with 19 research centers in different countries and 501 patents registered in the last year. The research is focused in three different fields: Hair, skin and color. This Research and Innovation model is organized around three major entities:

- Advanced Research, the research division aimed to discover new active ingredients, develop new evaluation methods and increase the knowledge of the skins and hairs.
- Applied Research, which develops formulation systems, which are then played out in the different families of products;
- Finally, Development, which provides the brands with the new formulas adapted to their identity and to consumer expectations.

Each of these entities is divided in several sections and departments:



**Figure 1. Scheme with the distribution of the research and innovation department in L'Oréal**

### Service of Molecular modeling

The aim of the molecular modeling service is building mechanistic models based on chemistry, physics and biology. This service is oriented to cutting edge innovation, exploring new fields and simulating processes never done before, that are going to be applied to the different products. Thanks to the work of this service, it's possible to anticipate different effects of the products and diminish the time it takes to put them in the market.

One of the advantages of molecular modeling is the possibility of calculating properties of compounds before the synthesis and measurement and giving information that could be difficult to obtain otherwise. Because of this, this service collaborates closely with other departments: analysis, biotechnology, chemistry, biophysics, etc.

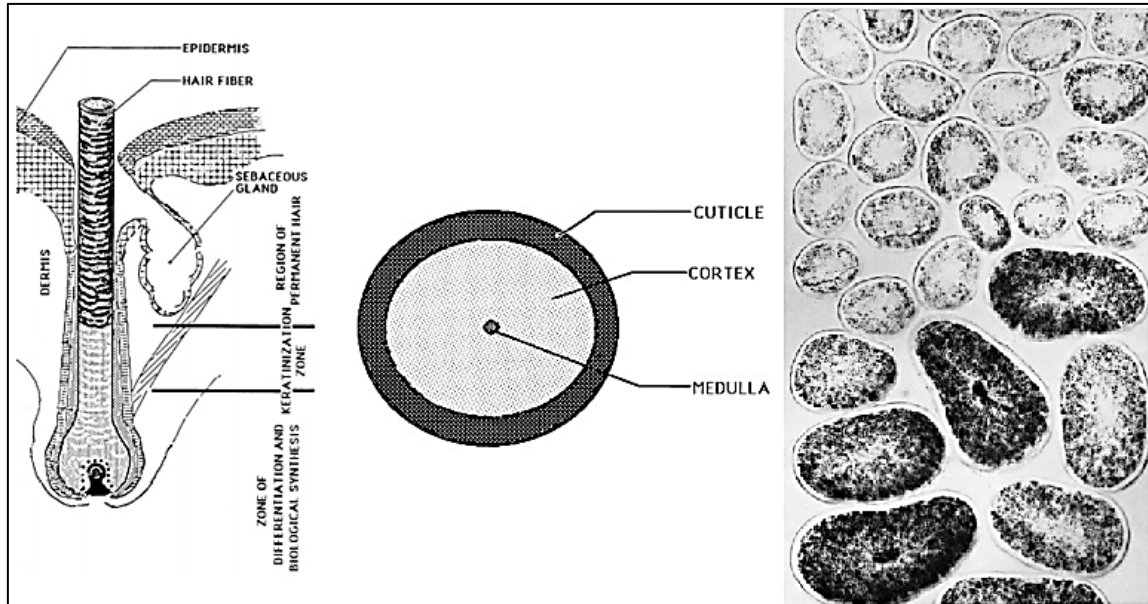
## 2. - Coloration of human hair

Coloration of human hair has always been one of the most important cosmetic treatments. For example, in ancient Greece, people were dyeing their hair in red because it represented honor and courage [1]. Nowadays, hair dyes are still very important for cosmetic companies. Finding new dye technologies to satisfy every expectation of consumers is one of the main priorities.

### 2.1. - The hair

Human hair is a keratin-containing appendage that grows from large cavities called follicles. Hair follicles extend from the surface of the skin through the epidermis into the dermis. [2]

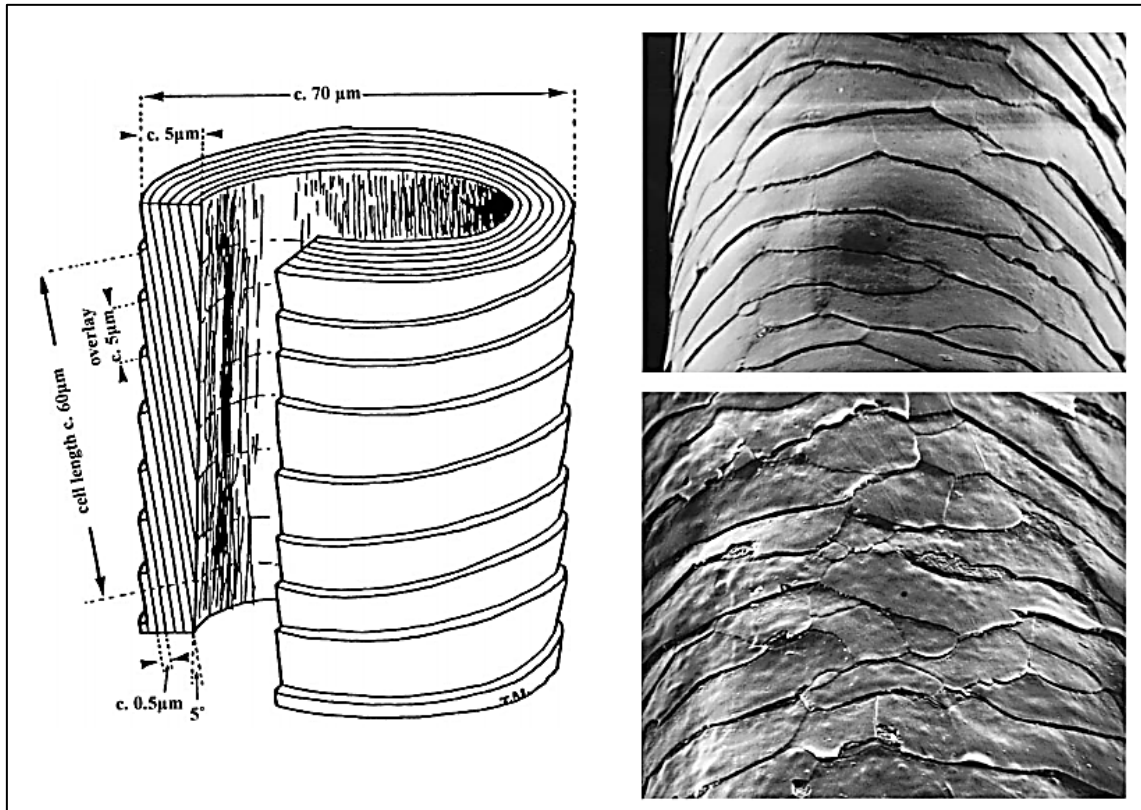
The human hair fiber can be divided in 3 different regions (Fig. 2 left-hand side): zone of differentiation and biological synthesis, keratinization zone and region of permanent hair (the most external one). There is a wide range of different composition (i.e. pigmentation), fiber shapes and diameters (Fig. 2 right-hand side); however, three distinct regions containing different types of cells are generally apparent in cross sections of human hair fibers: cuticle, cortex and medulla (Fig. 2 center-hand side).



**Figure 2.** On the left, hair follicle with its fiber; on the center, schematic diagram of a cross section of a human hair fiber. On the right, light micrograph of a hair fiber cross section. [2] Notice the lack of pigmentation in the cuticle.

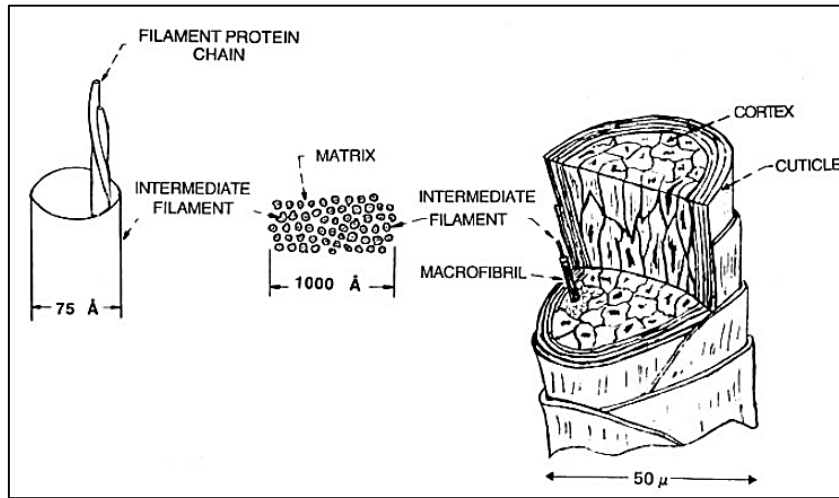


The cuticle is a chemically resistant region surrounding the cortex in hair fibers. It consists of flat overlapping cells (scales) that are attached at the root end of the fiber and point towards the tip end. The cuticle of human hair contains smooth unbroken scale edges at the root end near the scalp. However, cuticle damage as evidenced by broken scale edges can usually be observed due to weathering and mechanical damage from the effects of normal grooming actions (combing, brushing and shampooing).



**Figure 3. On the left, a schematic diagram of the human hair cuticle illustrating its dimensions and layering. [3] On the right, differences of the cuticle near the root (top) with the one near the tips (bottom). [2]**

The cortex constitutes the major part of the fiber mass of human hair. It consists of cortical cells and intercellular binding material. Cortical cells are composed by keratin bundles (or macrofibriles) and also contains nuclear remnants and pigment granules (more on this in the next section). Each macrofibril consists of intermediate filaments originally called microfibrils and matrix, a less organized structure that surrounds them.



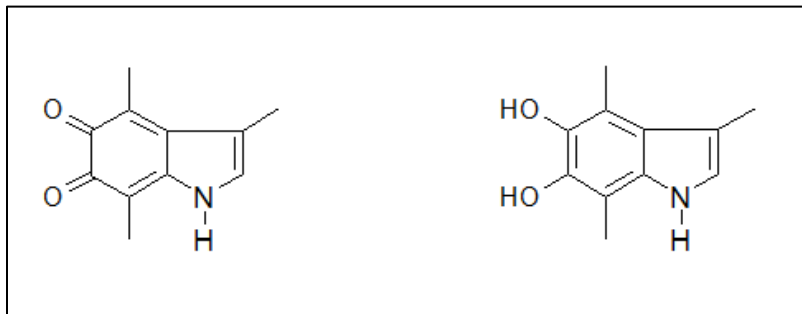
**Figure 4. Scheme of human hair fiber including intermediate filament/matrix structures.**

The medulla in human hair generally comprises only a small percentage of the fiber's mass. Medullary cells are spherical and hollow inside and are bound together by a cell membrane complex type material. It is believed that the medulla contribution to the chemical and mechanical properties of human hair fibers is negligible.

## 2.2. - Pigmentation of hair

As it was said before, in scalp hair, the pigments reside within the cortex and medulla in ovoid or spherical granules that generally range in size from 0.2 to 0.8mm along their major axis. The principal pigments of human hair are the brown-black melanins (eumelanins) and the less prevalent red pigments (pheomelanins). For simplicity reasons, this section is only going to focus on eumelanin (referenced just as melanin from now on).

The general composition of melanin granules consists of pigment, protein, and minerals. [4]. There is however, not a clear knowledge of the structure of melanin, and there are 2 theories considered; one proposes that is a random polymer [5], and the other one is a homopolymer [6]. In any case, both hypotheses propose that there an indole quinone grouping (or its reduced form) is a recurrent unit in its structure.



**Figure 5. Indole quinona and its reduced form.**

### 2.3. - Chemistry of hair bleaching

Bleaching of human hair involves the solubilization (partial or complete) of melanin pigments by oxidation at high pH. The degree of lightening is controlled by the type and concentration of oxidant, the temperature, and the duration of treatment [7].

Experimental work on oxidizing melanin has been done, and it shows a different behavior depending if it's done on isolated melanin granules or on soluble melanin [8]. Strong oxidants as permanganate or perchlorate failed to provide a detectable physical change when dealing with the granules, but they could oxidize the soluble melanin. However, treatment of the granules with hydrogen peroxide at high pH produces disintegration and dissolution of the granules.

Because of the severe reaction conditions required for destruction of the melanin, side reactions with the hair proteins occur simultaneously. The process involves several amino acid residues, but one major consequence is the reduction of the crosslinking capacity of the cysteine as a result of its oxidation to cysteic acid [9]. In addition, hydrogen bonds and ionic bonds can be destroyed by hydrolysis. The hydroxyl and amino side chains of various keratin amino acids offer points of attack for oxidative degradation. [7]

## 3. - Context and objectives

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### 3.1. - Context

Bleaching of natural hair color can be done as a single cosmetic application, but is also part of oxidative hair coloring. This is currently the most commonly used technique for permanent hair dyeing.

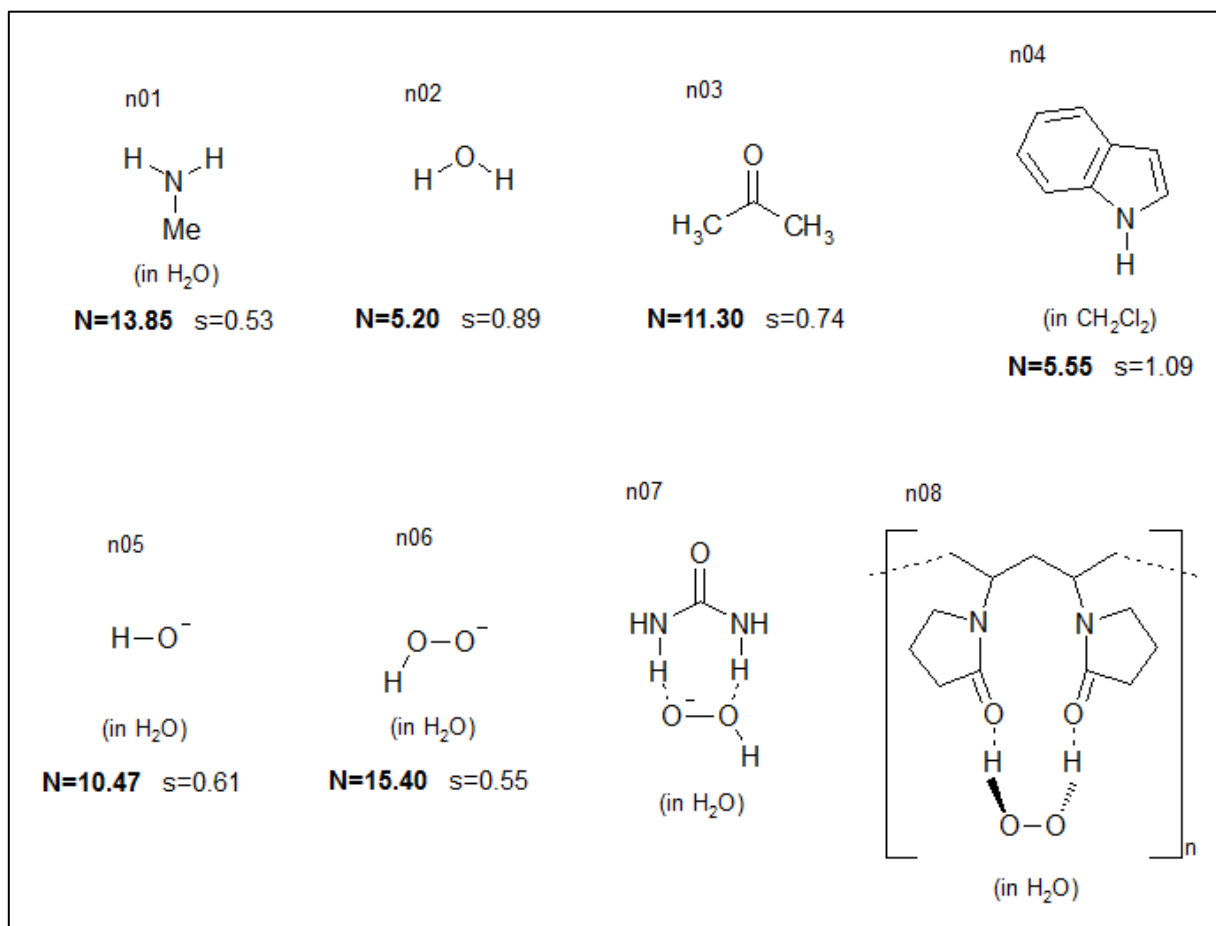
However, the current oxidation dyes in the market present 2 challenges: keep the hair quality at highest level and guarantee the safety of the ingredients. As it was explained in the previous section, depending on the conditions of use, the bleaching process may modify the chemical properties of the fiber. This produces modifications of the physical properties: a higher extensibility and thus lower mechanical strength; a rough, straw like feel when dry; and a spongy feeling when wet.

It's in the best interest of hair dye makers finding an oxidizing agent that is able to oxidize and solubilize the melanin pigments and, at the same time, keeping the damage done to the hair fiber at a lower level in comparison with the actual hair treatments. This is something that could be determined with enough experimental data on the reactivity of the different oxidizing agents. However, these reactants are, most of the times, very unstable at the high pH conditions where the reaction takes place, which makes the measurements of the rate constants difficult. This is why a theoretical method to obtain the rate constants could be very important to classify and rank the reactivities of the different compounds and find the more appropriate bleaching agent.

### 3.2. - Objectives

The main purpose of this study is finding a computational method able to predict the reactivity of nucleophilic compounds and apply this method to different oxidizing agents for hair bleaching.

The nucleophiles used for the study are:

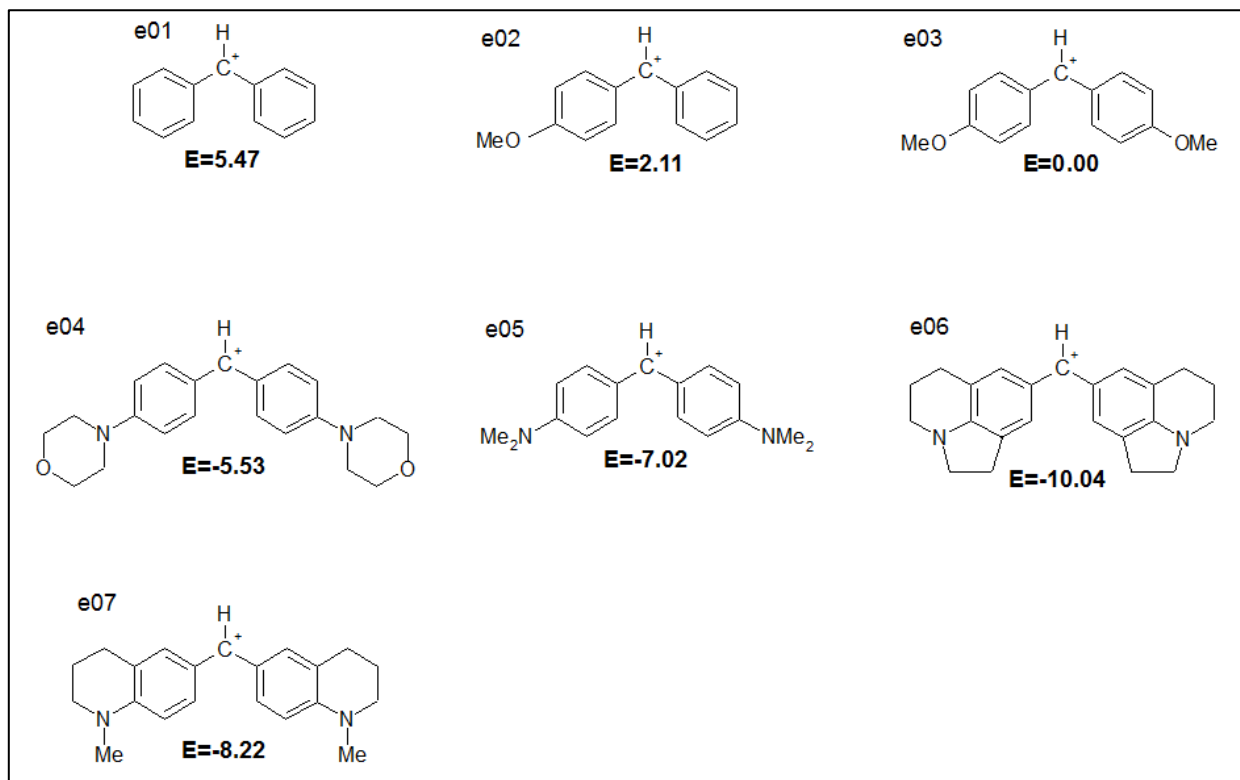


**Figure 6: Set of nucleophiles studied. N and s parameters (explained later) were obtained from Pr H. Mayr's experimental findings<sup>[10] [11] [12] [13] [14]</sup>. Note that the parameters for Urea-H<sub>2</sub>O<sub>2</sub> and the PVP-H<sub>2</sub>O<sub>2</sub> complexes (n07 and n08 respectively), haven't been measured yet.**

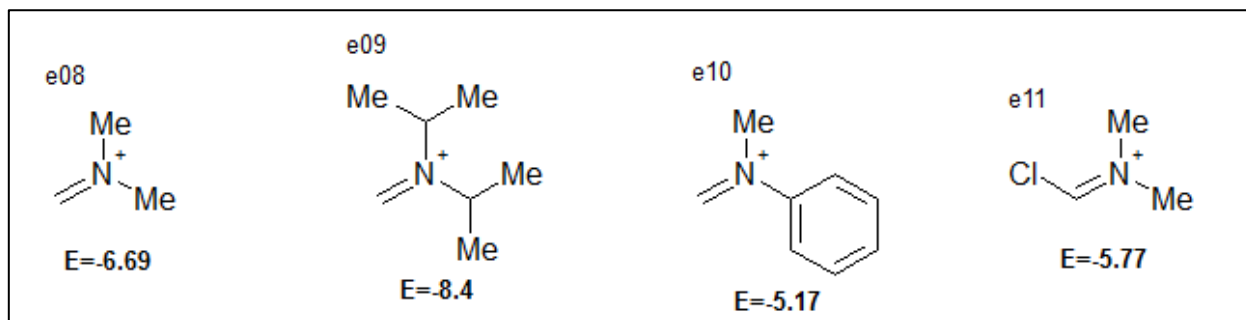
The electrophiles with known parameters are going to be used to determine the correct method. Once that method is decided, it's going to be used with the peroxide complexes to predict their reactivity.

## 4. - Procedure

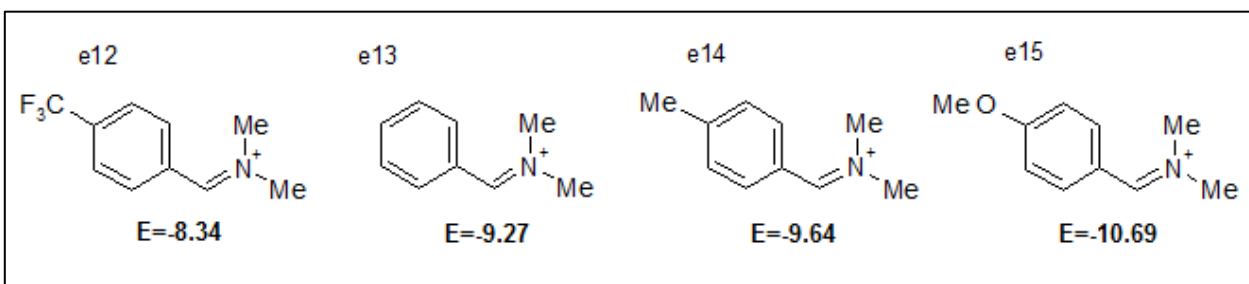
To study the nucleophilicity of these compounds, they were paired with a wide variety of electrophiles with known Electrophilicity parameters (E):



**Figure 7: Set of benzhydrylium electrophiles with their corresponding parameters [15]. These are reference electrophiles in Pr. H. Mayr's scale.**



**Figure 8: Set of iminium electrophiles.**

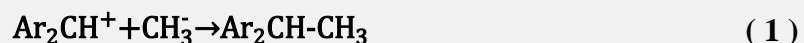


**Figure 9: Set of additional iminium electrophiles**

Two different approaches were used for the determination of the parameters. In both cases, the process involves fitting the results to satisfy a linear free energy relationship:

#### 4.1. - First study: "Affinities"

This initial method was based on the findings of C. Schindele, K. N. Houk and H. Mayr [16]. In which, for the reaction between a given set of carbocationic electrophiles and the methyl anion, there is a good correlation between the E parameter and the reaction energy.



The reaction energy values are, in this case, calculated with the next expression:

$$\Delta E_{\text{reac}} = E(\text{ArCHCH}_3) + \text{ZPE}(\text{ArCHCH}_3) - E(\text{ArCH}^+) - \text{ZPE}(\text{ArCH}^+) - E(\text{CH}_3) - \text{ZPE}(\text{CH}_3) \quad (2)$$

With E being the electronic energy and ZPE the zero point energy correction. It must be taken into account that this method imposes the electrophile so its applicability is only useful to check the behavior of the set of carbocationic electrophiles. This study will also be used to test different functionals and the inclusion of solvent.

## 4.2. - Second study: Pr. H. Mayr's reactivity scale

This method is based on the observations of Pr. H. Mayr and coworkers [17] that, in the last 20 years, have demonstrated that a 3 parameter equation is enough to be able to describe, semi quantitatively, the rate constant of a large variety of electrophile-nucleophile combinations:

$$\log k_{20^{\circ}\text{C}} = s_{\text{N}}(N + E) \quad (3)$$

**E** = electrophilicity parameter

**N** = nucleophilicity parameter (solvent dependent)

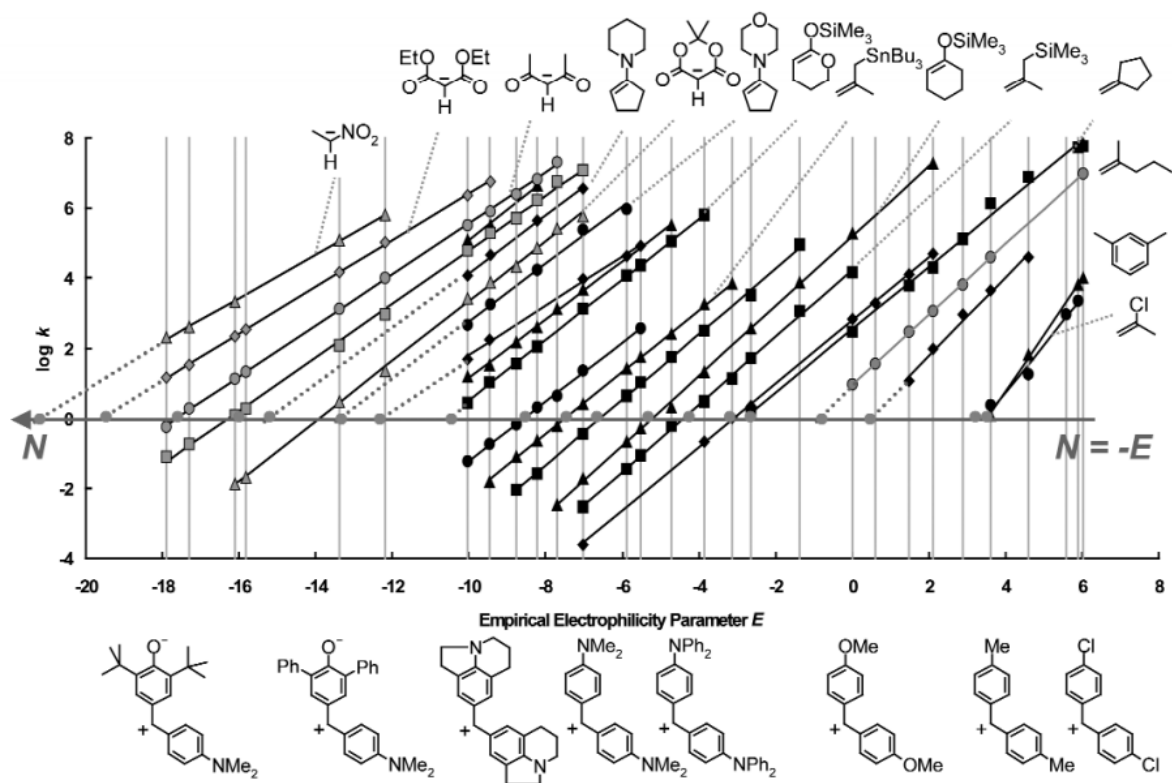
**s<sub>N</sub>** = nucleophile-specific sensitivity parameter (solvent dependent)

As Pr. H. Mayr indicates, this 3 parameter equation “does not include steric effects and, therefore, can only be used for semiquantitative predictions of rate constants. [...] As carbon-centered electrophiles and carbon-centered nucleophiles have been used for the parameterization, [the equation] is only applicable when one or both reaction centers are carbon.”

Following those indications, this formula can cover a reactivity range of 40 orders of magnitude, according to the experimental data obtained by Pr. H. Mayr.

For building what we are calling Pr. H. Mayr's scale, he and coworkers selected a series of 29 para- and meta-substituted benzhydrylium ions and structurally related quinone methides as reference electrophiles and studied the kinetics of their reactions with a variety of carbon nucleophiles. In this way, they obtained 29 nucleophilicity scales (Figure 10), in which each electrophile is characterized by one parameter E [taking as reference E=0 for (p-MeOC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CH<sup>+</sup>] while nucleophiles are characterized by two parameters N and s<sub>N</sub> (s = 1 for 2-methyl-1-pentene). N is defined as the negative intercept of a correlation line with the abscissa.





**Figure 10. Second-order rate constants for electrophile nucleophile combinations. [18]**

The rest of electrophiles and nucleophiles tested in subsequent experiments by Pr. H. Mayr and coworkers were obtained taking these electrophiles as reference and are classified and organized in an online database of reactivity parameter<sup>1</sup>, which currently contains 993 nucleophiles and 254 electrophiles.

Since the  $S_N$  parameter values are strongly dependent of the nature of the solvent and the  $N$  parameter values are more closely related to the intrinsic properties of the nucleophile, the  $N$  parameter was chosen to rank the reagents modelled. To obtain it, the  $E$  parameters are going to be taken from the experimental values registered on Pr. H. Mayr's database.

The connection between energies obtained from electronic structure calculations and the rate constants could be done using the Transition State Theory (TST). This theory, published almost at the same time by H. Eyring and M.G.Evans and M.Polanyi in 1935 assumes:

<sup>1</sup> <http://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/>

- Molecular systems that have gone over the activation energy barrier cannot turn back and form reactants again.
- Reactants are in chemical equilibrium with the transition state.
- It is possible to separate the motion of the system over the activation energy barrier from the other motions associated with the transition state.
- Classical motions over the barrier are reliable (quantum effects are being ignored).

One of the expressions that can be obtained taken all the previous points into account is:

$$k = \frac{k_b T}{h} e^{\left(\frac{-\Delta G^{\ddagger}}{RT}\right)} \quad (4)$$

With  $\Delta G^{\ddagger}$  being:

$$\Delta G^{\ddagger} = \Delta G^{\circ}_{TS} - \Delta G^{\circ}_R \quad (5)$$

Nucleophiles from n01 to n06 (that have experimentally obtained parameters), are going to be tested to check the appropriate computational approach to the problem. Once the method has been tested with those nucleophiles, it's going to be applied to two different peroxides (Urea-H<sub>2</sub>O<sub>2</sub> complex and PVP-H<sub>2</sub>O<sub>2</sub> complex) as possible hair bleaching agents. To compare the reactivity and possible competitive processes, results from the free HOO<sup>-</sup> and HO<sup>-</sup> calculations are going to be taken into account, since those are two species that are expected to be found in the strong basic medium of the bleaching process.

#### 4.4. - Computational details

DFT was picked as the method that should be used since it provides a good compromise between the speed of the calculation and the precision required for this study.

DFT is a quantum mechanical modelling method that is used in theoretical chemistry to study the electronic structure of atoms and molecules. This method is based on Hohenberg–Kohn theorems [19] that prove the following:

- With a nondegenerate ground state, the ground-state molecular energy, wave function and all other molecular properties are uniquely determined by the ground-state electron probability  $\rho_0(x, y, z)$ .
- The ground state density can be calculated, in principle exactly, using the variational method involving only density.

Taken this into account, it's possible to describe the ground state energy of the system in terms of the electronic density:

$$E_e[\rho] = T_e[\rho] + V_{ext}[\rho] + U_{ee}[\rho] \quad (6)$$

where,

$T_e$  is the kinetic energy of electrons,

$V_{ext}$  is the external potential (the electrostatic potential from the nuclei in this case)

$U_{ee}$  is the electrostatic repulsion between electrons.

However, the expressions relating the kinetic energy in terms of the density are not known with accuracy for atoms and molecules. To avoid this problem, Kohn and Sham [20] proposed a different split of the terms of the energy functional:

$$E_e[\rho] = T_0[\rho] + \int [\hat{V}_{ext}(\mathbf{r}) + \hat{U}_{cl}(\mathbf{r})] \rho(\mathbf{r}) d\mathbf{r} + E_{xc}[\rho] \quad (7)$$

$T_0[\rho]$  is the kinetic energy of the electrons in a system that has the same density as the real system, but without the interactions between electrons.

$\hat{U}_{cl}(\mathbf{r})$  is the Coulomb “classical” interaction between electrons.

$E_{xc}[\rho]$  is the Exchange-correlation energy, which includes all the energy contributions, not included in the other terms:

- The electron exchange
- The electron correlation (not taken into account in the kinetic energy term since non-interacting electrons have to correlate their movements)
- A portion of the kinetic energy that corrects  $T_0[\rho]$  to obtain the kinetic energy of the real system  $T_e[\rho]$ .
- A correction of the self-interaction that was introduced by the Coulomb potential.

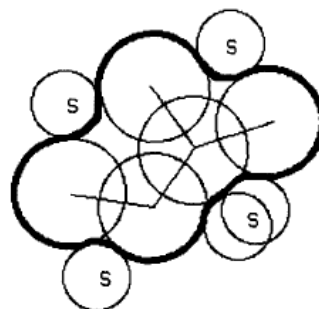
The Kohn Sham equations are solved self consistently (taking an initial guess of the electron density) until convergence, giving as result the ground state density and the ground state

energy of the system. However, the exact exchange-correlation functional is only known for the free electron gas, so an approximation needs to be used to cover that part of the functional when dealing with molecules. To choose the right functional, 3 different ones were tested in the first calculation: B3LYP, B3PW91 and M06-2X. The 3 of them are hybrid functionals that mix a part of the exact exchange from Hartree-Fock theory into the DFT exchange functional. B3LYP and B3PW91 share the same exchange functional (Becke's three-parameter hybrid functional B3) with different correlation functionals. M06 functionals are constructed with empirical fitting of their parameters, but constraining to the uniform electron gas.

The basis set selected was the 6-311+G(d,p), a Pople basis set flexible enough to represent all the structures, with polarization and diffuse functions, and it's in line with the size of basis set seen in the bibliography for similar problems.

In addition to calculations in gas phase, calculations with the different solvents were also carried out. For taking into account the solvent effects, the method chosen was including a self-consistent reactive-field via a continuum solvent model in the optimizations of the structures.

In this method, the molecular structure of the solvent is ignored and the solvent is modeled as a continuous dielectric of infinite extent that surrounds a cavity containing the solute structure. This continuous dielectric is characterized by its dielectric constant  $\epsilon$ , whose value is the experimental dielectric constant of the solvent at the temperature of the solution. The particular method used was SMD [21], which takes as the cavity a superposition of nuclear-centered spheres with radii  $\rho_k$ . These radii are called intrinsic Coulomb radii and are only dependent on the atomic numbers of the atoms.



**Figure 11.**  
**Example of solvent cavity**

Other factor that was taken into account in some of the calculations was adding an empirical dispersion term. This is an additional potential that is used to include long-range dispersion contributions. Since it is an add-on term, it does not directly alter the wave function or any other molecular property. However, geometry optimizations with dispersion correction will

lead to a different geometry than without because the dispersion correction contributes to the forces acting on the atoms.

There are several types of different empirical dispersion, but in this particular case, the one used is the GD3BJ, which, consists in adding the D3 version of Grimme's dispersion [22] with Becke-Johnson damping. This gives better results for nonbonded distances and more clear effects of intramolecular dispersion [23].

The strategy followed for each pair electrophile-nucleophile tested was doing optimization calculations of the 2 reactants individually, the final product, and from that point, obtaining the transition state. The optimizations were carried out using Gaussian09's version of Berny's algorithm in redundant internal coordinates [24].

In order to validate that the structures obtained are the correct ones, force constants and the resulting vibrational frequencies were calculated for every structure. Force constants were determined analytically and vibrational frequencies are computed by determining the second derivatives of the energy with respect to the Cartesian nuclear coordinates.

Intrinsic reaction coordinate calculations were done to check that the transition states obtained were the ones corresponding to the nucleophile-electrophile reaction. The algorithm used to follow the transition vector is the Hessian-based Predictor-Corrector integrator [25].

All these calculations were carried out with the Revision D of the electronic structure calculation software Gaussian09 [26].

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