DOI: 10.1002/ange.201208045

**Nucleophilic Substitution**

# Revisiting the Hammett ρ Parameter for the Determination of Philicity: Nucleophilic Substitution with Inverse Charge Interaction**

*Giulia Licini and Cristiano Zonta**

*In memory of Giorgio Modena*

Oxidation chemistry has always been one of the most important arenas for the interpretation and mastering of reactivity.[1] Since the beginning of the last century, the interest of scientists in this area has been driven by the strong implications that this reactivity has in biological systems, and also because oxidations are an essential tool in functional-group transformations. Over the years, two alternative mechanistic pathways for oxygen transfer (OT) reactions, oxidations which proceed by an heterolytic cleavage of the oxygen–oxygen bond of the oxidant, have been proposed: electrophilic OT, in which the transferred oxygen attacks the substrate electrophilically and nucleophilic OT, which is usually described as a two-step process involving the addition of the peroxo compound to the substrate. This philicity scheme is nowadays well accepted and used to interpret oxidative reactivities in both artificial and biological systems.[2]

However, although more than one hundred years of studies on OT reactions have offered a large number of examples which consolidate this framework, several experimental "exceptions" have made the philicity of oxidants is still a discussed, and in some way, a controversial subject.[3,4] Examples of outliers are represented by: strong electrophilic oxidants performing exceptionally well in nucleophilic OT reactions,[4a] substrates oxidized with unexpected philicity,[4b,c] complete switch in oxidant philicity as a consequence of minor transformations in the substrate,[4d] substrates displaying non-linear Hammett correlations in OT reactivity,[4e,f] and a still difficult comprehension of the OT processes involving metal peroxo complexes.[4g] All these experimental results call for a reinterpretation of the mechanisms of OT.

The interest in a unified vision emerged from the first pioneering studies in OT reactivity and, among the various substrates, sulfoxides have attracted extensive attention due to their capability to react following either philicity pathways.[5] In early studies, it has been shown that substituents bonded to aromatic sulfoxides have opposite effects on the rates of oxidation depending on oxidant philicity (Figure 1).[6]

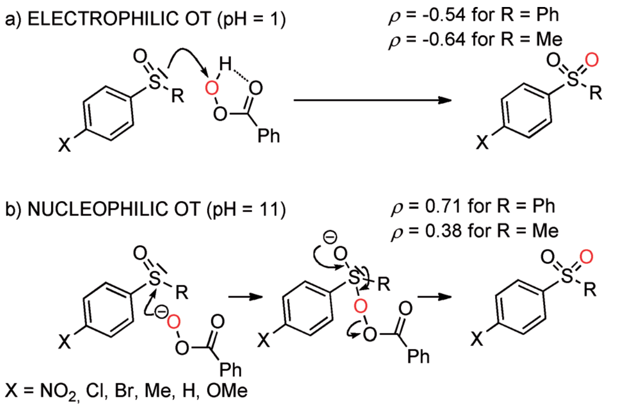

*Figure 1.* Experimental ρ values for OT on aryl alkyl sulfoxides with a) perbenzoic acid (**P-CID**) and b) perbenzoate (**P-ATE**) and historically proposed mechanisms.

In particular, linear Hammett correlations with negative slopes were obtained for the oxidation of *p*-substituted sulfoxides when the reaction was carried out with perbenzoic acid at low pH value (pH 1). This result was interpreted as the tendency of the reacting oxygen atom of perbenzoic acid, in its protonated form, to act as an electrophile. In contrast, positive Hammett slopes were observed on the same substrates when the reactions were carried out with perbenzoic acid at higher pH values (pH 11). This case was interpreted as the capability of the sulfoxide to act as an electrophile and the perbenzoate anion as a nucleophile. As a consequence of their peculiar "ambiphilic" reactivity, sulfoxides are considered unique probes for the description of the oxidant philicity in chemistry and molecular biology.[7]

Herein, we decided to tackle the mechanisms of OT investigating theoretically the original studies that are at the base of the interpretation of the ambiphilicity of sulfoxides. This gave us the possibility to reinterpret the original results paving the way for a new description of OT reactivity which extends, and to some extent redefines, the basic concept of nucleophilic substitution and highlights severe limitations on the information which can be gathered from Hammett ρ parameter.

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[*] Prof. Dr. G. Licini, Dr. C. Zonta
Department of Chemical Sciences, University of Padova
via Marzolo 1, 35131 Padova (Italy)
E-mail: cristiano.zonta@unipd.it

[**] The research was funded by Università di Padova (PRAT-CPDA099121), Fondazione CARIPARO (Nano-Mode). Computational resources were provided by the Laboratorio Interdipartimentale di Chimica Computazionale (LICC) at the Department of Chemical Sciences (Padova). We thank Prof. Dr. F. M. Bickelhaupt (Amsterdam), Dr. M. Bonchio (Padova), Prof. R. Curci (Brown), Prof. Dr. C. A. Hunter (Sheffield) and Dr. A. Sartorel (Padova) for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201208045.

To investigate the OT of sulfoxides, density functional theory (DFT) calculations[8] on the oxidation of substituted methyl phenyl sulfoxides **1** by perbenzoic acid **P-CID** and perbenzoate anion **P-ATE** have been carried out to reproduce the experimental data reported by Modena and Curci.[6,9] Among the possible attacks, Figure 2a shows the most stable geometry for the OT transition state for the attack of **P-CID** on **1-H**. Good correlation between experimental and calculated energies is observed (Supporting Information Table S1). In line with previous theoretical studies, the transition state is representative of a nucleophilic attack of the **1-H** sulfur lone pair (LP) on the empty σ* oxygen–oxygen orbital of the oxidant. This step is confirmed by natural bond orbital (NBO) analysis which shows a strong $LP_S \rightarrow \sigma^*_{OO}$ donor–acceptor delocalization (67.2 kcal mol$^{-1}$) between the two reacting fragments.[10] Interestingly, the geometrical characteristics of the transition state for the peranion P-ATE strongly resemble those of **P-CID** (Figure 2b). Also in this case a good agreement between experimental and calculated energies is observed. The similar geometry can suggest an attack that involves the same orbitals observed for **P-CID**, and the confirmation comes from NBO analysis. The main donor–acceptor delocalization between the two reacting partners is $LP_S \rightarrow \sigma^*_{OO}$; this interaction is stronger than the **P-CID** case (79.0 kcal mol$^{-1}$) and it confirms that the sulfoxide **1**-H is acting as nucleophile with respect to the negatively charged oxygen atom of the peranion **P-ATE**.

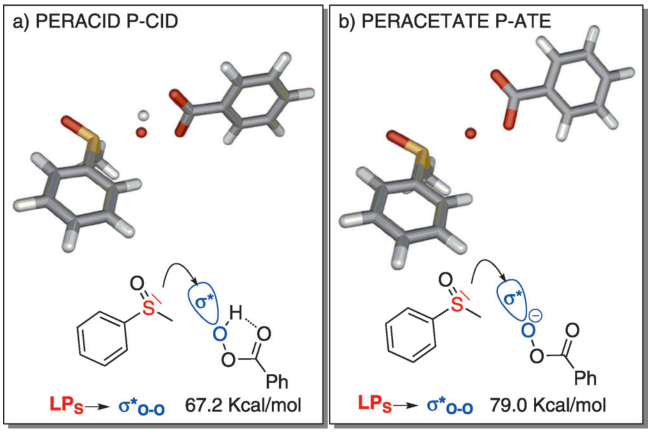

***Figure 2.*** Transition-state structures and main delocalization energies among the reacting fragments for OT of **P-CID** and **P-ATE** to **1-H**. LP = lone pair, yellow S, red O, white H, gray C.

To analyze the mechanism in more in detail, and to confirm that the observed transition states are representing the experimental data, the role of substitution on the aromatic ring has been investigated. Energies and main geometrical parameters for the oxidation of *p*-nitro **1-NO$_2$**, *p*-bromo **1-Br**, *p*-chloro **1-Cl**, *p*-methyl **1-Me** and *p*-methoxy **1-OMe** substituted phenyl methyl sulfoxides have been calculated. Substituents were chosen to compare the calculated systems with the original experiments and they offer a wide variation in the reactivity of the sulfoxides in terms of Hammett parameters,[11] spanning from electron-donating ($\sigma_{OMe} = -0.27$) to electron-withdrawing ($\sigma_{NO_2} = +0.78$) substitutents. Moreover, *para* substitution eliminates proximity effects on the reaction center. All the calculated transition-state structures have common geometrical features in terms of bond lengths and angles (Supporting Information, Table S1). Linear Hammett correlations were found between calculated $\log(k/k_0)$ and $\sigma$. The values for $\rho$ are $-1.20$ in the case of the **P-CID**, in agreement with the experimental value of $-0.64$, and $+1.29$ for the peranionic **P-ATE** which is in line with the experimental $+0.38$ (Figure S2).[12] The correlation for both the activation energies and Hammett correlation values is indicative that the calculated structures reproduce well situation during the reaction in solution. Frontier-orbital NBO analysis along the substituted series for both oxidants confirms that the main delocalization interaction in the transition state is between the lone pair of the sulfoxide and the empty orbital of the oxidant (Supporting Information, Table S2).[13] Nonetheless, the description of orbital overlap, besides showing that sulfoxides are always the nucleophiles, is not sufficient to interpret the inversion in the slope of the Hammett correlation.

What is then the cause of the inversion of the slopes passing from **P-CID** to **P-ATE** being both oxidants acting as electrophiles? Since the seminal work of Hammett,[14] it is assumed that reactions with a negative $\rho$ value are characterized by a decrease in electron density at the reactive site of the substrate during the reaction. This change translates into the substrate under consideration being the nucleophile, which is activated by the presence of electron-donating groups and deactivated by electron-withdrawing groups. This effect can be seen as a consequence of the variation of the HOMO–LUMO gap and/or the electrostatic interactions among the reacting partners. For example, electron-donating groups conjugated with the reactive site of an "electrostatically negative" nucleophile favor both the orbital overlap, reducing the HOMO–LUMO gap, and/or the electrostatic interaction between the interacting partners (Figure 3a).[15] The observed trends for sulfoxides cannot be accommodated in this scheme: different substituents have opposite effects on

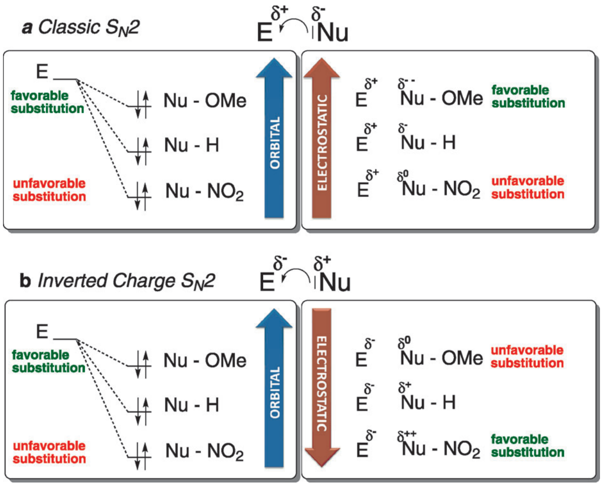

***Figure 3.*** Orbital and electrostatic trends in nucleophilic substitutions.

the rates of oxidation even though sulfoxides are always acting as nucleophiles.

A plausible explanation is offered by the analysis of the contribution from the electrostatic interactions which have been investigated by performing natural population analysis (Table S2), natural energy decomposition analysis (Table S4 and S5) combined with the activation strain model (Table S6 and S7).[16,17] In the ground state, the transferred oxygen atoms are characterized by a negative charge and, as expected, the negative charge is higher in the anionic oxidant **P-ATE**. Sulfoxide sulfur atoms are instead characterized by a positive charge which is influenced linearly by aromatic ring substitution in accordance to their $\sigma$ value. In the transition state, the attacking oxygen atom of the oxidant becomes more negative and the sulfur more positive, confirming the direction of the charge transfer (Figure 4). The reaction can be thus described as an "electrostatically positive nucleophile", the sulfur atom, reacting with an "electrostatically negative electrophile" the oxidant. As a consequence, in this nucleophilic substitution with inverse charge interaction, the substituents along the Hammett correlation give rise to opposing effects in the frontier orbitals and in the electrostatic interactions between the reactive fragments (Figure 3b). For example, electron-withdrawing substituents conjugated with the nucleophile disfavor the orbital interactions, increasing the HOMO–LUMO gap, while they cause a more favorable electrostatic interaction. The observed reactivities can be thus interpreted as the balance between these two components: in the case of **P-CID**, the higher influence of the orbital component is reflected by the negative $\rho$ value, in the case of **P-ATE**, in which the electrophile is formally a negative charge, the electrostatic component predominates and a positive $\rho$ value is observed. Sulfoxides are not switching philicity, the $\sigma^*_{SO}$ empty orbital is barely involved in these reactions even when a formally negative oxygen atom is attacking, but they are involved in an orbital or charge-driven reaction. The substituents on the aryl moiety have the opposite effect on the observed rates depending on the dominant interaction in the transition state. This scheme links both experimental and theoretical results.

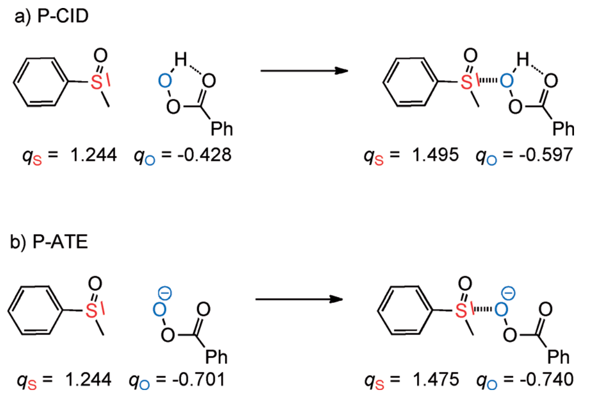

***Figure 4.*** Natural charges $q$, in the ground state and transition state.

The philicity assessment of a reaction using the Hammett correlation method should also be considered.[14] At first glance the reported results can be seen as a flaw in one of the most important tools in physical organic chemistry. However, it should be noted that for all the calculated values, either related to the thermodynamics or geometry of the process (Table S1–S6), good correlations are obtained along the substitution series. This confirms that the reactive centers are influenced by substitution according to empirical Hammett parameters. In other words, the nitro group remains an electron-withdrawing group, and it remains electron-withdrawing with the same "$\sigma$ intensity". A reinterpretation is needed instead for the $\rho$ value which cannot be associated with the increase, or decrease, of electron density at the reactive center in the transition state. The electrostatic-interaction contribution to the reactivity can be predominant and/or opposite in direction, disguising the contributions of orbital overlaps to the reactivity. The direct consequence is the low $\rho$ value, in terms of absolute values, observed for both oxidants, which is a consequence of the two counterbalancing contributions interplaying in the building of the transition-state barrier rather than a lower contribution of frontier orbitals.

The analysis leads to the following conclusions: 1) the reactions studied are examples of electrostatically positive nucleophiles reacting with electrostatically negative electrophiles; 2) in this nucleophilic substitution with inverse charge interaction, the presence of a substituent conjugated with the nucleophile displays opposite effects in the frontier-orbital interaction and in the electrostatic component; 3) it is the charge versus orbital counterbalancing effect, and not the nucleophilic versus electrophilic reactivity, that is responsible for the observed trends in reactivities. In addition to the fact that controversial cases[4] can now be revisited according to the proposed reactivity scheme, the new interpretation has broader implications. The results described should encourage scientists to consider nucleophilic substitution with inverse charge interaction as a possible route to explain already observed reactivities and to investigate new chemical problems.

Received: October 5, 2012
Published online: February 1, 2013

**Keywords:** Hammett plots · nucleophilic substitution · oxidation · peroxides · substituent effects

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[12] Calculations for sodium perbenzoate as the oxidizing agent have furnished similar results in term of geometry and orbital overlap. Calculated $\rho$ is 0.46 (Figure S1 and Table S3).

[13] NBO analysis shows that orbital interactions among the reacting fragments become stronger when electron-withdrawing groups are present in the sulfoxide, both for **P-CID** and **P-ATE**. This is the consequence of the greater extent of reaction, which results in shorter distances between the reactive fragments and, as a result, in higher overlap among the orbitals. As expected, HOMO–LUMO gaps for the $LP_S \rightarrow \sigma^*_{OO}$ interaction are larger with sulfoxides bearing electron-withdrawing substituents. Orbital and electrostatic interactions interplay with the deformation energy as explained by the activation strain model of Bickelhaupt (Tables S6 and S7).[17]

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