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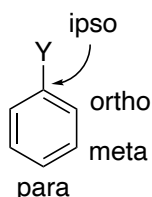Perrin, Charles L

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Charles L. Perrin

Department of Chemistry & Biochemistry

Univ. Calif. San Diego, La Jolla, CA 92093-0358

cperrin@ucsd.edu

Abstract. On a substituted benzene ring the position that bears the substituent is designated as the ipso position. This Perspective presents the history behind that designation.

The prefixes ortho, meta, and para, designating positions relative to a substituent on a benzene ring (**1**) are very well known, even to beginning students in organic chemistry.[1] The terms arose in the 1830s primarily to classify inorganic compounds, and around 1870 Wilhelm Körner proposed them to describe the substitution pattern in disubstituted benzenes. All three terms have a Greek etymology, ortho meaning straight, meta meaning following, and para meaning similar. But the connection of those meanings with molecular structure is vague. Nevertheless those designations are universally accepted.
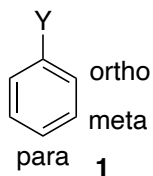
These terms are essential to our designation of directive effects in electrophilic aromatic substitution. Not only do we distinguish activators from deactivators but we also distinguish ortho/para directors from meta directors. Historically this was interpreted in terms of the electron distribution in the substrate, which either attracts or repels an electrophile, as illustrated in Figure 1. More properly it is due to the stabilization or destabilization of the transition state, as approximated by the intermediates in Figure 2.

Figure 1. Electron distribution in a substrate with (a) an ortho/para director. (b) a meta director.
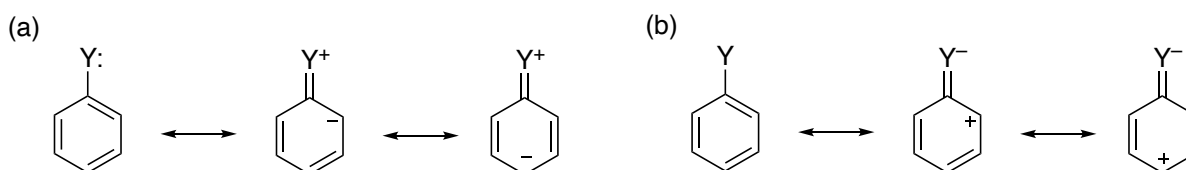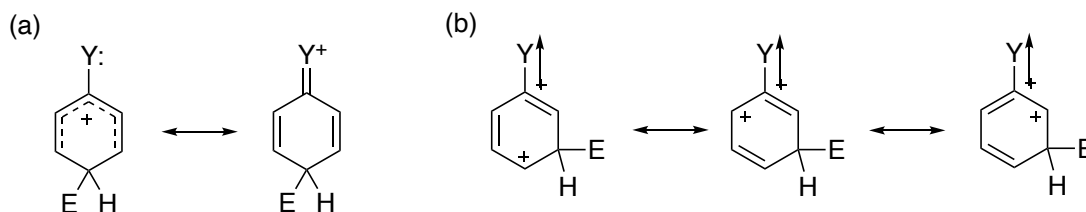

Figure 2. Stabilization or destabilization of the intermediate from electrophilic attack on a substrate with (a) an ortho/para director. (b) a meta director.

Directive effects can be expressed quantitatively by partial rate factors,[2] defined as the rate of substitution at one specific site in a monosubstituted aromatic relative to the rate of substitution at a single position in benzene. For example, the partial rate factor p_f^Z for para substitution in C_6H_5Z is given in eq 1, where $k(C_6H_5Z)$ and $k(C_6H_6)$ are the total rate constants for reaction of C_6H_5Z and C_6H_6, respectively, and %para is the percentage of para-product formed from C_6H_5Z. Similarly, the meta partial rate factor (more concisely called the meta factor) m_f^Z is as shown in eq 2.

$$p_f^Z = 6 \frac{k(\text{C6H5Z})}{k(\text{C6H6})} \frac{\%para}{100} \tag{1}$$

$$m_f^Z = 3 \frac{k(\text{C6H5Z})}{k(\text{C6H6})} \frac{\%meta}{100} \tag{2}$$

But how is the position bearing the substituent designated? The answer is ipso.

Although many people assume that this designation is contemporary with ortho/meta/para, it was

introduced only in 1971.[3] The purpose of this Perspective is to tell how the ipso designation

came about.

HISTORICAL

During World War II Frank Westheimer studied the mechanism of the oxynitration

reaction, used to synthesize the explosives 2,4-dinitrophenol and picric acid (2,4,6-

trinitrophenol) from benzene. The procedure uses nitric acid, with mercuric nitrate as catalyst.

The mechanism that they elucidated is shown in Scheme 1.[4] Mercuration is the first step. This is

simply an electrophilic aromatic substitution, with Hg^{+2} as electrophile, to form $PhHg^+$. In the

next step, NO^+, formed from nitrous acid present in the nitric acid, acts as an electrophile to

replace the Hg^{+2}. The resulting PhN=O is then converted to phenyldiazonium ion, $PhN^+\equiv N$.

That next hydrolyzes to phenol, PhOH, which is readily nitrated.

Scheme 1. The oxynitration reaction.
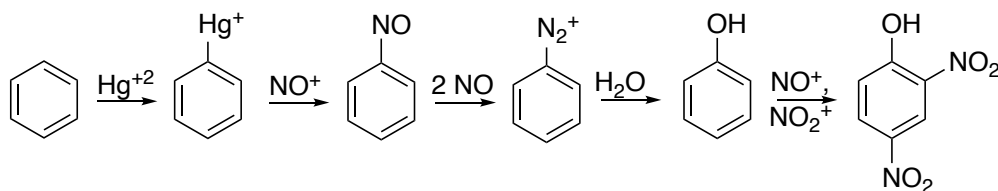
One of the puzzles in that study was that the rate of the initial mercuration increases with

the concentration of acid, which can be nitric, sulfuric, or perchloric. The rate increase was

initially attributed to acid catalysis, but there is no obvious role for acid to catalyze the reaction. Moreover, salts also accelerate the reaction,[5] so that the catalysis was tentatively attributed to the supposedly greater reactivity of an ion pair between Hg^{+2} and the anion of the salt. That became the topic for my PhD thesis. Eventually we attributed the apparent catalysis to a dependence of rate on the thermodynamic activity of water, measured independently.[6] The rate increase occurs because removal of water desolvates both H^+ and Hg^{+2} and increases their reactivity but increases the reactivity of Hg^{+2} to a greater extent.

A further feature of the mercuration reaction is that it is subject to polymercuration, meaning that the $PhHg^+$ can be further mercurated. Is that initial Hg^+ substituent an activator or a deactivator, an ortho/para director or a meta director? To answer this, products were precipitated as their chlorides and then brominated to the corresponding bromobenzenes. The ratios of mono- to di- to tri-bromobenzene were determined by GC, and the isomeric proportions of the dibromobenzenes were estimated by IR. The σ^+ constant of the Hg^+ substituent was thereby evaluated as varying from 0.09 to 0.15, corresponding to a weak deactivator, despite a positive charge that might have conferred a strong deactivation. The further question arose as to the isomer distribution that results from that second mercuration. It was found that comparable quantities of all three isomers were produced, which could be confirmed by GC with a column that provided better separations. It may be noted that this result differs from the 82:18 m:p ratio found under conditions of isomer equilibration.[7]

A further aspect that intrigued me was the bromodemercuration that converted ArHgCl to ArBr. A similar feature is shown by the second step of Scheme 1, which is a nitrosodemercuration. Both reactions involve electrophilic substitution directly at the position

bearing the mercury substituent, rather than ortho, meta, or para to that substituent. How should

that position be designated?

Consistent with ortho/meta/para, the Greek for "itself" is "auto". But that has

connotations (automatic, automobile) that make it unsuitable as a designation for the position

bearing a substituent. Initially I considered "alpha", but in carboxylic acids that refers to the

adjacent carbon, not the carboxyl itself. Therefore I chose "ipso", even though it is a solecism to

mix Greek and Latin. I was familiar with this term because my law-student friend would toss off

"res ipsa loquitur" (the thing speaks for itself), "ipso facto" (by that very fact), and "ipse dixit"

(he himself said it).

NITRATION OF HALOANISOLES

For my first independent research project as an Assistant Professor at UC San Diego I

chose to investigate the directive effect of a substituent Z for electrophilic substitution at the

position bearing the substituent. That is described by an ipso partial rate factor i_f^Z, or "ipso

factor", defined in eq 3 (analogous to eq 1-2), where $k(ArZ)$ and $k(ArH)$ are the total rate

constants for reaction of ArZ and ArH, respectively, and %attack at Z and H are the percentages

of product formed by ipso attack at Z or at one H.

$$i_f^Z = \frac{k(\text{ArZ})}{k(\text{ArH})} \frac{\%attack\ at\ Z}{\%attack\ at\ H} \tag{3}$$

I chose iodo, bromo, and chloro as the substituents, nitration as the reaction, and an

additional p-methoxy substituent to help direct the electrophilic NO_2^+ to the ipso position. Thus

the chosen reaction was nitration of p-iodo, p-bromo-, and p-chloroanisole. I expected the

reactions to occur as in Scheme 2. Normal nitration ortho to the methoxy would produce 4-halo-

2-nitroanisole, but ipso attack would lead to halogen migration and rearranged product, 2-halo-4-

nitroanisole. I envisioned that this reaction would become known as the Perrin Rearrangement, but soon realized that I had been scooped by Frédéric Reverdin, who had discovered the Reverdin Rearrangement in 1896.[8]

Scheme 2. Expected nitrations of p-haloanisoles.
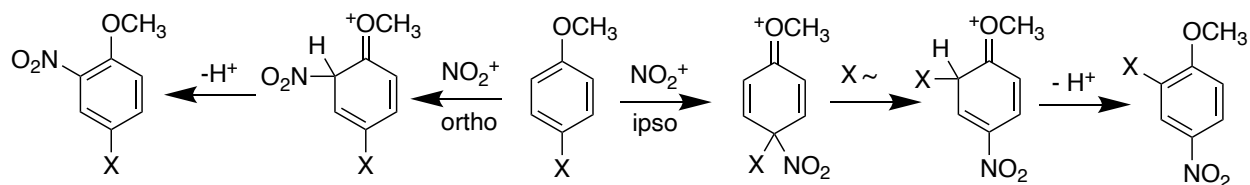
We therefore studied the nitration of anisole and three p-haloanisoles in acetic anhydride. The reactions are not entirely as expected but are shown in Scheme 3. Nitration ortho to the methoxy does produce 4-halo-2-nitroanisole, There is also p-nitro product, to the extent of 30.6, 40, 31, and <0.2%, from anisole, p-iodoanisole, p-bromoanisole, and p-chloroanisole, respectively, as determined by GC. However, in each case the p-nitro product was simply p-nitroanisole, without halogen migration. Instead the halogen is transferred to solvent and halogenates another molecule of p-haloanisole. Consequently the amount of 2,4-dihaloanisole equals the amount of p-nitroanisole.

Scheme 3. Observed nitrations of p-haloanisoles.
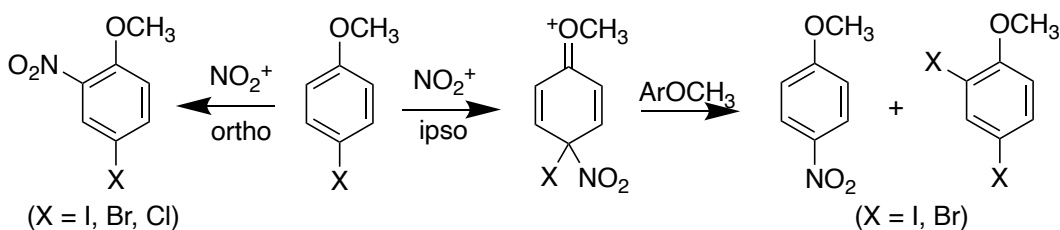
Why though is 4-chloro-2-nitroanisole the only product from nitration of *p*-chloroanisole? Why is there neither *p*-nitroanisole nor 2,4-dichloroanisole? Does that mean that there was no ipso attack? That might have been the case, but why should the reactivity at the position ipso to chlorine be so different from that ipso to bromine or iodine? Another possibility is that ipso attack does occur, but the resulting intermediate undergoes a nitro migration rather than dehalogenation.

To test the ease of nitro migration relative to dechlorination or debromination, ketone **2** (X = Br, Cl) was synthesized by nitration of 1-halo-2-naphthol, separated, and treated with HCl in acetic acid-acetic anhydride.[9] Indeed, as shown in Scheme 4, when X = Br only debromination occurs (even in the absence of HCl), leading to 1-nitro-2-naphthol (as its acetate). In contrast, when X = Cl the product is 1-chloro-6-nitro-2-naphthol (as its acetate), formed by a nitro migration. Therefore the ease of leaving/migrating abilities is $Br^+ > NO_2^+ > Cl^+$. Notice that these leaving abilities represent electrofugalities, as appropriate for cationic species, which leave without a bonding electron pair, in contrast to the more common sense of (nucleofugic) leaving abilities of anions in nucleophilic substitutions and eliminations, where $I^- > Br^- > Cl^- \gg F^-$.

Scheme 4. Reactions of 1-halo-1-nitro-2-oxo-1,2-dihydronaphthalenes (**2**, X = Br, Cl) in acid.
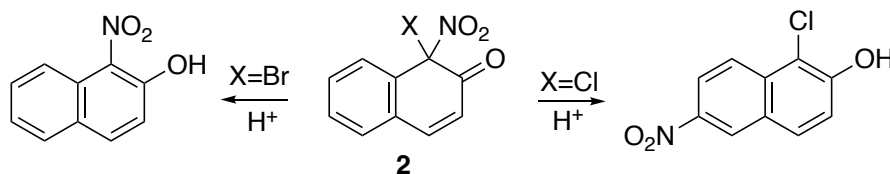

How then can ipso attack on *p*-chloroanisole be detected (if it occurs)? If the ipso intermediate undergoes nitro migration rather than dehalogenation, then the 4-chloro-2-

nitroanisole product is the same as from direct ortho nitration. A clue was the observation that a small amount of 4-chloro-2-nitrophenol was produced, especially if the acetic anhydride was replaced by acetic acid or water, and increasing to a maximum of 37% in aqueous HNO_3 containing 11 M H_2O.

Formation of this phenolic product was interpreted in terms of trapping of the ipso intermediate, as outlined in Scheme 5. In acetic anhydride that intermediate undergoes nitro migration to 4-chloro-2-nitroanisole, indistinguishable from the product of direct ortho nitration. But in more aqueous media the migration must compete with demethoxylation, via addition of water to the carbonyl carbon (as in ketal hydrolysis,[10] rather than attack at methyl carbon). That product corresponds to 37% ipso attack on p-chloroanisole, quite comparable to the 40% and 31% seen for p-iodo- and p-bromo-anisole.

Scheme 5. Trapping of the intermediate from ipso nitration of p-chloroanisole.
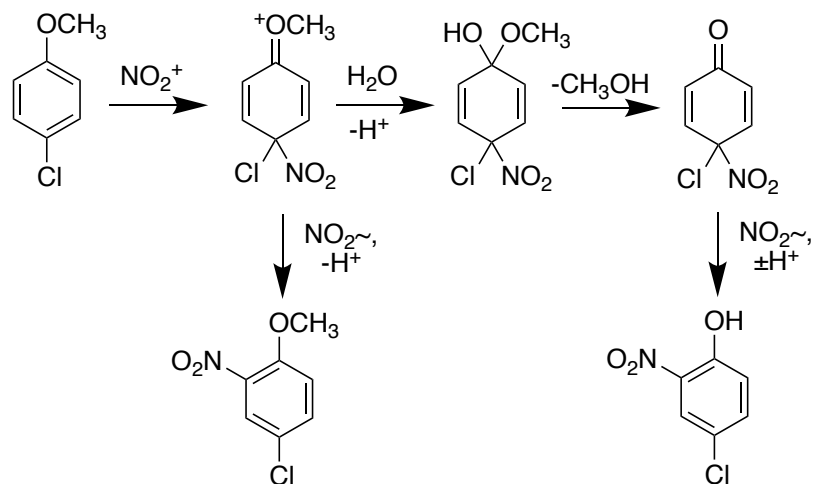
IPSO FACTORS

Having solved the puzzle of why there is no dechlorination or chlorine migration, we returned to measure ipso factors. Because the rate-limiting step in these nitrations is the

formation of NO_2^+, all substrates react at the same rate. Consequently, in order to measure

relative reactivities it was necessary to apply competition kinetics with a mixture of two anisoles.

From the relative amounts of the two *o*-nitroanisole products it was then possible to evaluate the

extent to which a halogen deactivates that ortho position meta to it, although it was necessary to

correct for the nitro migration in *p*-chloroanisole. Thus the ipso factors i_f^X were evaluated as

0.18 for iodo, 0.08 for bromo, and 0.06 for chloro. These electron-withdrawing halogens are

deactivating toward nitration at the ipso position bearing the halogen, but less so than in

halobenzenes themselves (i.e., C_6H_5X) because the methoxy group makes the reaction less

selective.

Now that the ipso position has been defined, we return to the intriguing aspect of the ease

of both the bromodemercuration that converted ArHgCl to ArBr and the nitrosodemercuration in

Scheme 1. Why are those reactions, which involve electrophilic substitution at the position

bearing the mercury substituent, so facile? They imply that the ipso factor i_f^{Hg} is fairly large,

corresponding to an activating substituent. Moreover, mercuration of benzene shows a kinetic

isotope effect k_{C6H6}/k_{C6D6} that varies from 4.68 to 6.75, depending on the concentration of acid.[6]

Therefore the deprotonation is partially rate-limiting, meaning that the initial mercuration is

reversible, as suggested in Scheme 6, with $k_{-1} \sim k_2$.

Scheme 6. Two-step mechanism for aromatic mercuration, via intermediate **3**.
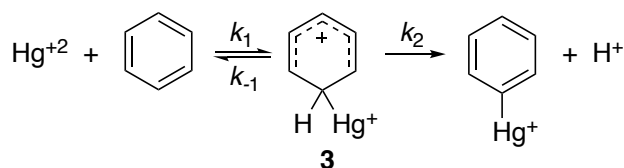
All those reactions, bromodemercuration, nitrosodemercuration, and the k_{-1} in Scheme 5, show that a mercury group can be a good electrofuge (leaving group that leaves without an electron pair). That is no surprise, because organometallics are very reactive to protiodemetallation. The familiar examples are ArLi and ArMgX. However, their reactivity resides in their carbon-metal sigma bonds, which are very rapidly cleaved by a protic acid. In contrast, the cleavage of an arylmercurial is stepwise, via initial conversion of the carbon bonded to mercury from sp^2 to sp^3, to create intermediate **4** (E = Br, NO, or H). Indeed, such arenemercurinium ions have been observed by ^{1}H and ^{13}C NMR, although on the NMR timescale the mercury may migrate from one position to another.[11]


E Hg$^+$ E Hg^{+2}

4
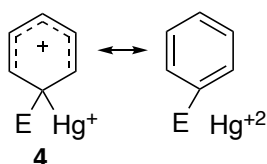
The question then becomes why is **4** so easily formed by electrophilic addition to the ipso position of PhHg$^+$. What stabilizes it? Why is the ipso factor i_f^{Hg} so large and positive, corresponding to an activating substituent? The reason is that carbocation intermediate **4** is stabilized by hyperconjugation. Hyperconjugation is the delocalization of electrons in sigma bonds, here the C-Hg bond, as described by the additional resonance form shown for **4** (where the Hg^{+2} does not dissociate but remains at bonding distance from the ipso carbon). This same situation applies to arylsilanes, which are readily cleaved by electrophilic substitution at the ipso position, owing to hyperconjugation of the C-Si bond in the reaction intermediate.[12]

CONCLUSIONS

In fifty years the designation ipso has become fully established. This nomenclature is included in the Glossary of Terms Used in Physical Organic Chemistry,[13] and it is approved by

the International Union of Pure and Applied Chemistry.[14] It is useful for indicating the position

on an aromatic ring that bears a substituent and for expressing relative reactivities. A rich

chemistry is associated with the ipso position, as evidenced by 235,000 entries in Google Scholar

on August 26, 2021. Although it was introduced in the context of electrophilic substitution,

which continues,[15] it has been extended to heterocycles,[16] to metal-catalyzed reactions,[17] and to

radical substitutions,[18] and it helps to codify computations and correlations with NMR data.[19] In

summary, the goal of this Perspective was to tell my personal story regarding the thinking and

the experiments that led to the designation ipso, which continues to be useful across a wide range

of research areas.

AUTHOR INFORMATION
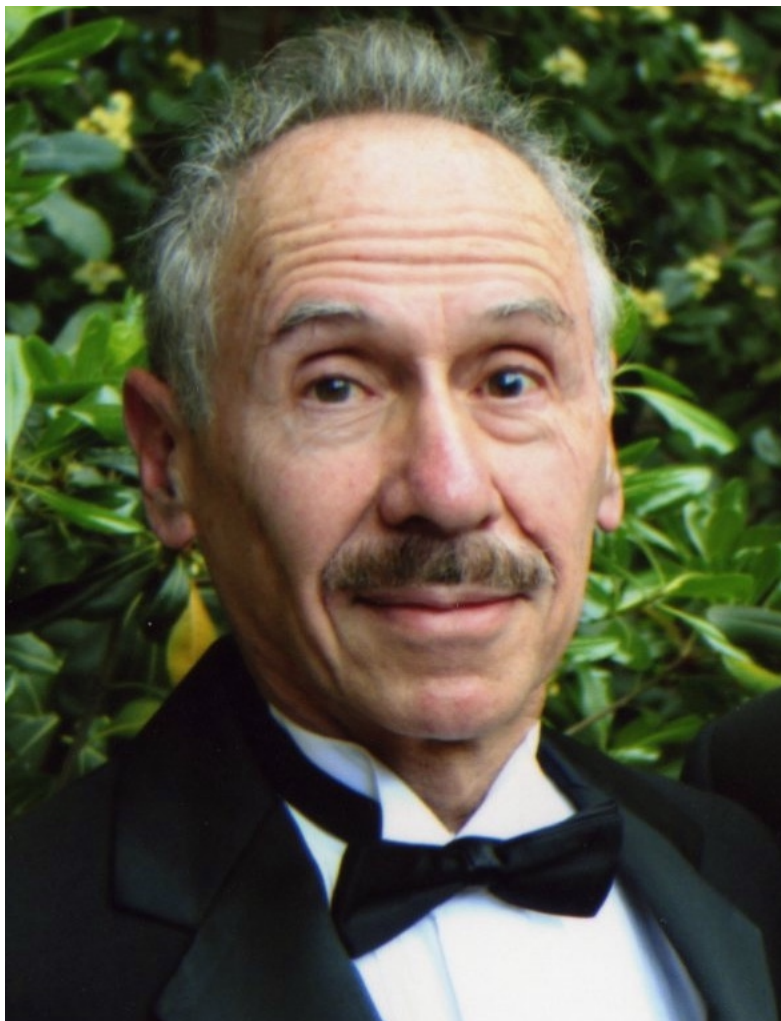
Born in Pittsburgh, Charles L. Perrin graduated from Harvard College in 1959 and received his PhD in 1963 from Harvard University, under the direction of F. H. Westheimer. Following an NSF Postdoctoral Fellowship at UC Berkeley, he joined the founders of the new campus at UC San Diego, where he is now Distinguished Professor of Chemistry (emeritus, recalled to active service). His research spans a broad range of structural and mechanistic chemistry, including malonic anhydrides, anomeric effects, stereoelectronic control, isotope effects, dynamic NMR, solvation, hydrogen bonding, and *p*-benzynes.

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