Through-Space Activation Can Override Substituent Effects in Electrophilic Aromatic Substitution

Guan, L.; Holl, M. G. Pitts, G. C.; Struble, M. D.; Siegler, M. A. Lectka, T. 
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John Milligan
Wipf Group Meeting

Current Literature
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Non-covalent arene interactions

Many types of interactions have been characterized, including:
- Arene-arene “edge to face”
- Arene-arene “stacking”
- CH-arene
- OH-arene
- S-arene
- Cation-arene

Non-covalent arene interactions

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Torsion balances: tools for studying these interactions

$\Delta G$ of ”edge to face” interaction can be deduced through relative population of the rotomers (observable by NMR)

Previous work by Lectka group

OH-alkene interaction

F-arene interaction

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OH-alkene interaction

F-arene interaction

Can an –OH-arene interaction impact reactivity?

Electrophilic Aromatic Substitution

Absent any differentiation, both rings react equally
Electrophilic Aromatic Substitution

A directing group will bias reactivity:
Non-covalent influence of electrophilic aromatic substitution?

Can reactivity be biased by a non-covalent interaction?
Synthesis of test substrate

Synthesis of substrate

1. 
   Cl$_3$C\(\text{NH}\)O\(\text{Ph}\)
   TFOH (cat.)
   2. LiOH, H$_2$O/THF
   3. TFAA
   29% (3 steps)

1. anthracene, 160 °C
2. H$_2$, Pd/C
43% (2 steps)

1. PCC, CH$_2$Cl$_2$
2. LiAlH$_4$, THF
64% (2 steps)
Model compound

-OH IR shift red shifted 32 cm\(^{-1}\) compared to diastereomer
-\(^1\)H NMR: \(\delta\) -0.21 (sharp s)
Nitration

Bromination and nitration occur only at the “activated” aryl ring
Bromination

Tetrabromination of the “activated” ring occurs before any bromination of the bottom ring!
-CF$_3$ substrate

1. PCC, CH$_2$Cl$_2$

2. LiAlH$_4$, THF

3. preparative HPLC

\[ \text{o-DCB, 160 °C then H}_2, \text{ Pd/C 61%} \]

\[ 1.2 : 1 \text{ (inseparable)} \]
-CF$_3$ substrate

Non-covalent activation overrides –CF$_3$ deactivation!
-CF₃ substrate

Non-covalent activation overrides –CF₃ deactivation!
Activation through a “Meisenheimer complex”? 

\[
\begin{align*}
\text{Br}_2, \text{Fe} \\
\text{CH}_2\text{Cl}_2, \text{reflux} \\
57\%
\end{align*}
\]


Figure 2. Optimized structure of 6A, the σ-complex intermediate for endobromination of 6, at ωB97XD/6-311+G**.
Biological Relevance

Donepezil (Alzheimer’s drug) bound to acetylcholineesterase

Glutathione S-transferase active site pocket

Possible future direction

Can synthetically useful differentiation be achieved through enzymatic/supramolecular non-covalent activation?

Ron Breslow (1931-2017)

\[
\begin{align*}
&\text{OMe} \\ &\alpha\text{-cyclodextrin} \\ &\text{HOCl} \\ &\text{water, rt} \\ &\text{OMe} \\ &\text{Cl}
\end{align*}
\]

96:4 \text{para : ortho}

rate and selectivity decrease without cyclodextrin

Figure 1. Schematic representation of an anisole molecule in the cavity of cyclohexaamylose. Eighteen hydroxyl groups (not shown) ring the mouths of the cavity, one of which is written as its hypochlorite ester to indicate a mechanism by which the increased rate of chlorination in the complex may be explained.