Year 1 CHEM40006
Reactivity at Carbon Centres

LECTURE 14 - Reactivity at sp² Centres: Aromatic Compounds as Nucleophiles

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Format and scope of presentation

• **Electrophilic aromatic substitution (S<sub>E</sub>Ar):**
  – Directing effects
    • *meta-*directing groups (*deactivating*)
    • *ortho-*/*para-*directing groups which *deactivate*
    • *ortho-*/*para-*directing groups which *activate*
    • *ortho-*/*para-*ratios
    • *ipso-*directing groups
  – Polysubstituted aromatics
    • cooperating and competing directing influences

**Key further reading:** Clayden, Greeves & Warren, *Organic Chemistry*, 2<sup>nd</sup> Ed., Chapter 21
• *directing effects* – pages 479 - 492
Aromatics as ambident nucleophiles – *directing effects*

- **Substituted aromatics are ‘ambident’ nucleophiles**
  - *i.e.* they can potentially react at various positions

  substituent as nucleophile (*e.g.* $X = NH_2$)

  ![Diagram showing ambident nucleophilic reactivity]

  - *ipso*-carbon as nucleophile
  - *ortho*-carbon as nucleophile
  - *meta*-carbon as nucleophile
  - *para*-carbon as nucleophile

- **What governs the position of reactivity?**
  - The ‘directing effect’ of the substituent $X$
  - These fall into two broad categories:
    - *meta*-directing groups
    - *ortho-/para*-directing groups…
Directing effects

- Electrophilic substitution is under kinetic control - i.e. fastest formed product predominates
- The fastest formed product will be formed via the lowest energy transition state:

How can we estimate which transition state has lowest energy?

HAMMONDS POSTULATE: ‘energy of TS# will resemble that of Wheland intermediate more closely than the starting materials or products’

We can estimate the energies of the Wheland intermediates from their resonance forms...
**meta-Directing groups (deactivating)**

- **‘Deactivated’** – *i.e. less reactive than benzene (overall more electron deficient)*

- **CF₃, NR₃⁺, NH₃⁺**
  *induction deactivates overall & destabilizes o-/p-WIs*

- **NO₂, CN, SO₃H, SO₂R, CHO, COR, CO₂R, CO₂H**
  *conjugation deactivates overall & decreases relative reactivity of o-/p- positions; induction deactivates overall & destabilizes o-/p-WIs*
**ortho-/para-Directing (deactivating)**

- **Deactivating** – *i.e. less reactive than benzene (overall more electron deficient)*

- **I, Br, Cl, NO**
  
  (*conjugation* increases relative reactivity of *o*-/*p*- positions; *induction* deactivates overall)

  *i.e. conjugation dominates relative reactivity of *o*-/*p*- vs. *m*- but induction deactivates overall*
**ortho-/para-Directing (activating)**

- **Activating** – i.e. more reactive than benzene (overall more electron rich)
  - NR$_2$, NH$_2$, OH, OR, NHCOR, OCOR
    (conjugation activates overall & increases relative reactivity of o-/p- positions)
  - **Alkenyl, aryl**
    (conjugation activates overall & stabilizes o-/p-WIs)
  - **Alkyl**
    (sigma conjugation activates overall & stabilizes o-/p-WIs)
ortho-/para-Ratios

- Statistically we expect ~2:1 ortho- : para-
- Theoretical charge density studies favour the para-:

- Steric effects (large $E^+$ or directing substituent or both) disfavour the ortho-

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<th>$E$</th>
<th>% o-</th>
<th>% p-</th>
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<td>55</td>
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<td>Br</td>
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<td>SO₃</td>
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<table>
<thead>
<tr>
<th>$X$</th>
<th>% o-</th>
<th>% p-</th>
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<tbody>
<tr>
<td>Me</td>
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<td>37</td>
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<tr>
<td>Et</td>
<td>45</td>
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<tr>
<td>iBu</td>
<td>16</td>
<td>73</td>
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</table>

- Complexation (chaperone) effects can favour the ortho-
  - Strazzolini J. Org. Chem. 1998, 63, 952 (DOI)

- Solvent effects are difficult to predict
**ipso-Substitution**

- **Proto-desulfonylation:**
  
  ![Reaction Scheme]

- **Utility of SO$_3$H as temporary directing group**

  ![Reaction Scheme]

- **Desilylation, degermylation & destannylation:**
  
  - **Review:** Eaborn J. Organometal. Chem. 1975, 100, 43 (DOI)
Polysubstituted Aromatics

- **Two substituents direct to the same positions - cooperation:**
  - \( o-/p \)-directing
    - \( o-/p \)-directing
      - \( \text{OH} \)
      - \( \text{Br} \)
      - \( \text{FeBr}_3 \)
      - \( \text{Br} \)
      - \( \text{Br} \)
    - \( \text{OH} \)
    - \( \text{Br} \)
      - \( \text{EtCOCl} \)
      - \( \text{AlCl}_3 \)
      - \( \text{Cl} \)
      - \( \text{CO}_2\text{Me} \)
    - \( \text{major prod (+ some o-)} \)

- **Two substituents activate different positions – competition:**
  - two activating groups – the more powerful director dominates:
    - \( o-/p \)-directing
      - \( \text{OH} \)
      - \( \text{SO}_3 \)
      - \( \text{H}_2\text{SO}_4 \)
      - \( \text{OH} \)
      - \( \text{SO}_3\text{H} \)
      - \( \text{activation by conjugation overrides activation by sigma-conjugation} \)
      - \( \text{NHAc} \)
      - \( \text{HNO}_3 \)
      - \( \text{NHAc} \)
      - \( \text{NO}_2 \)
      - \( \text{Me} \)
      - \( \text{Me} \)
      - \( \text{Me} \)
      - \( \text{Me} \)
      - \( \text{...even when the conjugation is diluted in an amide} \)

  - an activating & a deactivating group: in general, activating effects override deactivating effects:
    - \( o-/p \)-directing
      - \( \text{OMe} \)
      - \( \text{OMe} \)
      - \( \text{c.HNO}_3 \)
      - \( \text{c.H}_2\text{SO}_4 \)
      - \( \text{OMe} \)
      - \( \text{OMe} \)
      - \( \text{O}_2\text{N} \)
      - \( \text{H} \)
      - \( \text{H} \)
      - \( \text{the aldehyde deactivates C5, C6 is preferred on account of being para activated and on steric grounds} \)
Synthetic ‘check list’ for \( S_{E}Ar \)

- **Will** \( E^+ \) **react at ring carbon or elsewhere** (e.g. at amine substituent \( \rightarrow \) diazonium salt)?

- **Is the** \( E^+ \) **sufficiently reactive to react with a ring carbon?**

- **If reaction at a ring carbon is expected, what orientation relative to existing group(s) (i.e. directing effects)?**
  - ortho-/para- or meta- or ipso-?
  - If ortho-/para- …which?
  - Do directing effects of existing groups cooperate or compete?
  - Use a temporary directing group to get desired orientation?

- **Mono- or multiple substitution?**
  - Will introduction of \( E \) activate or deactivate the ring relative to the starting material?