Neighbouring group participation

By
Hasibur Rahaman

Department of Chemistry
Prof. Petri Pihko’s Research Group
University of Jyväskylä
Email: hasibur.h.rahaman@jyu.fi, rahman.ncl08@gmail.com
**Definition:**

**Neighbouring group participation** or NGP in organic chemistry has been defined by IUPAC as the interaction of a reaction centre with a lone pair of electrons in an atom or the electrons present in a sigma bond or pi bond.

*When NGP is in operation:*

1) It is normal for the reaction rate to be increased.
2) It is also possible for the stereochemistry of the reaction to be abnormal (or unexpected) when compared with a normal reaction.

**Who does participate?**

-Cl, -Br, -I, -NH₂, -OH, -OR, -S-, -OOCR.

*Mechanism:*

\[
\begin{align*}
\text{G} & \quad \text{X} \\
\text{G} & \quad \text{Nu-} \quad \text{Fast} \\
\text{G} & \quad \text{Nu} \quad \text{slow}
\end{align*}
\]
Halide participation in NGP

S - Bridged complexes: Alkyl Participation

\begin{align*}
(\text{CH}_3)_3\text{CCH}_2\text{OH} & \xrightarrow{\text{HBr}} \text{CH}_3\text{CCH}_2\text{CH}_3 \\
(\text{CH}_3)_3\text{CCH}_2\text{I} & \xrightarrow{\text{Ag}^+} \text{CH}_3\text{CCH}_2\text{CH}_3 + \text{AgI} \\
\text{Rational} \quad \text{CH}_3 & \xrightarrow{-\text{I} \quad \text{slow}} \text{CH}_3\text{CCH}_2\text{I} \quad \xrightarrow{\text{H}_2\text{O}} (\text{CH}_3)_2\text{CCH}_3 \quad \xrightarrow{\text{H}_2\text{O}} \text{alc. prod} \\
\text{Supporting evidence} \\
\text{B}_2\text{H}_6 & \\
\text{Al}_2(\text{CH}_3)_6 &
\end{align*}
NGP by Alkene

The II orbitals of an alkene can stabilize a transition state by helping to delocalize the positive charge of the carbocation.

Even, if the alkene is more remort from the reacting center the alkene can still act in this way.
NGP by Aromatic Ring

An aromatic ring can assist in the formation of a carbocationic intermediate called a phenonium ion by delocalising the positive charge.

Example:

Cram, D. J. JACS 1952, 74, 2129
Application in Carbohydrate Chemistry

Turnbull, W. B. et al. OBC 2009, 7, 4842
Remote Participation for $\beta$-Selectivity

**Five Membered Ring**

**Six membered Ring**

NGP: Solvent effect

<table>
<thead>
<tr>
<th>Solvent</th>
<th>% Yield</th>
<th>Ratio1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>29</td>
<td>1.1</td>
</tr>
<tr>
<td>Benzene</td>
<td>34</td>
<td>0.8</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>22</td>
<td>1.2</td>
</tr>
<tr>
<td>DMF</td>
<td>Trace</td>
<td>.........</td>
</tr>
</tbody>
</table>

Yoshimura, Y. et al. JOC 1998, 63, 6891
Classic Example of NGP
Temperature Dependence in NGP

<table>
<thead>
<tr>
<th>Reaction temperature</th>
<th>Ratio 1:2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 °C</td>
<td>22:78</td>
</tr>
<tr>
<td>25 °C</td>
<td>32:68</td>
</tr>
<tr>
<td>70 °C</td>
<td>46:54</td>
</tr>
</tbody>
</table>

**Synthesis of Surfactants**

Grindley, T. B. et al. *JOC* 2009, 74, 7762
Hydroxyl Group in NGP

When $R = R' = H$: only deacyl pdt
$R = H; R' = Me$ only alkene pdt
$R = R' = Me$: on reaction

Braddock, D. C. *et al.* *TL* 2001, 42, 7527
Tuneable Method for N-Debenzylation by NGP

Davis, B. G. *et al.* *OL* **2005**, *7*, 2361
Conclusion

• Neighboring group participation is a useful tool for synthetic chemists. In $S_N^2$ reactions, retention of configuration of the reaction center can be obtained instead of the expected inversion of configuration.

• Also, if the neighboring group helps stabilize the intermediate produced in the rate determining step, rate acceleration occurs.

• In the case study, the effects of solvent polarity on the competition between neighboring group participation and $S_N^2$ direct substitution were addressed. It was observed that polar solvents increased neighboring group participation. Use of polar solvents seemed to help stabilize the cyclic cation intermediate.

• Also, the strength of the nucleophile was found to affect the reaction outcome. When strong nucleophiles were used, only direct substitution was observed.

Thank You