Microwave-Assisted Nucleoside Chemistry and Major Groove Functionalization of DNA

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Agenda

- DNA: A Structural Introduction
- Double-Headed Nucleosides
- Synthesis of Nucleoside Dimers
  - Ring Closing Metathesis
  - Dimers via Click Chemistry
- Functionalization of DNA
  - Minor Groove Functionalization
  - Major Groove Functionalization
- Future Perspectives
- Conclusion

DNA: A Structural Introduction
Double-Headed Nucleosides

Figure 1. Figures of the Watson–Crick double helix (A) and of a duplex containing double-headed DNA (B).

Jensen, B. and Nielsen, P., Unpublished results.

Pg = Protecting Group
Lg = Leaving Group

Synthesis of Nucleoside Dimers

- Stabilizing Secondary DNA and RNA Structures
  - Three-way Junctions
  - Bulged Duplexes
  - Targeting of Secondary Structures
- Artificial Model Systems
Nielsen, H. and Nielsen, P., unpublished results.

Nielsen, H. and Nielsen, P., unpublished results.

Nielsen, H. and Nielsen, P., unpublished results.
Ring Closing Metathesis

Liv S. Thomsen, and Poul Nielsen, Unpublished results


RCM catalysts used

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Total rx. Time (min)</th>
<th>Amount of cat. mol%</th>
<th>Catalyst</th>
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</thead>
<tbody>
<tr>
<td>9.6:8</td>
<td>15</td>
<td>10</td>
<td>Hoveyda-Grubbs'Generation 1</td>
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<tr>
<td>9.7:9</td>
<td>10</td>
<td>12</td>
<td>Hoveyda-Grubbs'Generation 2</td>
</tr>
</tbody>
</table>

Thomsen, L. S. and Nielsen, P., Unpublished results.
Diene 9.6

Andersen, N. K., Thomsen, L. S. and Nielsen, P., Unpublished results

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Diene 9.4

Andersen, N. K., Thomsen, L. S. and Nielsen, P., Unpublished results

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**Site Specific DNA Functionalization**

- Two Examples
  - Minor Groove Functionalization
    - 2'-Amino LNA thymine
  - Major Groove Functionalization
    - Functionalization of the nucleobase C5-position

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Minor Groove Functionalization

- Minor groove has been extensively modified
  - 2'-Amino-LNA
  - 2'-Amino-uridine

Functionalized 2’-amino-LNA

Major Groove Functionalization

- Aim
  - To obtain good spatial control of functionalities placed in the major groove
  - Functional Diversity
  - Increase duplex stability towards complementary DNA and RNA
  - Good mismatch discrimination
Introduction of Functionalities via Click Chemistry

- Easy access to a large variety of functionalities
- Tolerance to steric demands
- “Green Chemistry”
- Easy work-up/purification

The Building Blocks

Requirements:

- High stability
- Extended π-π stacking
- Chemoselective functionalization

Ab-initio Calculations

- The triazole-ring and nucleobase are found to be co-planar.
- No local minima are found only one global minimum indicating that a single conformation is dominant.
Determination of pKa

Absorption measured at 266nm


Multiple modified ON against DNA

DNA:DNA
DNA:RNA
RNA:RNA
5'-GTG XX X X GC:DNA
5'-GTG YYY YGC:DNA
5'-GTG ZZZ ZGC:DNA


Multiple modification ON against RNA

DNA:DNA
DNA:RNA
RNA:RNA
5'-GTG XX X X GC:RNA
5'-GTG YYY YGC:RNA
5'-GTG ZZZ ZGC:RNA


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Table 1. Distribution data.

|                      | Diol component 1 | Diol component 2
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<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>$N_{2001}$</td>
<td>$N_{2001}$</td>
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<tr>
<td>1-OH</td>
<td>360.0</td>
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</tr>
<tr>
<td>2-OH</td>
<td>325.0</td>
<td>325.0</td>
</tr>
<tr>
<td>1,2-Diol</td>
<td>325.0 (325.0 + 0)</td>
<td>325.0 (325.0 + 0)</td>
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<tr>
<td>1-CH$_{3}$-OH</td>
<td>325.0 (325.0 + 0)</td>
<td>325.0 (325.0 + 0)</td>
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<tr>
<td>2-CH$_{3}$-OH</td>
<td>325.0 (325.0 + 0)</td>
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Table 2. Structural data.

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<th>Diol component 1</th>
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Exploring the potential of fully modified duplex structures

Possible application in triplex systems

Increased use of microwave reactions

Future Perspectives

• Exploring the potential of fully modified duplex structures

• Possible application in triplex systems

• Increased use of microwave reactions

Conclusion

• Rate increase for standard reactions

• Good perspectives for reactions with high activation energy

• High temperatures can be used

• Not always the optimal method
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