Atropisomerism: The Axis of Chirality

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Outline of the presentation

1. Introduction
2. Conditions for Atropisomerism
3. Nomenclature of Atropisomers
4. Classification of Atropisomers
5. Methods to study Atropisomerism
6. Methods for Atroposelective Conversion
7. Uses of Atropisomers
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Introduction

Though “optical activity due to axial chirality” was first reported by Christie and Kenner in 1922,¹ but the term “Atropisomerism” was coined by Richard Kuhn later in 1933.²

From Greek: a – not
tropos – to turn

Atropisomerism is that kind of isomerism, where the conformers (called atropisomers) can be isolated as separate chemical species and which arise from restricted rotation about a single bond.

Axis of Chirality: An axis about which a set of atoms/functional groups/ligands is held so that it results in a spatial arrangement that is not superimposable on its mirror image.

²Kuhn, R. Stereochemie (Ed.: K. Freudenberg), 1933, 803
1. Two necessary preconditions for axial chirality are:
   i. a rotationally stable axis
   ii. Presence of different substituents on both sides of the axis

2. Atropisomers are recognised as physically separable species when, at a given temperature, they have a half life of at least 1000 s (16.7 min) \([t \geq 1000 \text{ s}]\).

3. The minimum required free energy barriers at different temperatures are as below.
   \[\Delta G_{200K} = 61.6 \text{ kJmol}^{-1}\]
   \[\Delta G_{300K} = 93.5 \text{ kJmol}^{-1}\]
   \[\Delta G_{350K} = 109 \text{ kJmol}^{-1}\]

4. The configurational stability of axially chiral biaryl compounds is mainly determined by three following factors:
   i. The **combined steric demand of the substituents** in the proximity of the axis
   ii. The **existence, length, and rigidity of bridges**
   iii. Atropsiomerization **mechanism different from a merely physical rotation** about the axis, e.g. photochemically or chemically induced processes.
Nomenclature of Atropisomers

1. Notations used for Atropisomers:
   - \( aR \) (axially Rectus) or \( P \) (plus)
   - \( aS \) (axially Sinister) or \( M \) (minus)

2. Priority of the substituents are determined by the CIP rule.

3. Here it is assumed that priority of \( A>B \) and \( A'>B' \).

*same descriptor results, regardless of the position of the observer

Classification of Atropisomers

The following classification is based upon the basic structure of the “Biaryl Atropisomers”.

- **Biaryl Atropisomers**
  - Bridged Biaryls
    - Bridged biaryl lignans
    - All-carbon bridged biaryls
    - Biaryl lactones
    - Biaryl cyclopeptides
    - Multicyclic bridged biaryls
  - Nonbridged Biaryls
    - Isocyclic biaryls
    - Fused heterocycles
    - Heterobiaryls
    - Multiply Coupled biaryls

Examples of Natural Bridged Atropisomers

Bridged biaryl lignans

\( \text{MeO} \)
\( \text{MeO} \)
\( \text{Me} \)
\( \text{Me} \)
\( (M)\text{-}(+)\text{-steganone} \)
\( \text{antihepatotoxic, Microtubulin-aggregation inhibiting activity} \)
\( \text{J. Am. Chem. Soc. 1973, 95, 1335} \)

All-carbon bridged biaryls

\( \text{OH} \)
\( \text{OH} \)
\( (P)\text{-}(+)\text{-isoplagiochin C} \)
\( \text{antitumoral, antibacterial and antymycotic activities} \)
\( \text{J. Am. Chem. Soc. 2004, 126, 9283} \)

Biaryl Lactones

\( \text{OH} \)
\( \text{OH} \)
\( (P)\text{-Tellimagrandin} \)
\( \text{anti-herpesvirus activity} \)
\( \text{Phytochemistry 1976, 15, 211} \)

Multicyclic Biaryls

\( \text{Cl} \)
\( \text{Cl} \)
\( (P,M,M)\text{-Diazonamide A} \)
\( \text{Potent cytotoxic activity} \)
\( \text{J. Am. Chem. Soc. 1991, 113, 2303} \)

Biaryl cyclopeptides

\( \text{NH}_2 \)
\( \text{NH} \)
\( (M)\text{-Biphenomycin A} \)
\( \text{antibiotic with potent antibacterial activity against gram-positive bacteria} \)
\( \text{J. Am. Chem. Soc. 1989, 111, 7328} \)
Examples of Natural non-bridged Atropisomers

**Isocyclic Biaryl**

(\(P\))-Mastigophorene A
Nerve growth stimulator

**Fused Heterocycles**

(\(P\))-\(\Delta\)-Kotonin
Fungal Metabolites
*J. Org. Chem.* 1977, 42, 244

**Heterobiaryl**

(\(M\))-Murrastifoline-F

**Multiply Coupled Biaryl**

(\(P\))-\(\Delta\)-Phleichrome
Phytotoxic activity
*Agric. Biol. Chem.* 1975, 39, 1683
**Methods to Study Atropisomerism**

1. **X-ray crystallography**: Though X-ray (or neutron) diffraction provides only a static picture of atropisomerism, yet that is essential for knowing the torsional angle and the preferred conformation.

   ![11a (trans)](image1) ![11b (cis)](image2)

   A single-crystal X-ray diffraction analysis on crystals selected from the sublimed product of the above hole-transport molecule for organic light-emitting diodes shows two orientations in solid state. The occupancy factors for the two sites were found to be 0.50:0.50.

2. **Electron Diffraction**: Almenningen et al. used this method for 2,2'-dithienyl in finding the angle of twist of 34°.

   ![2,2'-dithienyl](image3)

   Angle of Twist = 34°

3. **Electronic Spectra (UV and Visible)**: Hindering the planarity (steric inhibition of resonance) modified the absorption (hypsochromic-blue shift-and hypochromic effects). Braude's equation \( \cos^2 \theta = \epsilon / \epsilon_0 \) has been used to find the torsional angles in 2-arylinodes, 1-aryl imidazoles etc.

   ![2-arylinodes](image4) ![1-aryl imidazoles](image5)

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Methods to Study Atropisomerism\textsuperscript{5}

4. **Dipole moment**: Dipole moments can be estimated by a vector sum that depends upon the conformation.

5. **Depolarised Rayleigh Scattering (DRS)**: Rioux and Clement used this method to calculate the dihedral angles of 1-arylpyrazoles.

6. **Basic Measurements (pKa) and reactivity**: Steric inhibition of resonance increases the basicity, e.g. the basicity of N-arylpyrazoles increases by about 0.5 pKa units, when a methyl group is introduced at position-5.

7. **Substituent Constants (Hammett & Taft values)**: The hammett and Taft values are sensitive to steric hindrance and they suggest the degree of non-planarity of both the aryl groups.

8. **Static and Dynamic NMR**: Together with crystallography, HPLC, and theoretical calculations, NMR is the technique that has contributed most to the understanding of this phenomenon. Atropisomers are detectable by NMR if half lives exceed 0,001 s.

Methods for Atroposelective Conversion

There are conceptually four different strategies:

1. Atropodiastereoselective biaryl coupling reactions of chirally modified arenes with \textit{internal asymmetric induction}. In this case the stereogenic element remains in the target molecule.

2. Atropodiastereoselective coupling of arenes by applying an \textit{artificial chiral bridge}.

3. Dynamic \textit{kinetic resolutions} of configurationally labile biaryls.

4. The efficient \textit{atropoenantioselective} biaryl coupling.
Methods for Atroposelective Conversion

Atropodiastereoselective biaryl couplings using artificial Chiral Auxiliary:6,7

Methods for Atroposelective Conversion

By Metal catalysed Asymmetric Cross Coupling (Kumuda Coupling):^8

\[ \text{34 Br} + \text{MgBr} \rightarrow \text{35 Me}\]

\[ \text{MeO} \]

\[ \text{36 Ph}_2\text{P Fe} \]

\[ \text{(4-10 mol-%)} \]

\[ \text{NiBr}_2 \text{ (2-5 mol-%)} \]

\[ \text{Et}_2\text{O/Toluene, -10 °C} \]

\[ \text{dr = 98:2} \]

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Methods for Atroposelective Conversion

By Metal catalysed Asymmetric Cross Coupling (Suzuki Coupling):^9

\[
\begin{align*}
\text{R} & \quad \text{Br} & \quad \text{P} & \quad \text{OR'} & \quad \text{OR'} & \quad \text{P} & \quad \text{Cy}_2 \\
\text{B(OH)}_2 & \quad \text{R} & \quad & & & \\
\text{NMe}_2 & \quad & \text{PCy}_2 & \quad & \text{Me} & \quad & \text{Me}
\end{align*}
\]

\[
Pd_2(dba)_3 (0.2-0.5 \text{ mol-\%}) \quad \text{K}_3\text{PO}_4, \text{Toluene, 60-80 }^\circ\text{C}
\]

* Configuration Unknown

**Methods for Atroposelective Conversion**

Atropodiestereoselective biaryl couplings using artificial Chiral Auxiliary:

\[ 	ext{R}^1 \text{MeO} + \text{Br} - \text{R}^1 \text{R}^2 \text{MeO} \xrightarrow{\text{Mg, THF, Heat}} \text{R}^1 \text{MeO} + \text{R}^1 \text{R}^2 \text{MeO} \xrightarrow{\text{Removal of chiral auxiliary}} \]

Mechanism:

\[ 	ext{R}^1 \text{MeO} + \text{Mg} \xrightarrow{\text{Better chelation by OMe}} \text{R}^1 \text{R}^2 \text{MeO} \]

\[ \text{R}^1 \text{MeO} + \text{Mg} \xrightarrow{\text{Prefered product}} \text{R}^1 \text{R}^2 \text{MeO} \]

\[ \text{Meyers, A. I. et al. Tetrahedron 2004, 60, 4459} \]
Methods for Atroposelective Conversion

Dynamic Kinetic Resolution of Atropisomeric Amides:¹¹

Axially Racemic

Proposed Transition States:

¹¹Patrick J. Walsh and co-workers  *Org. Lett.* 2004, 6, 2051
Methods for Atroposelective Conversion

3. Direct Kinetic Resolution of Configurationally Labile Biaryls:¹²

\[
\begin{align*}
\text{Br} & \quad \text{non-stereoselective biaryl coupling} \\
48 & \quad \text{Atropoenantiomers}
\end{align*}
\]

4. Atropoenantioselective Homocouplings:¹³

\[
\begin{align*}
\text{X} & = \text{CO}_2\text{R}', \text{CONR}_2', \text{COR}', \text{PO(O(R')}_2, \text{SO}_2\text{R}'
\end{align*}
\]

Uses of Atropisomers

Kinetic Resolution of Secondary Alcohols:\(^\text{14}\)

\[
\begin{align*}
\text{Ph-Me} & \xrightarrow{5 \text{ mol-\% cat-56}} \text{Ph-Me} \\
\text{Me} & \xrightarrow{60 \text{ mol-\% AcCl}} \text{Me} \\
\text{55} & \xrightarrow{65 \text{ mol-\% DABCO}} \text{57} + \text{58} \\
\text{Et}_2\text{O, -20 °C, 5 h} & \xrightarrow{51\%} \\
\text{96:4 er} & \xrightarrow{s = 54} \\
\text{94:6 er} & \\
\end{align*}
\]

As Hydrogen Bond Catalyst in three component Domino Reaction:\(^\text{15}\)

\[
\begin{align*}
\text{R}^1\text{OH} & \xrightarrow{59} \xrightarrow{\text{CH}_3\text{NO}_2} \xrightarrow{\text{Cat 61}} \\
\text{CHCl}_3, 40 \text{ °C} & \xrightarrow{\text{Cat 61}} \\
\text{R}^2\text{H} & \xrightarrow{63} \text{64} \\
\text{CF}_3 & \\
\text{CF}_3 & \\
\end{align*}
\]


\(^{15}\)Pihko, P. M. and co-workers Angew. Chem. Int. Ed. 2011, 50, 6123
Uses of Atropisomers

Asymmetric Mizoroki-Heck Reaction of Benzylic Electrophiles:\textsuperscript{16}

\begin{align*}
\text{Pd(dba)}_2 \text{ (10 mol-%)} & \quad \text{Ligand-72} \text{ (12 mol-%)} \\
\text{Li}_2\text{CO}_3, \text{ 2-MeTHF} & \\
\text{OCOCF}_3 & \\
\text{65} & \\
\text{40 °C} & \\
\text{66} & \\
\text{96\%, 92\% ee} & \\
\text{s 41:1} & \\
\text{Boc} & \\
\text{67} & \\
\text{40 °C} & \\
\text{60 °C} & \\
\text{69} & \\
\text{96\%, 92\% ee} & \\
\text{s > 100:1} & \\
\text{70} & \\
\text{Boc} & \\
\text{68} & \\
\text{66} & \\
\text{90\%, 92\% ee} & \\
\text{s > 100:1} & \\
\text{71} & \\
\text{96\%, 91\% ee} & \\
\text{s > 100:1} & \\
\end{align*}

\textsuperscript{16}Yang, Z. \textit{et al.} \textit{J. Am. Chem. Soc.} 2012, 134, 11833
Uses of Atropisomers

Atroposelective conversion with atropisomer:

\[
\begin{align*}
\text{R}_1 \text{NH} &+ \text{Ar-l} \\
\text{73} &\xrightarrow{5 \text{ mol-\% (R)-DTBM-SEGPHOS}} \text{R}_1 \text{N}^+ \text{Bu}^t
\end{align*}
\]

3.3 mol-\% Pd(OAc)\textsubscript{2} + 140 mol-\% t-BuOK

toluene, 80 °C

Intramolecular

Optically Active Atropisomeric Anilides

\[
\begin{align*}
\text{R}_1 \text{N}^+ \text{Bu}^t &\xrightarrow{40 \text{ mol-\% (S)-BINAP}} \text{R}_1 \text{N}^+ \text{Ar}
\end{align*}
\]

5 mol-\% Pd(OAc)\textsubscript{2} + 140 mol-\% Cs\textsubscript{2}CO\textsubscript{3}

toluene, 80 °C

Intermolecular

Axially Chiral

\[\text{(S)-BINAP}\]

\[\text{77}\]

\[\text{78}\]

\[\text{75}\]

\[\text{74}\]

\[\text{73}\]

\[\text{76}\]

\[\text{17}\]

Takeo Taguchi and co-workers J. Am. Chem. Soc. 2012, 134, 11833
Conclusion

1. Based on the famous atropisomer antibiotic "VANCOMYCIN", it is explained in a limerick.
   
   It's a chemical stroke of good luck
   When a hindered rotation gets stuck.
   If conformers are cool,
   **Atropisomers** rule
   When Gram-positive germs run amuck.

2. Atropisomers are abundant in nature and their structural variety is broad ranging from simple biphenyls to highly complex glycopeptides.

3. Quite a number of powerful and reliable methods have been developed for the construction of the chiral biaryl axis.

4. However, atropoenantrioselective methods are still rare.

5. With the steadily growing number of natural products with chiral biaryl axis, both further refinement of the existing methods and development of novel strategies are necessary to address their syntheses.

**Literature:**

THANK YOU