Investigating the relationship between the rotational barriers of N(2’-hydroxybenzyl) anisidine analogues and their unusual $^1$H NMR chemical shifts.

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BACKGROUND

- Cyclooxygenase-2 (COX-2) produces prostaglandin E2 (PGE2) which increases aromatase activity.

- Aromatase is an enzyme involved in the biosynthesis of estrogens.

- COX-2 inhibition suppresses aromatase activity.

- Low aromatase activity leads to low estrogen levels, providing a means of treating breast cancer.
BACKGROUND STUDIES

• 2-amino-5-nitrophenol was used to synthesize N-(2-benzyloxy-4-nitrophenyl)methanesulfanomide (nimesulide), a COX-2 inhibitor

• N-methyl derivative exhibits no COX-2 inhibition, but is an aromatase inhibitor

References:
Original Purpose of Research

- Preparation of alternative COX-2 inhibitors from o- and m-anisidine
- Test the COX-2 inhibitory potential of analogues

\[ \text{salicylaldehyde} \quad + \quad \text{m-anisidine} \quad \rightarrow \quad \text{o-anisidine} \quad \rightarrow \quad \text{ED1-Compounds} \]
- ortho-anisidine and meta-anisidine and their reaction with salicylaldehyde
- one-pot procedure for amination
- alkylation with benzyl chloride
- reduction of amide to amine

Reference:
Reductive amination of *meta*-substituted anisidine

salicylaldehyde

*m*-anisidine

nucleophilic addition to carbonyl

proton transfer

elimination of H$_2$O

imine
Reductive amination of *meta*-substituted anisidine-continued
$^1$H NMR of *meta*-substituted anisidine
Reductive amination of ortho-substituted anisidine

\[
\begin{align*}
\text{salicylaldehyde} & \quad \text{o-anisidine} \\
\text{imine} & \quad \text{proton transfer} \\
\end{align*}
\]
Reductive amination of ortho-substituted anisidine-continued

1) NaBH₄, CH₃CH₂OH
2) CH₃COOH

Proton transfer

-imine-
$^1$H NMR of ortho-substituted anisidine: unexpected results

- methylene H’s appear as non-equivalent H’s in spectrum, suggesting restricted rotation about N-Ar bond
- IR spectra of ortho- and meta-derivatives are nearly identical suggesting similar structures
Alternative explanation for unexpected $^1$H NMR results

- If cyclization occurred, chiral center produced creates nonequivalent diastereotopic methylene H’s
Future Direction of Research

- determine which product formed upon reductive amination of ortho-anisidine by

  1) conducting temperature-dependent 1H NMR studies

  2) comparing the calculated barrier of rotation about the N-Ar bond of the meta- and ortho-anisidine derivatives

  3) comparing calculated 1H NMR spectra of two possible products with observed 1H NMR spectrum

possible products
Calculating rotational barrier of N-Ar bond

- the structures of both the *ortho*- and *meta*- derivative will be optimized while varying the C-N-C-C dihedral angle at fixed intervals

- an energy plot will be generated from these constrained optimizations for both the *ortho*- and *meta*- derivative

- the observance of a larger energy barrier to rotation in the *ortho*- derivative would be supportive of the hypothesis that restricted rotation about the N-Ar bond is causing the nonequivalence of the methylene H signals
Computational Details

- Initially structures will be optimized using a Semi-Empirical method with Spartan software
- Atomic coordinates generated from the aforementioned optimization will be used in subsequent constrained optimizations performed with GAMESS
- Structures will be visualized using MacMolPlt

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