Mechanism and Stereochemistry of the Alkaline Hydrolysis of a VX Simulant

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VX nerve agent

- O-ethyl S-(2-diisopropylaminoethyl) methylphosphonothiolate
- V-series (non-volatile)
- Banned 1997

VX and your body

- Acetylcholinesterase (AChE) inhibitor
- Prevents it from hydrolysing acetylcholine
- Results in constant muscle stimulation

Symptoms*
- Myosis
- Bradycardia
- Convulsions
- Respiratory depression

Result
- Death by asphyxiation

Trigonal Bipyramid (TBP)

- Electronegative groups preferentially occupy apical position
- Apical positions on TBP are primary cleavage spots
Nucleophilic attack

- Attack results in a TBP intermediate
- Attack opposite electronegative group preferred because this gives electronegative group in apical position
Alkaline Hydrolysis of VX

- Initial attack of hydroxide gives alkoxide group in apical position
- *Mixture of products*, but majority results from cleavage of P-S

\[ VX: R = \text{CH}_2\text{CH}_3, \ R' = (\text{CH}_2)_2\text{N}(\text{i-Pr})_2 \]
Pseudorotation of TBP

Bending of the structure

- Apical groups (2, 5) move toward equitorial plane
- Two equatorial (3, 4) groups move away from each other
- Square pyramid transition state
From the first intermediate TBP, there are three other TBP structures accessible by pseudorotation.
Stereochemistry

- Non-superimposable mirror images
- Pseudorotation gives inversion of stereochemistry around phosphorus
- (+) VX LD<sub>50</sub> (mouse, iv) 0.165 mg/kg
- (-) VX LD<sub>50</sub> (mouse, iv) 0.013 mg/kg
Research Goals

- To find the low energy reaction pathways by exploring the pseudorotations of the first intermediate TBP structure
- To predict the stereochemistry of the products by following the inversions along the low energy pathway
Methods

- Optimize geometry
- Get electronic energy at 0 K, gaseous phase
- Correct to enthalpy at room temperature
- Add energy of solvation
- Final energy is at 298 K, 1 M, aqueous
- Confirm transition states with IRC calculation
Methods

- Computational methods
  - Geometry/Vibs
    - mPW1K/MIDI!
  - Electronic Energy
    - MP2/6-31+G(d)
  - Solvation Energy
    - HF/6-31+G(d)

- Simulant
  - Use reduces computational time
  - Structure around P similar to that of VX
  - Similar reactivity to VX
Alkaline Hydrolysis of VX model

- Followed reaction through initial three pseudorotations
- From these, found P-S bond cleavage or further pseudorotation
- Eventually led to P-O bond cleavage pathways
Paths through TBP-O-Me

Relative energies (kcal/mol) are in parenthesis

* IRC shows problems with these structures
Paths through TBP-O-Me

![Graph showing paths through TBP-O-Me](image)
Paths through TBP-O-SMe

Relative energies (kcal/mol) are in parenthesis
Paths through TBP-O-SMe
Paths through TBP-Me-SMe

Relative energies (kcal/mol) are in parenthesis
Paths through TBP-Me-SMe

Reaction Coordinate
to SMe-loss
to OMe loss?
Comparison: Perhydrolysis of VX

- Initial attack of perhydroxide gives alkoxide in apical position
- Products result exclusively from cleavage of P-S bond

**VX:** $R = \text{CH}_2\text{CH}_3$, $R' = (\text{CH}_2)_2\text{N}(i-\text{Pr})_2$

100% Non-toxic
Comparison of Hydrolysis and Perhydrolysis Reactions

- Competing reactions in the alkaline hydrolysis
  - 3 kcal/mol difference
- Do NOT compete in the perhydrolysis reaction: P-S bond cleavage is highly favored
  - 25 kcal/mol difference
Discussion

- Energy barrier to P-S cleavage always lower than barrier to P-O cleavage
- Difference in energy between P-S and P-O bond cleavage is approximately 3 kcal/mol for hydrolysis, while 25 kcal/mol for perhydrolysis
- P-S bond cleavage results in mixture of stereoisomers, while P-O cleavage results only in (-) isomer
Future Work

- Find or confirm TS for:
  - P-O cleavage from TBP-O-OMe
  - Pseudorotation to TBP-SMe-OMe from TBP-O-Me
  - P-S cleavage from TBP-SMe-OMe

- Possibly find another stable geometry for TBP-SMe-OMe
Acknowledgements

- Grant provided by NSF-STEP
- Knowledge provided by Dr. Patterson
- Foundation provided by Jessica Menke, *et. al.*
- Facilities provided by Truman State University
- Distractions provided by Pattagan lab rats and puppies