Hydroperoxidolysis of the Chemical Warfare Agent VX

Laura Kopff
Faculty Mentor: Eric Patterson
Truman State University
History of Nerve Agents: G-Series

› 1932-Potency of organophosphorus compounds realized by Lange and Krueger
› 1936-Schrader synthesized 1st nerve agent, Tabun
› 1938-Schrader developed 2nd nerve agent, Sarin, named after Schrader, Ambros, Rudriger, and van der Linde
› Volatile liquids
› “G” = Germany
› Crude Sarin was used by the Aum Shinriko cult to attack the Tokyo subway in 1995
› Non-volatile liquids
› Clean-up and detoxification becomes a large concern
VX Nerve Agent

› 1952-53 - Discovered by Ghosh of ICI (Great Britain)
› 1961-1968 - Produced in US
  › Obtained formula in trade for thermonuclear technology
› 1970’s - Structure no longer a secret
› 1997 - Banned*

VX and Your Body

- Acetylcholinesterase (AChE) inhibitor
- Prevents AChE from hydrolysing acetylcholine
- Results in constant muscle stimulation
- Symptoms*
  - Myosis
  - Convulsions
  - Respiratory depression
- Result
  - Death by asphyxiation

Nucleophilic Attack

- Attack results in a TBP intermediate
- Attack opposite electronegative group preferred because this gives electronegative group in apical position
Trigonal Bipyramid (TBP)

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

a = apical (or axial)
e = equatorial
Pseudorotation of TBP

Bending of the structure

- Apical groups (2, 5) move toward equatorial plane
- Two equatorial (3, 4) groups move away from each other
- Square pyramid transition state
Initial attack of hydroxide gives alkoxide group in apical position

Mixture of products, but majority results from cleavage of P-S

Hydroperoxidolysis of VX Simulant

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

Research Goals

- To determine:
  - the mechanism for the hydroperoxidolysis of VX
  - the role of the diisopropylamine sidechain in this reaction
  - the significance of the oxidation-rearrangement
Methods

- Optimize geometry (MPW1K/MIDI!)
- Get electronic energy at 0 K, gaseous phase. Also get thermodynamic corrections.
- Use MP2/6-31+G* to get more accurate single-point energy
- Add energy of solvation (IEF-PCM)
- Final energy is at 298 K, 1 M, aqueous
- Confirm transition states with IRC calculation
Reaction Energy Diagram

› The relative energies of structures are plotted

› This allows for comparison between reaction pathways

› For VX:
  › Two main pathways resulting from attack opposite either OEt or SR
Reaction Energy Diagram for the Hydroperoxidolysis of VX

The diagram shows the relative energy (in kcal/mol) as a function of the reaction coordinate. The energy values are indicated at the end of each reaction pathway:

- Attack opposite OEt: -47.02 kcal/mol
- Pseudorotation: -20.99 kcal/mol
- Attack opposite SR: -54.87 kcal/mol
- Direct P-O cleavage: -54.87 kcal/mol
Conclusions

- Initial attack of hydroperoxide opposite SR is more favorable by 2.69 kcal/mol, thus a 94:1 product ratio of P-S cleavage to P-O cleavage is expected.

- With attack opposite OEt, the reaction still proceeds to P-S bond cleavage through an oxidation/insertion and pseudorotation.

- This explains why the hydroperoxidolysis of VX yields exclusive P-S bond cleavage.
Acknowledgements

› Grant provided by Truman State University
› Dr. Patterson
› Past Patterson Research Students