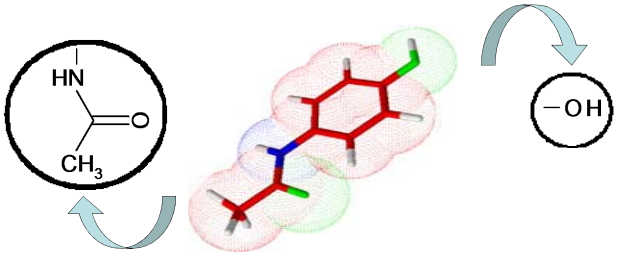
Acetaminophen (Tylenol) : A Pain to the Environment!

CHEM 331: Environmental Organic Chemistry
March 20, 2008

Introduction:

Pharmaceuticals and Personal Care Products (PPCP's) have become an increasing environmental issue over the last decade. Their sources stem mainly from anthropogenic means and are destined for most aquatic environments. Along the way they may be volatilized, phototransformed, physicochemically or environmentally altered, and degraded into other forms which may or may not be seen as harmful environmental contaminants (1).

- Acetaminophen recognized as one of 95 wastewater contaminants by a National Reconnaissance completed in 1999-2000 in 139 U.S. streams (2).
- Non prescription drugs found in 81% of streams tested (2).
- Acetaminophen found at concentrations as high as 10 ppb (2).



Acetaminophen (4-hydroxyacetanilide)

Current Research:

Until recently, there were no proposed mechanisms for the photodegradation of Acetaminophen. In January 2008, Zhang *et al*. proposed to degrade Acetaminophen in a TiO_2 suspended solution with a 250W metal halide lamp (14). Efforts were successful with respect to the degradation at a 95% decomposition level and the rates at which the molecule adsorbed to the suspended solution were quantified according to pH. Adsorption was measured at pH's 3.5, 6.9 and 9.5 and was found to have the fastest rate at pH 3.5. The authors are confident that future efforts can be made to remove Acetaminophen from wastewater and drinking water through this method without any generation of more toxic byproducts (14).

Distributions in the Environment:

Vapor Pressure:

•$P°(L) = 9.0 \times 10^{-9}$ atm @ 25° C (3)

- The vapor pressure of a molecule indicates the pressure at which the vapor of a compound is in equilibrium with its pure condensed phase (4).
- Values vary greatly depending on the type of intermolecular forces (IMF's) present.
- Acetaminophen is involved in London Dispersion Forces as well as H-bonding which contribute to a lower vapor pressure.
- This value is quite small in comparison to that of phenol ($P°(L) = 4.6 \times 10^{-4}$ atm @ 25° C (5)) which lacks the amide functional group and therefore exhibits weaker IMF's than Acetaminophen.

Water Solubility:

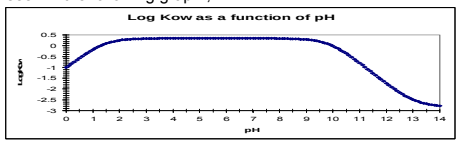
$C_w^{sat} = 0.0843$ M @ 25°C (9)

- Since Acetaminophen is found predominantly in aqueous environments it is therefore necessary to understand its water solubility.
- In comparison to phenol (Cwsat = 0.879 M @ 25°C (10)), Acetaminophen is ~10X less soluble!
- A smaller solubility may be due to the increased size of the molecule and the increased chance of H-bonding between molecules.
- Extra H-bonding from amide group increases the energy necessary to separate solute molecules which will decrease the water solubility.

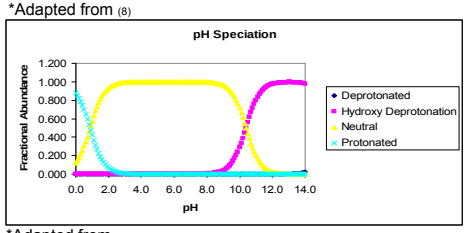
Octanol-Water Partitioning:

Log $K_{ow} = 0.46$ (6)
$K_{ow} = 2.88$ (7)

- Calculated values consistent (Log $K_{ow} = 0.34$) (8)
- Phenol has a $K_{ow} = 28.8$ (3) which is 10X larger than Acetaminophen and therefore phenol is more likely to partition into octanol (organic environments) than Acetaminophen
- Since K_{ow} strongly correlated with C_w^{sat}, it is also largely pH dependent and more Acetaminophen will associate with organic environments when the pH is between 2 and 10 as seen in the following graph ;



*Adapted from (8)



*Adapted from (8)

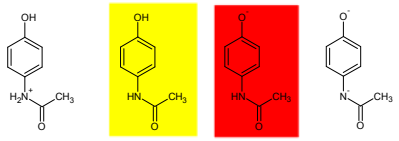
Henry's Law Constant:

Log $K_H = -8.3038$ @ 25°C
$K_H = 5.0 \times 10\text{-}9$ (calculated with bond contributions (11))
$K_H = 4.4 \times 10\text{-}9$ (calculated from C_w^{sat} , P°(L))

- The partitioning of a molecule from the liquid into the gas phase is determined by the K_H.
- Acetaminophen will favor partitioning from air → water as it has a fairly large C_w^{sat} and a relatively small P°(L) (smaller K_H).
- Since KH is highly temperature dependent, less Acetaminophen will partition from the air into the water as the temperature is increased (K_H ↑, T ↑).

pH Dependence:

- pKa = 9.71 (3) for the acidic hydrogen of the hydroxy group. It is at this pH where half of the molecules will be in the protonated form (yellow box) and half will be in a deprotonated form (red box).
- Below the pKa and between pH 2 and 10 the majority of the molecule will be present in the neutral form as seen in the yellow box and the pH speciation diagram.



Transformations in the Environment:

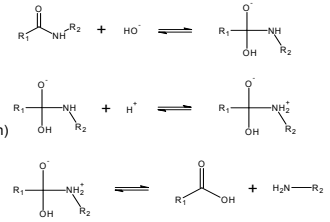
When emitted out into the environment organic contaminants are able to undergo multiple physicochemical processes including, but not limited to, hydrolysis, oxidation, reduction and photochemical processes. Although, not all contaminants react through these processes and therefore Acetaminophen has been studied in its reactions of hydrolysis and chlorination.

Amide Hydrolysis:

$B_{AC}2$ Mechanism (Base Catalyzed) (12)

R_1	R_2	R_3	K_a ($M^{-1}s^{-1}$)
CH_3	H	H	8.36×10^{-6}
CH_3	CH_3	H	3.2×10^{-7}

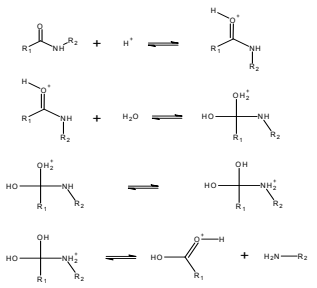
*Adding a methyl group at R_2 slows the rxn 10X
(Similar results may be found for Acetaminophen)



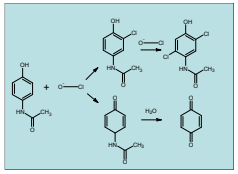
$A_{AC}2$ Mechanism (Acid Catalyzed) (12)

R_1	R_2	R_3	K_a ($M^{-1}s^{-1}$)
CH_3	H	H	4.71×10^{-5}
CH_3	CH_3	H	4.56×10^{-6}

*Adding a methyl group at R_2 slows rxn 10X
(Similar results may be found for Acetaminophen)



Chlorination of Acetaminophen:



- In wastewater treatment plants where Acetaminophen will inevitably end up, the process of chlorination generates more toxic products that the reactant itself.
- Reactions with hypochlorite produces products *N*-acetyl-*p*-benzoquinone imine and 1,4-benzoquinone both of which are toxic metabolites that have shown to result in hepatic necrosis (*13*).

Discussion:

One of the most important questions that environmental chemists are asking themselves these days is "Are they recalcitrant and ubiquitous in the environment?". When analyzing organic contaminants in the environment it is essential to define their distribution (where they are) and their transformations (where they go) in the environment. Armed with this knowledge, methods to remove, degrade, or dispose of such contaminants can be more easily facilitated.

Acetaminophen is an emerging persistent organic pollutant which has come to the forefront of environmental issues. A National Reconnaissance completed in 1999-2000 on 139 US streams found it to not only be present at low levels but to be present in almost all the streams sampled (2). Though it is being found only at low levels, the measure of unknowns is countless. From interactions with other organic environmental contaminants, interactions with medications through drinking water, or simply chemical transformations which are yet to be discovered, the list of possibilities is infinite. Since it is continually being introduced into the environment the concern may lie in the event that its removal is counteracted by its continual daily replenishment. Efforts to remove Acetaminophen have only just been suggested but it seems the trend of research is heading in that direction. Changes made today will only strengthen our knowledge and ultimately our ability to deal with these impacts to environmental health.

References:

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