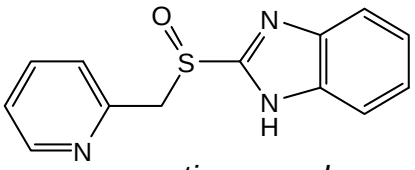
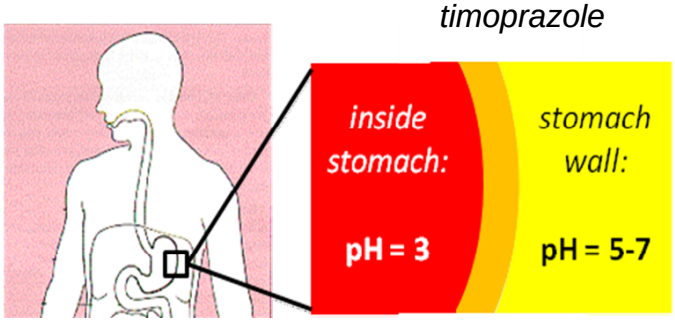
Chemistry 2331H Friday, September 13

At-Home Exercise:
The Pharmacology of Organic Acids and Bases

Most drugs are taken orally, and so it is important to understand the acid-base properties of these drugs as they pass through the acidic stomach on their way to the neutral pH of the rest of the body. It is even more important to understand the acid-base properties of drugs that are intended to stay in the stomach. Through the 1970's, the pharmaceutical company AstraZeneca researched molecules that could treat acid reflux disease by blocking the proteins that pump acid into the stomach. One molecule they discovered in 1974, timoprazole, was effective but toxic; the protonated form is active and safe in the stomach, but the molecule is deprotonated at the more neutral pH near the stomach wall to regenerate neutral, cytotoxic timoprazole.

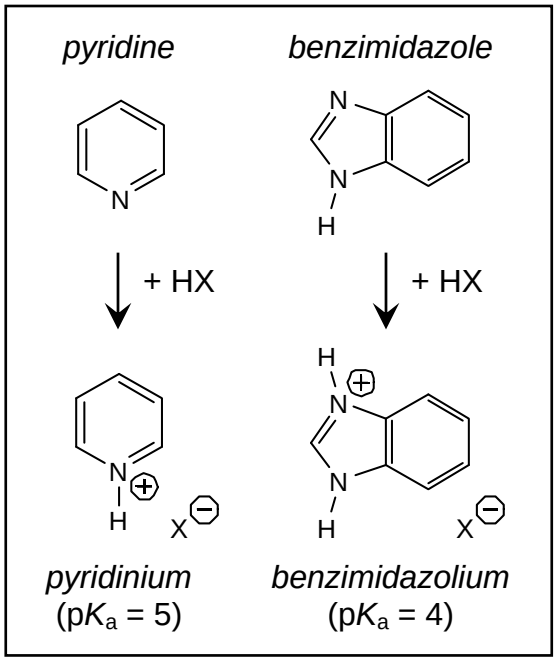


timoprazole

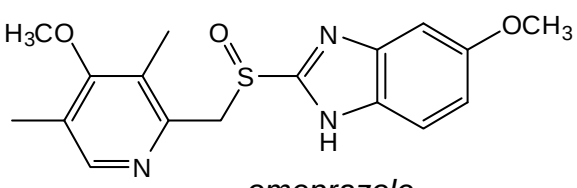


a. The left- and right-hand sides of timoprazole can each be protonated independently (each with its own pK_a), and we can assume that each side will be about as basic as the simple molecules pyridine and benzimidazole. Using "electron pushing", show how each side of timoprazole would be protonated by $(H_3O^+)Cl^-$, the most prevalent component of stomach acid.

b. One easy way to define "pK_a" is "the pH at which half of an acid is protonated, and half is deprotonated". So what would most timoprazole molecules look like at pH = 3, in the stomach? At pH = 4.5, as the molecule diffuses through the stomach lining? At pH = 6, in the stomach wall?



c. In 1979, AstraZeneca created omeprazole, a modified version of timoprazole, and found that it was much less toxic. (This molecule is now sold as Nexium by AstraZeneca.) Omeprazole is more basic than timoprazole, so it remains protonated even at pH = 7. Looking at just the left-hand (pyridine) side of omeprazole, why whould this be more basic than the left side of timoprazole?



omeprazole