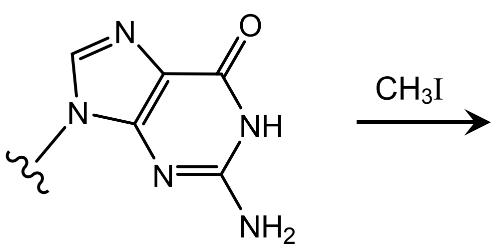
Chemistry 2301

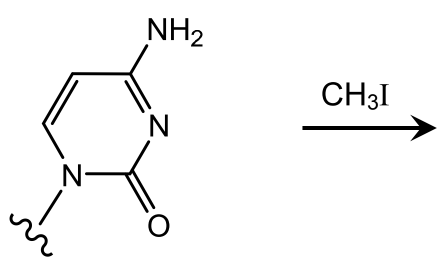
Workshop 12
S_N2 Chemistry: Causing Cancer, and Curing It

1. Cancer is caused by chemical reactions that alter the DNA molecules in our cells, and that lead those cells to reproduce out of control. DNA is particularly vulnerable to S_N2 substitution reactions in which a DNA "base" serves as a nucleophile, and that means that the most reactive S_N2 electrophiles are often carcinogenic.

   How might the bases guanine and cytosine—shown below—react with the carcinogen methyl iodide (CH_3I)? Draw mechanisms that show how each lone pair in each base might react via S_N2, and draw the product of each reaction. Which products would you predict to be most stable? What does that say about which electron pairs from these two bases will be most reactive as S_N2 donors?



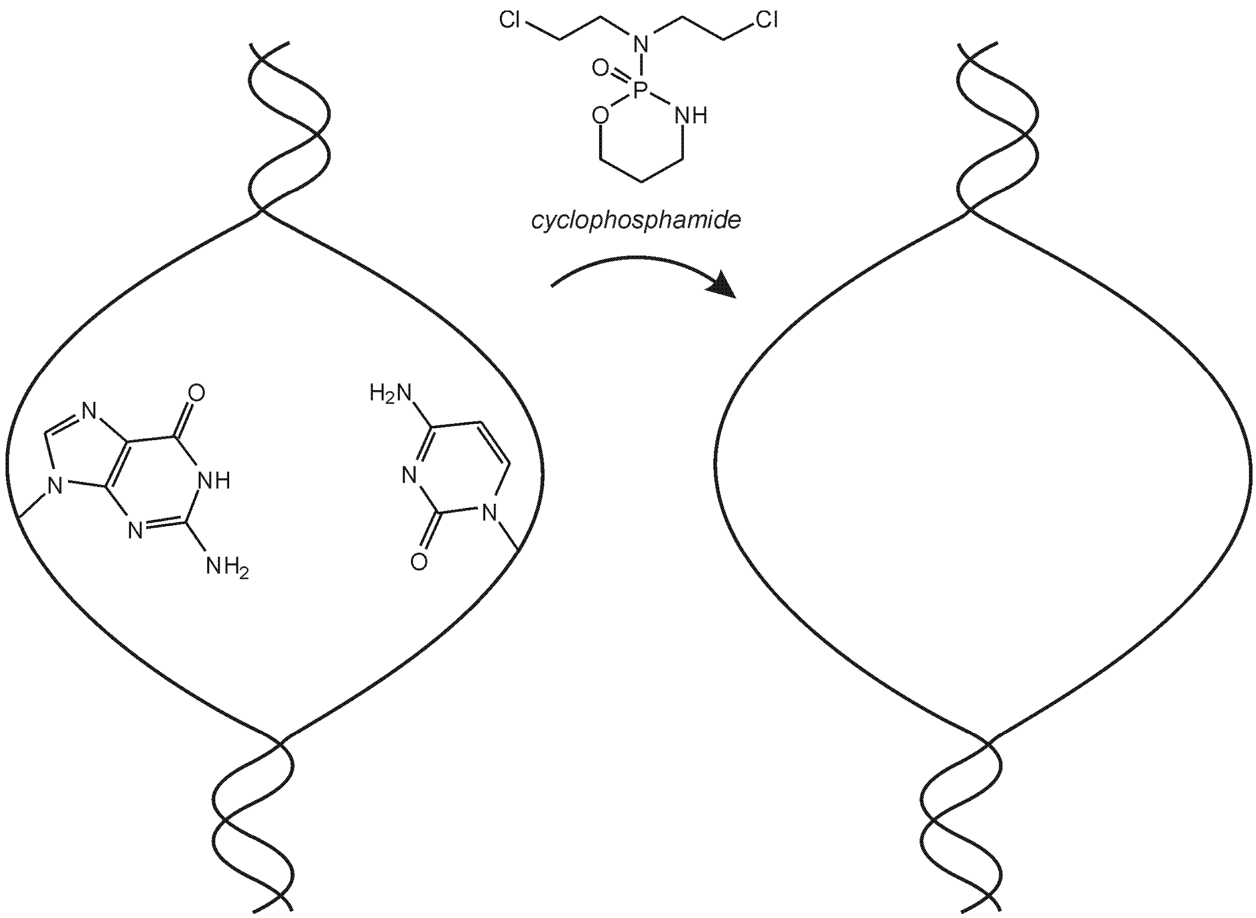
guanine



cytosine

(Molecules that are written above a reaction arrow—as I did above with CH_3I—are available as reactants.)

2. Cancerous cells have two characteristics in common: (i) they multiply more rapidly than normal cells, resulting in tumor growth; and (ii) they absorb more nutrients than normal cells to fuel this growth. When cancer patients are treated with cyclophosphamide, a chemotherapy agent, the molecule is rapidly absorbed by cancer cells, and then reacts with the cell's DNA via two successive S_N2 reactions.[1] After the reaction is done, the cancer cell's DNA can no longer replicate because its double helix is tied together.



Draw a multi-step mechanism for one possible reaction between cyclophosphamide and both fragments. Then, draw the result of your reaction in the DNA helix on the right. (The molecules are flexible—don't worry about trying to "fit" the reaction into the hole I've drawn.)

[1] I lied here, but just a little. Cyclophosphamide is actually converted in the cytoplasm to a few different molecules, all of which look a lot like cyclophosphamide. For simplicity's sake, we'll pretend that cyclophosphamide is the active agent.