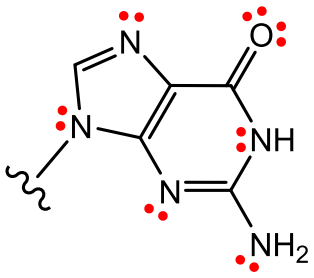
Chemistry 2301

Workshop 12 Solutions
S_N2 Chemistry: Causing Cancer, and Curing It

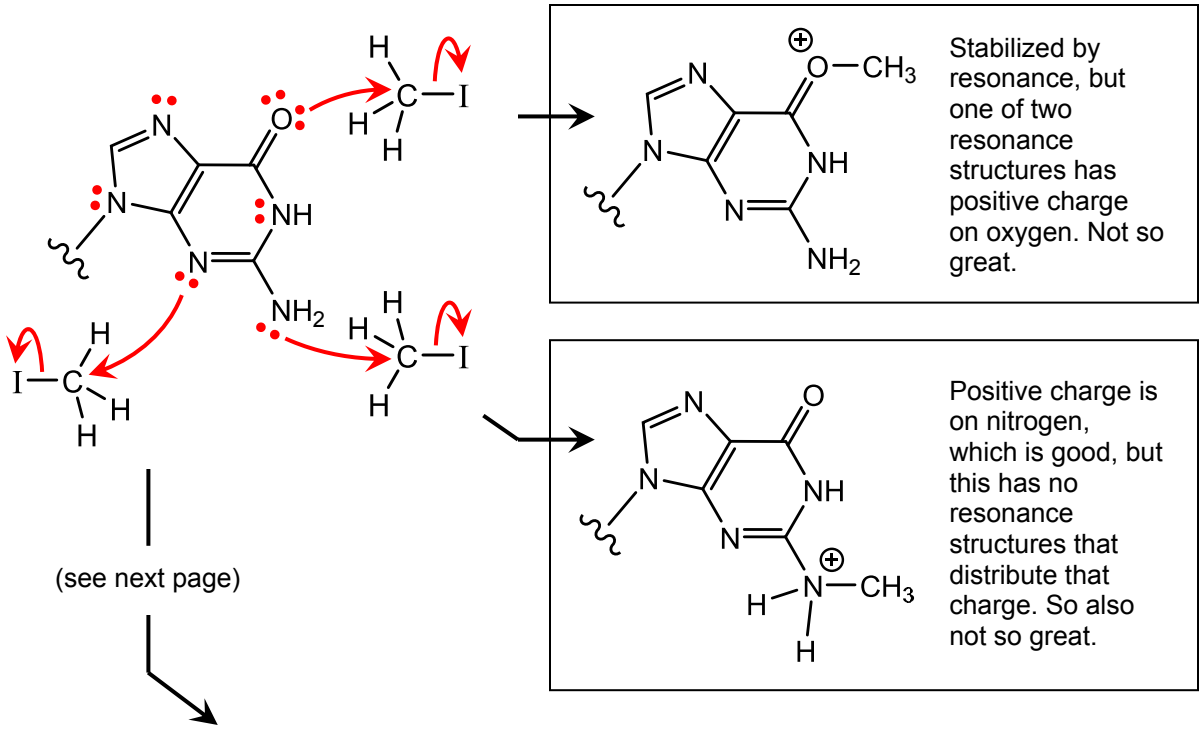
a) S_N2 reactions involve a nucleophile donating a lone pair of electrons, and result in a product being formed between this nucleophile and the electrophile. Any lone pair of electrons could serve as the nucleophile, so we have to consider them all. I think we can judge S_N2 reactions both on how good an electron donor the nucleophile is, and on how stable the product would be, for each potential reaction.

Thinking about nucleophile quality:



Oxygen is much more electronegative than nitrogen. Out of all the electron donors here, I might rule out oxygen based on electronegativity alone. I think we still need to think about the products that the oxygen nucleophile might make, just in case they are a lot more stable than others. But our best nucleophile will probably be a nitrogen atom.

Thinking about product stability:



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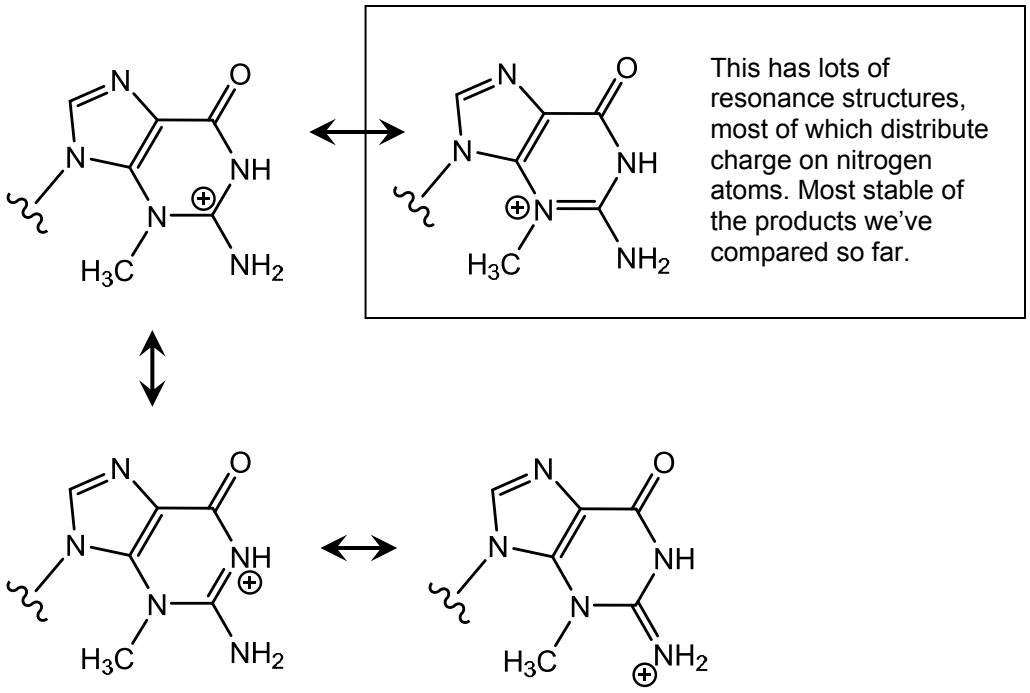
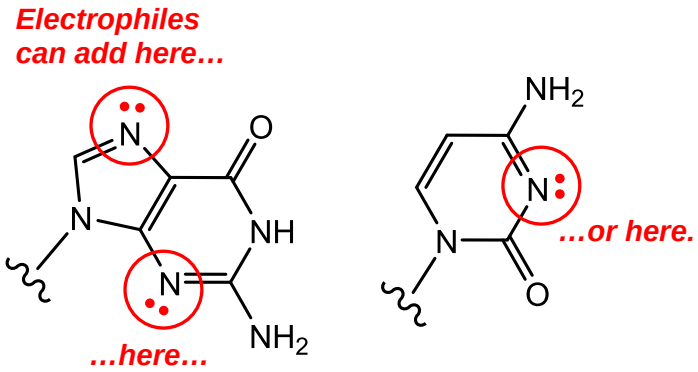
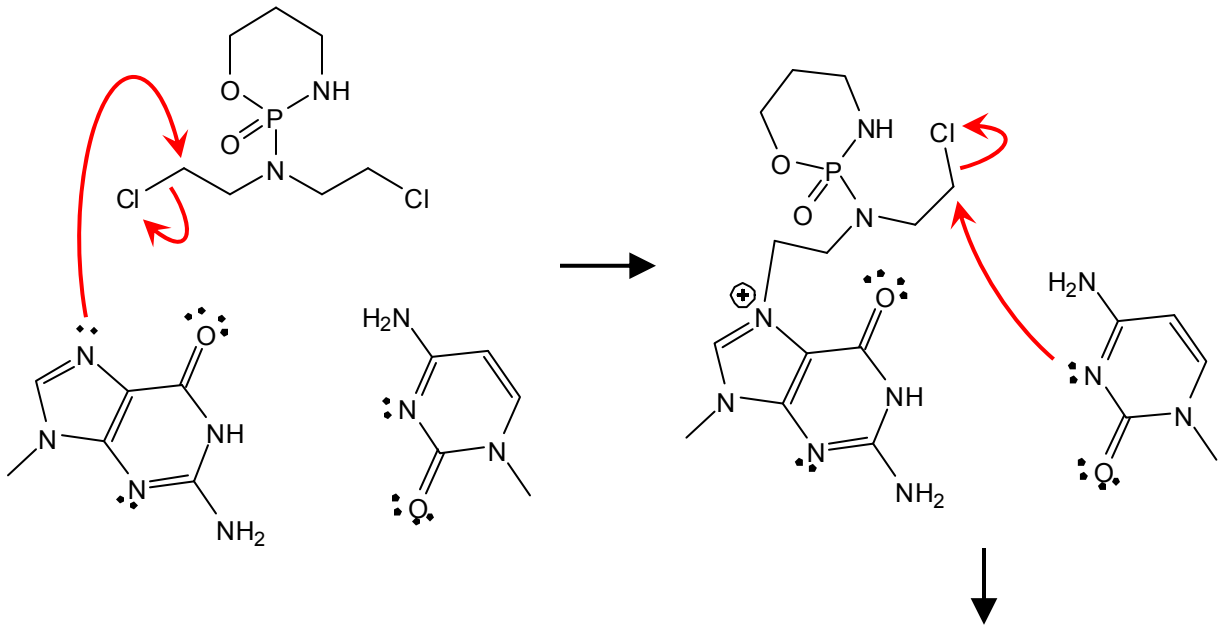


We can do this same analysis for all of the nucleophilic centers on both bases, and that allows us to identify three good nucleophiles:



This all makes sense, as long as reaction kinetics correlate with product stabilities. Technically, this isn't necessarily the case; kinetics and rates are determined by transition-state energies, not product energies. But Hammond's Postulate gives us the license to base our conclusions on product energies, because the favorable things we see in products are usually also present in transition states.

b)



This ties the two DNA strands together and makes the chemotherapeutic work.

Note that I've drawn this mechanism as two separate S_N2 steps, instead of proposing that both S_N2 reactions happen at once. I think there is no way that three molecules—the two DNA strands and cyclophosphamide—would all be in the same place at the same time, in perfect position to react. In fact, that's characteristic of molecular reactions; they can never really involve the collision and reaction of more than two species.