Carcinogenesis by Alkylating agents

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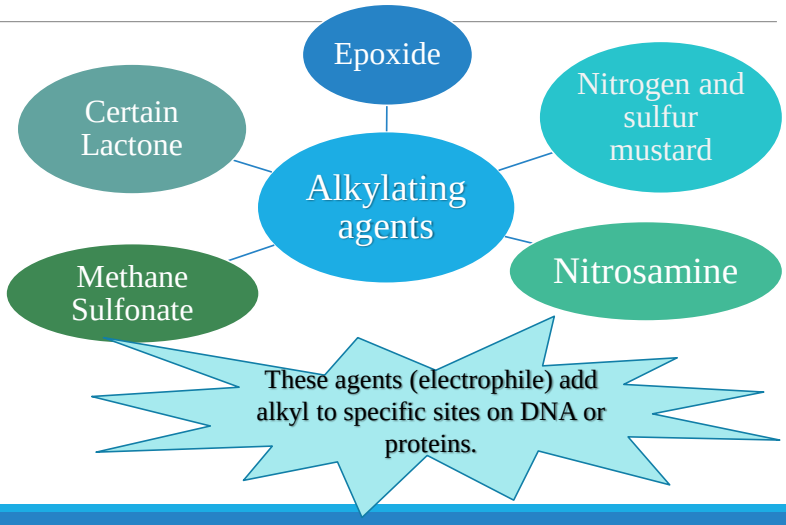


Alkylating Agents

Alkylating agents include a large variety of chemicals, some of which are potent mutagens and carcinogens.

They are highly reactive compounds and can be activation-independent and act directly on target sites.

They react aggressively with cell components and block vital cell functions.

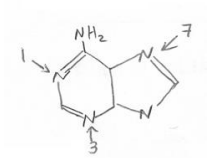
The most common alkylating agents are alkyl sulfates, alkyl sulfonates, alkyl halides, di-alkyl nitrosamine, alkyl nitrosoureas, and mustards.

In World War I, Mustard gas was used as a chemical weapon.

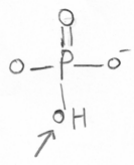
The effects of mustard gas include severe burning of the skin, fatal lung damage, and severe damage to intestinal mucosa and bone marrow (all rapidly proliferating tissue).

Sites of alkylation

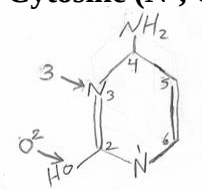
Adenine (N^1,N^3,N^7)



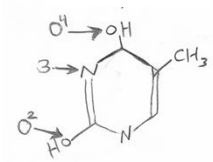
Phosphate



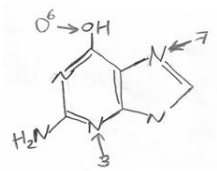
Cytosine (N^3, O^2)



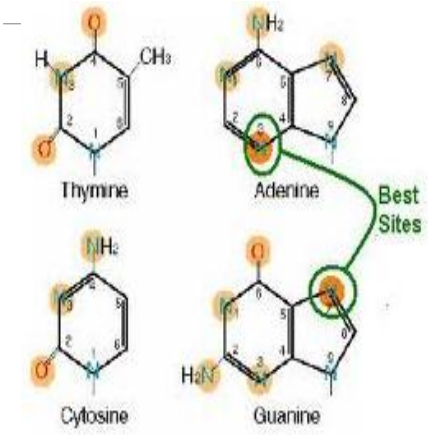
Thymine (O^4,N^3,O^2)

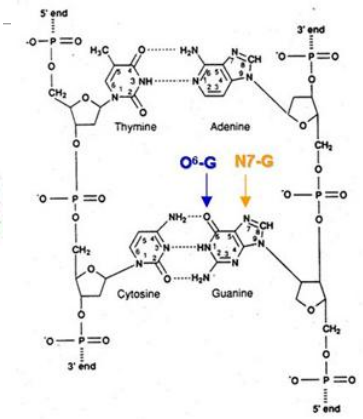


Guanine (N^7,N^3,O^6)



Sites of alkylation





Chemistry of the Alkylating Agents

The alkylating agents are compounds that react with electron-rich atoms in biologic molecules to form covalent bonds.

Traditionally, these agents have been divided into two types: those that react directly with biologic molecules and those that form a reactive intermediate, which then reacts with the biologic molecules. These types are termed SN1 and SN2 respectively.

Chemistry of the Alkylating Agents (cont.)

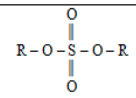
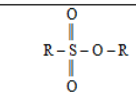
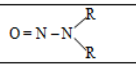
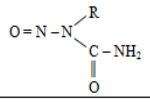
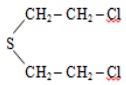
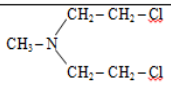
Alkylating agents were found to react particularly with cysteinyl derivatives, as well as with alpha carboxyl, aspartyl, Glutamyl and imidaxole (histidine) groups at physiological pH and low concentrations

Variability of particular biological effects according to species or experimental preparations

Initially, variance in biological effects became apparent related to the species used or other aspects of the experimental preparation.

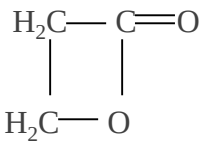
- This became especially evident during the attempts to establish whether it is the rate of synthesis of DNA on the one hand, or the integrity of the mitotic process or chromosomes on the other, which is the primary cell biological "target" of alkylating agents.

Structure of selected alkylating agents

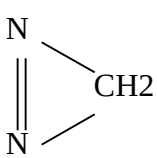
	Dialkyl sulfate
	Alkyl alkane sulfonate
	Dialkyl nitrosamine
	N-Alkyl-N-nitrosureas
	Sulfur mustard (mustard gas)
	Nitrogen mustard

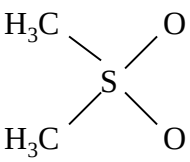
Structure of selected alkylating gents(cont.)

Lactones like propiolactone



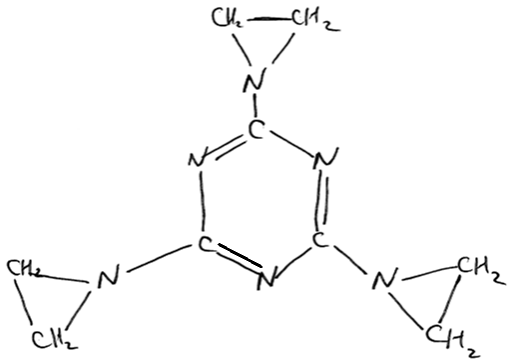
Methylating agents s Diazomethane and Dimethyl Sulfate



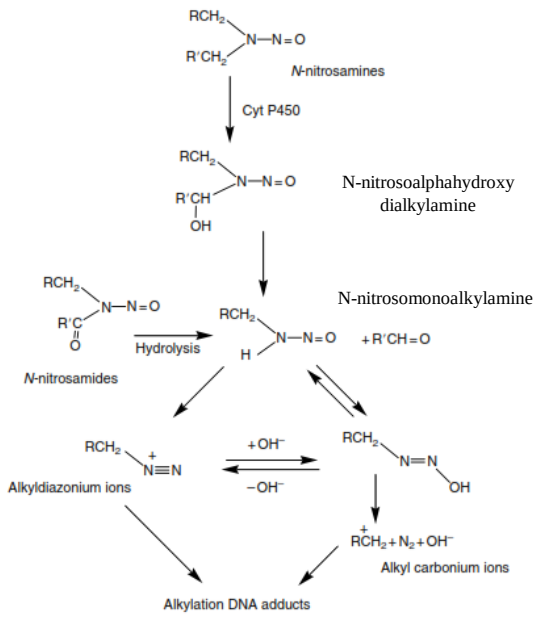


Structure of selected alkylating agents(cont)

Ethyleneimines (Triethyl-melamine)

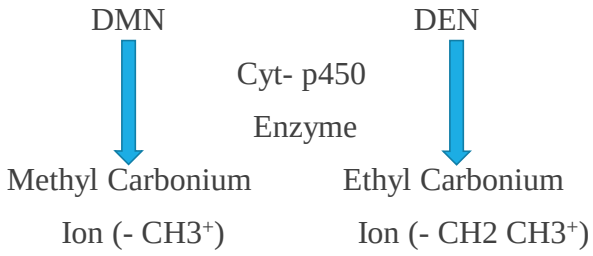


Metabolism of Nitrosamines



N.B

- Alkylated guanine is a major alkylated base in the DNA



***Dimethyl nitrosamine(DMN)** ***Diethyl nitrosamine (DEN)**

Effect of DNA alkylation

- Modify DNA template properties, by blocking DNA synthesis. Or by potentiating the synthesis of DNA with a changed base sequence.
- Induces cross-links between Guanine bases in opposite strands or within single strands of DNA. (Nitrogen mustard).

Effect of DNA alkylation by (cont.)

- Cross-link DNA ⟹ prevent DNA separation.(Ethyleneimines)
- Causing miss-pair of nucleotides ⟹ Mutation.
- Causing mutation GC ⟶ AT (transition).

Cancer Treatment by Alkylating Agents

Alkylating agents are also used for the treatment of cancer (to kill cancer cells).

The classical sulfur mustard is too toxic for therapeutic use.

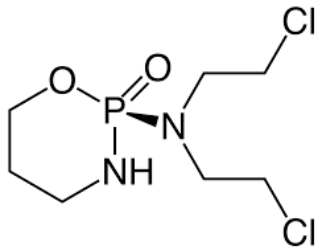
Nitrogen mustard is useful for the treatment of some forms of leukemia.

The highly reactive mustard compounds have difficulty in reaching the tumor, while underway they react with other cells and serum components.

Cancer Treatment by Alkylating Agents

To overcome this problem, a derivative that would release active mustard only to the tumor (latent activity) was developed. The best example is cyclophosphamide (a nitrogen mustard).

Cyclophosphamide



Mechanism of Toxicity

Alkylating reagents react with many compounds including proteins and nucleic acids. Their reactivity with DNA plays a key role in its biological effects.

Alkylating agents are divided into 2 major groups: mono-functional and bi-functional.

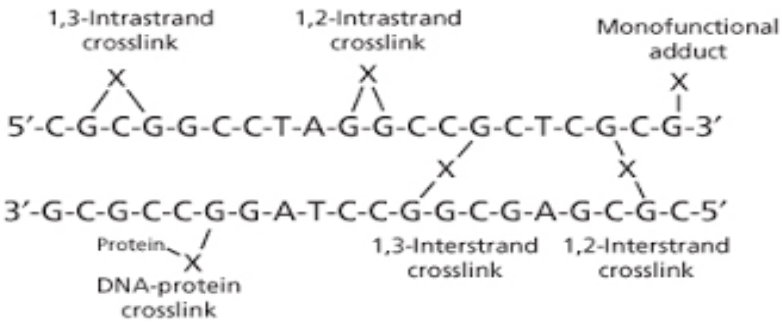
The monofunctional agents have only one reactive group which is involved in covalent interaction with the single center on DNA.

Mechanism of Toxicity

The bifunctional agents have 2 reactive groups and can react with two centers on DNA. If the two centers are on opposite strands of DNA, the reaction of a bifunctional agent (e.g. mustard) can produce an inter-strand cross-link.

Inter-strand cross-linking prevents DNA strand separation which is crucial for replication. Thus, DNA synthesis is inhibited.

DNA Crosslinks



Toxicity on Cancer Cells

Anticancer drugs are more toxic to cancer cells than normal cells due to the following reasons:

- Cancerous tissue has comparatively more blood supply (by angiogenesis), thus more drug is concentrated in cancer tissue.
- Cancer cells have poor repair systems.
- Cancer cells divide faster thus subjected to more DNA damage.

Toxicity on Normal Cells

Some normal fast-growing cells are also affected by anticancer drugs.

- Degeneration of hair cells leads to fall of hair (alopecia).
- Degeneration of sperms (aspermia).
- Degeneration of erythropoietic cells (anemia).
- Degeneration of gastric mucosal cells (gastrointestinal problems).