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# ADDUCTS OF DEOXYRIBONUCLEIC ACID WITH POLYCYCLIC AROMATIC HYDROCARBONS AND ACRIDINIC DERIVATIVES

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## Abstract

*Investigations initiated in the 6th decade of the 20th century on the compounds resulted from the interaction between the DNA macromolecule and small molecules led to the idea of appearance of some bioincompatible structures. The resulted compounds have been named, for the first time, as "molecular complexes", an incompatible denomination because such compounds exist in chemistry and inorganic biochemistry. It was also used the term "molecular associations" (Bergman, 1968), but it does not explain the existence of such compounds. During years of physical-chemical investigations and mecanic-quantum calculations over the electronic density in the donor-acceptor relationship between DNA and small molecules, the term "adducts" was preferred (Stich and Dunn, 1988; Gârban, 2001). This term is used in the present paper following the biogenesis of adducts of DNA with polycyclic aromatic hydrocarbons (PAH), respectively of DNA with acridinic compounds, and the aspects connected to patobiochemistry, connex to the appearance of these incompatible structures.*

***Keywords**: DNA-PAH and DNA-acridine adducts; structural peculiarities*

## Structural Peculiarities of the DNA Double Helix

Discovery of double chain structure of DNA is of major importance in the development of molecular biology, allowing the interpretation of data from classical genetic and the initiation of important studies in molecular biology, genetics, biochemistry, biochemical pathology, etc.

Physico-chemical investigations and quantum mechanic calculations showed that between the different DNA types appear great

conformational differences characterized by the variation of topological properties in the DNA stereo structure (Arnott, 1978; Jack, 1979). Structural peculiarities of double chain DNA facilitate the interaction of the macromolecule with small molecules. Such interactions are generated between DNA and PAH as well as between DNA acridine derivatives. The study of the biogenesis of the formed adducts is of interest for the processes of biotransformation of xenobiotics from the class of HPA and acridine (Gârban et al., 2004). Xenobiotransformation leads to the appearance of some compounds with bioincompatible structures, which are studied by biochemical pathology and, evidently, subsequently by physiopathology.

In Biochemistry and Molecular biology are considered the theoretical and applicative aspects of interest for the interactions between macromolecules of nucleic acids and small molecules of some organic compounds (e.g. polycyclic aromatic hydrocarbons, acridine and derivatives, nitroderivatives) and anorganic compounds (biometals and metals with toxicogen potential). The formed compounds have been studied by physico-chemical methods (UV spectroscopy, mass spectroscopy, radiochemistry) and evaluated by quantum-mechanics calculations (establishing the differences of electronic density that influence interactions)

## Structural Characteristics of Some Biologic-Active Compounds

Theoretic calculations and experimental investigations using different physical and physico-chemical methods over some mutagenic and carcinogenic agents established that they form with DNA characteristic molecular associations, named adduct. After the nature of interaction and the type of bindings were described two types of adducts: labile and stable.

In the case of labile adducts interactions are characterized by weak bonding of the type of Van der Waals forces, charge transfer, hydrogen bondings. These types of bondings appear at sandwich type compounds, characteristic for some cancerigene polycyclic aromatic hydrocarbons and some acridinic type compounds with effects mostly mutagenic. The labile complex is better observed in the case of acridinic colouring agents, binding being made parallel or perpendicular to the axes of the DNA molecule. Stable adducts are

generated by interactions in which covalent bonds appear. Their formation can be preceded by the appearance of some labile adducts.

Molecular interactions that appear in duplication and transcription processes have as consequence the appearance of bioincompatible neoformations.

The aromatic structure is implied in biotransformation processes. That is why, a special importance is given to physico-chemical studies on the aromatic structures and on the specific bioactivation reactions (Dunn, 1982; Mănescu et al., 1982; Gârban, 1985; Baumann and Harsbarger, 1995).

**Structure of PAHs**

Polycyclic aromatic hydrocarbons (PAH) have two characteristics: a planar molecule and π delocalised electrons. The planarity of the molecule is important for the biologic activity. Deviations of the planar form can lead to the modification of the relation chemical structure – biological activity. Structure of main polycyclic compounds is given in Figure 1.

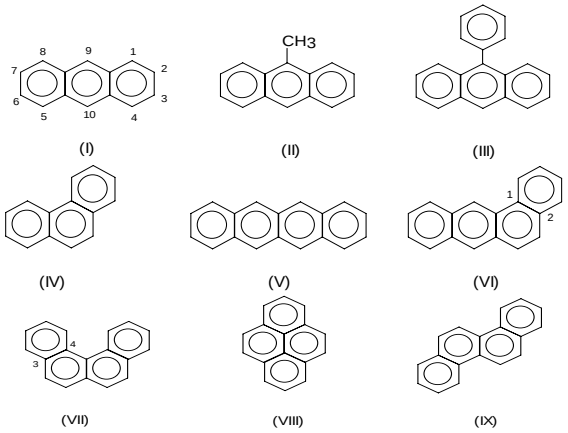


**Fig. 1**. Polycyclic aromatic hydrocarbons (tri and tetra cyclic) – structural formula

The π-delocalised electrons are present in a great number in the molecule, excepting the transanneal bonds. Steric features of PAH and degradation products can influence the biologic activity, facilitating the initiation of the carcinogenic process. (Bergman, 1968; Grunberger and Weinstein, 1979; Gârban et al., 1981; Lee et al., 1998; Gârban,

2003). Groups of compounds PAH represent the greatest class of substances among the carcinogenic polycyclic compounds.

Polycyclic aromatic hydrocarbons (PAH) have two characteristics: a planar molecule and Π delocalised electrons. The planarity of the molecule is important for the biologic activity. Deviations of the planar form can lead to the modification of the relation chemical structure - biological activity. The main polycyclic compounds are: antracene (I); 9-metilantracene (II); 9-fenilantracene (III); fenantrene (IV); tetracene (V); 1,2-benzantracene (VI); 3,4-benzfenantrene (VII); piren (VIII); crisen (IX) witch chemical structures is given in fig. 1 and pentacene (X); 1,2,3,4-dibenzantracene (XI); 1,2,5,6-dibenzantracene (XII); 1,2,7,8-dibenzantracene (XIII); 1,2,5,6-dibenzfenatrene (XIV); 1,2,3,4-dibenzfenantrene (XV); 3,4-benzipirene (XVI); 20-metilcolantrene (XVII); 1,2,3,4-dibenzpirene (XVIII); 1,2,6,7-dibenzpirene (XIX); 3,4,8,9-dibenzpirene (XX); 1,2,7,8-dibenztetracene (XXI); coronene (XXII) – their chemical structure is shown in fig. 2.

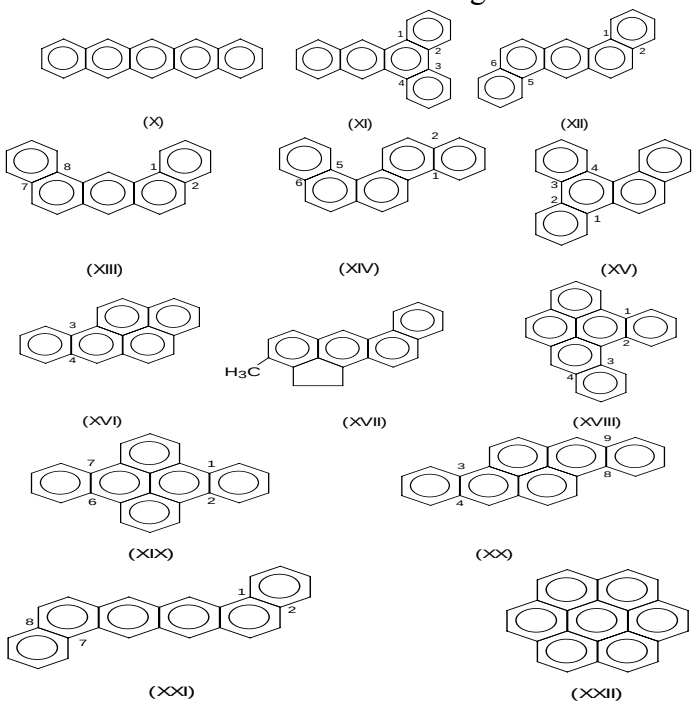


**Fig. 2.** Polycyclic aromatic hydrocarbons (penta, hexa and hepta cyclic) – structural formula

**Structure of acridine and acridinic derivatives**

As to the chemical structure, acridine is a dibenzopyridine, which forms yellow crystals, its solutions having a blue fluorescence. It is a weak base that can ionize resulting acridine salts. Introducing an auxochrome group ($NH_2$) in positions 3 and 6 acridinic colouring agents are obtained. Acridine (XXIII) and most important derivatives are: 9-aminoacridine (XXIV); 9-amino-1,2,3,4-tetrahydrine (XXV); proflavine (XXVI); acridin orange (XXVII); acrylflavine (XXVIII); acranil (XXIX); acridinylthiourea (XXX); mepacrine (XXXI); 9-amino-6-chloro-2-methoxyacridine – ACMA (XXXII). All these can be presented as cations whose chemical structure is given in figure 3.

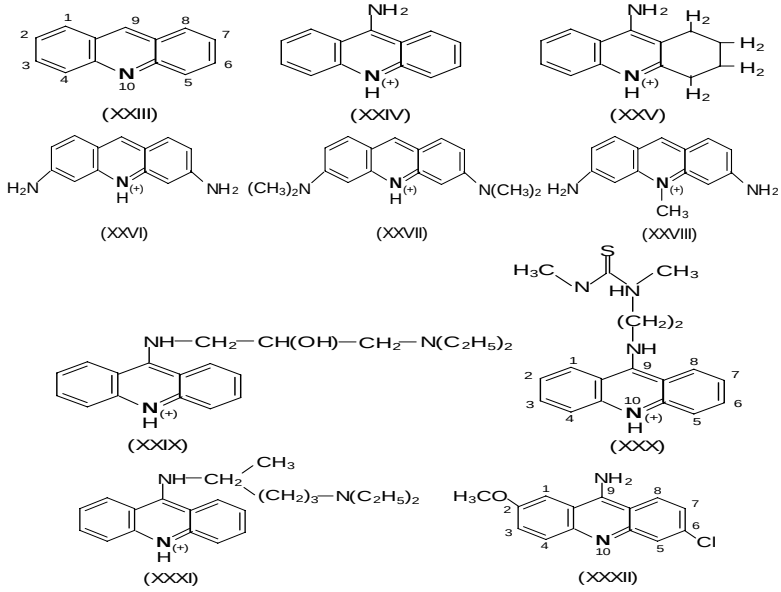


**Fig. 3.** Acridine and acridinic derivatives – structural formulas

These chemical compounds are mostly used as bactericides, bacteriostatics or colorants.

## Biogenesis of DNA Adducts

**Specificity of DNA-HPA type of adducts**

Adducts biogenesis has as origin the formation of some bindings between DNA nucleobases, prevailing guanine (G) and cytosine (C) in

regions with critical electron density. Following examples shows the denomination of adducts and their abbreviations (fig. 4).

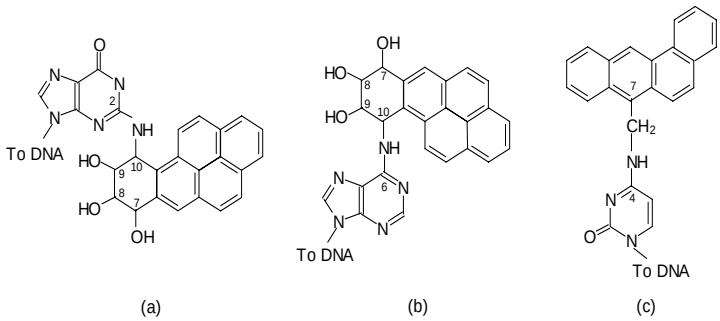


**Fig. 4.** Structure of some adducts between DNA nucleobases and diverse HPA a) N2dGu-B(a)P; b) N6dAd-B(a)P; c) N4dCi-MB(a)A

The position of the nitrogen atom in nucleotides is given in brackets. Binding of PAH, especially of benz(a)pyren is made at the level of deoxyriboguanosine (dGu) or deoxyriboadenosine (dAd).
The following adducts are formed:

- adduct (a): 2'-deoxy-$N_2$-(7,8,9,10-tetrahydro-7, 8, 9-trihydroxy-benzon(a)pyren-10-il)-guano-sine, noted **$N_2$dGu-B(a)P** ;
- adduct (b): 2'-deoxy-$N_6$-(7,8,9,10)-tetrahydro-7,8-trihydroxyben-zon(a)pyren-10-il)-adenosine, noted **$N_6$dAd-B(a)P** ;
- in the case of the adduct PAH-DNA the molecule of PAH is methyl-benz(a)antracen, i.e. MB(a)A which binds at deoxyribocytidine (dCi) of DNA, forming: adduct (c): $N_4$-(benzantracenyl-7 methyl) citidine, noted **$N_4$dCi-MB(a)A** .

Building of such adducts is followed by the destabilization of the macromolecular structure of DNA. This fact contributes to the perturbation of genetic information during replication-transcription-translation processes, leading to the appearance of mutagene and/or carcinogene processes. In the case of concept uses, the effects of adducts' building can stand at the origin of teratogene processes.

Native DNA nucleobases show known bondings. An interaction with planar heterocyclic ions of acridinic type implies a distorsion of the native double helix and an extension of the DNA molecule. These processes are conditioned by the saturation state of DNA.

**Specificity of DNA-acridine type of adducts**

Like polycyclic aromatic hydrocarbons, substances of this group show a fusion of π electrons in extended molecular orbitals. Chemical behaviour of N heterocycles differs due to specific properties of the nitrogen atom, its molecular charge being greater than that of carbon atoms. The greater electronegativity of N determines the non-uniform repartition of electrons in the molecule. Due to this structure ionic forms can appear. A type of adduct is presented in fig. 5.

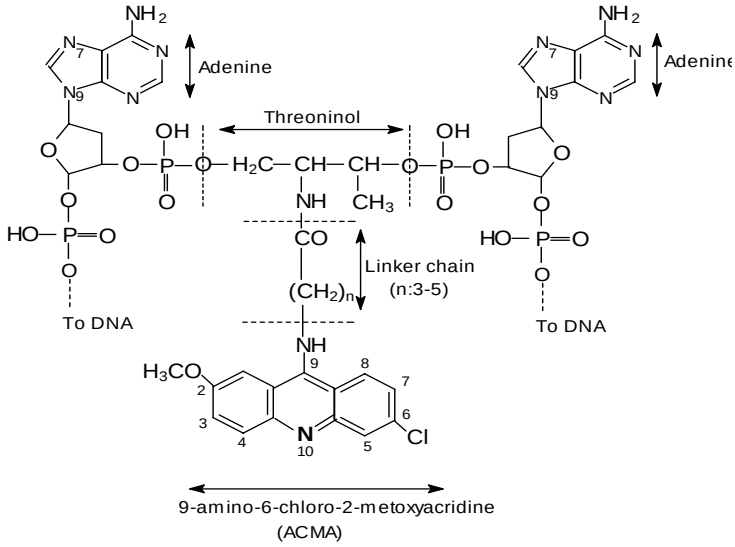


**Fig.5.** Structure of the adduct between DNA nucleobases and the derivative 9-amino-6-chloro-2-metoxyacridine

An interaction of DNA with planar heterocyclic anions of acridinic type determines a distorsion of the native double helix and an extension of the molecule. Molecular associations between the acridinic heterocycle, its derivatives and DNA have a mutagen influence observed in the case of DNA replication by influencing the deletion or insertion of the pairs of nucleobases. Thus, the genetic message is perturbated and mutations may appear.

The capability of acridinic compounds to form adducts with DNA can be related to the anticancer drugs that interact directly with DNA.

Figure 6 shows a cytotoxic agent platinum conjugate of acridinylthiourea (PT-ACRAMTU) that binds to nucleobases.

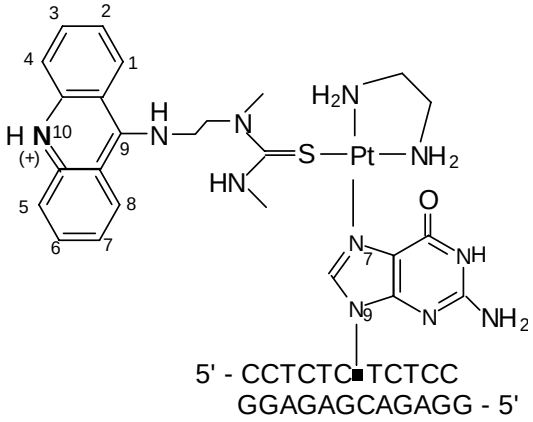


**Fig. 6.** Adduct between DNA and the platinum conjugate of acridinylthiourea

As a result a purine-metal coordinative bond appears that is in contrast with the mechanism of action of cisplatinum, a drug used currently in chemotherapy. Bindings of this compound are made at the level of guanine and adenine.

## Conclusions

Adducts of DNA-HPA type are formed due to the destabilization of electronic structures of HPA with the appearance of intermediary compounds with oxygen of epoxidic type. These ones precede the basic interaction DNA-HPA.

Acridinic compounds bind mostly to adenine and guanine; their mutagen influence is reflected on the transmission of the genetic information.

Interactions between DNA and HPA and respectively DNA and acridinic compounds are at the origin of biogenesis of some bioincompatible compounds that can be implied in processes of teratogenesis, mutagenesis and/or oncogenesis.

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