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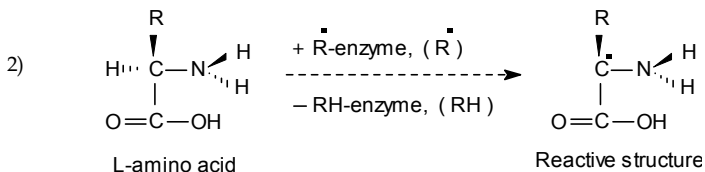
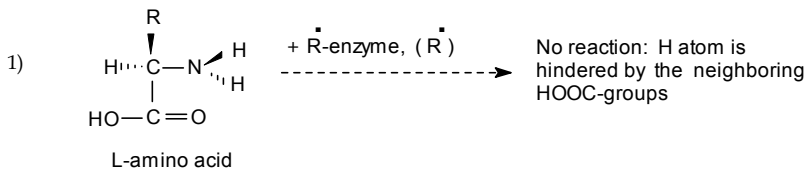
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IS IT POSSIBLE TO PREDICT BIOLOGICAL ACTIVITY OF ANY CHEMICAL, AND IF SO, HOW?

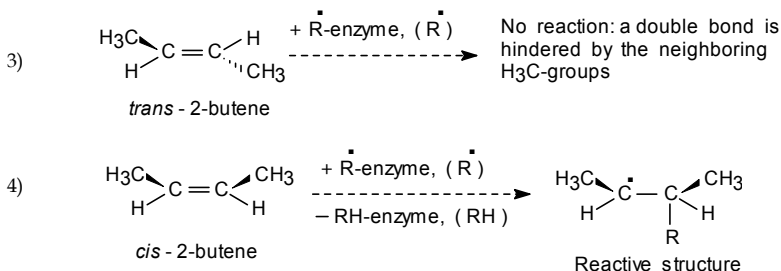
1. Understanding sterical structure

In the living system many kinds of organic molecules exist as L(S)– or D(R)– enantiomers. Enantiomers are stereoisomers that exhibit a property known as chirality. Usually, only one form of many chiral substances is present in biological systems. For example, 19 of the 20 amino acids (except glycine) presented in living organisms belong to L-forms and monosaccharides are presented by D-forms. Chirality is recognized by biologists as being an important factor that determines biological activity of large quantity of chemicals. Unfortunately, we still do not know much about the exact mechanism of such enantioselective recognitions in the living systems.

It is recognized that biochemical processes and activities depend on chemical reactions that play important roles in biological functions. In order for a biochemical reaction (the formation of new bond) to take place, the reacting molecules should possess in sufficient energy (activation energy). The speed or rate at which chemical reaction proceeds is dependent on the many reaction conditions [1]. One of the main ones is a sterical factor. Sterical hindrance (steric shielding) takes place when the size of groups within a molecule prevents the chemical reaction. Understanding steric effects is critical to chemical processes caused by biologically active substances: steric effects determine how and at what rate hormones, pesticides, drugs will interact with their target bio-molecules. An example of such phenomenon can be illustrated with amino acids: such reactions do not occur if an hydrogen atom is hindered by neighboring radicals (because they must collide in the correct orientation) and hence no biological effects are revealing (reactions 1 and 2).



This rule might also be applied to chemicals of *cis-trans*-configurations in the free radical addition reactions (reactions 3 and 4).



2. Sterical hindrance is the controlling factor in the relationship between steric structure and biological activity

It is very known that individual chemical properties of any chemical are all derived from the unique molecular structure of that chemical. These principles form the underlying basis for the prediction of biological activity from chemical structure. There are essentially several basic approaches to the prediction of toxicity/bioactivity from chemical structure. Among their, for example, are mechanistic and statistical approaches. Mechanistic approach is based on the analysis of physical, chemical or reactivity parameters to establish a structure/activity relationship (SAR). In statistical approach information is generated from collection of experimental (toxicological) data. Unfortunately, progress in prediction of toxicity/bioactivity from chemical structure has been slow over the past decades. Another approach that is currently being studied by us [2] is the use

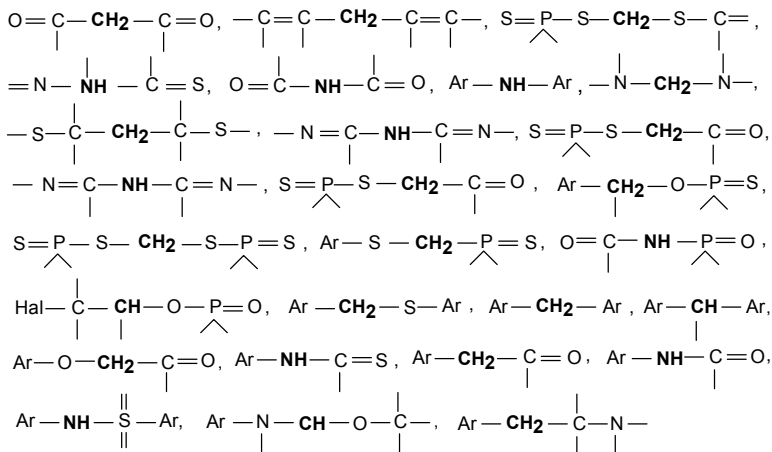
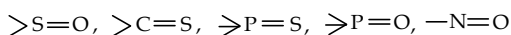
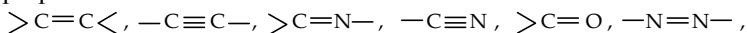


Figure. Chemical structure of D for diverse biologically active substances

of sterical properties and reactivity of the investigated substance. Our studies from the SAR suggest that this phenomenon is caused by the presence of an active hydrogen atom (at the C- or N-atoms) which sterically is not hindered by neighboring radicals. The fragment of the molecule that has the active hydrogen atom is termed as a functional reactive group (FRG or descriptor, D) is an essential factor determining biological activity of any given chemical. These chemicals to be reactive and to cause biological effects should be transformed into free radicals (by enzymes or endogenous metabolic free radicals) in the reactions of the hydrogen atom abstraction. Several D of diverse substances are presented in Figure.

Another FRG determining biological activity of chemicals are following:

(1) The functional groups having doubly or triply bonded atoms and likewise cyclopropane:



(2) The quaternary nitrogen atom in alkanes and cycloalkanes. *In vivo* these chemicals form olefins in accordance to the Hofmann's rule (Hofmann A.W.).

(3) The quaternary nitrogen atom in aromatic compounds. The substances of this class are readily converted into free radicals *in vivo*.

(4) The chemicals having active hydrogen atoms at two OH-groups in the non-aromatic cyclic structure. Abstractions of hydrogen atoms from these structures by another endogenous free radicals yield inert substances, that are termed as antioxidants.

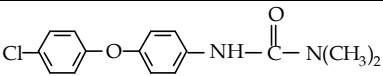
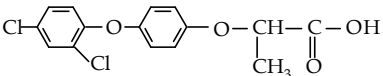
(5) The chemicals having one or more OH-groups. Abstraction of the hydrogen atom from such group by free radicals yields an oxygen centered radical.

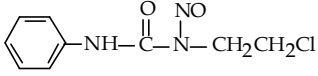
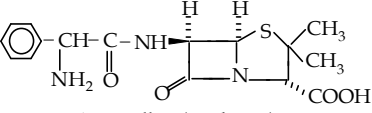
3. Flanking substitutes can influence the selective activity

The biological activity/toxicity is also caused by the presence of specific flanking substitutes (see table) [2]. These fragments of the molecule and FRG have essential impact on the toxicity to living systems.

Table

Summary of the important biologically active substances [2]

Structures (common name)	Descriptors	Typical flanking substitutes	Acute, oral toxicity LD ₅₀ , mg/kg
Herbicides			
 <p>Chloroxuron</p>	Ar-NH-C(=O)	-CH ₃	For rats 3000
 <p>Diclofop</p>	Ar-O-CH-C(=O)	-COOH	For rats 563-693

Structures (common name)	Descriptors	Typical flanking substitutes	Acute, oral toxicity LD ₅₀ , mg/kg
Insecticides			
$\begin{array}{c} (\text{H}_5\text{C}_2\text{O})_2\text{P} \text{ S } \text{CH}_2 \text{C} \text{ONH}_2 \\ \parallel \\ \text{S} \\ \text{Phosthion} \end{array}$	$\begin{array}{c} \text{S}=\text{P}-\text{S}-\text{CH}_2-\text{C}=\text{O} \\ \wedge \qquad \qquad \qquad \end{array}$	-NH ₂ -CH ₃	For mice 200
$\begin{array}{c} (\text{H}_5\text{C}_2\text{O})_2\text{P} \text{ S } \text{CH}_2 \text{COOH} \\ \parallel \\ \text{S} \\ \text{Acethion acid} \end{array}$	$\begin{array}{c} \text{S}=\text{P}-\text{S}-\text{CH}_2-\text{C}=\text{O} \\ \wedge \qquad \qquad \qquad \end{array}$	-COOH -CH ₃	630
Miscellaneous pharmaceutical substances			
 <p style="text-align: center;">CCNU (antineoplastic agent)</p>	$\begin{array}{c} -\text{N}=\text{O} \\ \text{Ar}-\text{NH}-\text{C}=\text{O} \\ \end{array}$	-CH ₂ Cl	For rats 38-51
 <p style="text-align: center;">Ampicillin (antibiotic)</p>	$\begin{array}{c} \text{Ar}-\text{CH}-\text{C}-\text{O}- \\ \qquad \qquad \\ \text{C}-\text{H} \\ \end{array}$	-COOH	For rats 10000

4. Answers to the question

1. The primary role of described Descriptors in the designing of novel bioregulators is to detect leads without performing experiments.

2. Substances having flanking substitutes such as -COOH, -OH, -COR and -COOR possess strong biological activity to plants and microbes whereas their toxicity to mammals is moderate or slight.

3. Chemicals having Descriptors which are formed by P and S atoms possess as very strong toxicity as biological activity.

4. Chemicals having Descriptors which are not formed by P and S atoms possess very/or strong biological activity, their toxicity is only moderate.

5. Bridgehead olefins which can form long-lived bridged free radicals *in vivo* possess analgesic activity.

6. In order to design potent bioregulators with strong biological effects it is need to chouse their *cis*-isomers.

7. Selection of Descriptors and flanking groups is the main condition that must be accountable factors in the designing of novel bioregulators.

8. Chemicals having lipophylic CH₃-groups as flanking substitutes possess strong toxicity to mammals.

9. Chemicals having oxygen in the ring of a molecule possess strong biological activity.

10. Substances that can form *in vivo* more than one free radical center simultaneously possess strong biological (analgesic) activity.

11. Factors which stabilize free radicals increase biological activity of chemicals.

Literature

1. *Ingold C.K.* Structure and metabolism in organic chemistry.— Ithaca and London: Cornell University Press, 1969.
2. *Kurchii B.A.* What Regulate the Growth Regulators? — Kiev: Logos Publisher, 1998.— 202 pp. (In Russian and English).

Summary

In this report we consider the role of several factors in the bioactivity/toxicity of hormones, pesticides and pharmaceutical substances. It is concluded that taking into account sterical factors, functional reactive groups and flanking substitutes is predictive tool in the prediction of bioactivity/toxicity of any given chemical.

В этом сообщении мы рассматриваем роль некоторых факторов, определяющих биологическую активность (токсичность) гормонов, пестицидов и фармацевтических препаратов. Сделано вывод, что учет стерических факторов, функционально активных групп и боковых заместителей является предиктивным инструментом в прогнозировании биологической активности (токсичности) любого химического соединения.

В цьому повідомленні ми розглядаємо роль деяких факторів, що визначають біологічну активність (токсичність) гормонів, пестицидів і фармацевтичних препаратів. Зроблено висновок, що врахування стеричних (просторових) факторів, функціонально активних груп і бокових замісників являється передбачуваним інструментом в прогнозуванні біологічної активності (токсичності) будь-якої хімічної сполуки.

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ГЕНЕТИЧЕСКОЕ ОБОСНОВАНИЕ СИСТЕМЫ РОДА ТРИТИКАЛЕ (×*TRITICOSECALE* WITTMACK)

Разработка классификации синтетических гибридогенных амфиплоидных видов, полученных экспериментально объединением дивергированных геномов, имеет особое значение и требует тщательного анализа. Каждый новый синтетический вид должен иметь название и место в системе рода.

Амфиплоидный род тритикале (×*Triticosecale* Wittmack = *Triticum* L. × *Secale* L.) относится к подтрибе пшеницевых (*Triticinae* Benth.) трибы *Triticeae* (*Hordeae*) семейства злаков (*Poaceae* Barnh., или *Gramineae* Juss.) порядка однодольных трав (*Poales* Small). Он включает синтетические виды фертильных реципрокных межродовых гибридов между представителями родов пшеницы (*Triticum* L.) и ржи (*Secale* L.), различающиеся плоидностью, происхождением и хромосомным составом геномов.

Реальность рода ×Тритикале (×*Triticosecale* Wittmack) не вызывает сомнений. Виды тритикале репродуктивно изолированы от исходных видов пшеницы и ржи и отличаются от них происхождением, кариотипически, по совокупности морфогенетических признаков, селекционной проработкой и ареалом распространения. За последние 40 лет интенсивной селекции создан обширный исходный материал и новые высокоурожайные сорта озимых и яровых тритикале. По данным ETDB (The European Triticale Database) объем мировой коллекции тритикале вырос с 5203 образцов из 9 генетических банков в 1999 г. до 11 721 образца из 23 генбанков 18 стран в 2006 г.: 2056 образцов зарегистрированы в SIMMYT (Мехико), 7788 образцов происходят из Европы, включая коллекцию из 3876 образцов ВИР (VIR) [1].

Тетраплоидные тритикале (*Triticosecale tetraploidii* (*lebedevii*) Kurk., AARR, BBRR, DDDR, A/B/DRR, $2n=4x=28$) включают в состав ядра диплоидный RR-геном ржи и диплоидный или рекомбинантный набор хромосом A-, B- и D-геномов пшеницы. Составляют около 3,2% генофонда тритикале. В коллекции ВИР представлены 124 образцами. Растения по морфологическим признакам занимают промежуточное положение между пшеницей и рожью. Признаки ржи выражены сильнее, чем у гексаплоидных и октоплоидных тритикале. Тетраплоидные тритикале — озимые, редко яровые, самоопылители, склонные к перекрестному опылению. Используются для реконструкции генома тритикале.

Гексаплоидные тритикале (*Triticosecale hexaploidii* (*derzhavinii*) Kurk. Et Filat., T/AABBRR, S/RRAABB, $2n=6x=42$) включают в состав ядра диплоидные наборы хромосом A-, B-геномов и R-генома ржи. Составляют более 90% генофонда тритикале. В коллекции ВИР представлены 3492 образцами.