QFL-0341 Estrutura e reatividade de compostos orgânicos

2019 (04/outubro)

https://blacktag.com.br/eventos/1973/aromaticos-we-are-all-mad-here

Compostos aromáticos

Hidrocarbonetos aromáticos

Nomenclatura de benzenos mono-substituídos

Nomenclatura de benzenos dissubstituídos e polissubstituídos

Critérios de aromaticidade

Anti-aromaticidade

Descrição da aromaticidade e da anti-aromaticidade pela teoria do orbital molecular

Substâncias heterocíclicas aromáticas

Os compostos contendo anel benzênico são em geral os compostos mais estáveis. Não surpreende que tenham sido os primeiros a serem isolados a partir de fontes naturais.

O próprio benzeno foi isolado a partir do resíduo resultante da queima de hidrocarbonetos (óleo de baleia) utilizados em iluminação pública em Londres.

Quase todos os produtos naturais inicialmente isolados continham anéis benzênicos.

Michael Faraday (1791-1867)

- Mais conhecido por suas descobertas sobre fenômenos elétricos. Contudo, iniciou sua carreira com estudos na área da química.

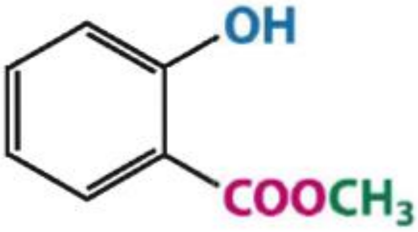
- **Isolou o benzeno** do resíduo oleoso encontrado na postes de iluminação à gás das ruas de Londres e determinou que a razão **C:H era de 1:1**.

- O nome do grupamento ***fenila***, usado quando o uma unidade de benzeno encontra-se como um substituinte, deriva de sua origem, pois a palavra grega ***pheno*** significa *"**Eu tenho a luz**"*.

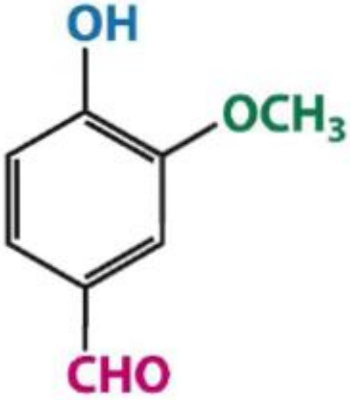
- O benzeno foi sintetizado em 1834 por Eilhard Mitscherlich, o qual determinou sua fórmula molecular como C_6H_6.

- Outros compostos com uma baixa razão **C:H apresentavam um aroma agradável, desta maneira foram classificados como aromáticos.**

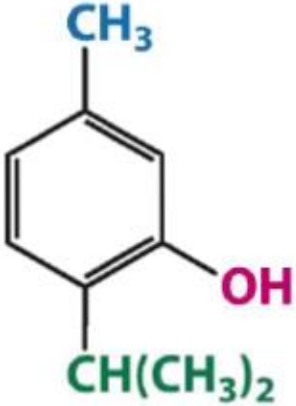
Early definition as ***aromatic*** was used to described some fragrant compounds in early 19th century.



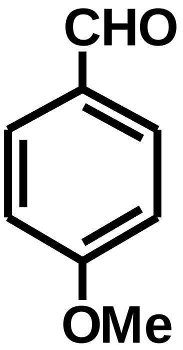
Methyl 2-hydroxy-
benzoate
(Methyl salicylate,
oil of wintergreen flavor)



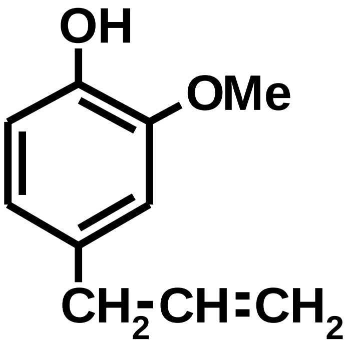
4-Hydroxy-3-methoxy-
benzaldehyde
(Vanillin, vanilla flavor)



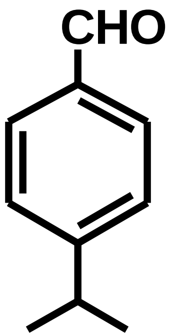
5-Methyl-2-(1-methyl-
ethyl)phenol
(Thymol, thyme flavor)



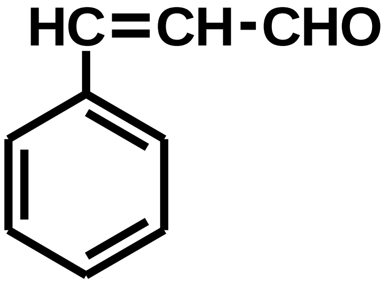
anisaldehyde
(anise)



eugenol
(cloves)

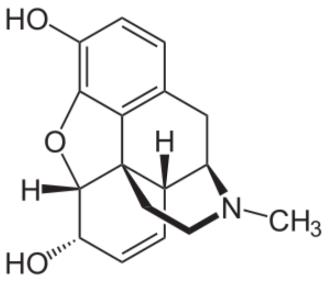


cuminaldehyde
(cumin)

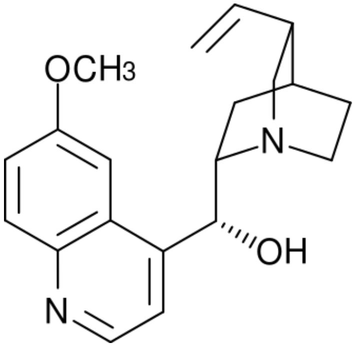


cinnamaldehyde
(cinnamon)

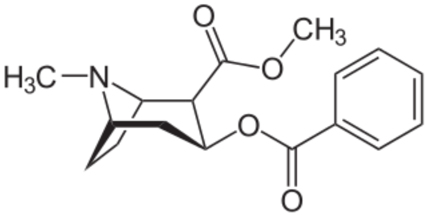
Exemplos de fármacos contendo anéis aromáticos



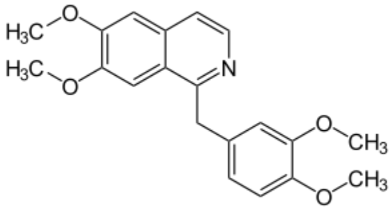
Morfina: Sertürner, 1805



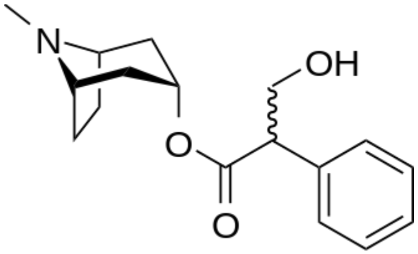
Quinina: Pelletier e Magendie, 1820



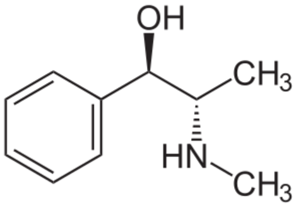
Cocaína: Wöhler, 1859.



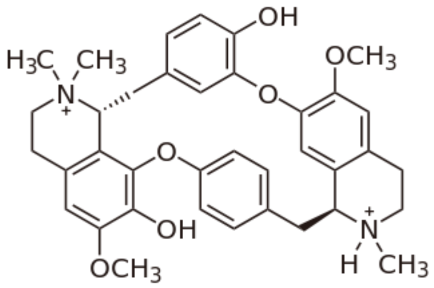
Papaverina: Merck, 1848.



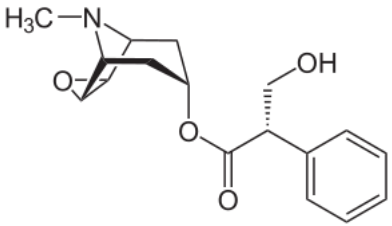
Atropina: Mein, 1831.



Efedrina: Nagai, 1885.

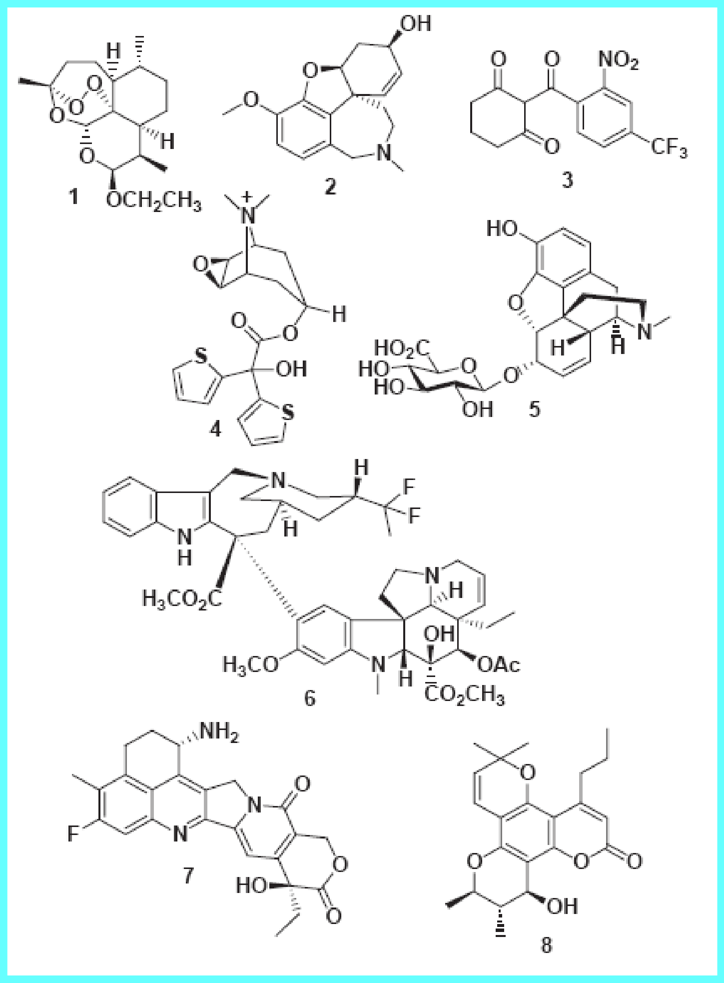


Tubocurarina: Boehm, 1895.



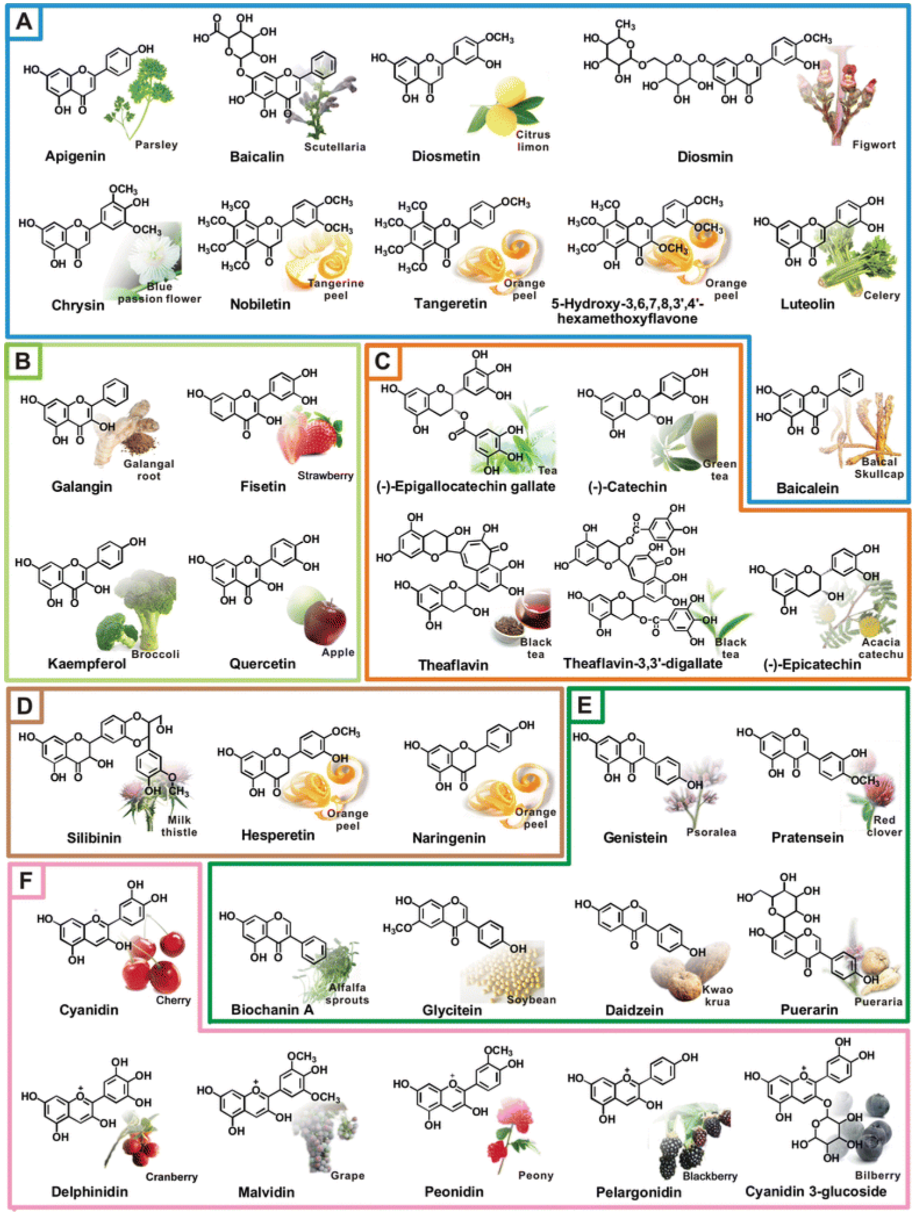
Escopolamina: Landenburg, 1881.

Examples of new medicinal drugs recently introduced to market or in late-phase clinical trials



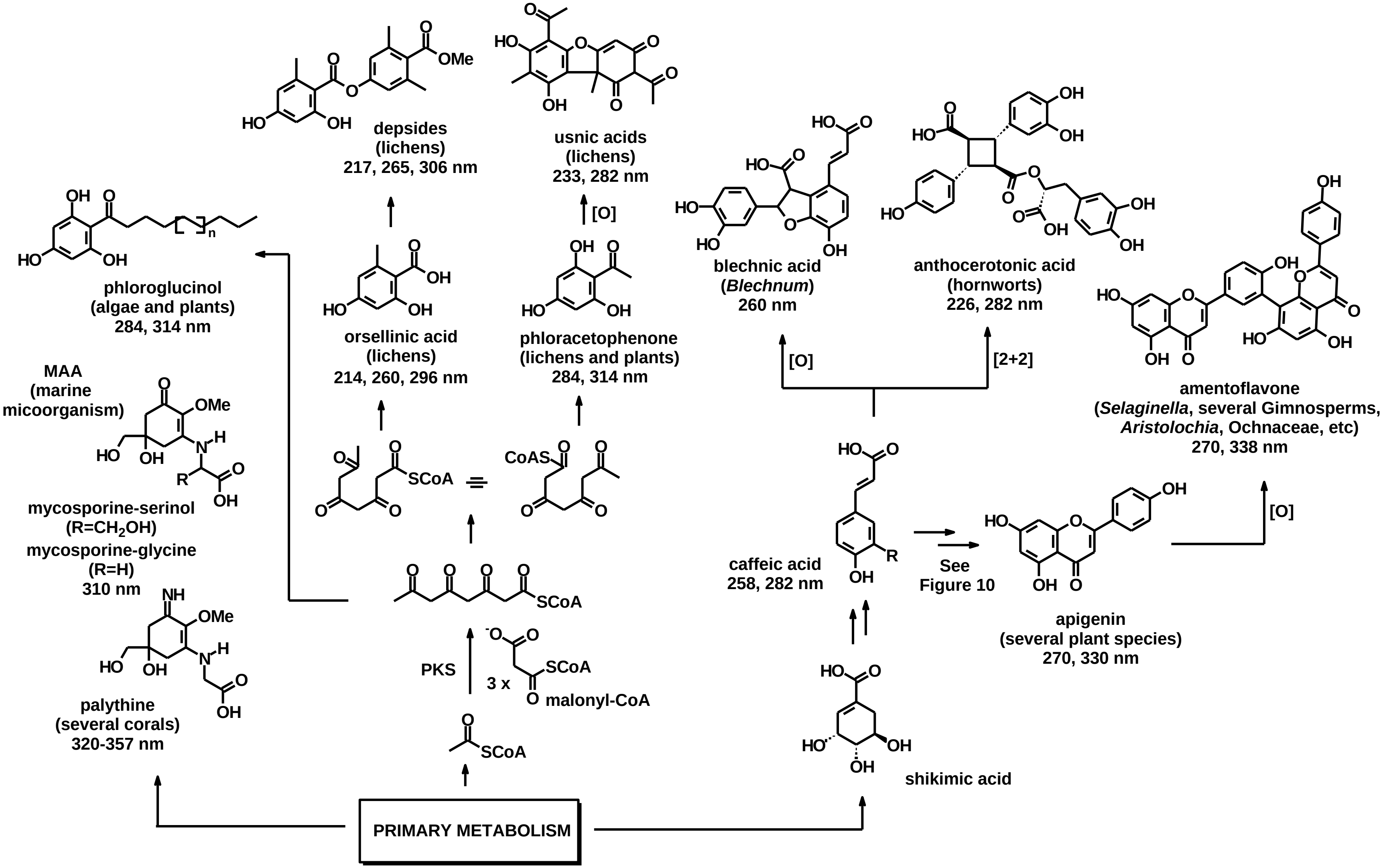
1 Artemether (Artemotil) – antimalarial, *Artemisia annua*
2 Galantamine (Reminiyl) – Alzheimer, *Galanthus woronowii*
3 Nitisinone (Orfadin) – tyrosinaemia, derived from mesotrione, an herbicide based on leptospermone, *Callistemon citrinus*
4 Tiotropium (Spiriva), chronic obstrutive disease, derivative of atropine, *Atropa belladona*
5 Morphine-6-glucuronide, pain medication, *Papaver somniferum*
6 Vinflunine, vinblastine derivative, anticancer, *Catharanthus roseus*
7 Exatecan, camptothecin analog, anticancer, *Camptoteca acuminata*
8 Calanolide, anti-HIV, *Calophyllum lanigerum*

Aromatic compounds in nature: Flavonoids



Major examples of UV-absorbing compounds that have evolved from aquatic to land plants (left to right).

The approximate range of UV maximum is indicated in each case.



phloroglucinol
(algae and plants)
284, 314 nm

depsides
(lichens)
217, 265, 306 nm

usnic acids
(lichens)
233, 282 nm

orsellinic acid
(lichens)
214, 260, 296 nm

phloracetophenone
(lichens and plants)
284, 314 nm

MAA
(marine
micoorganism)

mycosporine-serinol
($R=CH_2OH$)
mycosporine-glycine
(R=H)
310 nm

palythine
(several corals)
320-357 nm

blechnic acid
(*Blechnum*)
260 nm

anthocerotonic acid
(hornworts)
226, 282 nm

amentoflavone
(*Selaginella*, several Gimnosperms,
***Aristolochia*, Ochnaceae, etc)**
270, 338 nm

caffeic acid
258, 282 nm

apigenin
(several plant species)
270, 330 nm

shikimic acid

[O]: oxidative coupling;
[2+2]: photochemical reaction.

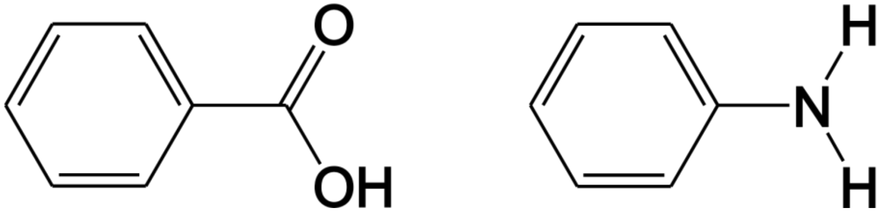
http://www.eolss.net/sample-chapters/c06/e6-151-00-00.pdf

As representações de compostos orgânicos não eram como conhecemos atualmente!

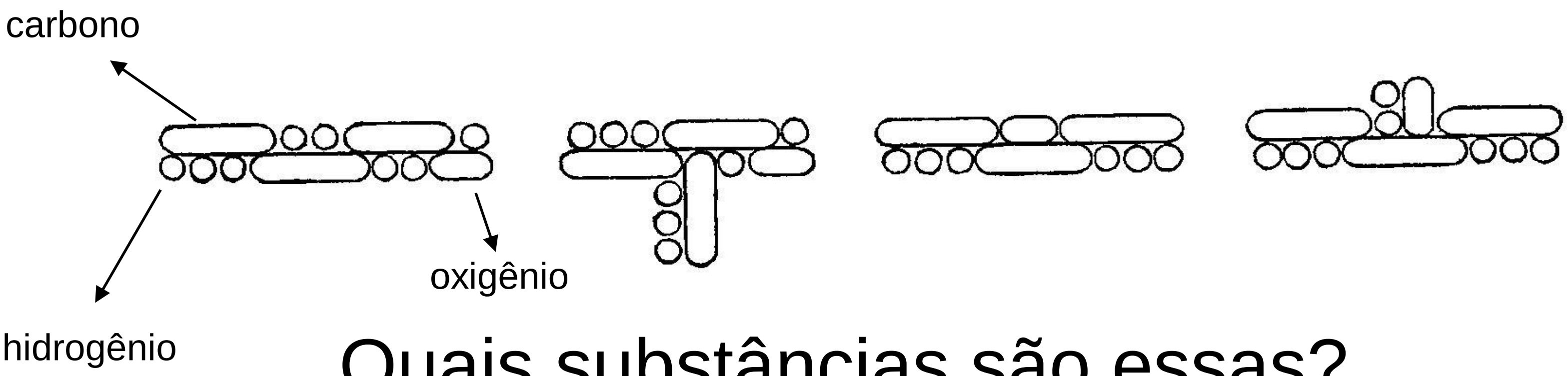
1824 - 1825 Isolated from burnt whale oil by Michael Faraday
1834 Eilhardt Mitscherlich finds benzene has formula of C_6H_6

1861 Loschmidt proposes structure for benzoic acid and aniline

benzoic acid aniline



1865 Kekule invokes sausage (*salsichas*) diagrams



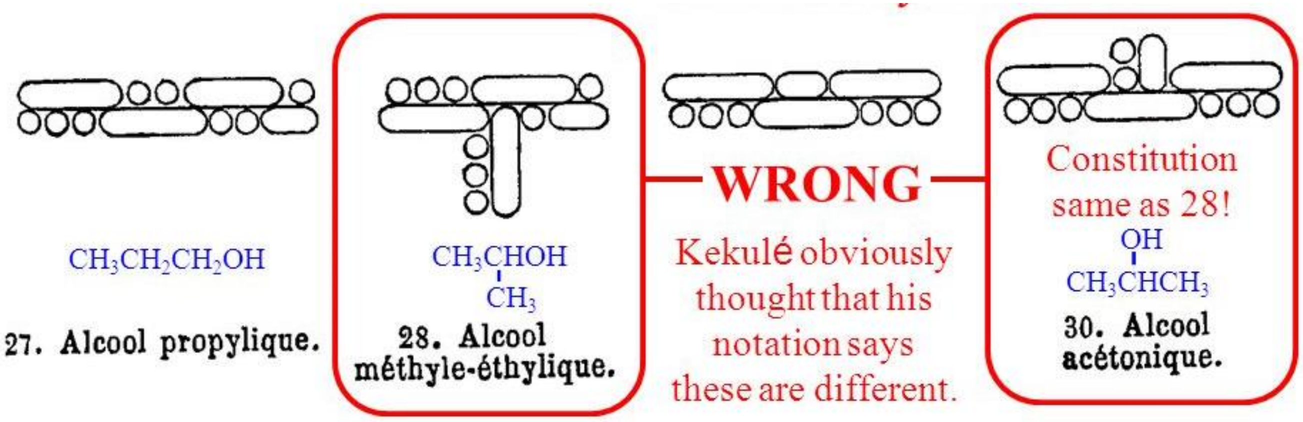
Quais substâncias são essas?

Alcool propylique.

28. Alcool méthyle-éthylique.

Acétone.

30. Alcool acétonique.



$CH_3CH_2CH_2OH$

27. Alcool propylique.

$CH_3\underset{CH_3}{C}HOH$

28. Alcool méthyle-éthylique.

WRONG

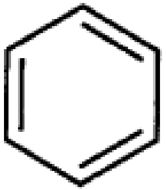
Kekulé obviously thought that his notation says these are different.

Constitution same as 28!

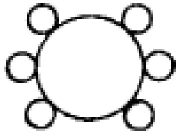
$CH_3\overset{OH}{C}HCH_3$

30. Alcool acétonique.

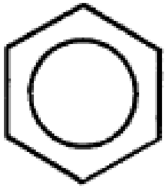
1865 Kekule published the structure **I** for benzene (and he had a dream…)



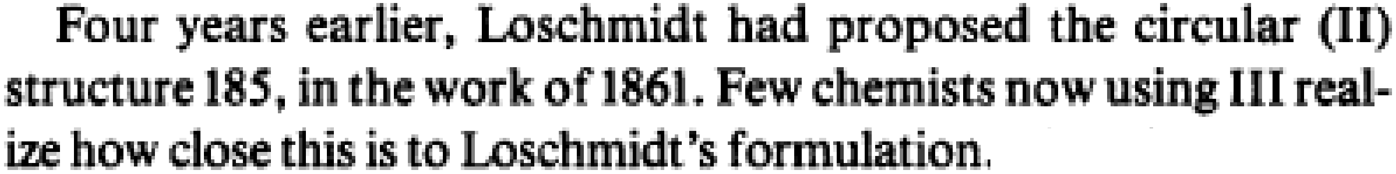
I



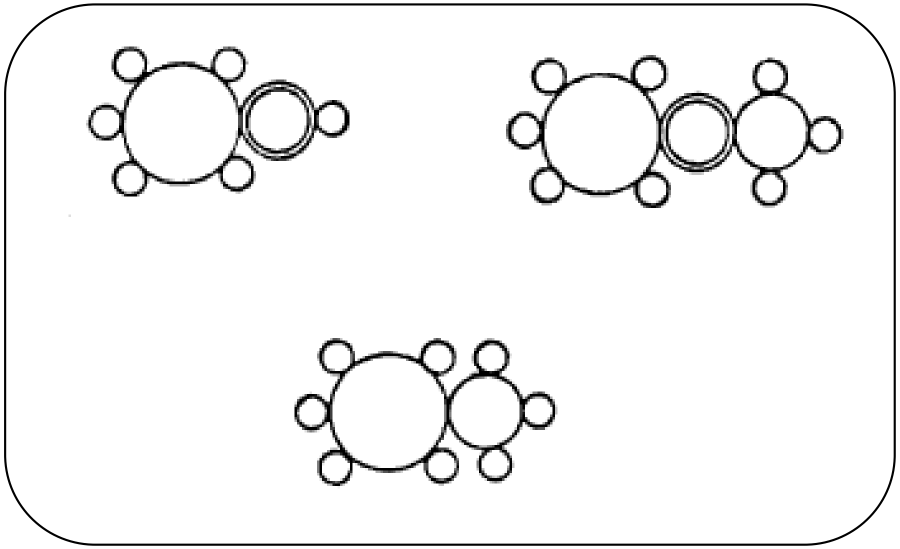
II



III



Four years earlier, Loschmidt had proposed the circular (II) structure 185, in the work of 1861. Few chemists now using III realize how close this is to Loschmidt's formulation.



→

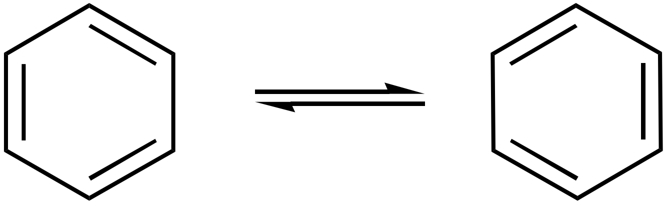
phenol

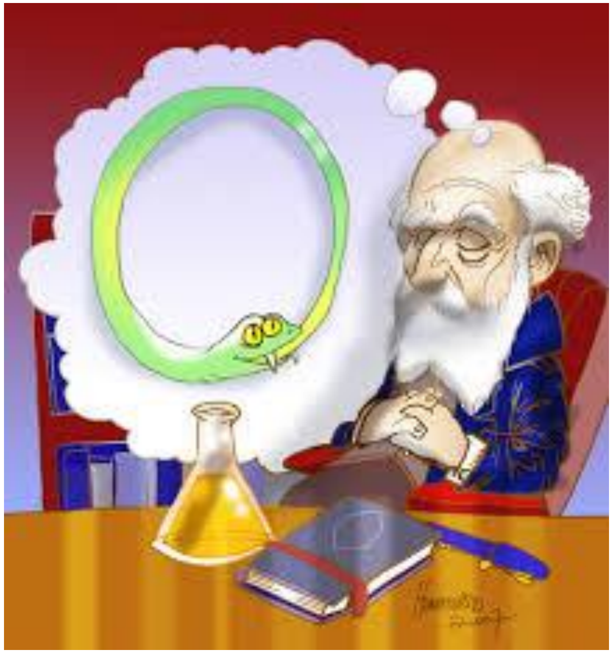
anisol

toluene

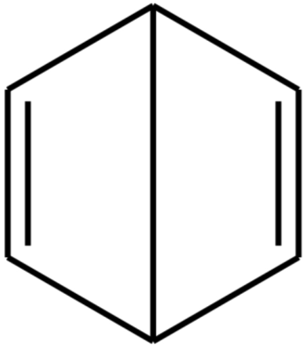
Structure of Benzene

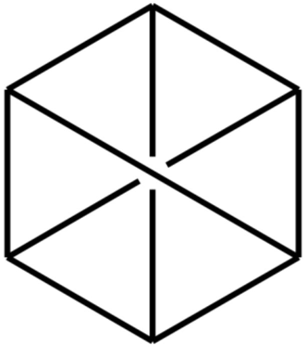
- The first structure of benzene was proposed by August Kekulé in 1865. He proposed that benzene was composed of three double bonds in a six-membered ring.
- These double bonds, he hypothesized, shift back and forth rapidly such that the two possible forms cannot be separated.





Alternate Benzene Structures





	Dewar	Claus	Landenburg Prismane
proposed	1867	1867	1869
synthesized	1972		1973

Katz, T. J.; Acton, N. (1973). "Synthesis of prismane". Journal of the American Chemical Society. 95 (8): 2738. doi:10.1021/ja00789a084.

Reactions of Benzene

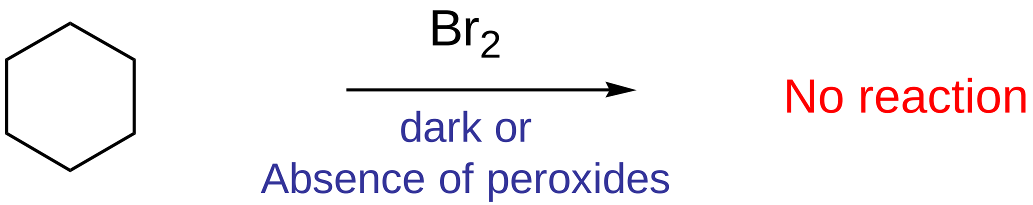
- At first it should be expected to react by electrophilic addition.

- But react by Aromatic electrophilic substitution

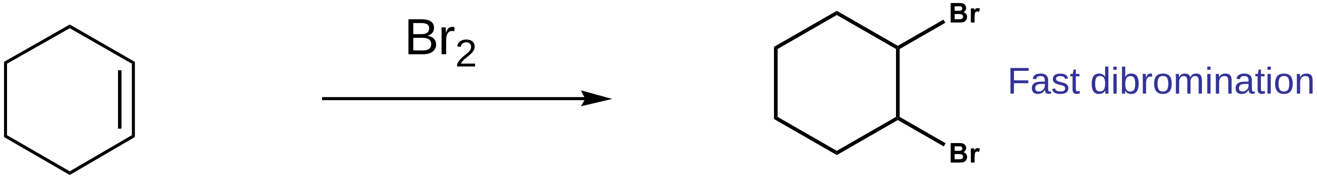
Addition of Bromine to Cyclohexane, Cyclohexene and Benzene

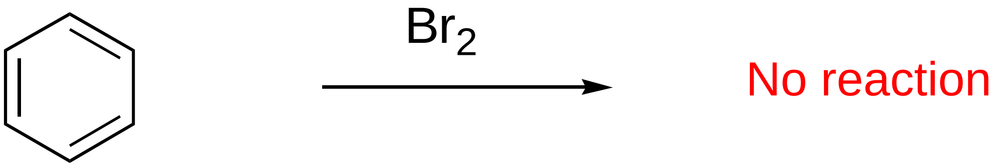
- vc tem que conhecer esses mecanísmos!!!

Reações
radicalares

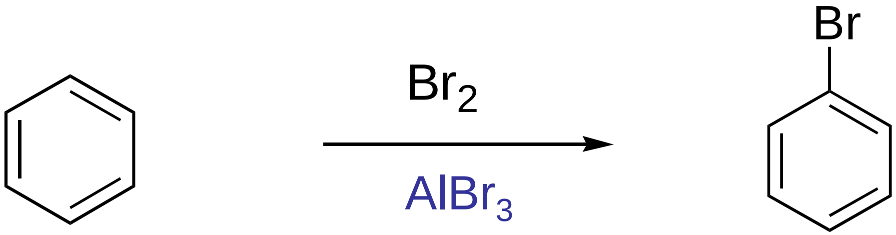


Reações
de adição
eletrofílica



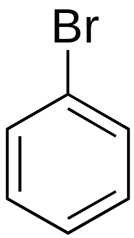


Reações
de substituição
Eletrofílica
aromática

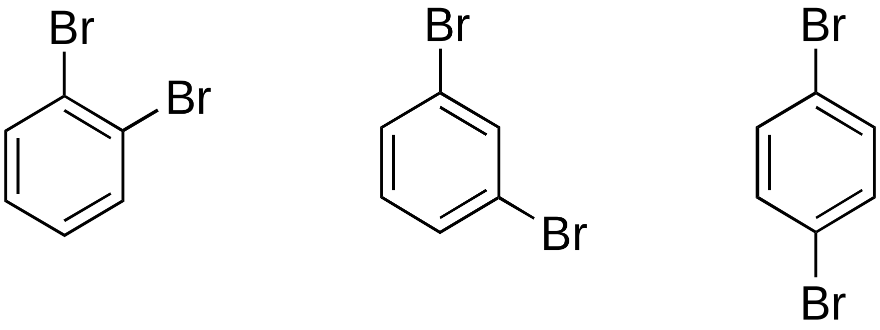


Structure of Benzene

- Kekulé’s structure accounts nicely for the observation that the bromination of bromobenzene gives three (and only three) isomers (and not four as should be expected).



Bromobenzene



Isomers of $C_6H_4Br_2$

Reações do benzeno

Reações de substituição eletrofílica aromática

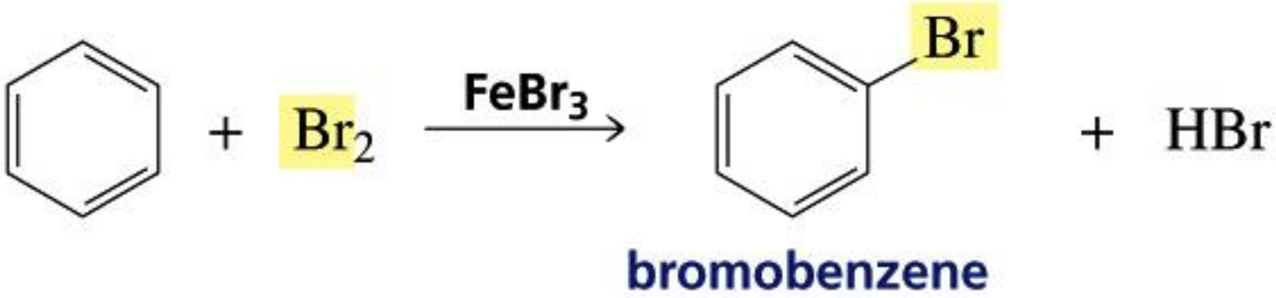
Reações de substituição nucleofílica aromática

São afetadas pelos substituíntes:

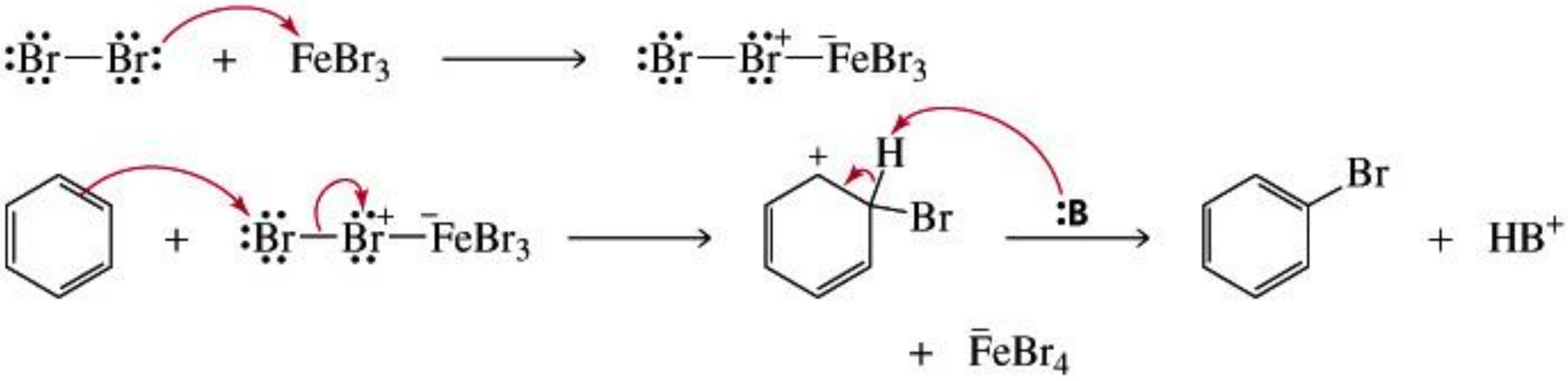
Ressonância e efeitos de ativação e orientação dos grupos substituintes nas reações.

Reações de S_EAr: Halogenação do Benzeno

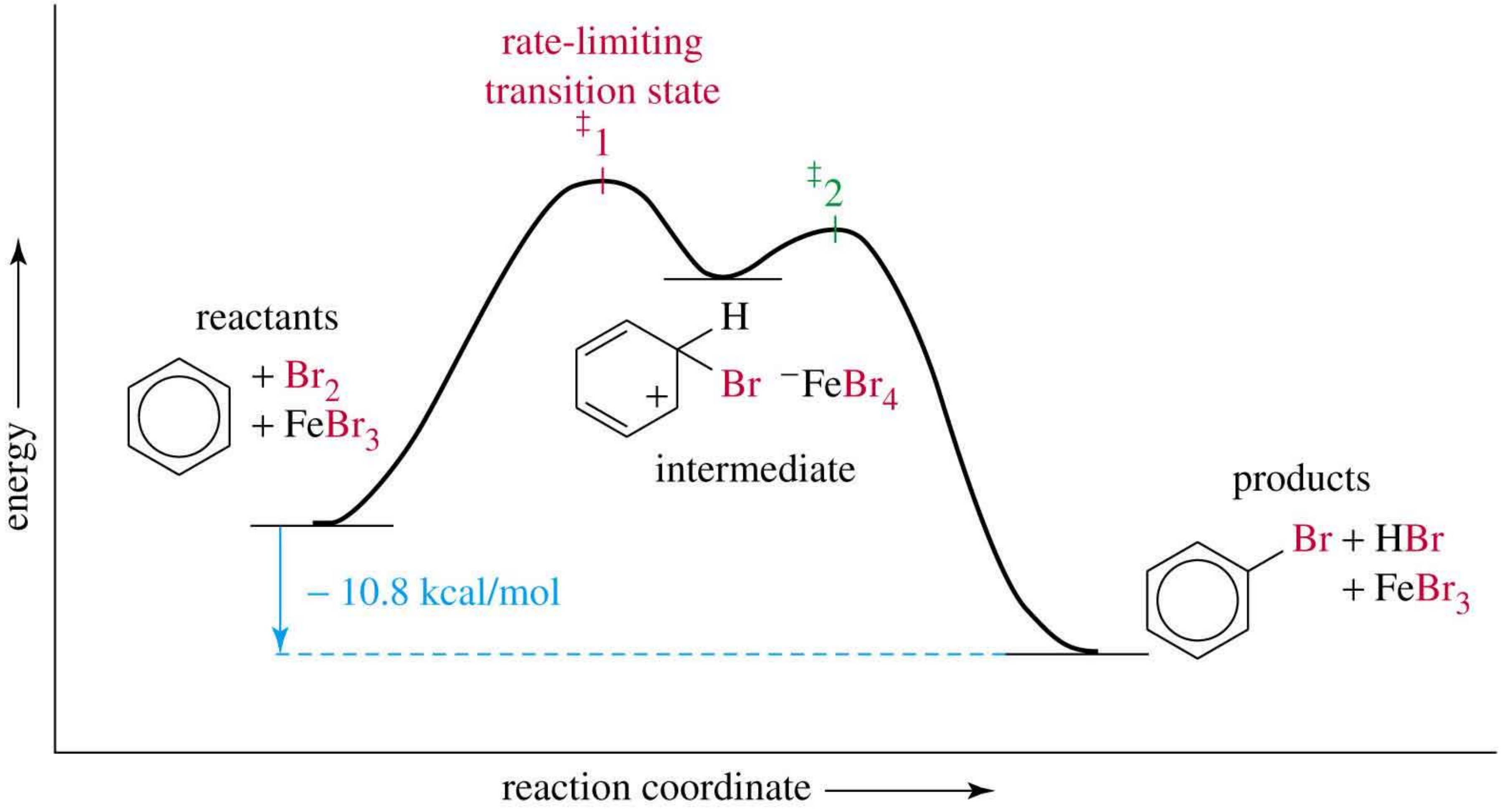
Bromação:



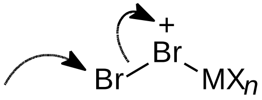
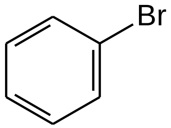
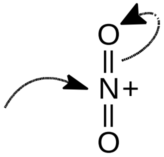
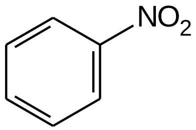
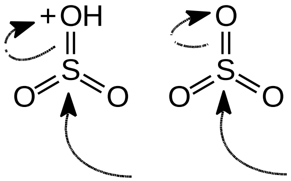
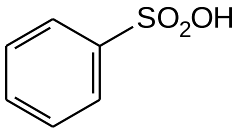
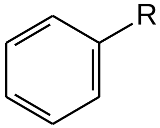
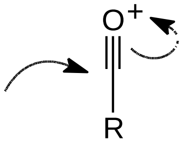
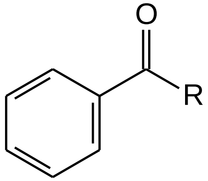
Mecanismo da Bromação:



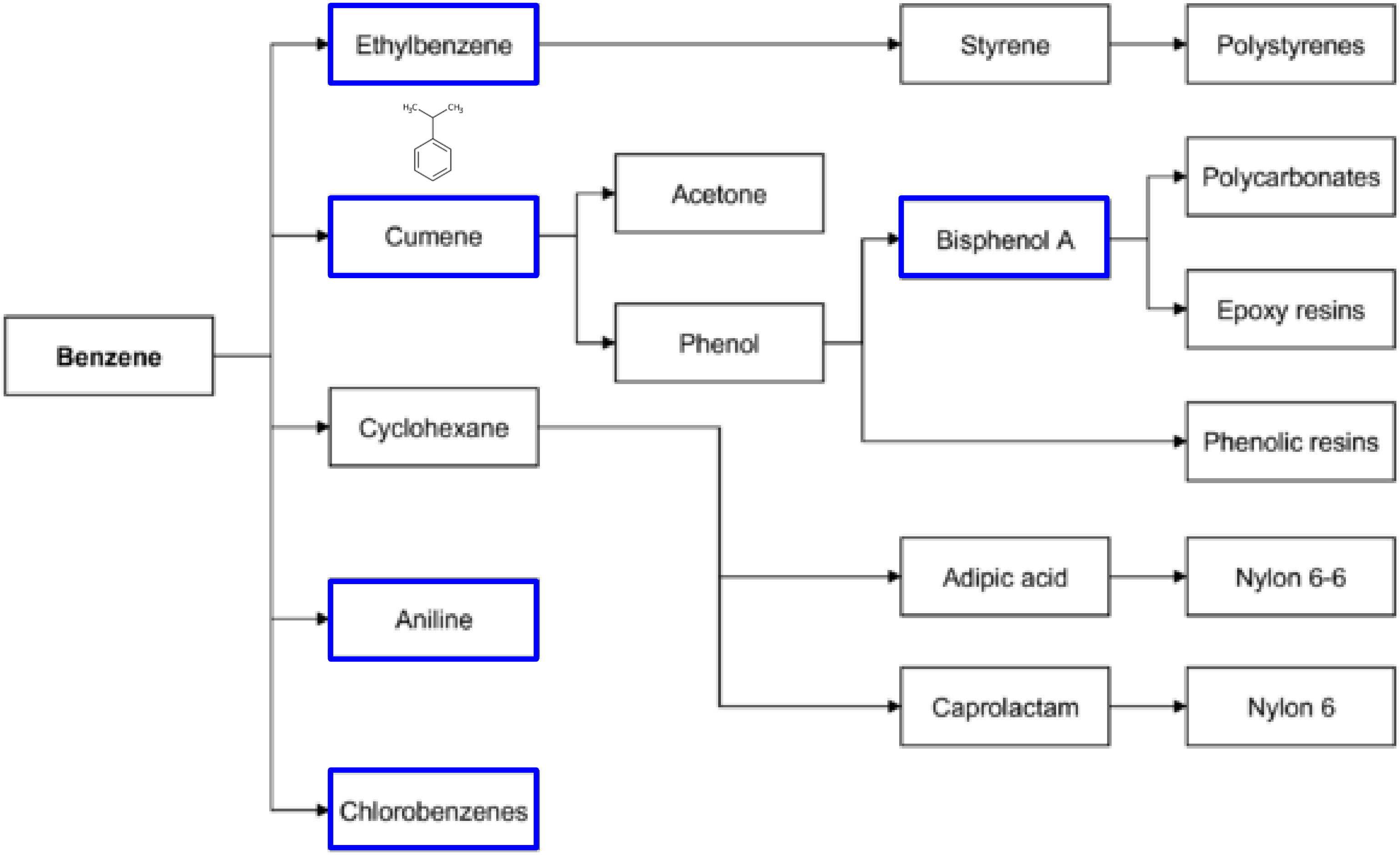
Energy Diagram for Bromination



S_EAr: Resumo das Reações

Reação	**Reagente**	**Eletrófilo**	**Produto**
Bromação	Br_2 + ácido de Lewis		
Nitração	HNO_3 + H_2SO_4		
Sulfonação	H_2SO_4 (conc.) ou H_2SO_4 + SO_3		
Alquilação de Friedel-Crafts	RX + ácido de Lewis		
Acilação de Friedel-Crafts	RCOCl + ácido de Lewis		

Major commodity chemicals and polymers derived from benzene



Benzene

Ethylbenzene

Cumene

Cyclohexane

Aniline

Chlorobenzenes

Acetone

Phenol

Styrene

Bisphenol A

Adipic acid

Caprolactam

Polystyrenes

Polycarbonates

Epoxy resins

Phenolic resins

Nylon 6-6

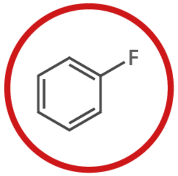
Nylon 6

☐ = envolve SEAr (reações de substituição eletrofílica aromática)

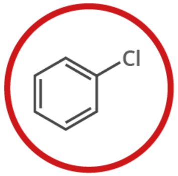
BENZENE DERIVATIVES IN ORGANIC CHEMISTRY

A WIDE VARIETY OF IMPORTANT ORGANIC COMPOUNDS ARE DERIVED FROM BENZENE, BY REPLACING ONE OF THE HYDROGENS WITH A DIFFERENT FUNCTIONAL GROUP. THEY CAN HAVE BOTH COMMON & SYSTEMATIC NAMES, WHICH CAN BE CONFUSING; HERE, COMMON NAMES ARE SHOWN PRIMARILY, WITH SYSTEMATIC NAMES SHOWN IN ITALICS.

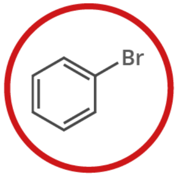
● HALOGEN-CONTAINING ● HYDROCARBON DERIVATIVES ● OXYGEN-CONTAINING ● NITROGEN-CONTAINING ● SULFUR-CONTAINING ● POLYAROMATICS



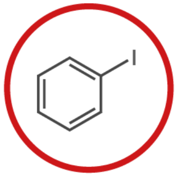
FLUOROBENZENE
Fluorobenzene
C_6H_5F



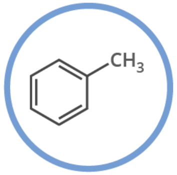
CHLOROBENZENE
Chlorobenzene
C_6H_5Cl



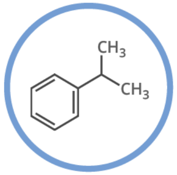
BROMOBENZENE
Bromobenzene
C_6H_5Br



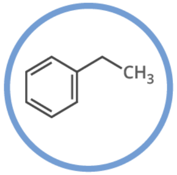
IODOBENZENE
Iodobenzene
C_6H_5I



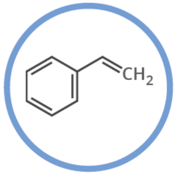
TOLUENE
Methylbenzene
C_7H_8



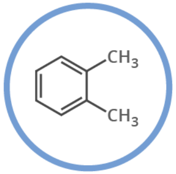
CUMENE
Isopropylbenzene
C_9H_{12}



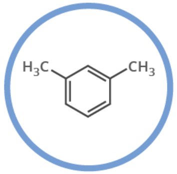
ETHYLBENZENE
Ethylbenzene
C_8H_{10}



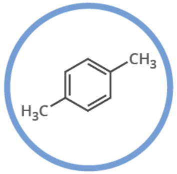
STYRENE
Vinylbenzene
C_8H_8



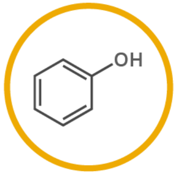
ORTHO-XYLENE
1,2-dimethylbenzene
C_8H_{10}



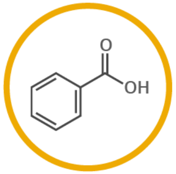
META-XYLENE
1,3-dimethylbenzene
C_8H_{10}



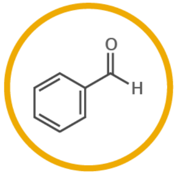
PARA-XYLENE
1,4-dimethylbenzene
C_8H_{10}



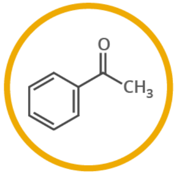
PHENOL
Hydroxybenzene
C_6H_5OH



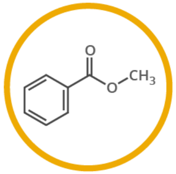
BENZOIC ACID
Benzenecarboxylic Acid
C_6H_5COOH



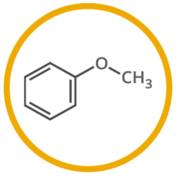
BENZALDEHYDE
Benzenecarbaldehyde
C_6H_5CHO



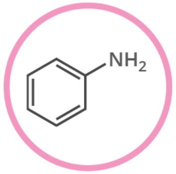
ACETOPHENONE
1-phenylethanone
$C_6H_5COCH_3$



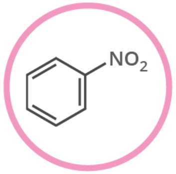
METHYL BENZOATE
Methyl Benzoate
$C_8H_8O_2$



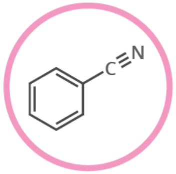
ANISOLE
Methoxybenzene
$C_6H_5OCH_3$



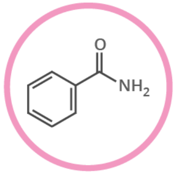
ANILINE
Aminobenzene
$C_6H_5NH_2$



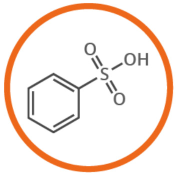
NITROBENZENE
Nitrobenzene
$C_6H_5NO_2$



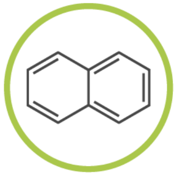
BENZONITRILE
Benzonitrile
C_6H_5CN



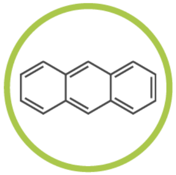
BENZAMIDE
Benzamide
$C_6H_5CONH_2$



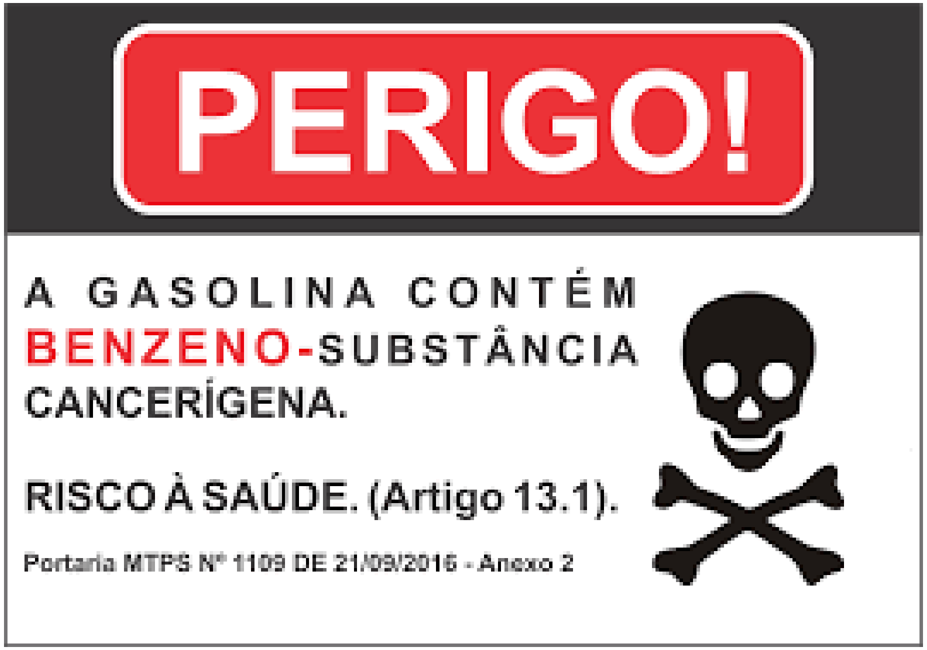
BENZENESULFONIC ACID
Benzenesulfonic Acid
$C_6H_5SO_3H$



NAPHTHALENE
Naphthalene
$C_{10}H_8$



ANTHRACENE
Anthracene
$C_{14}H_{10}$



PERIGO!

A GASOLINA CONTÉM **BENZENO**-SUBSTÂNCIA CANCERÍGENA.

RISCO À SAÚDE. (Artigo 13.1).

Portaria MTPS Nº 1109 DE 21/09/2016 - Anexo 2

EFEITOS DO BENZENO NO ORGANISMO

SISTEMA NERVOSO
Depressão, insônia, dor de cabeça, variações de atenção, percepção, memória, habilidades motoras e funções de raciocínio lógico

OLHOS
Pode causar danos ao córtex visual, como discriminação de cores

MEDULA
Pode atingir as células da medula óssea, causando diminuição de leucócitos

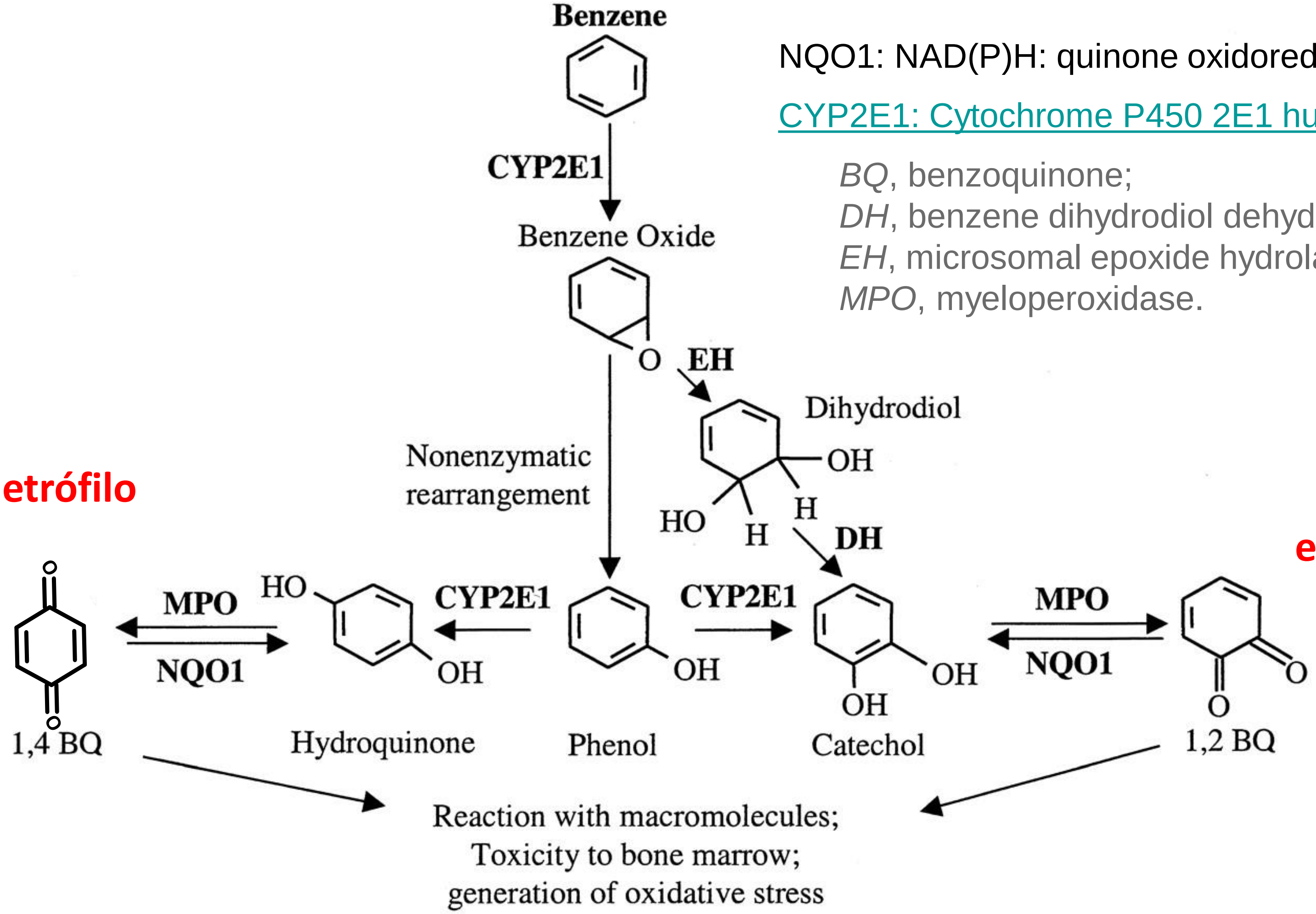
OUVIDOS
Redução de audição, zumbidos, vertigens e dificuldades de processamento de sons

PELE E MUCOSAS
Pode causar eritema e dermatite irritativa

Fonte Arte: Revista Galileu

Conselho Regional de Química da 5ª Região

Benzene metabolism in the liver and bone marrow (medula óssea)



eletrófilo

eletrófilo

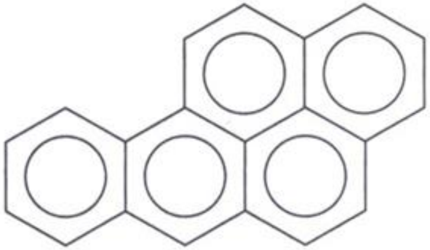
NQO1: NAD(P)H: quinone oxidoreductase-1

CYP2E1: Cytochrome P450 2E1 human recombinant

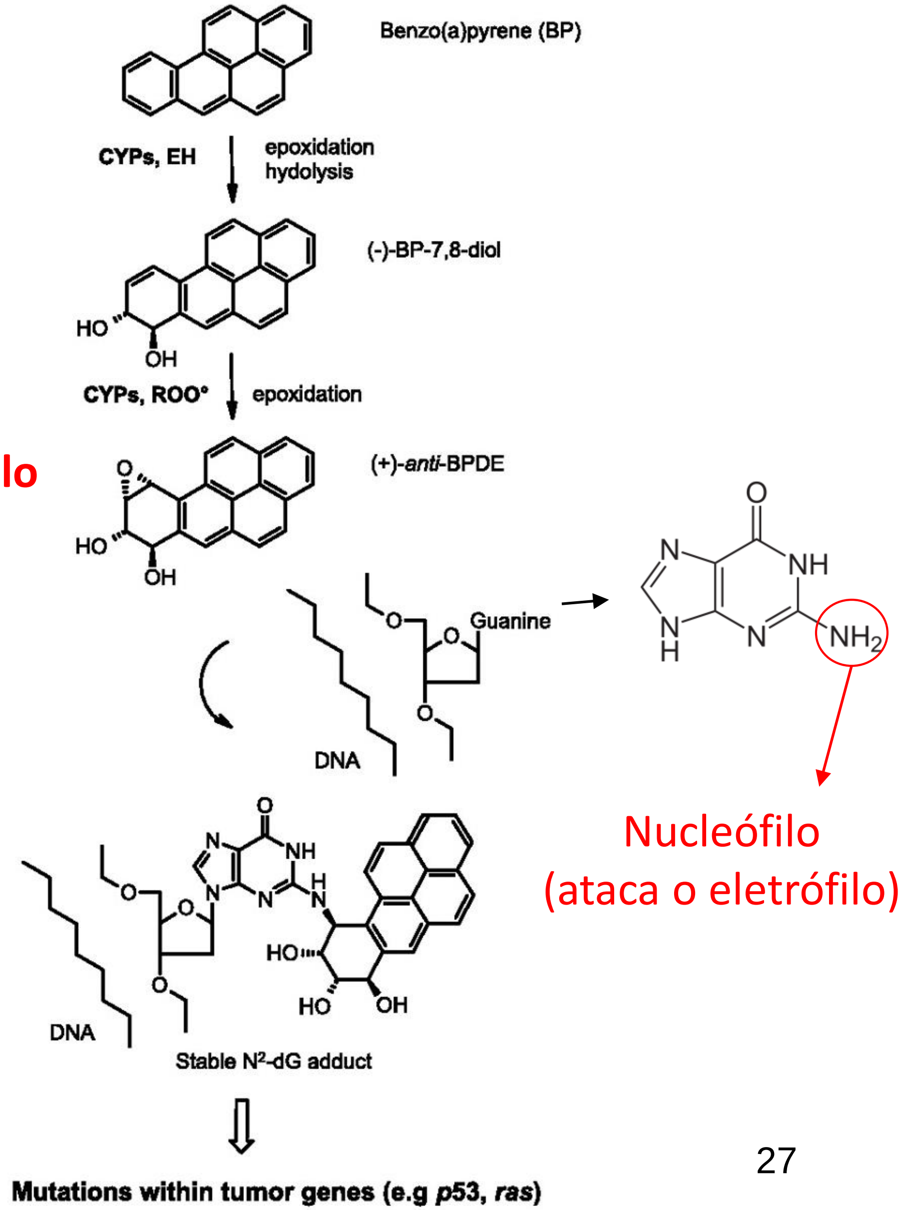
BQ, benzoquinone;
DH, benzene dihydrodiol dehydrogenase;
EH, microsomal epoxide hydrolase;
MPO, myeloperoxidase.

Smith M. T. The mechanism of benzene-induced leukemia: a hypothesis and speculations on the causes of leukemia. *Environ. Health Perspect.*, **104(Suppl. 6)**: 1219-1225, 1996.

O alcatrão é uma mistura de mais de 4000 substâncias.



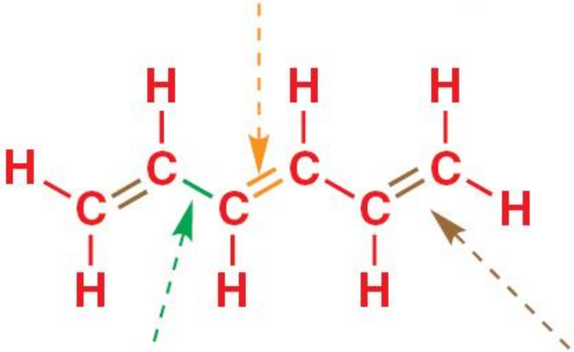
Benzopireno
(um dos constituintes do alcatrão)



eletrófilo

Nucleófilo
(ataca o eletrófilo)

Bond lenght for C=C of benzene



this double bond is 137 pm

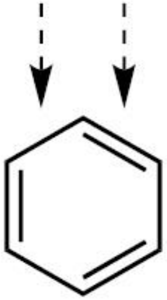
both single bonds are 146 pm

both end double bonds are 134 pm

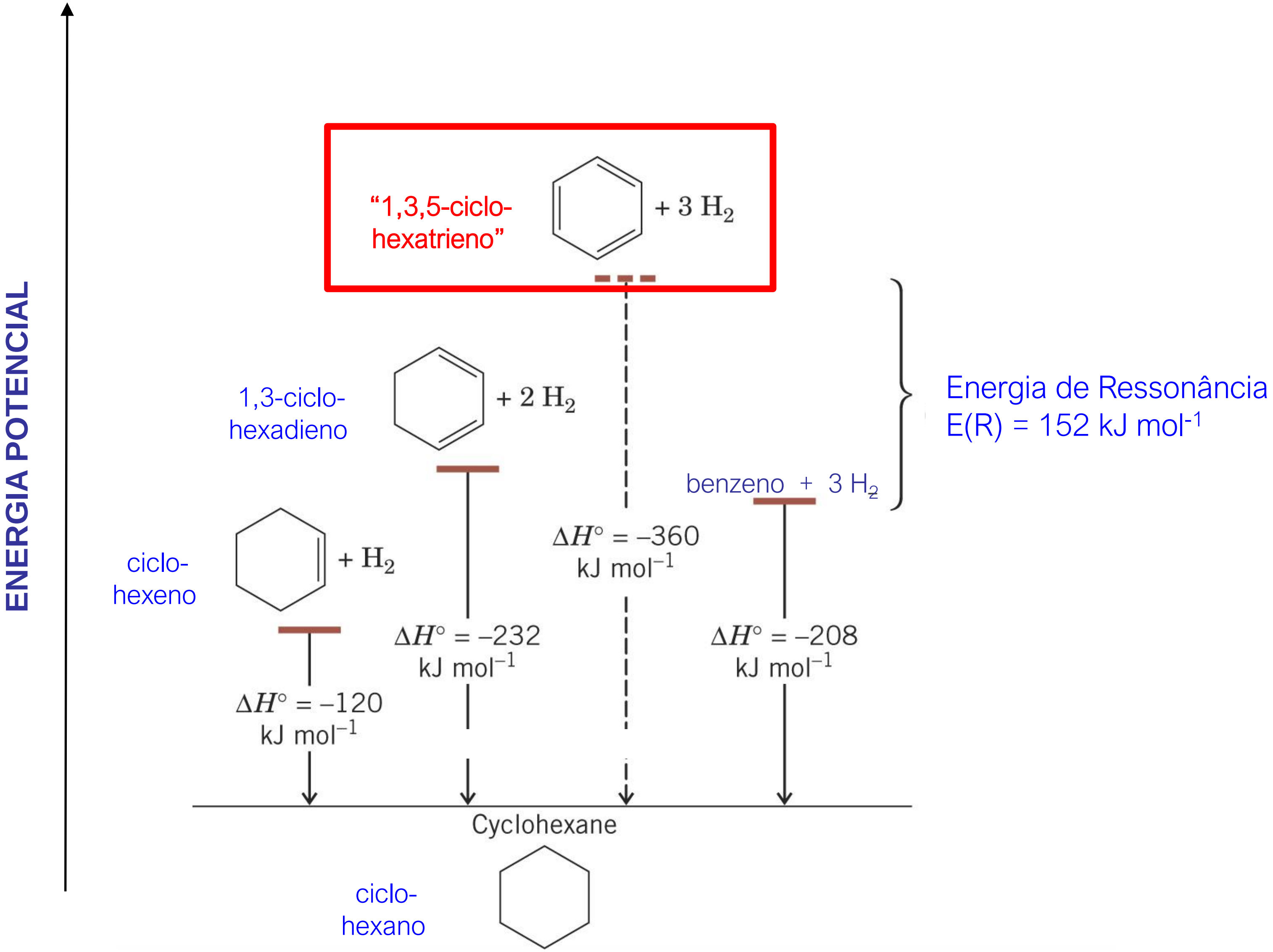
typical values:

single bond: 154 pm
double bond: 134 pm

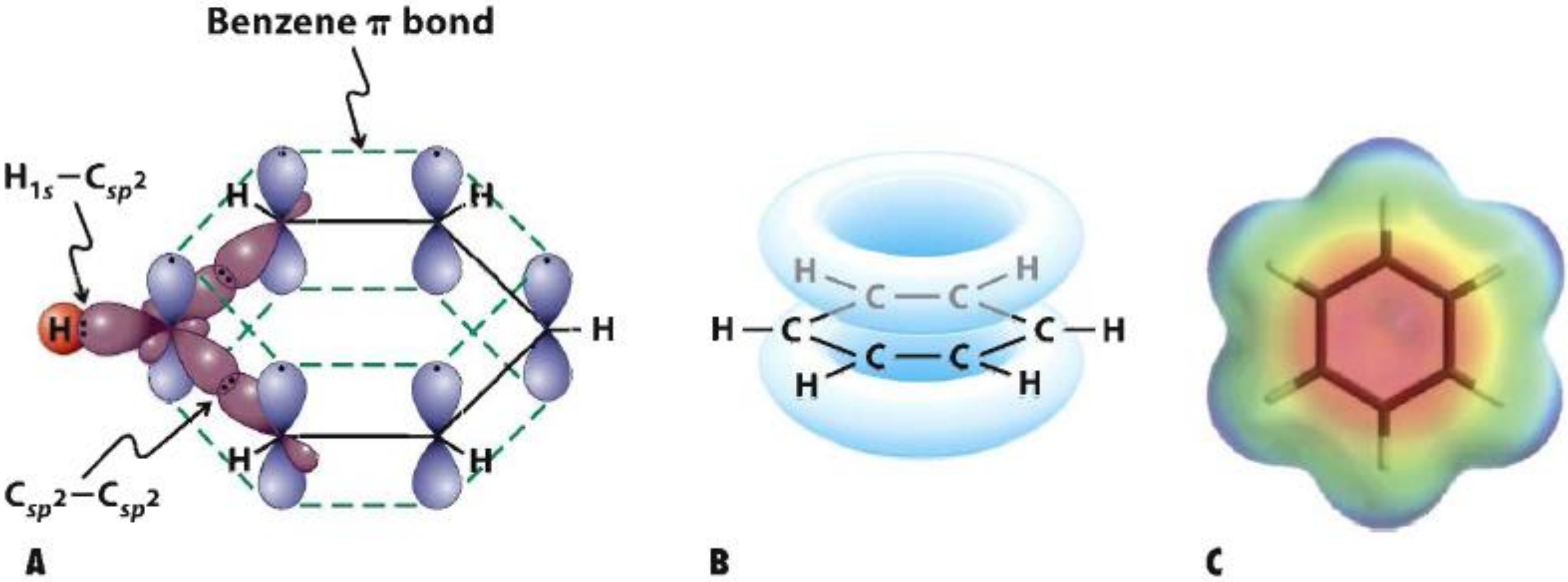
All C–C bonds 139.5 pm



Aromaticidade - estabilidade

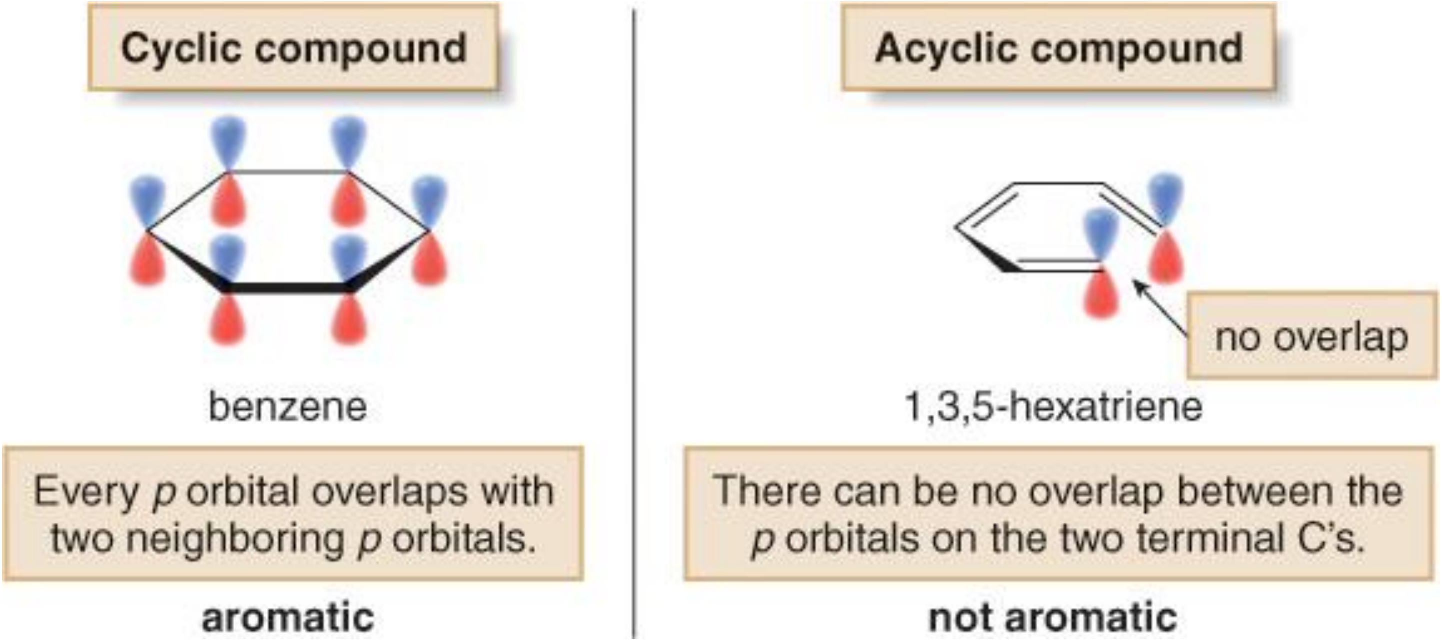


Orbitais do benzeno



Critérios para aromaticidade

1. O composto deve ter uma nuvem cíclica e ininterrupta de elétrons π



Cyclic compound

benzene

Every *p* orbital overlaps with two neighboring *p* orbitals.

aromatic

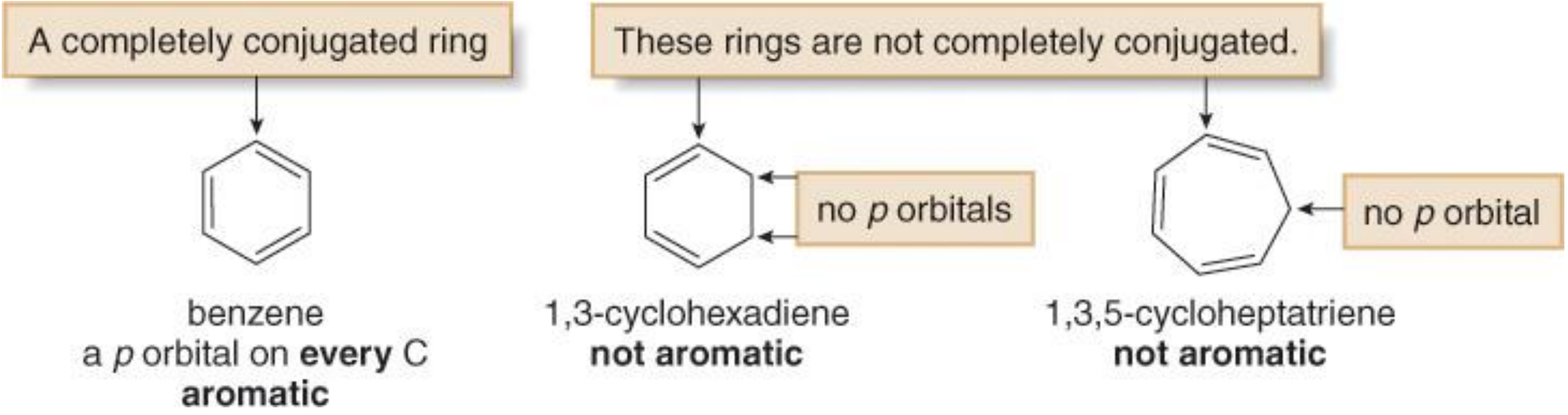
Acyclic compound

1,3,5-hexatriene

There can be no overlap between the *p* orbitals on the two terminal C’s.

not aromatic

1. O composto deve ter uma nuvem cíclica e ininterrupta de elétrons π (ser completamente conjugada)



A completely conjugated ring

These rings are not completely conjugated.

no *p* orbitals

no *p* orbital

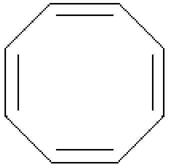
benzene
a *p* orbital on **every** C
aromatic

1,3-cyclohexadiene
not aromatic

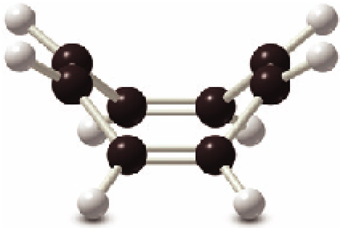
1,3,5-cycloheptatriene
not aromatic

Critérios para aromaticidade

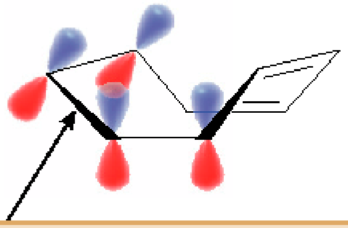
2) Além da sobreposição de orbitais p, a molécula deve ser planar.



cyclooctatetraene
not aromatic

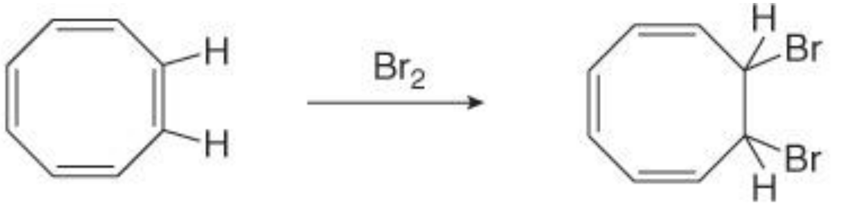


a tub-shaped,
eight-membered ring



Adjacent *p* orbitals cannot overlap.
Electrons cannot delocalize.

Since cyclooctatetraene is non-planar, it is not aromatic, and it undergoes addition reactions just like those of other alkenes.



cyclooctatetraene

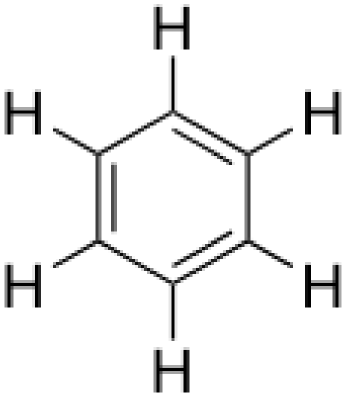
addition product

Critérios para aromaticidade

3) Deve cumprir com a Regra de Hückel ($4n + 2$)

Para uma substância cíclica planar ser aromática, sua nuvem π ininterrupta deve conter ($4n + 2$) elétrons π, onde n é um número inteiro qualquer

2 elétrons π	($n = 0$)	1 par
6 elétrons π	($n = 1$)	3 pares
10 elétrons π	($n = 2$)	5 pares
14 elétrons π	($n = 3$)	7 pares



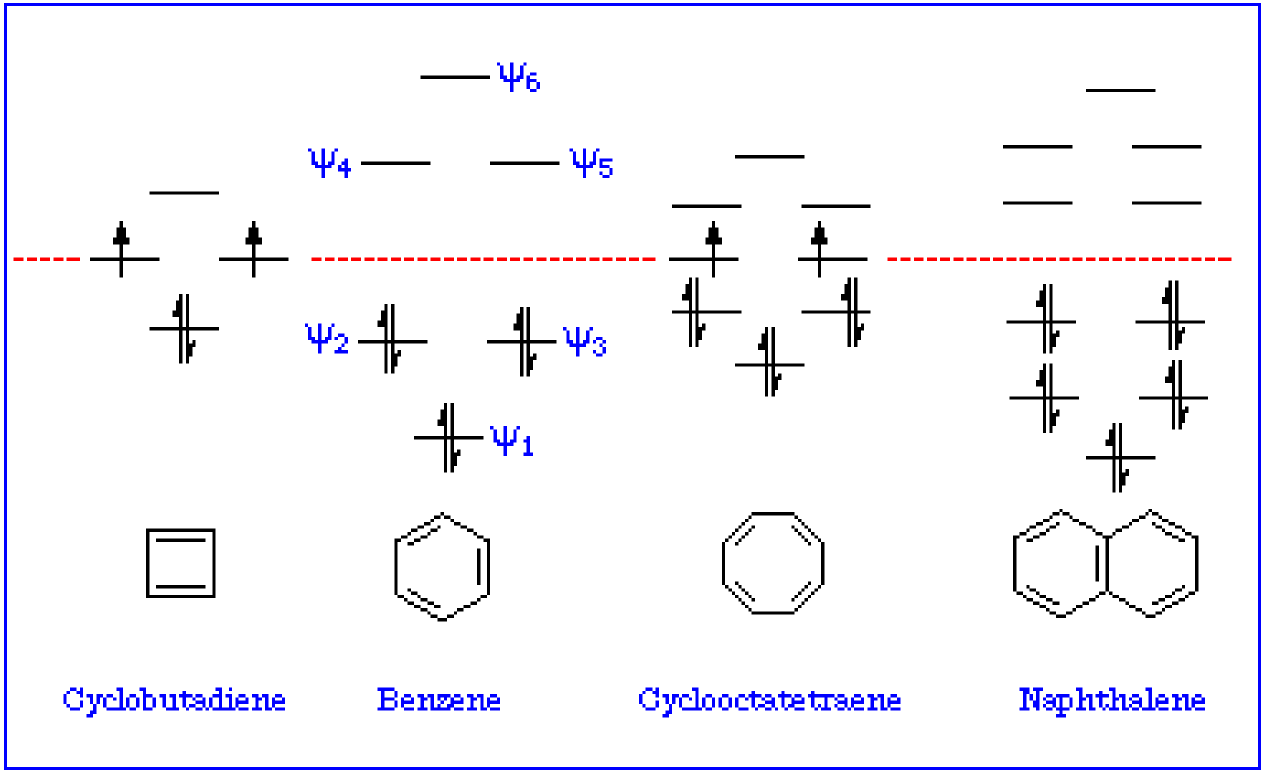
$$4n + 2 = \mathbf{6}$$

The term '**antiaromaticity**' was first proposed by Ronald Breslow in 1967 as "a situation in which a cyclic delocalisation of electrons is destabilising"

The IUPAC criteria for antiaromaticity are as follows:

1. The molecule must be cyclic.
2. The molecule must be planar.
3. The molecule must have a complete conjugated π-electron system within the ring.
4. The molecule must have ***4n*** π-electrons where *n* is any integer within the conjugated π-system.

Huckel rules and aromatic stabilization



Huckel rule
4n + 2

(6 e, n=1)

(10 e, n=2)

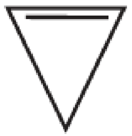
Huckel rule
4n

(4 e)

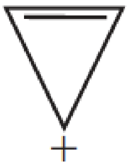
(8 e, n=2)

Comparing Aromaticity, Antiaromaticity and Non-aromaticity

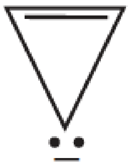
	Aromatic	Antiaromatic	Non-aromatic
Cyclic?	Yes	Yes	Will fail at least one of these
Has completely conjugated system of p orbitals in ring of molecule?	Yes	Yes	
Planar?	Yes	Yes	
How many π electrons in the conjugated system?	4n+2 (i.e., 2, 6, 10, …)	4n (4, 8, 12, …)	N/A



cyclopropene



cyclopropenyl
cation



cyclopropenyl
anion

Ciclopropeno: não aromático

- não tem um anel ininterrupto de átomo que contenham orbitais *p*
- um dos átomos do anel tem hibridização *sp*^{3} (somente carbonos hibridizados *sp*^{2} e *sp* têm orbitais *p*)

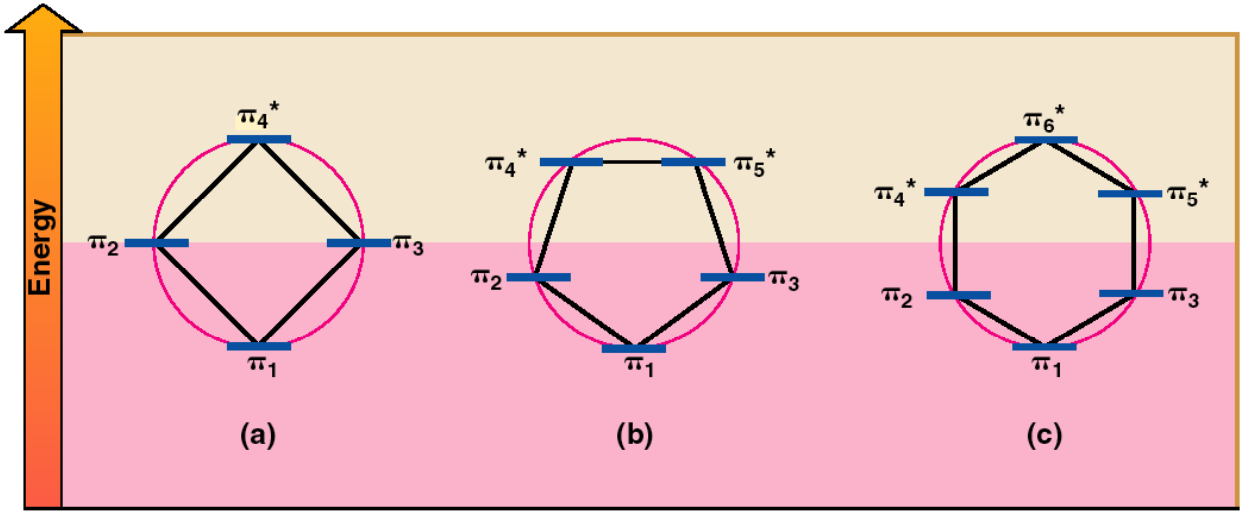
Cátion ciclopropeno: aromático

- tem um anel ininterrupto de átomo que contenham orbitais *p*
- a nuvem π contém um (número impar) par de elétrons π deslocalizados (4n+2) (n=0)

Ânion ciclopropeno: anti-aromático

- sua nuvem π tem dois (número par) pares de elétrons π deslocalizados **(4n)**

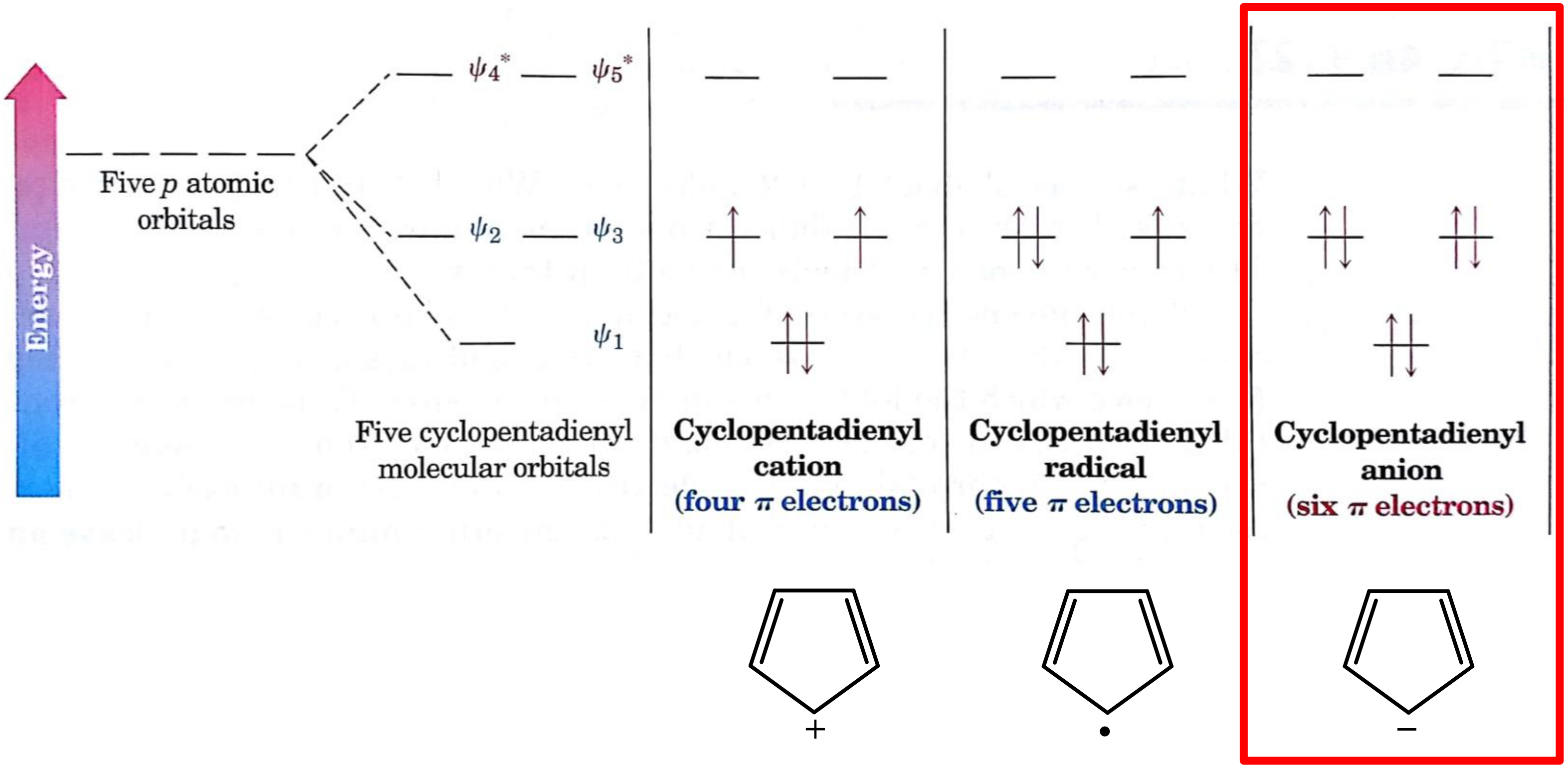
Frost Circles



Frost circles for four, five and six fully conjugated, monocyclic systems.

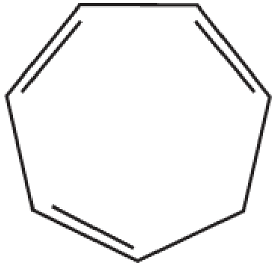
A. A. Frost [J. Chem. Phys., 1953, 21, 572

Energy levels of the five cyclopentadienyl molecular orbitals. Only the six-π-electron cyclopentadienyl anion has a filled-shell configuration leading to aromaticity.



Anti aromatic

aromatic

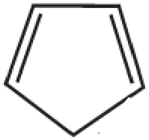


cycloheptatriene

Não aromático

Apesar de ter 6 elétrons π

O anel está interrompido por um C sp_3



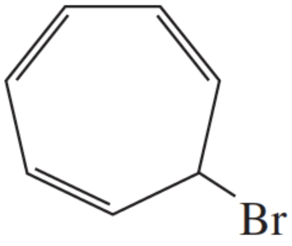
cyclopentadiene

Não aromático

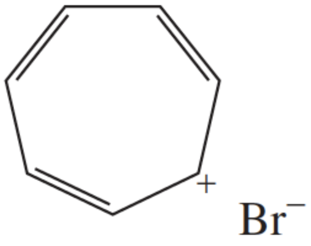
número par

de pares de elétrons π

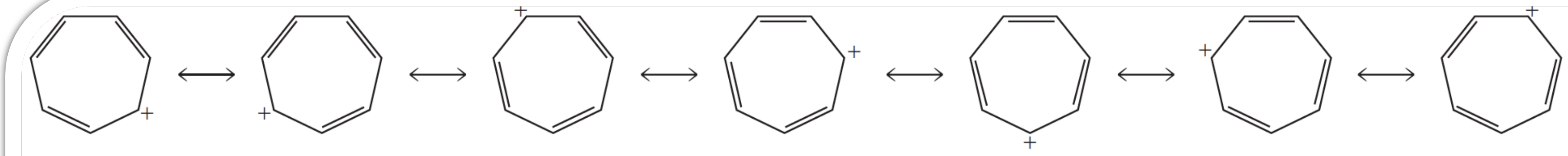
Cation *tropylium*



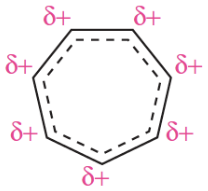
covalent
cycloheptatrienyl bromide



ionic
cycloheptatrienyl bromide
tropylium bromide



resonance contributors of the cycloheptatrienyl cation

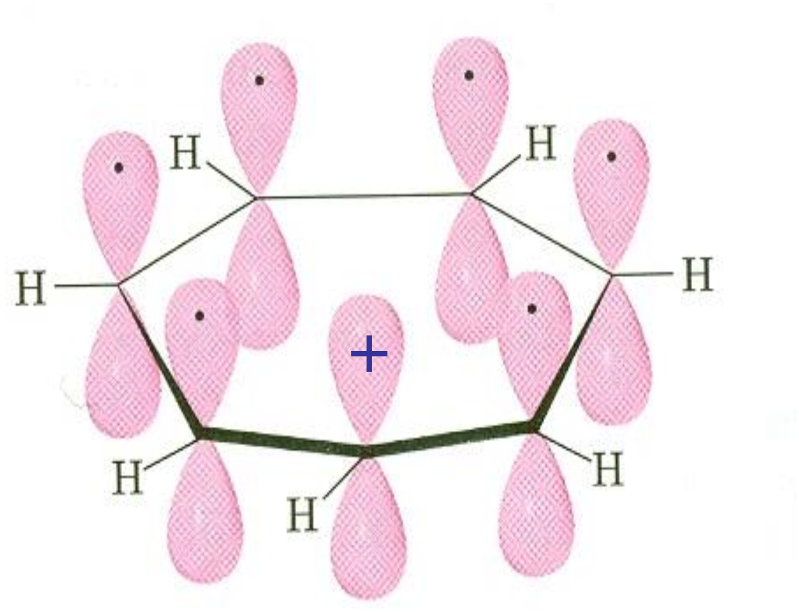


resonance hybrid

Cycloheptatrienyl Cation

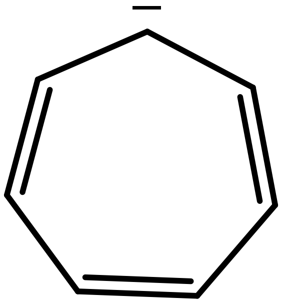
- The cycloheptatrienyl cation has six pi electrons

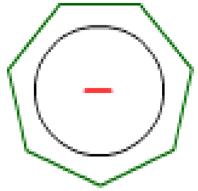
- Its radical and anion have seven and eight pi electrons, respectively (not Huckel numbers)

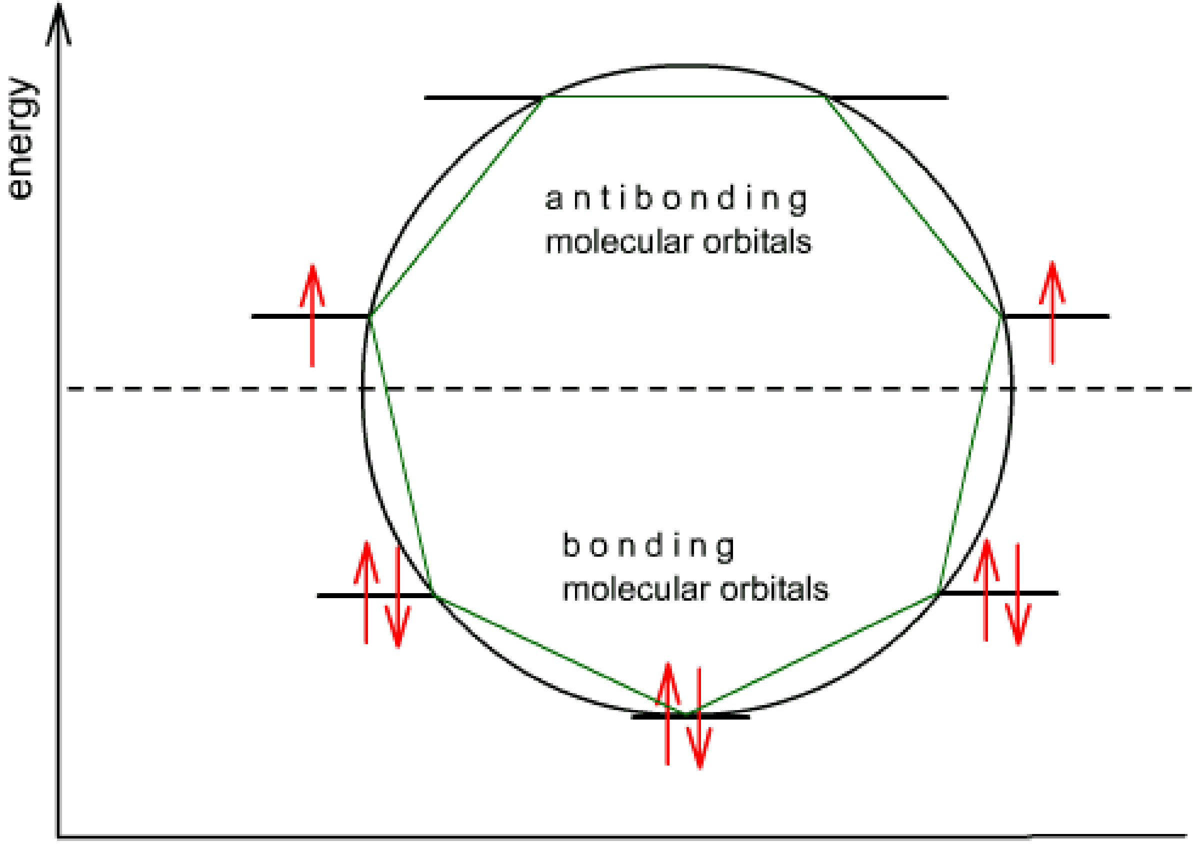


Cycloheptatrienyl cation
six π electrons

What about cyclopentatrienyl anion?





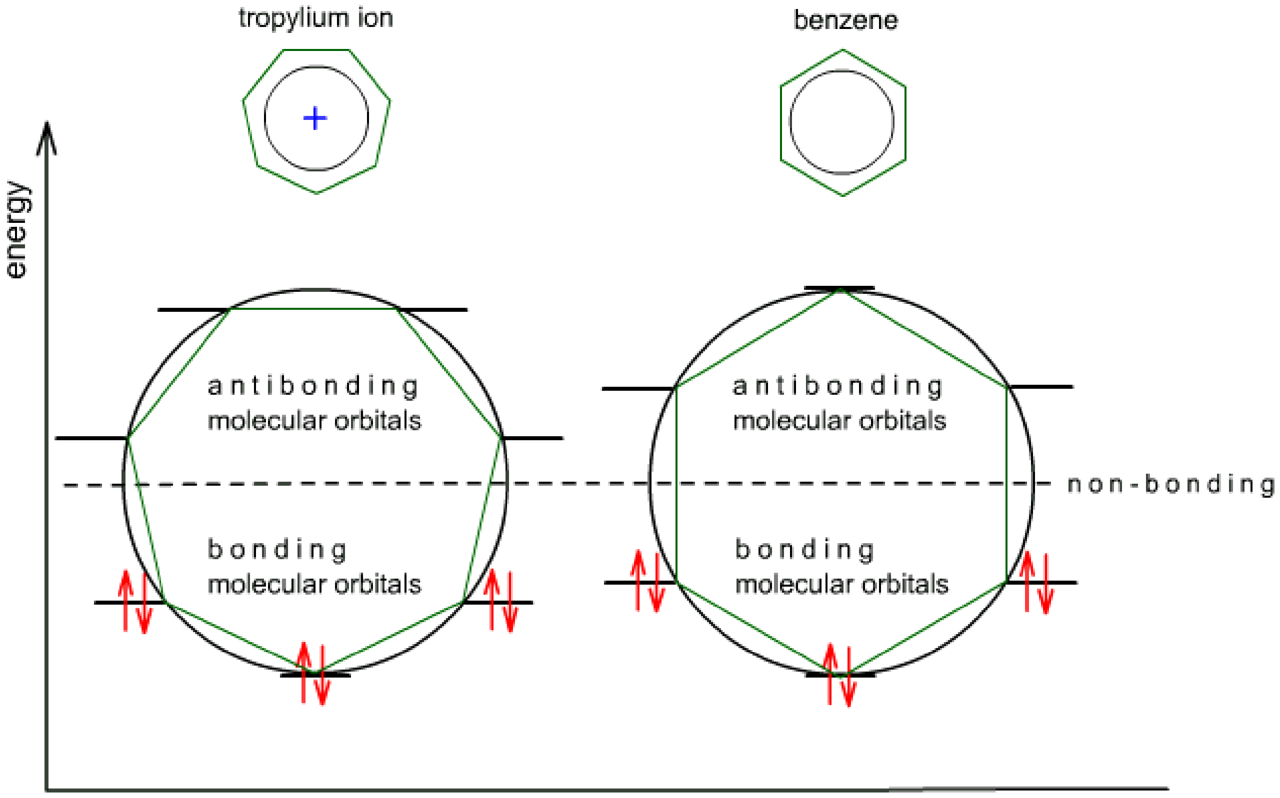


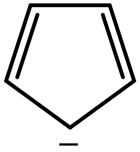
8 electrons π
(4n) (n=2)
(Antiaromático)

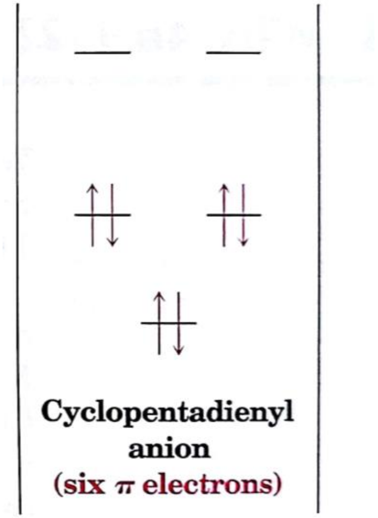
tropylium ion

benzene

cyclopentadienyl anion

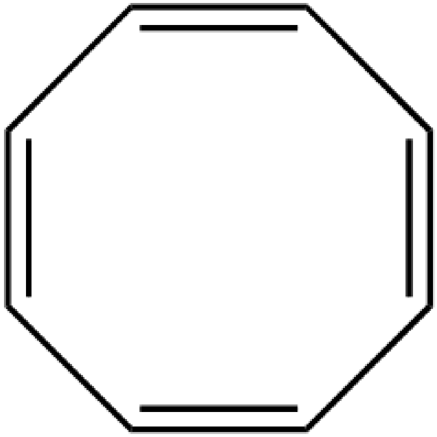






Examples of aromatic compounds in the Frost circle.

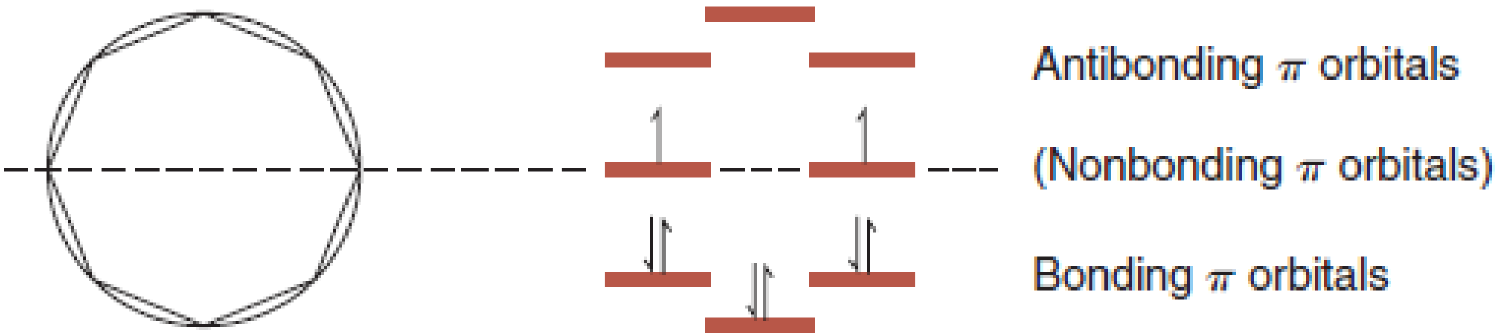
Is cyclooctatetraene aromatic?



Huckel’s rule ?

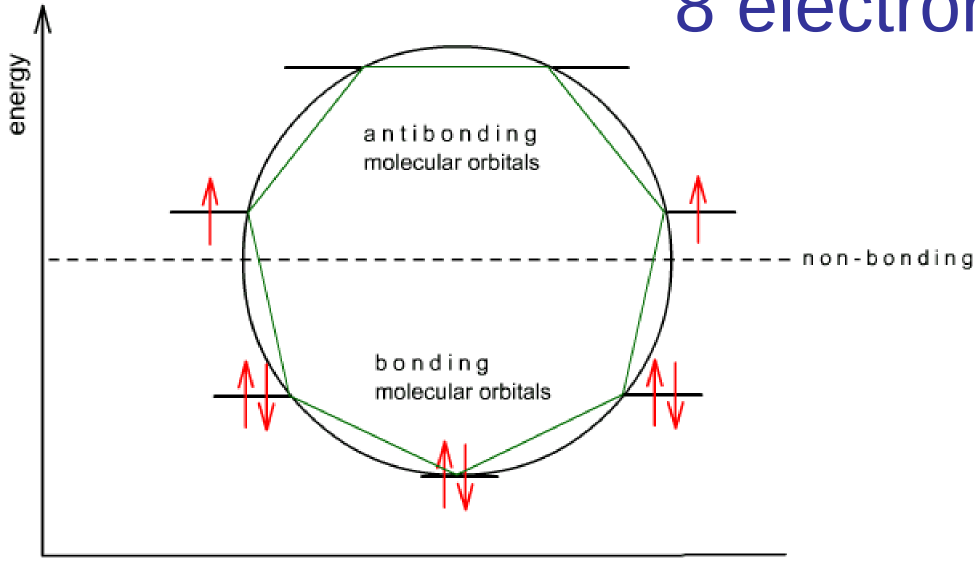
Cycloctatetraene

8 electrons



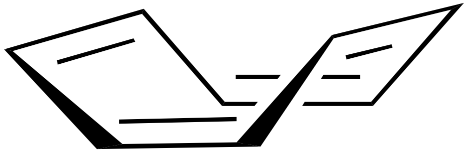
Cycloheptatriene anion

8 electrons

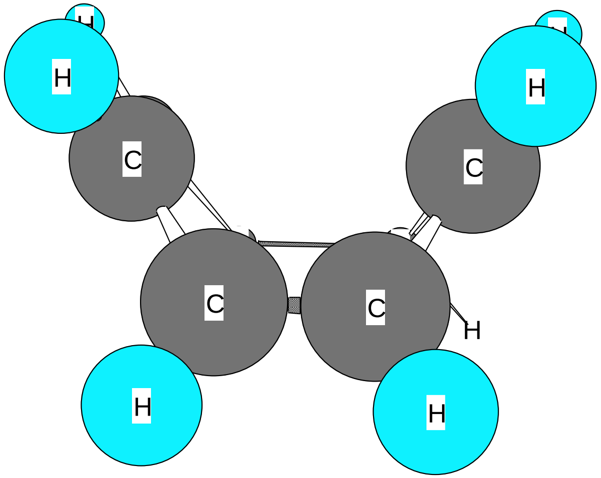


Cyclooctatetraene:

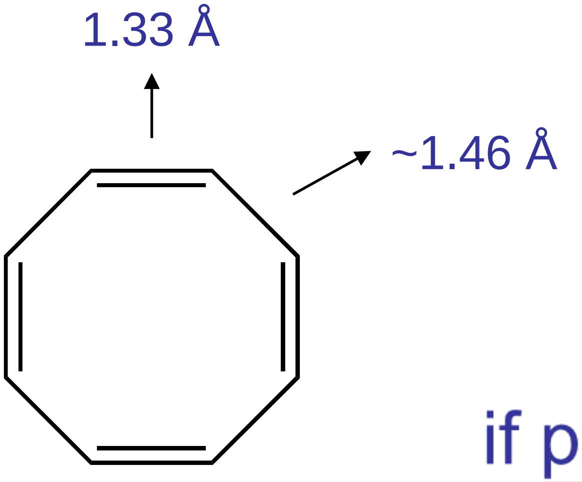
- Cyclooctatetraene: not a planar molecule and therefore **not aromatic** either.



Cyclooctatetraene
8π electrons
non aromatic

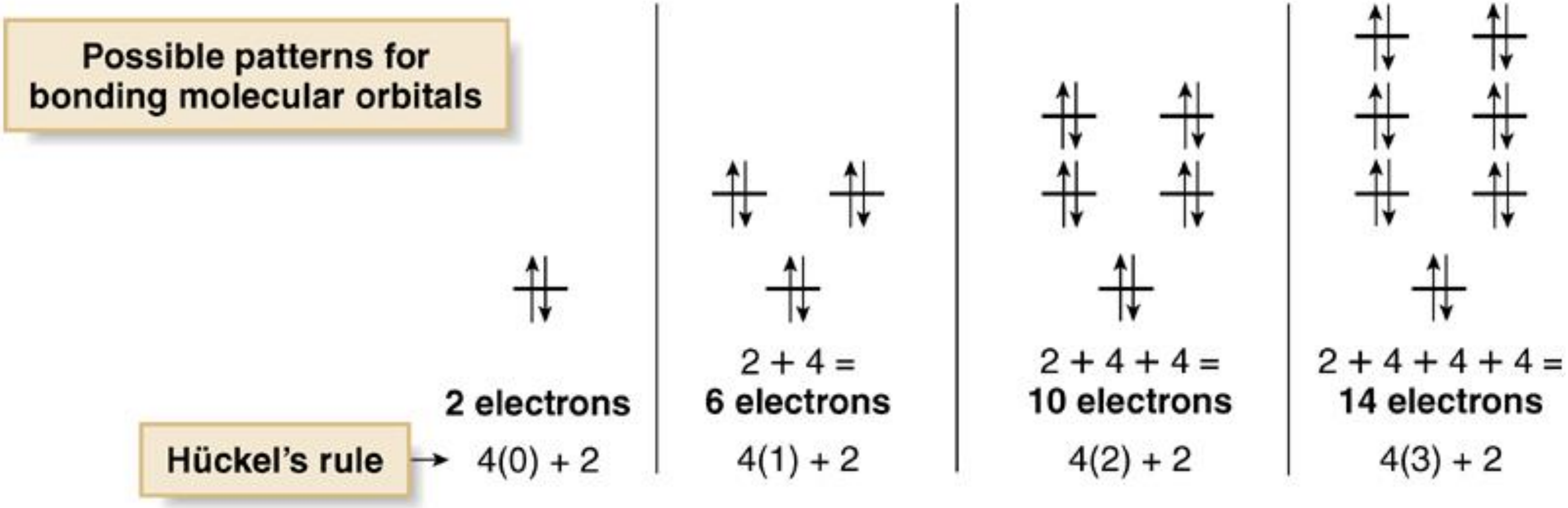


Cyclooctatetraene
8π electrons
Side view



if planar cyclooctatetraene existed it would be classified as antiaromatic.

MO patterns for cyclic, completely conjugated systems



Possible patterns for bonding molecular orbitals

2 electrons

4(0) + 2

2 + 4 =
6 electrons

4(1) + 2

2 + 4 + 4 =
10 electrons

4(2) + 2

2 + 4 + 4 + 4 =
14 electrons

4(3) + 2

Hückel's rule →

MOs completely filled with electrons, so the “magic numbers” for aromaticity fit Hückel’s 4*n* + 2 rule.

HÜCKEL 4n+2 RULE

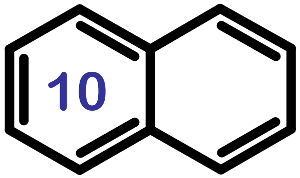
Prediction: Compounds that have 4n+2 pi electrons in a cyclic array will be aromatic.

4n+2 series = 2, 6, 10, 14, 18, 22, 26, 30 …….. etc.

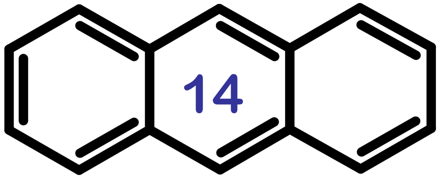
The rule was derived by observation of

POLYCYCLIC AROMATIC COMPOUNDS

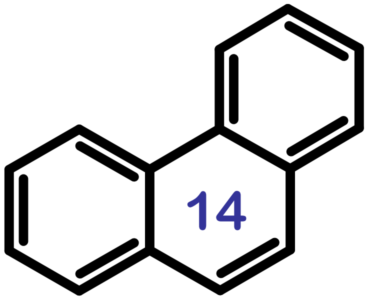
benzene

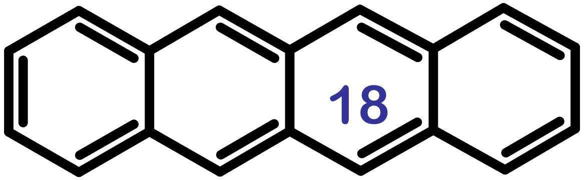


naphthalene

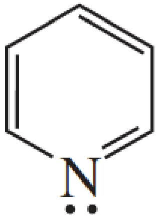


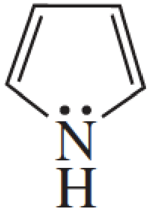
anthracene

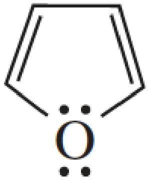


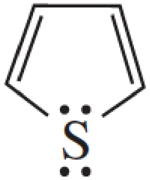


Substâncias **heterocíclicas** aromáticas

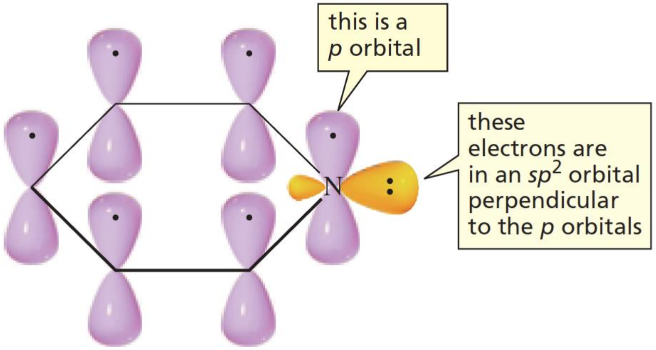

pyridine


pyrrole


furan


thiophene

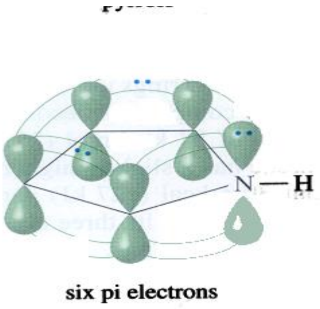
Substância heterocíclica: composto cíclico onde pelo menos um dos átomos do anel é um átomo diferente do carbono.



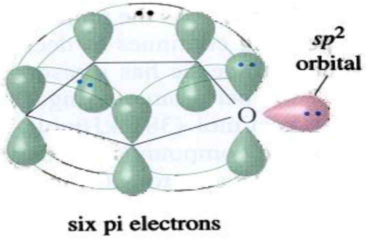
this is a *p* orbital

these electrons are in an sp^2 orbital perpendicular to the *p* orbitals

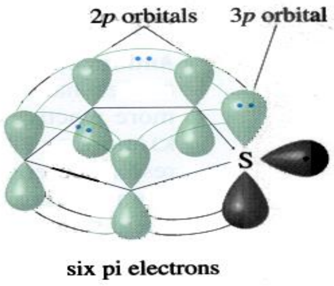
orbital structure of pyridine



pyrrole

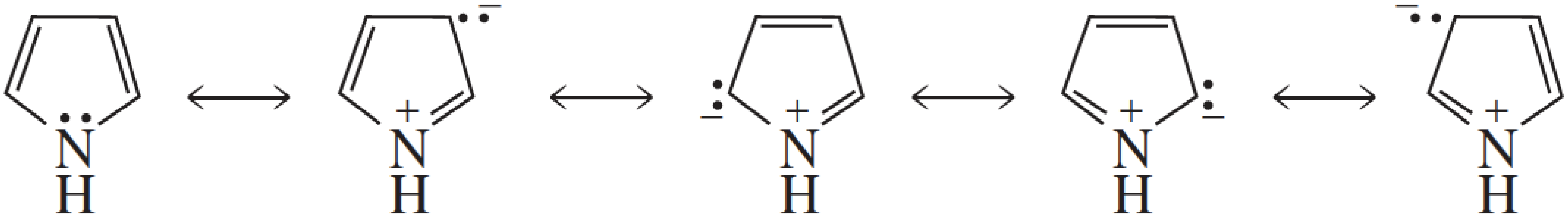


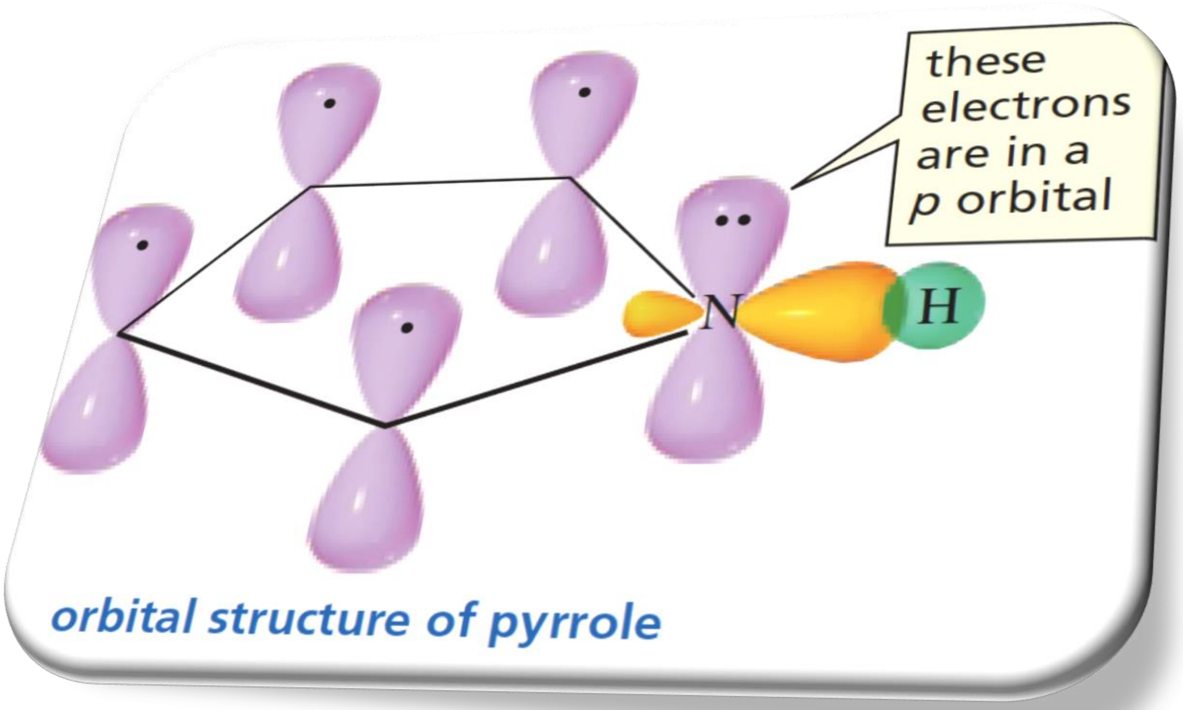
furan



thiophene

Pirrol é aromático

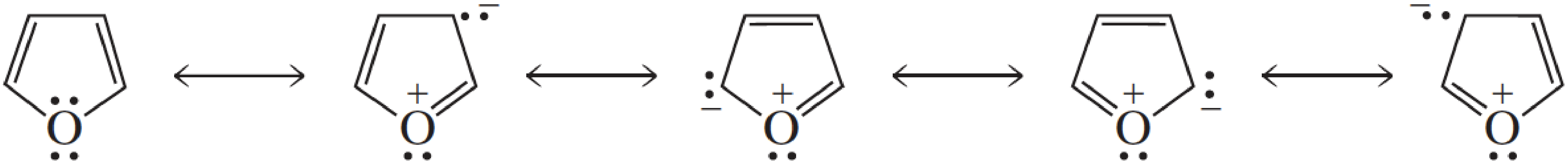


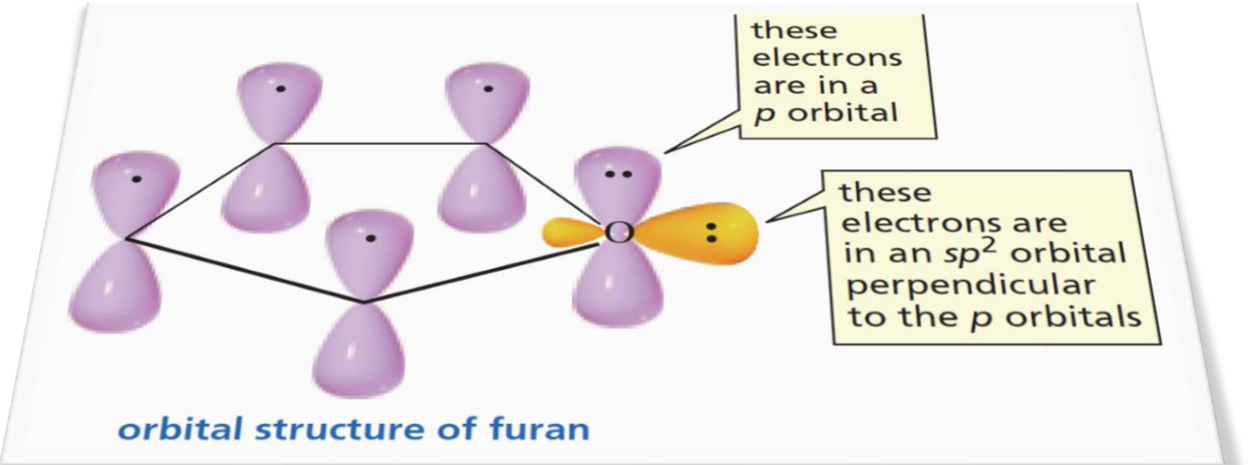


these electrons are in a *p* orbital

orbital structure of pyrrole

Furano é aromático



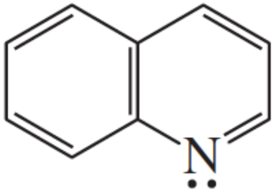


these electrons are in a *p* orbital

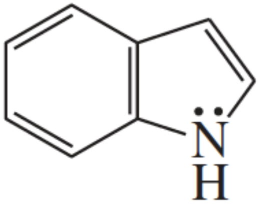
these electrons are in an sp^2 orbital perpendicular to the *p* orbitals

orbital structure of furan

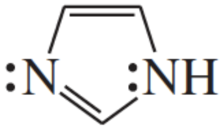
Exemplos de outras substâncias heterocíclicas aromáticas:



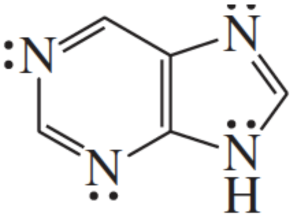
quinoline



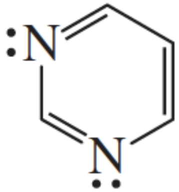
indole



imidazole

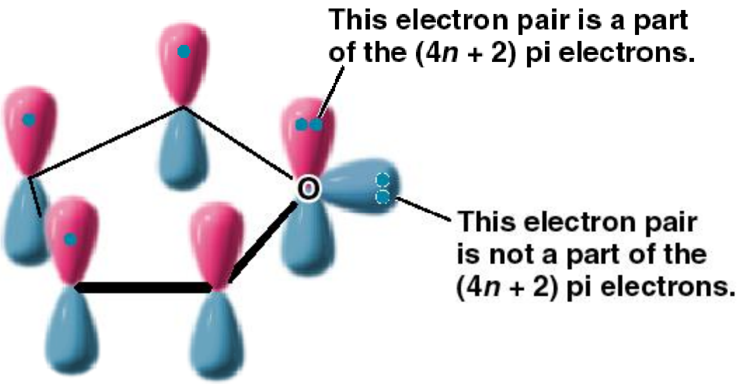


purine

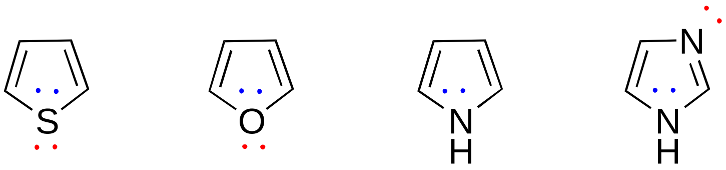


pyrimidine

- The five membered systems, pyrrole, imidazole, thiophene and furan are also aromatic. In these systems, additional *heterocycles,* an unshared pair of electrons participates in the aromatic system.

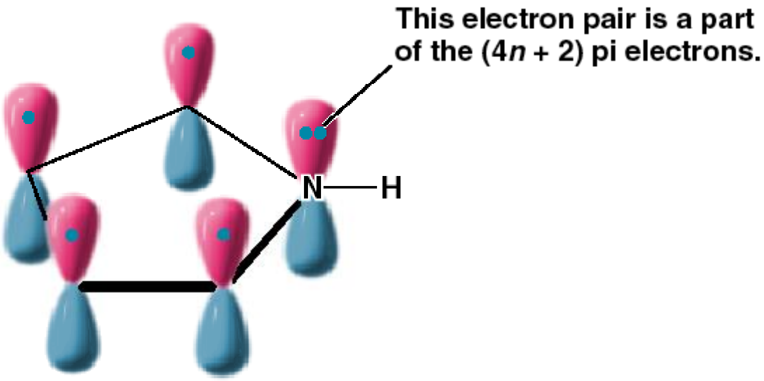


Furan

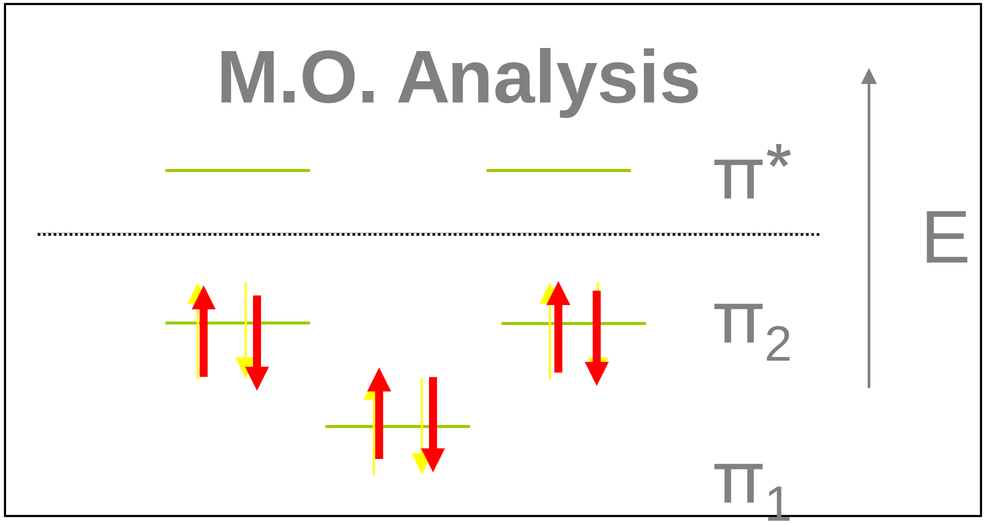


red electron pair does not participate in the aromatic pi system

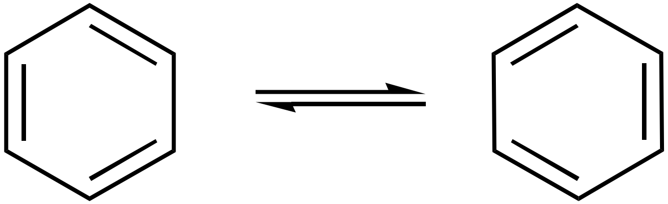
blue electran pair participates in aromatic system

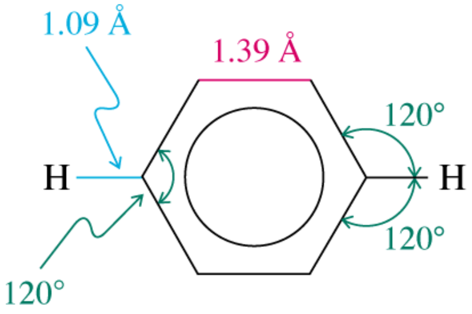


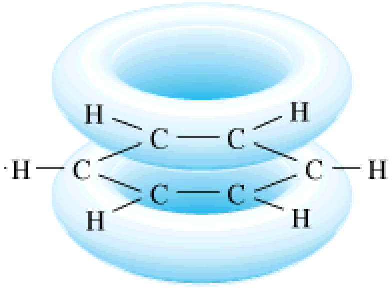
Pyrrole



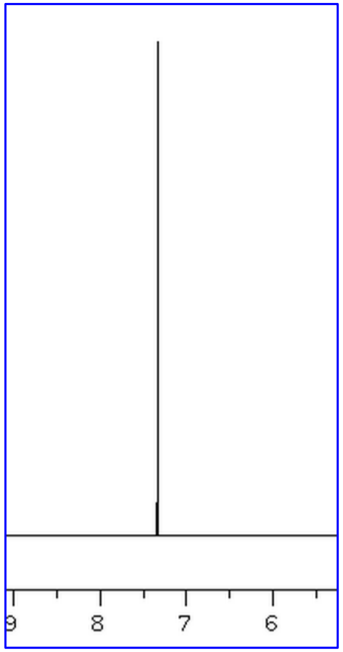
Evidências da circulação eletrônica na estrutura do benzeno (híbrido de ressonância) por RMN







One single signal at 7.2 δ



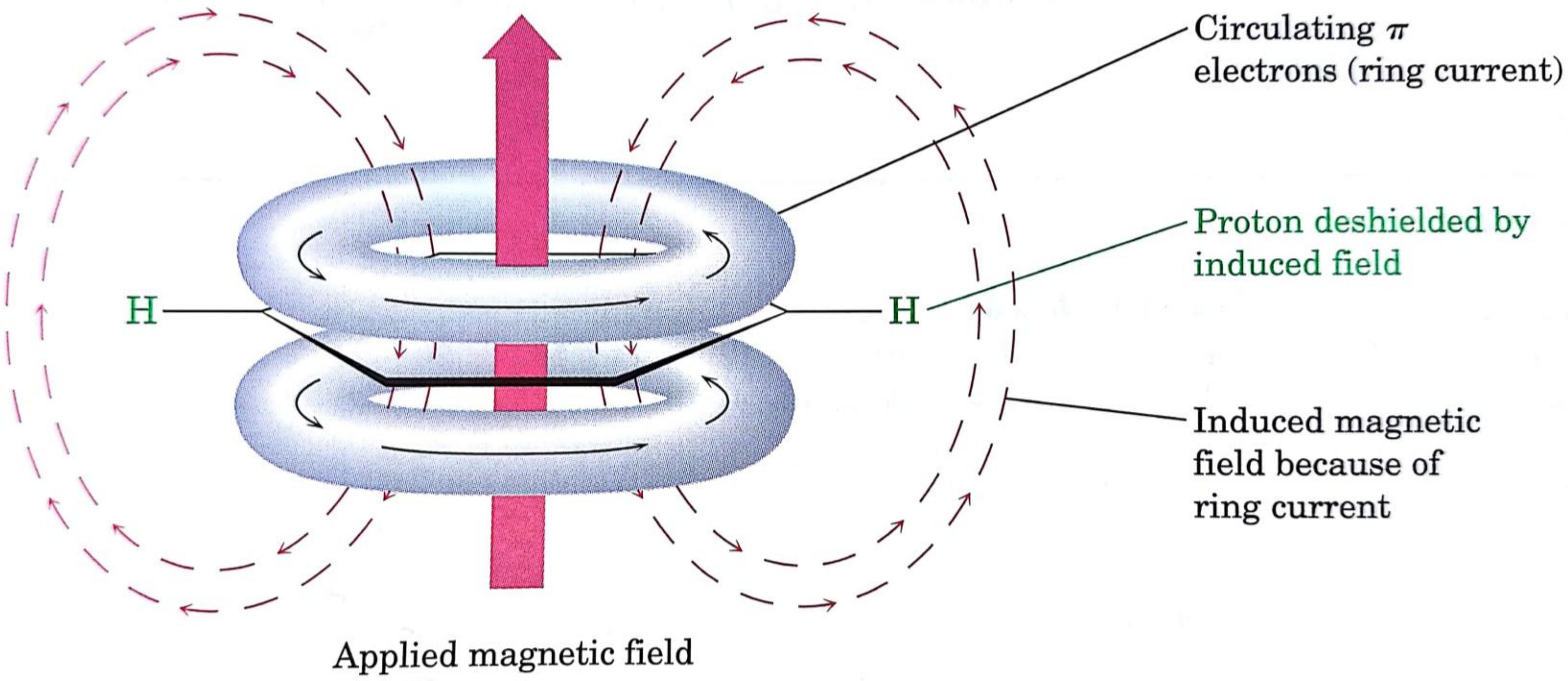
^{1}H NMR spectrum of benzene

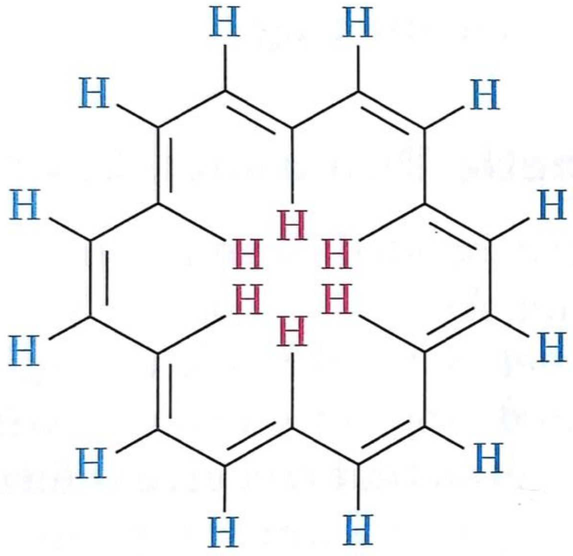
^{1}H NMR: the most powerful spectroscopic analysis to determine the substitution pattern of aromatic compounds

Evidências da circulação eletrônica na estrutura do benzeno por RMN

The origin of aromatic ring current. Aromatic protons are deshielded by the induced magnetic field caused by delocalized π electrons circulating in the molecular orbitals of the aromatic ring.

7.2 δ

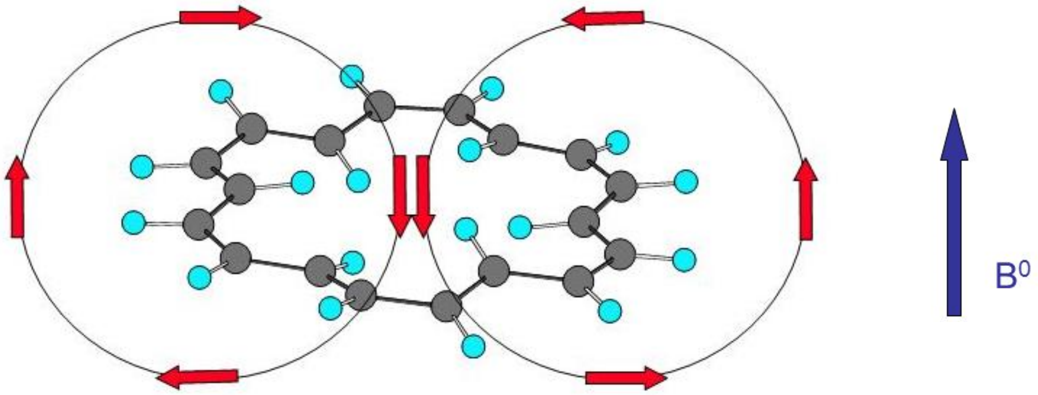




[18]Annulene

Inside H: −3.0 δ

Outside H: 9.3 δ



Direction of magnetic field

Reações do benzeno

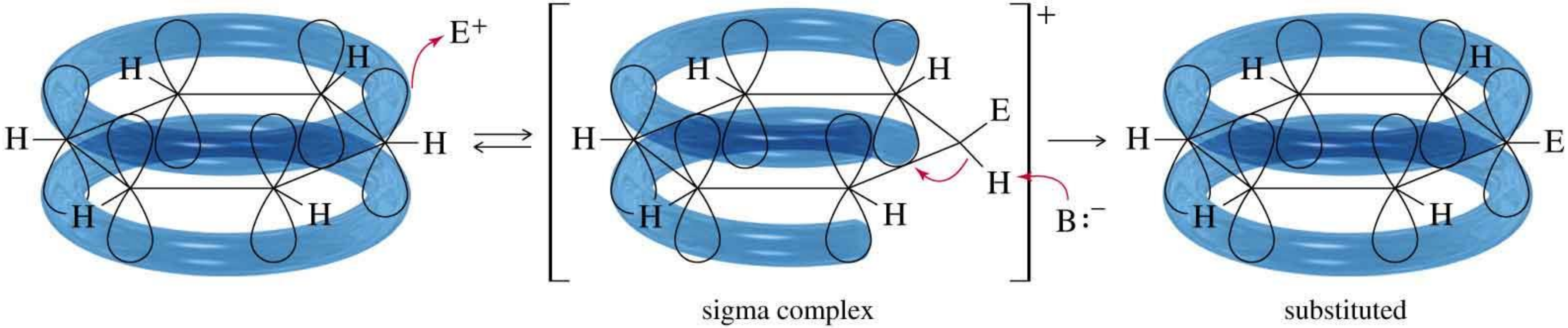
Reações de substituição eletrofílica aromática

Reações de substituição nucleofílica aromática

São afetadas pelos substituíntes:

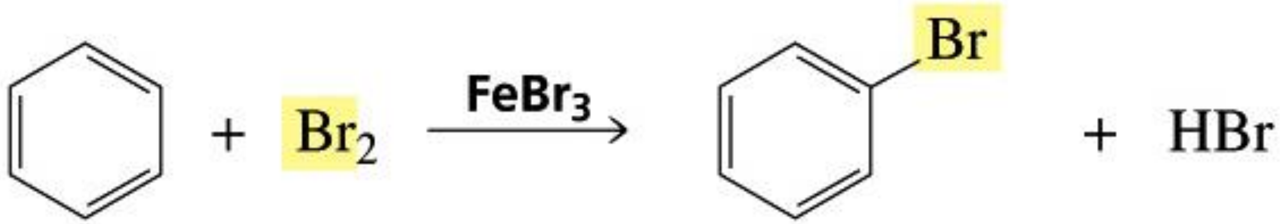
Ressonância e efeitos de ativação e orientação dos grupos substituintes nas reações.

Electrophilic Aromatic Substitution



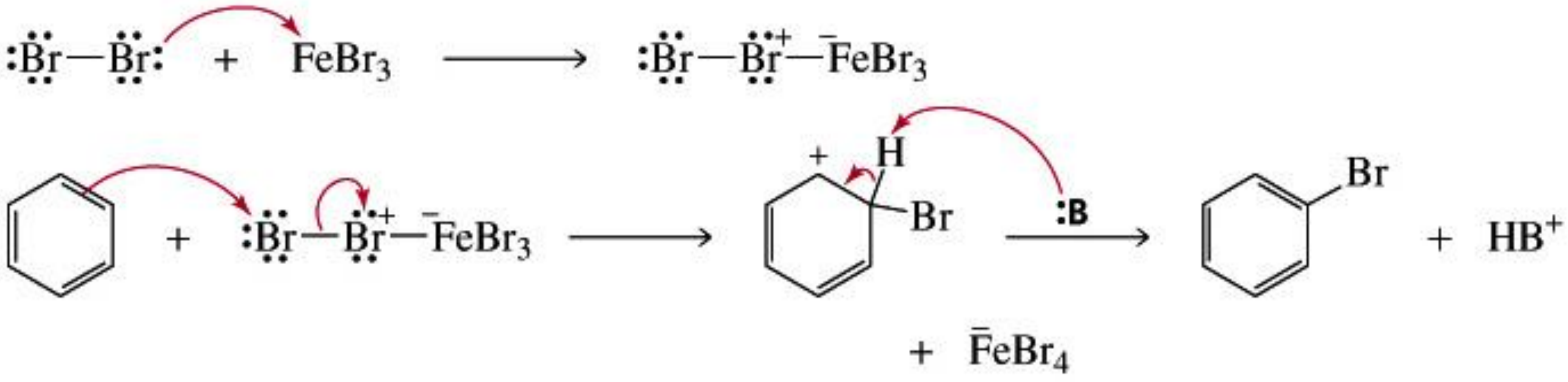
Reações de S_EAr: Halogenação do Benzeno

Bromação:

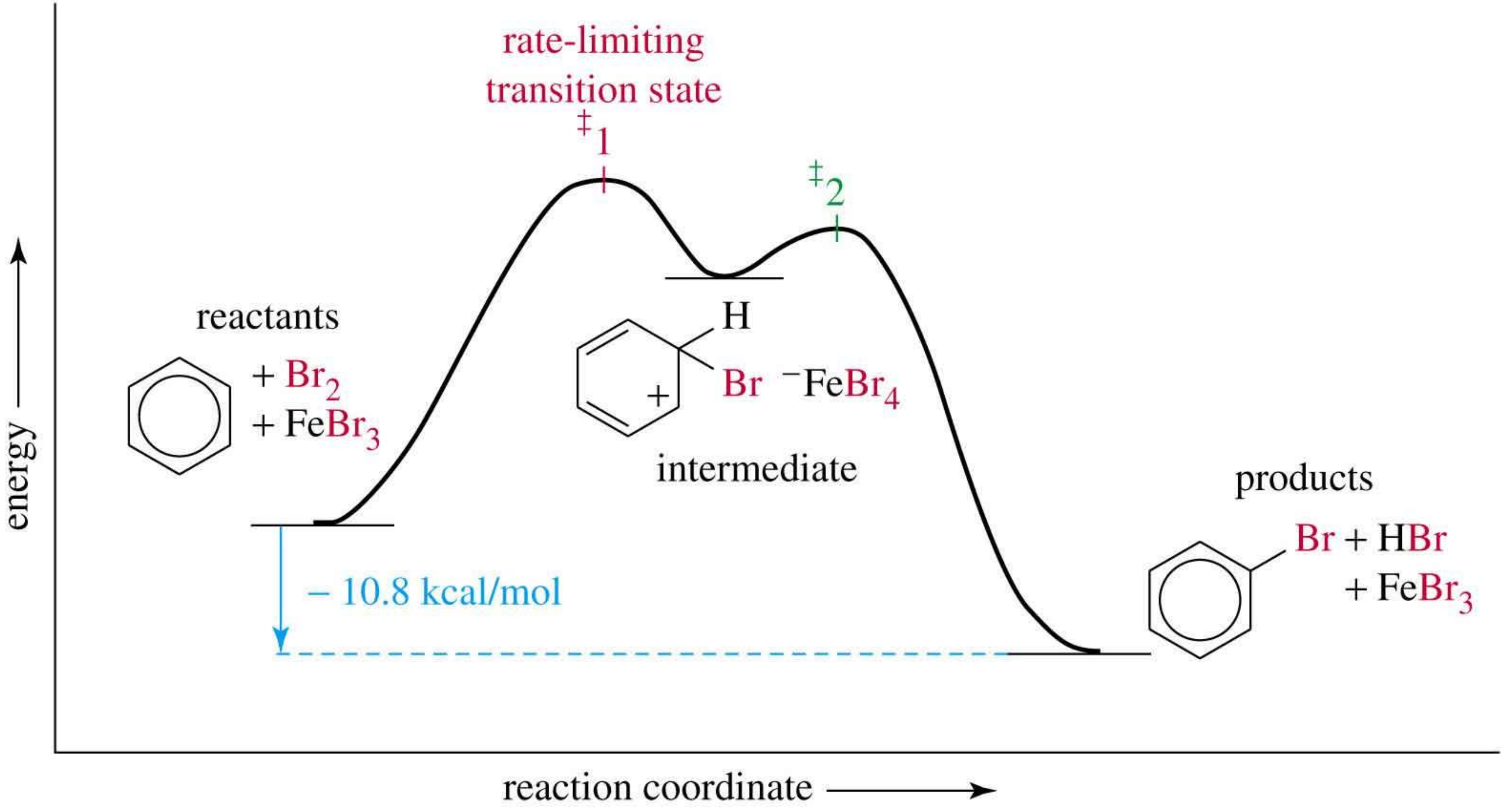


bromobenzene

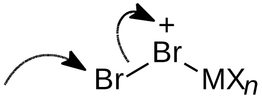
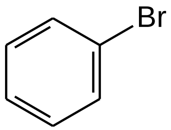
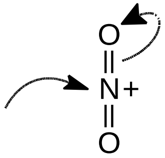
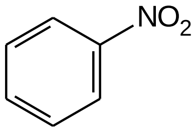
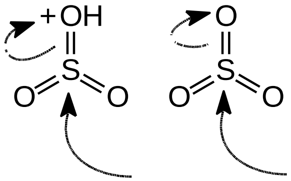
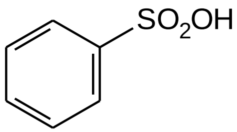
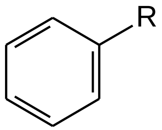
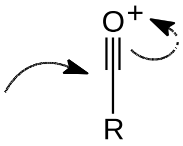
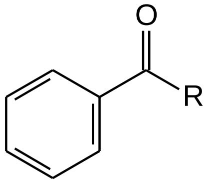
Mecanismo da Bromação:



Energy Diagram for Bromination

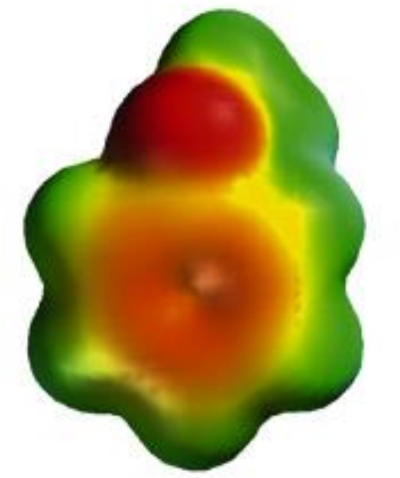


S_EAr: Resumo das Reações

Reação	**Reagente**	**Eletrófilo**	**Produto**
Bromação	Br_2 + ácido de Lewis		
Nitração	HNO_3 + H_2SO_4		
Sulfonação	H_2SO_4 (conc.) ou H_2SO_4 + SO_3		
Alquilação de Friedel-Crafts	RX + ácido de Lewis		
Acilação de Friedel-Crafts	RCOCl + ácido de Lewis		

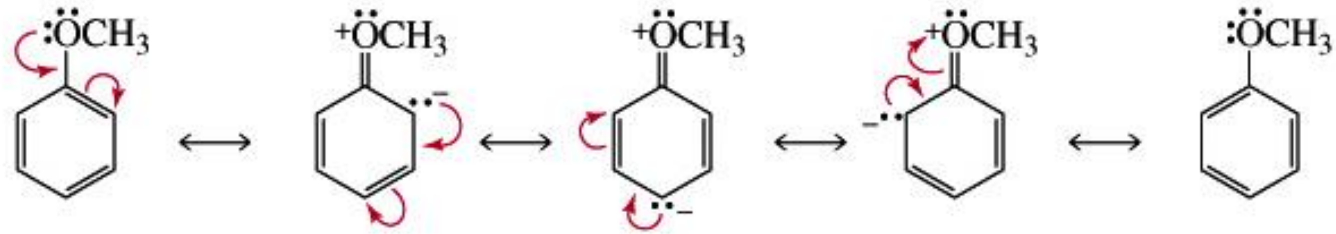
Efeito de Substituintes:

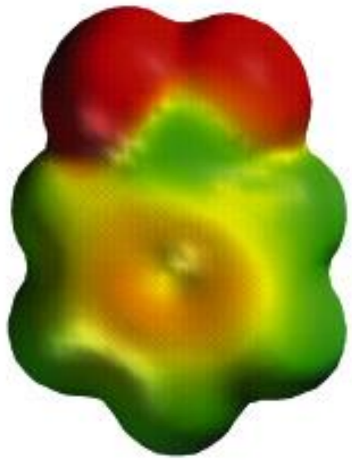
Efeitos de Ressonância



anisole

Doação de elétrons pelo efeito de ressonância (mesomérico)





nitrobenzene

Atração de elétrons pelo efeito de ressonância (mesomérico)