TO BE OR NOT TO BE … AROMATIC?

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Table of contents

## 1. INTRODUCTION

Aromaticity is a topic so vast that only a few features may be touched in a communication within a limited space. The selection of these features will therefore be quite subjective and personal.

A century ago, when chemists measured heats of combustion for non-branched alkanes and terminal alkenes or primary alcohols, they made a remarkable discovery: the difference between combustion heats for two successive members of each homologous series was constant, namely 157.4 kcal/mol (calculated for gaseous state at 25ºC and 1 atm.). Actually, this is the heat of reaction for the combustion of a CH_2 group, by which two homologs differ:

$$CH_2 + 1.5\ O_2 \rightarrow CO_2 + H_2O$$
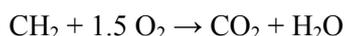
Many other chemical and thermodynamic phenomena taught generations of scientists that additivity was a general phenomenon. However, a few exceptions drew attention and contributed to the development of new theories. One of these exceptions is connected to what theoretical chemists call *conjugation*. The heat of hydrogenation for converting alkenes into alkanes is additive when two or more double bonds are present in the same molecule (28.6 kcal/mol for one double bond in cyclohexene or 1,4-cyclohexadiene), except for the cases when these double bonds have a common carbon atom or are separated by a single bond; in the latter case the double bonds are called *conjugated*. Heats of hydrogenation for conjugated double bonds are

slightly lower than those predicted by additivity, proving that conjugation stabilizes the isomeric 1,3-cyclohexadiene by about 2 kcal/mol (heat of hydrogenation 55.4 kcal/mol). Quite unexpected was what happens with benzene $(CH)_6$, which was first isolated and characterized by Michael Faraday, but had to wait for 40 years till its cyclic structure was deciphered: its cyclohexatriene (or [6]annulene) structure postulated by August Kekulé reveals a comparatively huge stabilization, and this phenomenon gave rise to what chemists call "aromaticity".[1] Using concepts developed by physicists and chemists (Niels Bohr, Linus Pauling, Wolfgang Pauli, Erwin Schrödinger, Erich Hückel) it was shown that delocalized valence electrons are responsible for this deviation from additivity. Similarly to Bohr's postulate for explaining the discrete energy levels in atoms owing to the wave nature of electrons. We now understand that aromatic stabilization requires the presence of an odd number of conjugated double bonds in annulenes, i. e. $4n + 2$ π-electrons in a planar ring (the celebrated Hückel Rule), was confirmed experimentally by Franz Sondheimer who synthesized large-size annulenes. The fact that some of the π-electrons could be supplied by heteroatoms with unshared electron pairs such as N, S, or O in five-membered heterocyclic rings (pyrrole, thiophene, or furan, respectively) had been adumbrated earlier by E. Bamberger. By contrast, annulenes with even numbers of double bonds avoid the corresponding antiaromatic destabilization by adopting non-planar geometries with alternating localized single and double bonds as in [8]annulene synthesized first by Richard Willstätter.

Before Kekulé's time, organic chemists had very few data for characterizing their substances. The first 3-volume edition of *Beistein's Handbuch* is revealing about the scarcity of information, by containing only elemental analyses (no structural formula, and names of compounds originating in the sources where these substances came from). Thus, chemists at that time were drawn to observe that "hydrogen-rich" substances (alkanes, alkyl derivatives) were characterized by additive thermodynamic properties and by a chemical reactivity based on substitution (e. g. of hydrogen by halogens) whereas "hydrogen-poor" substances such as alkenes, alkynes and their derivatives were characterized by addition reactions in which halogens instantly became incorporated into the organic compound. During Kekulé's time, the "carbon enrichment" of organic compounds with tar-extracted structures that belonged to the aromatic family led to the puzzling observation that although these compounds were "hydrogen-poor", they reacted preferentially by substitution and not by addition. Also, their thermodynamic properties were not additive, as shown above. Thus, the whole field of aromaticity was shrouded in mystery, till the advent of electronic theories provided the theoretical framework that we now possess, allowing us to understand aromaticity.

It should be mentioned that the *Chemical Abstracts* database available through *SciFinder* contains about 6×10^8 isolated and characterized compounds; more than 95% are organic compounds based on the element carbon, and among these more than 60% have aromatic moieties. Natural evolution has adopted many structural features benefitting from the enhanced stability of aromatic structures, especially among heterocyclic compounds, which will be discussed in a separate section. First and foremost are all five nucleotide bases (uracil, cytosine, adenine, and guanine in RNA, and thymine, cytosine, adenine, and guanine in DNA), then phenylalanine, tyrosine and tryptophan among amino acids, as well as countless natural products of vegetal or animal origin. The strongest synthetic polymers such as Kevlar and the wonderful electronic properties of graphene also benefit from the sturdiness and stability inherent in their aromatic character.

2. HOW MUCH AROMATICITY FOR A GIVEN CHEMICAL STRUCTURE?

In the 1930s some polycyclic aromatic hydrocarbons (PAHs or benzenoids) were found to be carcinogenic, and theoretical chemists discovered that a necessary but insufficient structural condition for these PAHs was to possess a "bay region", exemplified by benzo[*a*]pyrene. Paradoxically, the carcinogenic activity is due to efforts of cells in higher organisms to eliminate toxic molecules by oxidizing them with cytochrome P450 1A1 and then eliminating them as glycosylated, water-soluble compounds, but in the case of bay region aromatic hydrocarbons this process affords intermediate diol-epoxides. Ring opening of such strained epoxy rings in bay-region PAHs yields stabilized carbocations that interact with DNA and enzymes, and this process ends in the cell becoming malignant (Fig. 1). Thus PAHs became a focal point in biochemical research.[2,3] Graph-theoretical methods were crucial in enumerating all possible bay-region PAHs.[4]
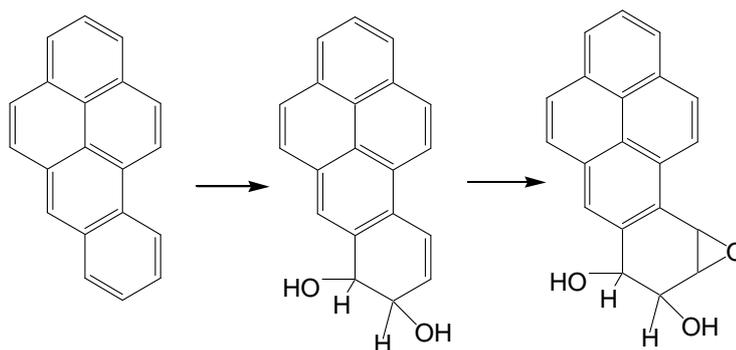
Fig. 1 – Benzo[*a*]pyrene, 7,8-dihydroxy-dihydro-benzo[*a*]pyrene,
and 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-benzo[*a*]pyrene.

For annulenes $(CH)_{2k}$, Erich Hückel's Rule states that aromatic monocyclic hydrocarbons (charged or neutral annulenes) have $4n+2$ π-electrons, and antiaromatic annulenes have $4n$ π-electrons. Whereas Hückel's Rule establishes a "yes-or-no" hierarchy, Eric Clar's approach[5] is more nuanced: the circle representing an aromatic sextet may be shared along an acenic portion of a polycyclic benzenoid so that various rings may have fractions of π-electron sextets, according to the global set of resonance (Kekulé) structures. As a result, the central ring of phenanthrene is entitled to only two of the 14 π-electrons while each of the marginal rings has a π-electron sextet. Oskar E. Polanski introduced the concept of local aromaticity in PAHs.[6] Equipartition of π-electrons in graphene assigns one π-electron to each carbon atom, or two π-electrons for each six-membered ring; for phenanthrene this type of reasoning would assign to central and marginal rings 4 and 5 π-electrons, respectively. A third way of partitioning π-electrons in rings of polycyclic aromatic hydrocarbons was devised by Milan Randić (two π-electrons for a non-shared double bond, and one π-electron for a shared double bond[7]), and was applied consistently by Randić and the present author;[8–10] it results in an intermediate set of values between the too-uniform equipartition and Clar's "winner-takes-all" assignments. Examples are seen in Fig. 2 for phenanthrene and triphenylene.
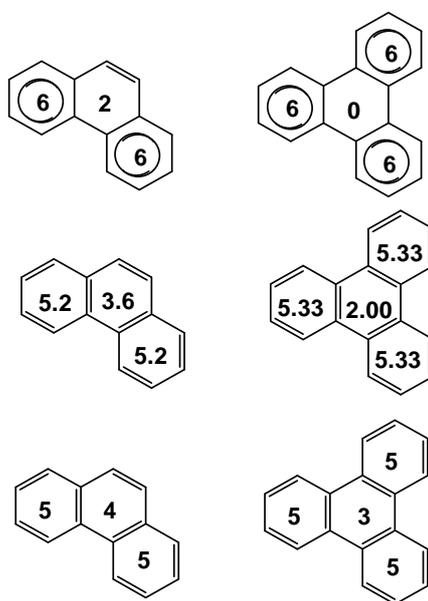

Fig. 2 – Left column: partition of phenanthrene's 14 π-electrons according to Clar,
Randić-Balaban, and equipartition. Right column: analogous partitions of triphenylene's 18 π-electrons.

A still debated problem concerns the local aromaticity of the rings in anthracene: the reactivity places the highest reactivity, i. e. the lower aromaticity, at the *meso* positions in the central ring and this is also the result of the Randić-Balaban partitions, with the 14 π-electrons assigned slightly less (4.5) than to the side-rings (4.75 π-electrons), while eqiupartition concurs placing four and five π-electrons, respectively.

However, the Clar structure appears to prefer the central ring with six π-electrons, leaving the marginal rings with four π-electrons each; similarly, HOMA indices (to be discussed later) and NICS values agree with the latter assignment.

In collaboration with Zeno Simon, the present author has attempted in the 1960s to add a quantitative basis to the qualitative framework of atoms that may form aromatic rings, in agreement with the Hückel Rule and the relative electronegativities with respect to the carbon electronegativity.[11] The "aromaticity constants" that had been devised at that time were based on electronegativities relative to carbon, and a similar approach was used for including heteroatoms in the topological index usually called "Balaban index J".[12]

A notable graph-theoretical application to benzenoids was classifying them according to their dualists (vertices in centers of hexagons, and edges connecting vertices that correspond to adjacent hexagons): catafusenes have acyclic dualists, perifusenes have dualists with triangles, and corona-fusenes have dualists that have larger rings.[13]

3. AROMATICITY CRITERIA

The stabilization energy associated with aromaticity evolved through successive approximations. The Hückel resonance energy having as reference isolated double bonds was considerably improved by Michael J. S. Dewar, who considered an acyclic conjugated polyene as reference. Later through the efforts of William C. Herndon, Haruo Hosoya, J.-I. Aihara, L. J. Schaad, B. A. Hess, Nenad Trinajstić, and Milan Randić, a parametrized topological resonance energy could be found for polycyclic aromatic benzenoid hydrocarbons. There is still room for finding and improving correlations with resonance energy of heterocyclic compounds.

A fairly recent bibliography on reviews of aromaticity is provided here, starting with books published during the last two decades,[14–17] and followed by special issues of journals.[18–24] *Aromaticity is a fuzzy concept of limited generality, yet it is emergent from a collection of properties* that will be examined in more detail below.

- Chemical reactivity
- Spectroscopic criteria
- Energetic criteria
- Magnetic criteria
- Geometric criteria

Chemical reactivity. The accepted dogma is that aromatic compounds react by substitution ("revert-to-type-reactions") rather than by addition like most unsaturated compounds. Thus, neutral (chargeless) compounds undergo electrophilic aromatic substitution of hydrogen atoms, whereas halogen atoms activated by strong electron-attracting groups such as nitro groups can undergo nucleophilic aromatic substitution of halogen atoms. An example is provided by various electrophilic substitutions of ring-attached hydrogens in toluene, but in homolytic reactions, under the influence of UV light or heat, the substitution occurs for hydrogens of side-chains. Heterogeneous catalysts (Raney nickel, platinum or palladium) can assist in addition reactions of hydrogen. Also, homolytic halogen additions can take place, affording for instance stereoisomeric hexachlorocyclohexanes. Of course, when charged cationic or anionic aromatic compounds are involved, the above generalizations no longer apply. For polycyclic aromatic hydrocarbons, the orientation of the electrophilic substitution can be rationalized by valence-bond methods, based on resonance structures (also called Kekulé structures). It is understandable that during the 1960s some chemists proposed to change the name "aromatic" into less outdated terms such as "strobilism" to indicate the potential ring current (C. K. Jorgensen, Jean-François Labarre) or meneidic to indicate the regenerative character (Douglas Lloyd). Some other chemists (Edgar Heilbronner) were even inclined to deny the usefulness of keeping the term "aromatic" because it is not an observable property and does not correspond to a unique definition (see the discussions on this topic in ref.[25]). However, the chemical community still finds the term "aromatic" useful, and students still learn about it. More on this topic will be presented in the section on heterocyclic aromatic compounds. Jokingly, people may like to think that women are more aromatic than men because estrogen hormones have one aromatic ring, whereas testosterone has none.

Spectroscopic criteria. By studying the electronic absorption spectra of polycyclic aromatic compounds, Gilbert N. Lewis and collaborators classified the absorption bands that are responsible for the

color of various benzenoids. Eric Clar [5] was able to infer the direction of polarization for the absorption bands, as they had been defined earlier by G. N. Lewis and M. Kasha.[26] The same directions were found to exist also in the electronic absorption spectra of six-membered heterocyclic aromatic compounds where a CH group was replaced by an N or O atom (pyridine and pyridinium or pyrylium cations). Taking as example several isomeric catafusenes with seven benzenoid rings, there is a direct correspondence between the number of linearly condensed benzenoid rings ("acenic portion"), the number C of Clar sextets, and the absorption wavelength (λ_{max} in nm) i. e. the color. For these benzenoids with one to five Clar sextets, Fig. 3 shows their colors. Other properties of PAHs such as redox potentials can also be correlated with the numbers of rings in the acenic portion.[27]
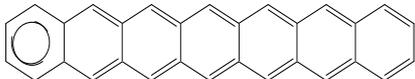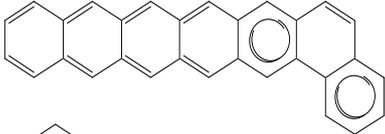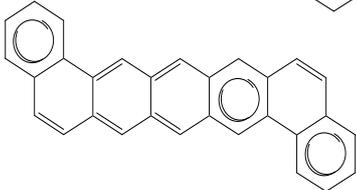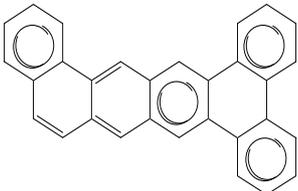
C	λ_{max}	color
1	840	green
2	651	blue
3	523	red
4	425	yellow
5	328	colorless
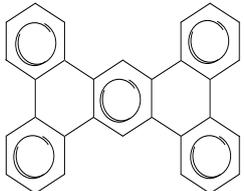
Fig. 3 – Cata-condensed PAHs with 7 benzenoid rings having from 1 to 5 Clar sextets.

Energetic criteria. According to Tadeusz Marek Krygowski and Michał K. Cyranski, this is the most fundamental of all criteria, and is manifested in thermodynamic stability due to resonance energy that can be measured (with respect to given reasonable structures that can also be measured) and then calculated so as to agree with experimental data. Following Dewar's argumentation that the resonance energy of an [n]annulene is to have as reference the acyclic polyene with the same number n of carbon atoms, various improvements were proposed by Trinajstić's Zagreb group, by Hess and Schaad, and by Aihara.

Magnetic criteria. An early observation was that in the proton magnetic resonance spectra, coplanar hydrogen atoms situated outside the planar aromatic ring of diatropic annulenes are strongly deshielded (for instance in [18]annulene at −60ºC for obtaining sharp spectra, 12 protons have δ = 9.22 ppm), whereas those

that are above or inside the ring are strongly shielded (for instance in [18]annulene six protons have $\delta = -2.99$ ppm).[28] This fact is due to the induced ring current in diatropic [4n+2]annulenes which causes the external protons to resonate at low fields . By contrast, in paratropic [4n]annulenes the external protons resonate at high fields: for instance, in [16]annulene shown in Fig. 4 at -120ºC the 12 outer protons appear at $\delta = 5.20$ ppm and the 4 inner protons at $\delta = 10.32$ ppm.
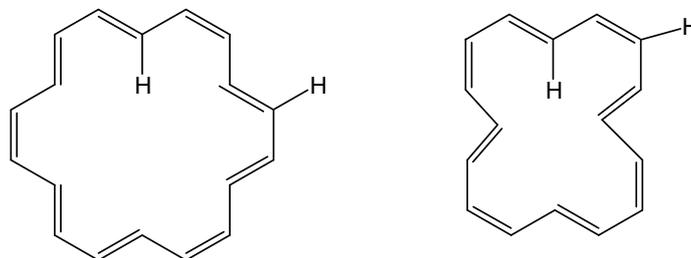

Fig. 4 – [18]Annulene and [16]annulene with inner and outer protons.

In order to introduce a general criterion for the presence of aromaticity or antiaromaticity, Schleyer and coworkers used initially the resonance of ^{3}He atoms in the vicinity of such cyclic structures, but soon afterwards they invented a computational method called "nucleus independent chemical shift" (NICS) at a given distance in the third dimension from the center of the planar ring.[29] Fowler and coworkers described ring currents by maps with small arrows pointing in directions of the induced magnetic field,[30] and connected these representations with theories of conjugated circuits.[31]

An interesting way of quantitatively evaluating the aromaticity of ring having amino substituents is to convert them into pyridinium salts (Fig. 5) by treatment with 2,4,6-trimethylpyrylium salts. The difference $\Delta\delta$ (ppm) between the chemical shifts of the three distant coplanar 4-methyl protons and the six closely situated 2- & 6-methyl protons is a measure for the aromaticity of the ring(s) attached to the nitrogen heteroatom:[32] $\Delta\delta$ values are intermediate, smallest, and largest for the three isomers shown in Fig. 5: 4-methyl protons are deshielded, and 2/6 methyl protons are shielded by the global ring current of the anthryl group.
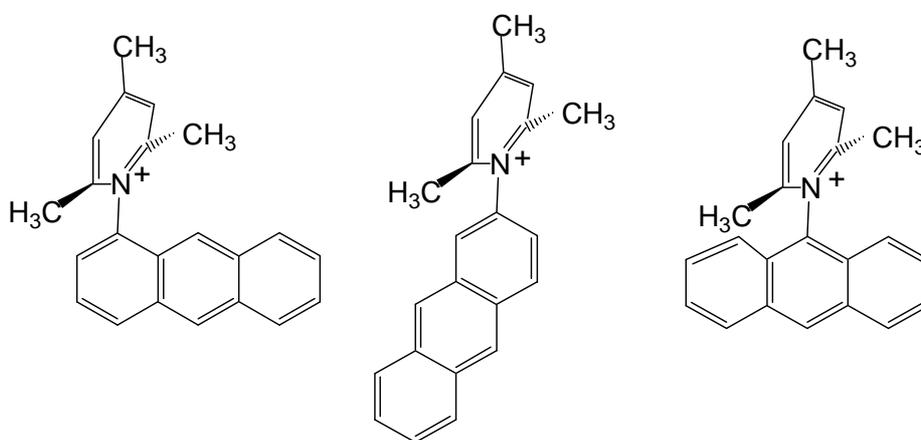

Fig. 5. 2,4,6 – Trimethylpyridinium cations with orthogonally situated N-anthryl substituents.

The circular sequence of 12 benzenoid rings surrounding [18]annulene was synthesized by Heinz A. Staab and coworkers, who named it "kekulene".[33] It is a normal PAH with six benzenoid rings having one internal and one external hydrogen atom (their chemical shifts are $\delta = 10.45$ and 8.37 ppm, respectively) and twelve olefinic protons with $\delta = 7.95$ ppm (see the middle structure of Fig. 6).

If a *para*-phenylene ring would bridge opposite sites of [18]annulene, an interesting structure ("choker-annulene") would result, as seen in Fig. 6. An analogous "choker-kekulene" can be imagined. Such structures are not yet known. An attempt to obtain a bis-pyridinium analog from phthalic aldehyde and 2,6-dimethyl-4-phenylpyrylium under ultra-dilution conditions was unsuccessful perhaps due to the insolubility of the product.[34,35]
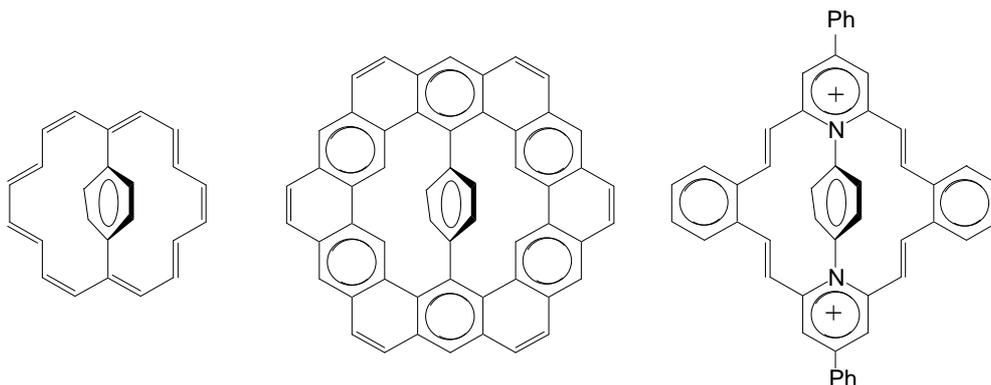
Fig. 6 – Challenges for experimental organic chemists: choker-[18]annulene, choker-kekulene, and a bis-pyridinium analog.

Conjugated circuits in polycyclic benzenoids combine ideas about energetic and magnetic criteria; they were introduced by Milan Randić [31] as a simple method for computing resonance energies, and are connected theoretically with diamagnetic ring currents when the number of alternating single and double bonds is odd ($4n+2$ π-electrons required by the Hückel rule for aromaticity) and paramagnetic ring currents when it is even ($4n$ π-electrons for antiaromaticity). Benzenoids have only the former types of conjugated circuits. By associating values for resonance energies computed by Dewar using semiempirical methods, conjugated circuits with odd numbers (3, 5, and 7) of double bonds have decreasing positive values (0.869, 0.247, and 0.100 eV, respectively) and negative values (–0.781, –0.222, and –0.090) for even numbers (2, 4, and 6, respectively) of double bonds in the conjugated circuit.[36]

Geometric criteria. Progress in understanding the reason why benzene adopts a D_{6h} geometry with equalized bond lengths is due to S. Shaik, P. C. Hiberty and their colleagues who emphasized the dominance of the strong force constant between the CC σ-bonds over the effect of the π-conjugation.[37] By contrast, cyclobutadiene and hexa-azabenzene are predicted to have alternating localized single and double bonds (the latter would also decompose instantly into 3 N_2 with a very small activation barrier). It is possible to synthesize benzene derivatives with D_{3h} geometry by means of added steric strain, confirming the above conclusions, as shown in the next paragraph and in Fig. 7.

The equalization of all CC bond lengths in benzene molecules with D_{6h} symmetry is in agreement with Linus Pauling's valence bond theory placing equal weights on the two Kekulé resonance structures. Pauling used the pair bonding ideas of Gilbert N. Lewis and the Heitler–London approach to covalent bonds for introducing the orbital hybridization and electronegativity concepts. More recently, Shaik and Hiberty showed that there is a "tug-of-war" fight between delocalized π- and localized σ-electron pairs of aromatic compounds.[37] Experimental evidence has been obtained for substituted benzene derivatives with D_{3h} symmetry having unequal bond lengths due to steric constraints: Vollhardt et al.[38,39] synthesized tris(benzocyclobutadieno)benzene and found that it has alternating bond lengths of 149.4 pm for the bond shared by the central 6-membered and the three 4-membered rings, whereas the remaining non-shared bonds measure 133.6 pm. When the strain is due to fusion with three bicyclo[2.1.1]pentanes, as in Siegel's hydrocarbon,[40] the shared and unshared bonds have lengths of 144.3 and 135.8 pm, respectively, as shown in Fig. 7.
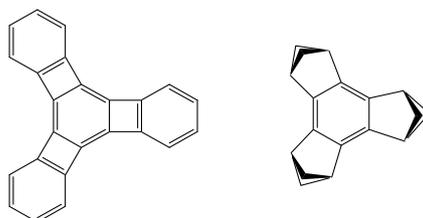

Fig. 7 – Benzene rings with D_{3h} symmetry caused by steric strain.

The tendency towards bond equalization due to electronic delocalization was used as a measure of aromaticity by Julg [41] who proposed a bond index based on bond lengths, and more recently by Krygowski and Cyranski who introduced the harmonic oscillator measure of aromaticity (HOMA).[42]

4. HETEROCYCLIC AROMATICITY

Aromatic heterocycles can be monocyclic or polycyclic (benzo-heterocycles are among the most interesting) and can have rings involving various numbers of heteroatoms. Fig. 8 contains six-membered aromatic neutral or cationic rings with one heteroatom, having N or O heteroatoms (and zero or one positive charge). Boron (in the boratabenzene anion) and many other heavier elements can also function as heteroatoms. A book chapter reviewed recently six-membered aromatic heterocycles (hetarenes) with one heteroatom,[43] and another book chapter was about monocyclic hetarenes with π-electron sextet.[44] Among the latter compounds, pyrylium cations distinguish themselves as having the strongest possible single-heteroatom perturbation.
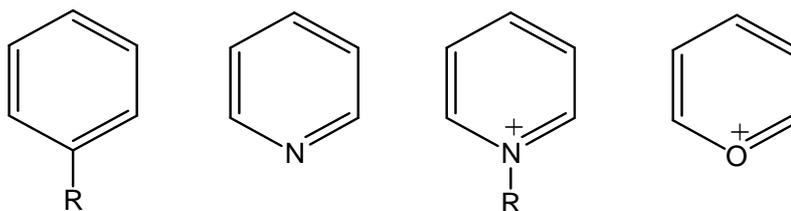
Fig. 8 – Six-membered aromatic monocyclic compounds: benzene (R = H),
pyridine, pyridinium cation, and pyrylium cation.

Pyrylium salts with alkyl or aryl substituents in 2 and 6 positions are well stabilized. A simple synthesis of such salts was discovered independently in Bucharest and London, and is known as the Balaban-Nenitzescu-Praill reaction.[45] In addition to a book on pyrylium salts,[46] several reviews exist on their synthesis, reactions, and properties;[47-49] the Houben-Weyl series which continues as "Science of Synthesis" publishes comprehensive chapters and updates them periodically.[50-52] The very electronegative oxygen heteroatom causes easy ring closing and ring opening. Nucleophiles add usually to 2/6 positions and the resulting pyran ring opens to a conjugated 2,4-pentadien-1-one that can recyclize yielding various carbocyclic or heterocycloic compounds. Therefore pyrylium salts behave as valuable synthons. In Fig. 9 one sees how 2,4,6-trimethylpyrylium salts can be in equilibrium with anhydrobases (methylenepyrans) explaining thereby the fast deuteration of the 4-methyl group in D_2O at 80ºC or the slower deuteration of all methyl groups at 100ºC. Quantum-chemical computations reveal the higher stability of 4-methylenepyrans than for 2-methylenepyrans, explaining the difference in reaction rates.[53] Also in Fig. 9 one sees how the pseudobase (*Z*-4-methyl-3-hepten-2,6-dione) can recyclize to 3,5-xylenol under dehydration on boiling with sodium hydroxide.

The influence of substituents on the reactivity of aromatic rings is well documented, and the lowering of reactivity towards oxidants by electron acceptors is well known. Nitrogen heteroatoms behave like acceptors and fortify hetarenes against oxidants such as $KMnO_4$ (permanganate destroys the phenyl group of N-phenylpyrazole, not the pyrazolyl group), but too many heteroatoms destabilize the molecule, and N_6 does not exist, decomposing into $3N_2$. Ivar Ugi and Rolf Huisgen succeeded to stabilize pentazole by attaching electron-donor substituents such as dialkylamino groups.[54]

In addition to the aromatic structures essential to life enumerated in the Introduction, an extraordinary role is associated to metal-atom-containing aromatic polycyclic structures: *porphyrin* (with four pyrrolic groups surrounding an iron atom in hemoglobin), and *chlorin* (with three pyrrolic and one pyrrolinic ring also coupled through four =CH− linkages and surrounding a magnesium atom in the chlorophylls that catalyze *the most important reaction on our planet*, photosynthesis, because it makes possible to have life on the surface of earth):

$$Energy + 6\ CO_2 + 6\ H_2O \rightarrow 6O_2 + C_6H_{12}O_6$$

It converts sunlight, gaseous water and carbon dioxide into the oxygen that we breathe and glucose that is further converted by vegetation into the food intake of the whole animal world. The reverse reaction,

oxidative processes of food in animal tissues, provides energy which in mammal cells is stored as adenosine triphosphate (adenine, one of the nucleoside bases, being an aromatic heterocycle).
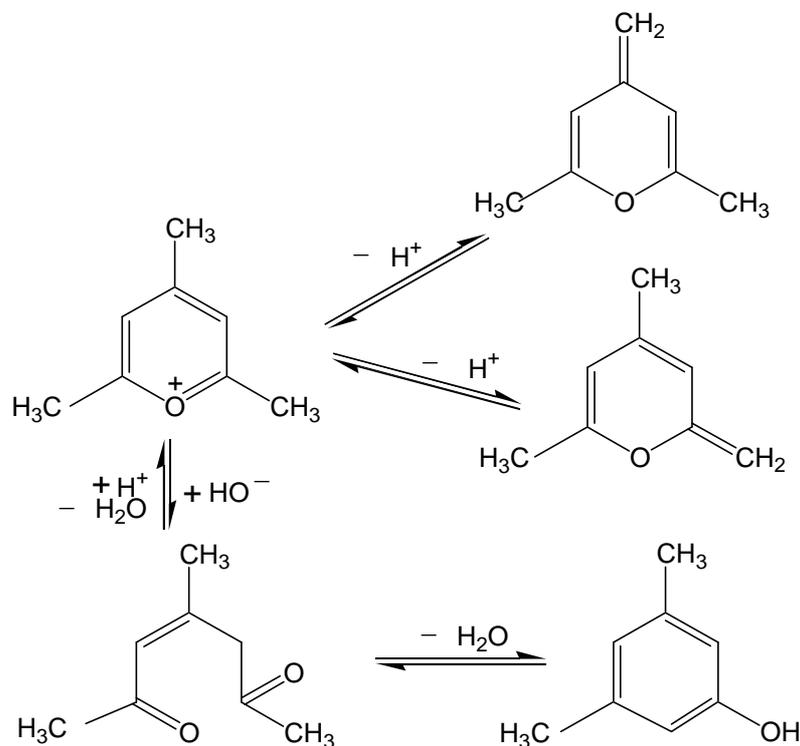

Fig. 9 – Upper formulas show how 2,4,6-trimethylpyrylium can be reversibly deprotonated below pH 6 to 4- or 2-methylenepyrans; lower formulas: at high pH values, a pseudobase results by addition of hydroxyl anion, followed by intramolecular cyclization to 3,5-dimethylphenol.

A controversy between Alan Katritzky (1928-2014) and Paul Schleyer (1930-2014) caused by contradictory effects on applying various criteria to 5-membered aromatic heterocycles resulted in several publications about the aromaticity of such heterocycles; it ended with a paper agreeing that aromaticity is a multidimensional phenomenon.[55] To the regret of the chemical community, these two giant figures of aromatic chemistry passed away recently.

5. CHEMICAL PROCESSES WITH AROMATIC TRANSITION STATES

The intramolecular rearrangements of 1,5-dienes discovered by Arthur C. Cope, and of allyl-aryl-ethers (Claisen rearrangement), 1,5-hydrogen transfers of 1,3-pentadienic chains, or the Diels-Alder cycloadditions proceed via aromatic transition states, as inferred by M. G. Evans, Michael J. S. Dewar, and Howard Zimmermann.[56] Fig. 10 displays some of these degenerate rearrangements (automerizations) and cycloadditions. The rationalization of the stereochemical outcome for such pericyclic reactions, due to Robert Woodward and Roald Hoffmann,[57] explains also why some of these degenerate reactions proceed with high rates, allowing bullvalene to behave as if it had ten equivalent CH groups, or semibullvalene to undergo fantastically fast automerizations even at low temperatures. An NMR study of crystalline deuterated bullvalene by Zimmermann and coworkers evidenced the automerization in solid state.[58] Bullvalene's unprecedented structure (a fluxional molecule with no permanent structure) was predicted by William v. E. Doering and Wolfgang Roth,[59] and its synthesis was reported shortly afterwards by Gerhard Schröder.[60] It is remarkable that both semibullvalene and bullvalene are valence isomers of annulenes with 8 and 10 CH groups. It was possible to display all possible types of 6-membered transition states.[61] Jiao and Schleyer brought strong arguments for the aromatic transition state, including NICS results.[29]
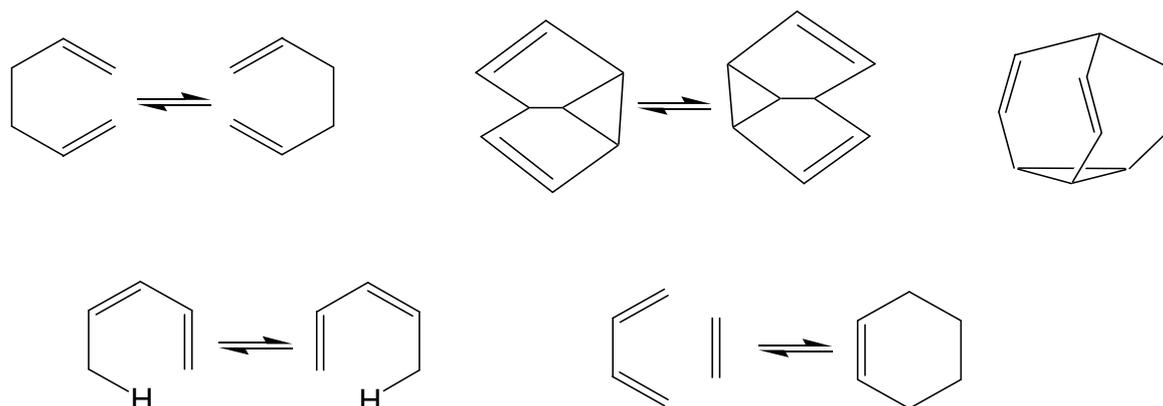
Fig. 10 – Pericyclic reactions. Upper row: Cope rearrangement; semibullvalene; bullvalene.
Lower row: 1,5-hydrogen transfer; Diels-Alder cycloaddition.

6. INORGANIC AND/OR ORGANOMETALLIC AROMATICITY

Borazine $B_3N_3H_6$ is the prototype of "inorganic benzene" based on the electronic similarity between CC and BN bonds, and on the fct that the electronegativity of carbon is approximately equal to the average between electronegativities of boron and nitrogen. However, borazine is much less stable than benzene, and chemists agree that its aromaticity is practically nil. Michael J. S. Dewar prepared "borazaro- and boroxaro-analogues" of benzenoid hydrocarbons, in which a CC bond was replaced by a BN or a BO bond, respectively.[62] Such compounds still inherit some aromaticity. Bortoxaropyrylium perchlorates were also reported,[63] but in crystals their anion was covalently attached to the cation.

The discovery of ferrocene by several independent groups came as a surprise,[64] but the X-ray crystal structure determination was the final argument[65] However, the rational approach by Wilkinson, Woodward and coworkers had already settled the problem.[66-68] Also, Ernst Otto Fischer was based on deductive reasoning when he and his research associates prepared bis-benzene-chromium,[69-71] sharing the 1973 Nobel Prize for Chemistry with Geoffrey Wilkinson for enriching the huge class of metallocenes. Later, Streitwieser and coworkers prepared bis(cyclooctatetraenyl)uranium (uranocene). also starting from theoretical induction.[72]

Mertallabenzenes such as osmabenzene or iridabenzene have been reviewed recently. An interesting discovery of aromaticity in all-metal dianion clusters such as Al_4^{2-} was recently reported by A. I. Boldyrev, L. S. Wang, and their coworkers (see their review [73]). The antiaromaticity of $Li_3Al_4^-$ is a logical consequence.[74]

7. THREE-DIMENSIONAL CARBON ALLOTROPE AROMATICITY

Chemists have for a long time considered that planarity is a necessary feature of aromaticity. However, after the remarkable discoveries of fullerenes, nanocones, and nanotubes, all of which are valid stable allotropes of carbon, one has to adopt 3D-aromaticity as yet another extension of this extraordinary stabilization. Of course, the higher the curvature, the lower the stabilization.

Eric Rohlfing, Donald Cox, and Andrew Kaldor at the Exxon Research and Engineering Co., then in Annandale, N.J., published in 1984 mass spectra of carbon aggregates and observed that they had always even numbers of atoms, not noting that C_{60} had a slightly higher intensity.[75] One year later, the formation of C_{60} and C_{70} fullerenes was discovered at Rice University by H. W. Kroto, R. F. Curl, R. E. Smalley and their coworkers.[76]. The structure of the former (C_{60}) is a truncated icosahedron like a soccer ball, whereas the latter (C_{70}) is similar to a rugby ball. This discovery was honored by the 1966 Nobel Prize for Chemistry awarded in 1966 to these three scientists. The isolation and purification of these compounds was performed first by W. Krätschmer, D. Huffman and their coworkers.[77] The X-ray diffraction results and ^{13}C-NMR spectra confirmed these structures. It was found by D. J. Klein [78] and H. W. Kroto [79] that among all polyhedra with faces consisting in 12 pentagons and arbitrary numbers of hexagons, as prescribed by Euler's Theorem, C_{60}

and C_{70} are the first and unique structures with isolated pentagons. Higher fullerenes obeying this "isolated pentagon rule" were enumerated by Fowler and Manolopoulos.[80] Obviously, the presence of adjacent pentagons whose outer contour is the antiaromatic cyclooctatetraene should lower the stability.

Even closer to practical applications are carbon nanotubes first identified by Ijima. They can be single-walled (SWNT) or multi-walled nanotubes (MWNT). Depending on how the graphene sheet is folded upon itself, SWNTs can behave as metallic conductors or semiconductors with zero or non-zero gap between the highest occupied and lowest unoccupied molecular orbitals. In vectorial notation along acenic linear strings of hexagons, one keeps track about how many hexagons $h \geq k \geq 0$ there are between initial and final destination, as seen in Fig. 11. Actually, there are three possibilities for the geometry of nanotubes: zigzag, armchair, and chiral.
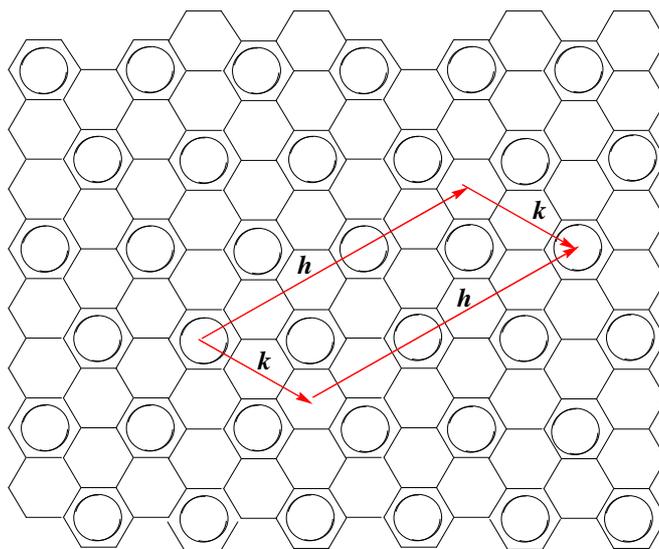

Fig. 11 – A graphene sheet with Clar sextets for the π-electrons; and vectors $h = 5$ and $k = 2$.

On folding such a graphene sheet so as to yield a single-wall nanotube (SWNT), the electrical conductivity of this SWNT depends on h and k: for $h = k$ one obtains an "armchair" nanotube and for $k = 0$ one obtains a "zigzag" SWNT. Both these types are achiral. When $h \neq k \neq 0$, the SWNT is chiral. When $h - k \equiv 0(\mathrm{mod}\ 3)$ the resulting bandgap is zero when curvature variations of the Hückel parameters are neglected, and the nanotube will have a metallic conductivity. Otherwise the SWNT is a semiconductor with non-zero bandgap. As a result, all armchair SWNTs and one-third of zigzag and chiral SWNTs are metallic, whereas two-thirds are semiconducting. The condition $h - k \equiv 0(\mathrm{mod}\ 3)$ can be interpreted as having a congruent overlap of Clar sextets after forming the graphene sheet.[81]

Interestingly, the same congruence condition also applies to folding graphene sheets into nanocones and nanotori. Douglas J. Klein has shown that there are eight classes of nanocones,[82] and the above congruence provides a simple explanation of this classification.[83]

8. HYPHENATED AROMATICITY AND MARGINAL AROMATICITY

Along with authentic aromaticity (even if unequal, according to various criteria examined earlier), several particular types of aromaticity have been described under various hyphenated names such as Craig's pseudo-aromaticity,[84] Lloyd and Marshall's quasi-aromaticity,[85] and Winstein's homo-aromaticity [86] (in addition to non-aromaticity and anti-aromaticity derived from systematic approaches based on the Molecular Orbital Theory). The success of MO methods was mainly motivated by the fact that they provide a simple approach for explaining the aromatic stabilization, in contrast to Valence Bond (VB) Theory.

Whereas tropylium and pyrylium cations are definitely aromatic, their related carbonyl derivatives (tropones, tropolones, α- and γ-pyrones) appear to possess zero aromaticity, probably because of insignificant contribution of their dipolar resonance structures.

In Fig. 12 one can see that by contrast, the contribution of aromatic diradicalic resonance structures is significant and has values of 17, 100, and 10% for *ortho*-, *meta*-, and *para*-xylylenes as a result of VB calculations by Hiberty et al.[87] and of more recent computations by Liebman and coworkers.[88]
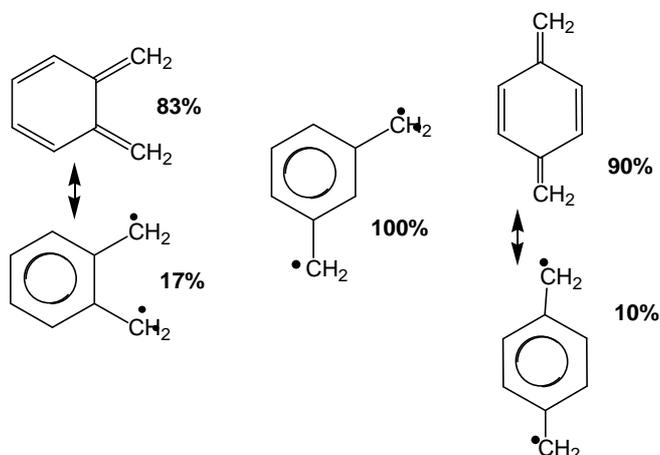

Fig. 12 – Valence-bond description of contributions of resonance formulas for xylylenes.

The high-yield intramolecular cycloadditions of benzocyclobutenes having alkene or alkyne substituents at convenient distances proceeds stereoselectively via valence-isomerization to xylylenes (Fig. 13). The driving force is the delocalization energy associated with aromatization; such reactions have acquired a high importance when they were shown to allow the synthesis of steroids and other biologically active compounds. Several reviews on this topic are available.[89–94]
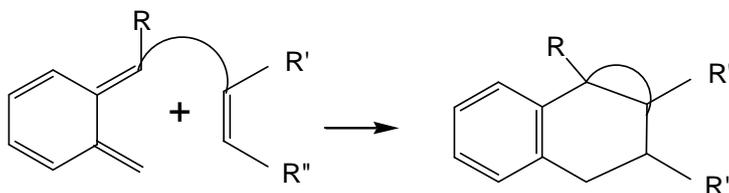

Fig. 13 – Regioselective intramolecular Diels-Alder cycloadditions of xylylene derivatives.

Fulvenes that have dialkylamino substituents at the exocyclic carbon atom have a detectable lowering of the activation barrier for intramolecular rotation than for dialkylfulvenes; this experimental finding agrees with calculations of delocalization energies in such compounds that have a non-negligible contribution of dipolar resonance formulas with a negatively-charged five-membered ring and a positively-charged exocyclic $CHNR_2$ group.[94] One can consider electrically-neutral structures with some contribution of aromatic dipolar resonance structures as "marginally-aromatic".

A spectacular and far-reaching discovery of the bacterial product caliceamicin γ_1^1 led to the development of a powerful new class of anti-cancer agents, enediynes.[95] As shown in Fig. 14, on hrating deuterated hex-3-en-1,5-diyne a 1,4-benzene diradical is reversibly formed, which yields benzene by abstracting two hydrogen atoms from surrounding molecules. The natural product has the ene-diyne moiety as part of a ten-membered ring preventing the cyclization, but when needed by the bacterium releases the "brake" of caliceamicin γ_1^1 and the resulting diradical destroys the attacking predator. In the case of ene-diyne anti-cancer agent Milotarg incorporated into a monoclonal antibody, the diradical destroys the DNA of malignant cells.[96]

Calculations of total energies for the two C_6H_4 structures on top of Fig. 15 by using the RHF/3-21G Gamess Program afford the values of −143,141 kcal/mol for 3-hexene-1,5-diyne and of −143,013 kcal/mol for the intramolecularly recombined diradical. For the three C_6H_6 structures at the bottom of Fig. 15 the corresponding total energies are −143,888 kcal/mol for 1,3-hexadien-5-yne, −143,868 kcal/mol for 1,2,4-cyclohexatriene, and −143,963 kcal/mol for benzene. Evidently, the release of enormous amounts of

energy (about 200 kcal/mol in Bergman cyclizations with low activation barriers) explains the high hopes placed in these novel chemotherapeutic agents. It remains to be seen whether reactions of molecules at the bottom of Fig. 15, which do not involve hydrogen addition, may offer any interest.
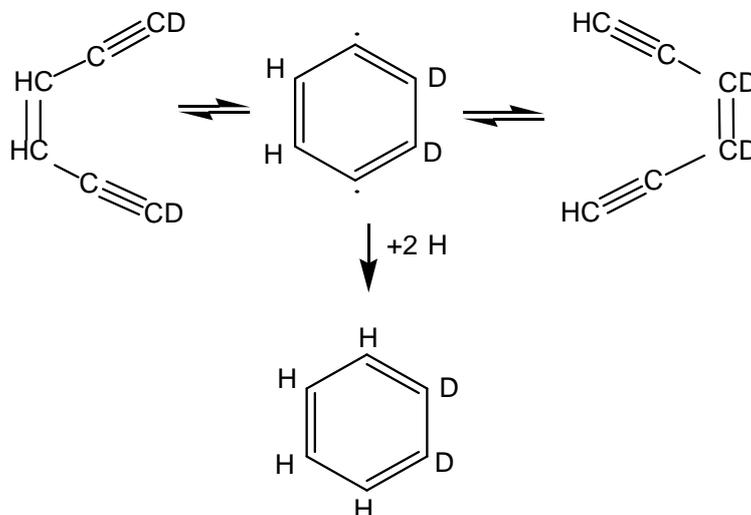

Fig. 14 – Thermal (200ºC) Bergman cycloaromatization of deuterated
hex-3-en-1,5-diyne to a diradical, which can abstract two hydrogen atoms yielding deuterated benzene.
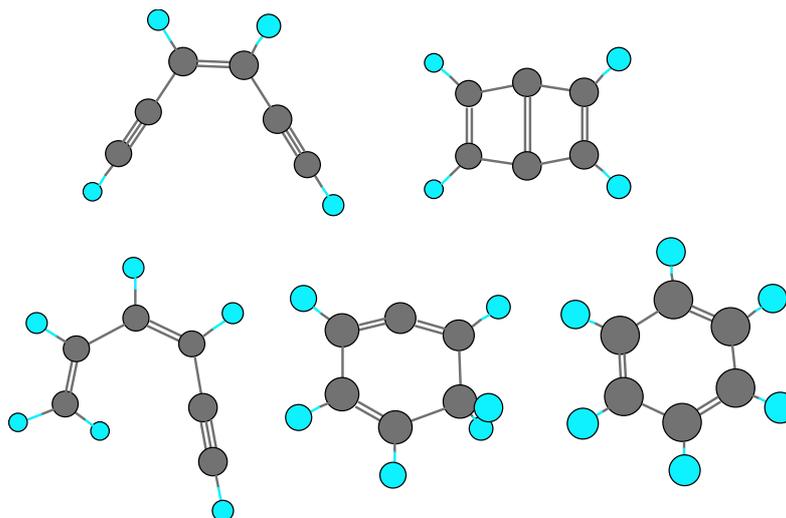
Fig. 15. Top row: C_6H_4 structures: 3-hexene-1,5-diyne and the virtual stabilization product of the cyclized diradical.
Bottom row: C_6H_6 structures: 1,3-hexadien-5-yne, 1,2,4-cyclohexatriene, and bemzene.

9. EFFECTS OF AROMATIC RINGS ON CHEMICAL STRUCTURES

It is well known that the aromaticity and conjugation involving aryl groups allows them to stabilize many chemical structures. Gomberg's discovery of triphenylmethyl *free radicals* is perhaps the most famous example.[97] The acidity of phenols is also a consequence of the stabilizing effect on the corresponding *anions*, made evident by the acidifying effect of electronegative substituents, leading for 2,4,6-trinitrophenol to the wrong name (picric acid, which does not have a carboxylic group as implied by the 'acid' name, yet its pK_a is in the corresponding range for carboxylic acids). The shift of keto-enol tautomerism to the (ph)enolic form is a powerful argument for the existence of aromatic conjugation energy. However, if other factors such as steric strain act as a counter-effect, then the cyclohexadenone tautomer becomes more stable, as shown by Vladimir Prelog who studied medium-size rings in *meta*-cyclophanes (Fig. 16): when the polymethylene chain has more than five CH_2 groups, the phenol is the stable tautomer, but with five methylene groups the

structure is cyclohexadienonic.[98] A similar effect was observed in the reaction of 2,6-diisopropyl-4-methylpyrylium salts with primary amines RNH_2, such as methylamine; instead of a normal pyridinium salt formed when the 2,6-dialkyl substituents are not bulky, the product is a 3,6,6-trimethyl-5-isopropyl-2,4-cyclohexadien-1-imine (Fig. 16),[99] because the pyridinium salt would have to squeeze an alkyl group between two isopropyl groups, which behave like *tertiary*-butyl groups due to their "Janus-effect".[100]
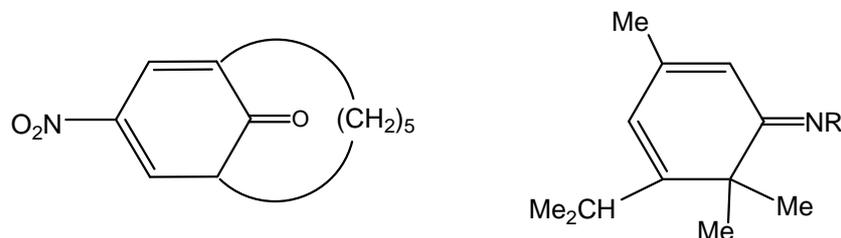

Fig. 16 – Left-hand structure: Prelog's product of condensation between nitro-malon-dialdehyde with cyclo-octanone.
Right-hand structure: Uncutza et al.'s product from 2,6-diisopropyl-4-methylpyrylium salts and alkylamines.

The colorful palette of triarylmethano and diarylamino dyestuffs proves the efficiency of electronic delocalization. Diarylhalonium and triaryloxonium *cations* [101] are much more stable than the corresponding polyalkyl derivatives and even diphenyl-*o,o'*-biphenyleneammonium iodide with high melting points have been prepared.[102] "Phenyl groups are crutches" was a favorite phrase of W. Treibs, who favored the unsubstituted structures, whenever they were possible.[103]

The remarkable "thermal stabilization" of diphenyl ether, polychlorobiphenyls, and "arochlor" allowed such compounds to be used as heat transfer fluids. Even more spectacular is the use of a mixture of *meta-* and *para*-terphenyl as neutron moderators in nuclear reactors, indicating also the "radiation stabilization" i. e. resilience of covalent bonds to nuclear radiation.

Returning to free radicals, the correct structure of the triphenylmethyl dimer was established only after NMR technology became available. Reversible dimerization of the triphenylmethyl free radical does not yield a sterically-hindered hexaphenylethane but a cyclohexadienic structure, whereas the reaction with dioxygen affords the normal peroxide, apparently because the intermediate radical $Ph_3C–O–O·$ has a small enough 'active site', able to connect with the central atom of the triphenylmethyl radical , as seen in Fig. 17.
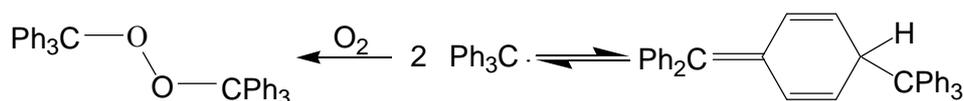

Fig. 17 – Triphenylmethyl free radicals are in equilibrium with dimers, but react with dioxygen.

Analogy reasoning led Wieland to investigate diarylaminyls,[104,105] and again the dimerization took an unexpected course, yielding N,N'-diphenylphenazine (after oxidative dehydrogenation of the initial dimer). Even more exciting was Goldschmidt's discovery [106] of the violet 2,2-diphenyl-1-picrylhydrazyl (DPPH) which is stubbornly monomeric even at liquid helium temperatures (about –270°C); in this case, the explanation is provided by the "push-pull effect", with an electron-donor diphenylamino group and an electron-acceptor picryl group which provides also steric shielding. Dewar had theoretically predicted stabilization of free radicals by push-pull effects [8] but recognizing that DPPH is such a radical happened a few years later.[107–110] Thus, the lone electron pair on nitrogen is delocalized on the acceptor group while the odd electron is mostly delocalized on the donor group. Linnett's theory [111,112] takes into account the fact the spin (α or β) of lone electron pairs of nitrogen atoms; it can be seen (Fig. 18) in the corresponding structure of DPPH that all non-hydrogen atoms in hydrazyls can have electron octets if the N–N bond has a bond order of 1.5. Since ESR spectra of DPPH are too complicated, a variable-temperature study of the rotation barrier around the N–N bond was undertaken with 1-benzoyl-2,2-bis-(3,5-di-tert-butylphenyl)hydrazyl, confirming the non-equivalence of the two aryl groups at low temperatures, in agreement with Linnett's theory. The rotation barrier at temperatures between –30° and +50°C is 31 kJ/mol, with coalescence of ESR spectral peaks at +60°C.[113]
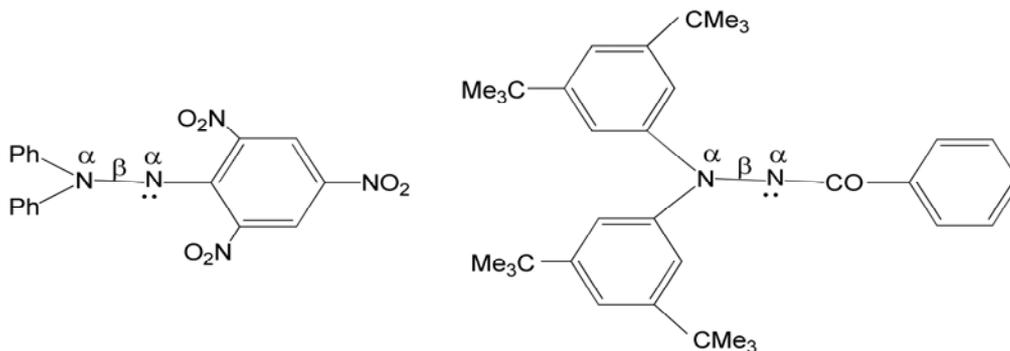
Fig. 18 – The stable free radical DPPH, and a related 2,2-diaryl-1-benzoylhydrazyl for dynamic ESR spectroscopic investigation revealing the high rotation barrier around the N–N bond.

Whereas in condensed phase dinitrogen molecules cannot be protonated and alkyldiazonium cations are transient reactive intermediates, aryldiazonium salts are stable and they function as the "working horse" for the manufacture of azo dyestuffs, or, after elimination of dinitrogen, for *arylation of nucleophiles*, just as alkyl halides are the agents for *alkylkation of nucleophiles*. Thus, aryl groups stabilize enormously chemical structures by electron delocalization, as discussed earlier for phenols and triarylmethyl free radicals. There is a marked contrast between the fairly stable hydrogen peroxide, *tert*-butyl hydroperoxide or di-*tert*-butyl peroxide on one hand, and on the other hand diphenyl peroxide, which does not exist. This is due to the stabilization energy of the phenoxyl radical (compensating for the weak O–O bond) and also to the tendency to mimic the benzidine rearrangement as argued by Rzepa[114] (the acid-catalyzed benzidine rearrangement has a vast literature [115,116]).

However, the red 2,4,6-triphenylphenoxyl is in equilibrium with its colorless *para*-quinol dimer, whereas the blue 2,4,6-tri-*tert*-butylphenoxyl radical does not dimerize. A physiologically and medicinally important phenolic antioxidant is vitamin E (α-tocopherol). Living cells have developed strong antioxidants and protecting enzymes (catalase, peroxidase) that catalyze the decomposition of hydrogen peroxide. Interestingly, Keith U. Ingold was able to devise phenols that are structurally similar to tocopherols but surpass the efficiency of the latter. [117–121]

In addition to the symmetrical homolytic O–O bond fission of a hypothetical diphenyl-peroxide that affords two phenoxyl free radicals, a non-symmetrical homolytic fission is also theoretically possible yielding a phenyl free radical and a phenyl-peroxy radical. Both these latter radicals are less stable than phenoxyl free radicals: decarboxylation of benzoyloxy free radicals formed from benzoyl peroxide on heating above 80°C leads indeed to the formation of phenyl free radicals, which are very reactive in initiating polymerizations of vinyl monomers. [122] Heterolytic O–O bond fissions of a hypothetical diphenyl-peroxide are even less plausible.

Phenols with bulky groups in 2, 4, and 6 positions afford stable aroxyls on oxidation, and when these groups are *tert*-butyl such phenols have been intensely studied for various applications as antioxidants.[123,124] 2,6-Di-*tert*-butyl-4-R-phenols with R = Me or t-Bu are the most studied compounds. [125–127] The red 2,4,6-triphenylphenoxyl [128–130] reacts with 2,4,6-tri-tert-butylphenol affording 2,4,6-triphenylphenol and the blue 2,4,6-tri-*tert*-butylphenoxyl.[131] Another interesting stable oxygen free radical is the deep blue galvinoxyl (Fig. 19) which is obtained by oxidizing 4,4'-dihydroxy-3,3',5,5'-tetra-*tert*-butyl-diphenylmethane with PbO$_2$; in colorimetric practical applications it competes with DPPH. The stabilization of the purple-black syrinoxyl is due to conjugation rather than steric shielding.
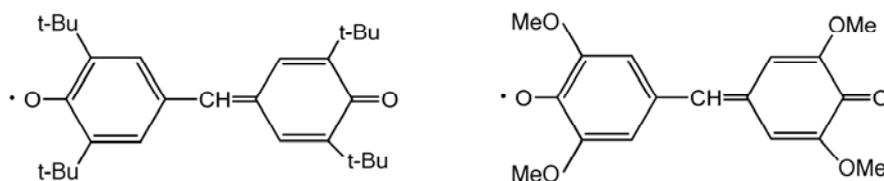

Fig. 19 – Stable oxygen free radicals: galvinoxyl (left) and syrinoxyl (right).

10. IMPORTANCE AND PRACTICAL APPLICATIONS OF AROMATIC COMPOUNDS

A book published in 1996[132] and a review[133] published in 2004 ("Aromaticity as a cornerstone in heterocyclic chemistry") were devoted only to a part of aromatic compounds, namely the substantial part of heterocyclics. Therefore it would be presumptuous to assume that one can enumerate even the most important of their applications in society.

Thinking first about aromatic hydrocarbons as raw materials, one has to recall that in the early 20th century, coal tar was the main raw material source for synthetic dyestuffs such as indigo and alizarin which used (earlier) to be extracted from plants, triarylmethane and azoic dyes. With the development of petrochemistry and of new methods for high-octane-number gasoline, petroleum became the main source for toluene, xylenes, and other aromatic hydrocarbons. Their functionalization to aniline, phenol, etc. allowed the development of other technological areas such as detergents and pharmaceuticals, including sulfanilamides and antibiotics that increased life expectancy by 20 years in the 20th century. Polymers for various uses such as polystyrene and Kevlar, textiles such as polyethylene terephtalate, have as raw materials simple aromatic hydrocarbons (benzene, *para*-xylene). The oldest local anesthetics for surgery such as procaine have *para*-substituted benzene rings.

A brief enumeration of technologically important aromatic heterocycles must include pesticides and insecticides (*para,para'*-dichlorodiphenyl-trichloroethane = DDT), insect repellants (N,N-diethyl-*meta*-toluamide) and herbicides, such as diquat and paraquat, applied for no-till farming.

11. RECENT DEVELOPMENTS

In 2015, Roald Hoffmann published an article titled "The Many Guises of Aromaticity. Is hype debasing a core chemical concept?" in which he argued against including as aromatics any observed or calculated fleeting molecules that have no chance of being bench-stable and "bottleable" under ambient conditions of pressure and temperature.[134] Examples of such "hype molecules" are the dianionic square-planar Al_4^{2-} and the cyclic or linear C_6 carbon cluster. As a reply, Alexander I. Boldyrev and Lai-Sheng Wang who had published extensively on Al_4^{2-}, stated that modern chemistry is able to compute, detect, and in some cases even isolate and bottle inorganic or organometallic substances that are connected by delocalized σ-,π-, and/or δ-electrons; in their opinion, such molecules deserve to be assimilated with aromatics.[135] As a counter-argument, R. Hoffmann offered as a rebuttal the H_3^+ cation, which is very reactive, despite its stability; it would be ludicrous to consider it as aromatic; several other chemists (F. A. Weinhold, G. Frenking, M. Solá, and D. Sundholm) joined the discussion under the auspices of *Chemical Engineeering News*.[136]

In the present author's opinion, as an experimental organic chemist, application of Occam's Razor would advise against extension of the well-established notion of aromaticity to substances that cannot be handled as kinetically stable *in condensed state* under normal bench conditions. The italicized part is important, since often one forgets it, for instance when discussing carbyne (the hypothetical carbon allotrope with long conjugated polyyne chains): these would explode in condensed state by exothermal polymerization, although they may exist indefinitely as isolated molecules in cosmic space.

Another aspect worthy of mentioning is the fact that small increments of parameters may cause large discontinuities, for example the fact that tropone and 4H-pyrone have practically zero aromaticity according to most indices, yet at low pH values they become aromatic as hydroxy-tropylium and 4-hydroxy-pyrylium cations, respectively. Along the same line of reasoning, the formation of aromatic pyridinium salts from primary amines and pyrylium cations proceeds normally, but with bulky substituents the product is not aromatic (Fig. 16).

It is astonishing how concepts can be in and out of fashion for a while. This is what happened with aromaticity: in the 1960s, various hyphenated aromaticities brought adverse criticism, restricting this ill-defined concept, even the suggestion to abandon the aromaticity notion;[25] by contrast, in the new millennium we witness the tendency to extend this concept to many of the known structures.

12. CONCLUSIONS

Chemistry is full of surprises, and one of these is that a single element (carbon) provides the skeleton of most known substances. Yet another source of wonder is that its two main allotropic forms (diamond and

graphite) are the hardest and one of the softest solids, respectively. Graphite and graphene contain aromatic rings and conduct electricity (unlike diamond); their tridimensional folded forms (fullerenes, nanotubes, nanocones, nanotori) have metallic conductivity or are semiconductors, depending on whether the Clar sextets are folded to afford congruence or incongruence. Thus carbon deserves to have an ode dedicated to it.[137] Several articles tried to provide answers to the question "What is aromaticity"?[138,139]

After the excursion into the various aspects of aromaticity, a comprehensive yet concise conclusion was formulated in the following IUPAC text about aromaticity:[140]

"The concept of spatial and electronic structure of cyclic molecular systems displaying the effects of cyclic electron delocalization which provide for their enhanced thermodynamic stability (relative to acyclic structural analogues) and tendency to retain the structural type in the course of chemical transformations. A quantitative assessment of the degree of aromaticity is given by the value of the resonance energy. It may also be evaluated by the energies of relevant isodesmic and homodesmotic reactions. Along with energetic criteria of aromaticity, important and complementary are also a structural criterion (the lesser the alternation of bond lengths in the rings, the greater is the aromaticity of the molecule) and a magnetic criterion (existence of the diamagnetic ring current induced in a conjugated cyclic molecule by an external magnetic field and manifested by an exaltation and anisotropy of magnetic susceptibility). Although originally introduced for characterization of peculiar properties of cyclic conjugated hydrocarbons and their ions, the concept of aromaticity has been extended to their homoderivatives (see homoaromaticity), conjugated heterocyclic compounds (heteroaromaticity), saturated cyclic compounds (σ-aromaticity) as well as to three-dimensional organic and organometallic compounds (three-dimensional aromaticity). A common feature of the electronic structure inherent in all aromatic molecules is the close nature of their valence electron shells, *i.e.*, double electron occupation of all bonding MOs with all antibonding and delocalized nonbonding Mos unfilled. The notion of aromaticity is applied also to transition states."

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