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Chemical Evolution, Biosynthesis, and Aromaticity

Jun-ichi Aihara
Department of Chemistry, Faculty of Science, Shizuoka University, Oya, Shizuoka 422
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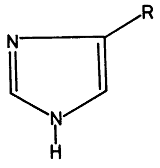
Naturally occurring heterocycles such as imidazole and thiophene do not conform to the rule of topological charge stabilization. Abiotic synthesis and biosynthesis of such heteroconjugated molecules can be rationalized in terms of aromatic stabilization. Antiaromatic molecules are formed neither in primitive-Earth-simulation experiments nor in living systems.

Many heterocyclic π-electron systems are formed in so-called primitive-Earth-simulation (PES) experiments.[1,2] Studies of chemical evolution have been based on various PES experiments. In previous papers,[3,4] we reported that unsaturated organic molecules produced in nature obeyed the rule of topological charge stabilization (TCS rule).[5] This rule states that an unsaturated molecule is relatively stable if heteroatoms of large electronegativity are located at those positions where charge density is high in the uniform reference frame (the URF, i.e., the isostructural, iso-π-electronic hydrocarbon).[5] Nucleoside bases, amino acids, and many carboxylic acids are formed in PES experiments and in living systems. All these molecules conform to the TCS rule.[3,4] All amine nitrogens, all ether (or alcohol) oxygens, all sulfide sulfurs, most imine nitrogens, and most ketone oxygens in these molecules occupy the sites of high charge density in the URFs.[3-6]

We recently noticed that a different kind of unsaturated molecules were also produced in PES experiments. Kobayashi and co-workers obtained imidazole (**1**, R=H) by exposing the gaseous mixture of CO, N_2, and H_2 to the high-energy proton ray.[7,8] High-energy proton ray was an imitation of cosmic ray. Histidine [**1**, R=-$CH_2CH(NH_2)COOH$] is a typical biomolecule, which has been produced in some PES experiments.[9,10] To our regret, these molecules do not conform to the TCS rule. Why are these unsaturated molecules formed in nature? It is the purpose of this paper to rationalize abiotic and biotic syntheses of such five-membered heterocycles in terms of aromaticity. Substituents not conjugated with a ring system are denoted by R or R_n (n=1, 2).

Results and Discussion

In general, an amine nitrogen behaves like a dication which attracts about two π electrons. This is the primary reason why nature tends to place this type of nitrogen atoms at the sites of high charge density in the URF.[2] However, imidazole (**1**, R=H) is exceptional in the sense that the amine nitrogen is not located at the site of comparatively high charge density in the URF. This molecule has a five-membered conjugated system with six π electrons. The URF for



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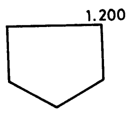

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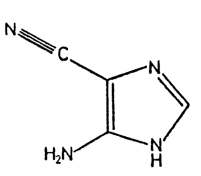
it is identical with the cyclopentadienide ion (**2**), in which π-electron density is uniform over all carbon atoms. The amine nitrogen in imidazole seems to be misplaced, disturbing the uniformity of the π-electron distribution in the URF. Substituted imidazoles such as 5-amino-4-imidazolecarbonitrile (**3**) and 5-amino-4-imidazolecarboxamide (**4**) are formed by the origomerization of HCN.[1,2] The URFs for **3** and **4** are shown in **5** and **6**, respectively. In contrast to imidazole, the entire π-electron systems of these molecules conform to the TCS rule.[3] All the heteroatoms are located at the sites of appreciably higher charge density in the URFs. No such regularity is discernible in unsubstituted imidazole.



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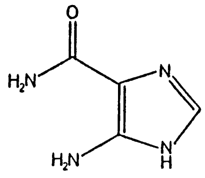

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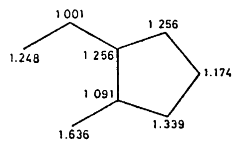

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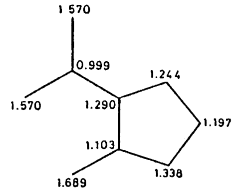

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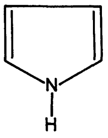
Kissel and Krueger reported that imidazole and pyrrole (**7**) were detectable in the mass spectra of the volatile species emitted from Comet Halley.[11] Petroleum contains thiophene (**8**) and alkyl-substituted thiophenes in large amounts.[12,13] The URFs for thiophene and pyrrole are the same as the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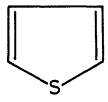
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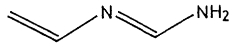
cyclopentadienide ion (**2**). These five-membered π-electron systems again disobey the TCS rule. A sulfide sulfur in thiophene and an amine nitrogen in pyrrole disturb the uniformity of the π-electron distribution retained in the URFs. Thus, these heterocycles must be destabilized by the presence of a heteroatom. Topological resonance energies (TREs) of five-membered heterocycles are smaller than that of the cyclopentadienide ion.[14,15]

In this context, coal, petroleum, and carbonaceous chondrites contain polycyclic aromatic hydrocarbons (PAHs) abundantly[16–19] Large compact PAHs dominate the interstellar medium exposed to intense ultraviolet radiation.[17,20,21] Shock and Schulte suggested that various organic compounds in carbonaceous chondrites might have been made from PAHs.[22] However, the occurrence of PAHs not only in nature but also in space cannot be rationalized in terms of the TCS rule. These molecules are alternant benzenoid hydrocarbons with a uniform π-electron distribution, in which there is no room for such heteroatoms as an amine nitrogen and an ether oxygen. Formation and stability of PAHs must therefore be interpreted in terms of aromaticity i.e., extra stabilization due to cyclic conjugation.[23] We have once pointed out that PAHs detectable in our environment and in space possess a relatively large TRE.[24,25]

In fact, antiaromatic molecules have neither been found in the products of PES experiments nor in the organic component of carbonaceous chondrite.[1,2,16] Coal and petroleum do not contain antiaromatic species.[16] Here, an antiaromatic molecule means a cyclic unsaturated species with a negative TRE.[14,15] There are many olefinic biomolecules but no antiaromatic ones. Considering that antiaromatic molecules never occur in nature, we postulate that the violation of the TCS rule may be compensated by aromatic stabilization. We previously analyzed aromatic stabilization and topological charge stabilization in some detail,[26] and showed that these two ways of stabilizing molecules are intrinsically different from each other. Aromatic stabilization arises primarily from the kinetic-energy term of π electrons, whereas topological charge stabilization is closely related to the potential-energy term of π electrons.[26] It is clear that these two stabilizing mechanisms are equally important, being complementary to each other.

It is very true that imidazole, pyrrole, and thiophene are stabilized by aromaticity. Although TREs of these heterocycles are somewhat smaller than that of the cyclopentadienide ion (**2**), they are still large in magnitude.[14,15] Therefore, we can say that aromatic species in principle are produced in nature because they are aromatic. Thus, one heteroatom with two π electrons in a five-membered, six-π-electron heterocycle contributes to the stability of the conjugated system. The heteroatom is utilized effectively not only to form an aromatic sextet, but also to attain charge neutralization.

Aromaticity of five-membered conjugated heterocycles (e.g., imidazole) can be associated with topological charge stabilization in the following manner. Every π bond in imidazole (**1**, R=H) must be stronger than like bonds in acyclic molecules such as **9** because the Dewar resonance energy (or the TRE) of imidazole is positive in sign.[27] The URF for **9** is given in **10**.



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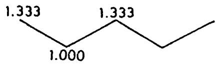

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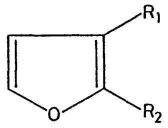
It is obvious that **9** conforms to the TCS rule. Therefore, we can say that imidazole is a sufficiently stable molecule since every bond in the molecule is more stable than like π bonds in acyclic molecules conforming to the TCS rule. The same interpretation applies to all five-membered, six-π-electron heterocycles. We have proved that these heterocycles are aromatic in nature.[28]

As exemplified by histidine, there are biomolecules which do not obey the TCS rule. They are all aromatic species, containing five-membered heterocycles with six π electrons. Histidine, histamine (**1**, R= -$CH_2CH_2NH_2$), and related species are synthesized and utilized by living organisms.[12] There are many terpenoids with an isolated furan conjugated system,[29] which are generally expressed as **11**. Porphyrinogens and related molecules contain isolated pyrrole conjugated systems.[30] Five-membered heterocycles in these biomolecules are not consistent with the TCS rule. Part of the bleomycin molecule[31,32] and the corresponding URF are shown in **12** and **13**, respectively. The amide linkage (-CONH-) in **12** is consistent with the pattern of the π-electron distribution in the URF (**13**). However, π-electron density is fairly uniform over the two five-membered carbocycles in the URF. Therefore, sulfide sulfurs in **12** are not placed at the sites of appreciably higher charge density



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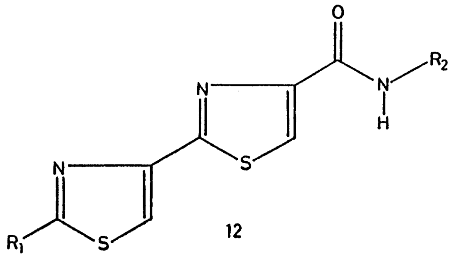

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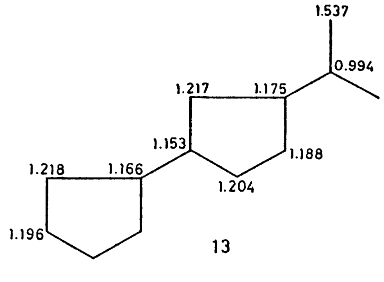

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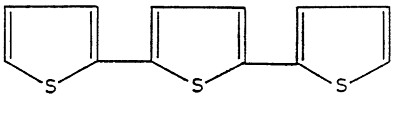
in the URF. Furthermore, this antibiotic has an isolated imidazole conjugated system in a different part of the molecule. Biosynthesis of such unsaturated molecules must again be rationalized in terms of aromatic stabilization.

Unsaturated organic molecules in nature and those formed in PES experiments are necessarily classified into two groups. One group consists of molecules whose entire conjugated systems conform to the TCS rule. Most of the unsaturated molecules produced in living systems and in PES experiments belong to this group.[3,4] Aromaticity and topological charge stabilization cooperatively enhance the stability of these molecules. The other group consists of organic molecules whose entire conjugated systems do not conform to the TCS rule. These molecules have one or more five-membered heterocycles not conforming to the TCS rule. Histidine, histamine, and bleomycin are typical examples. It goes without saying that imidazole, pyrrole, furan, and thiophene belong to this group. α-Terthienyl (2,2′ : 5′,2″-terthiophene, **14**) is a biocidal constituent of various species of marigolds.[12,33] 2,2′-Bithiophene (**15**) and its alkyl-substituted derivatives are present in petroleum.[13] Sulfur atoms in **14** and **15** do not match with the π-electron distribution in the URFs **16** and **17**, respectively.



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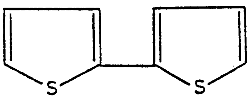

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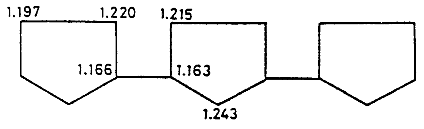

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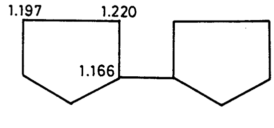

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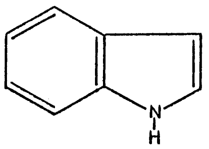

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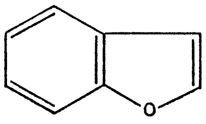

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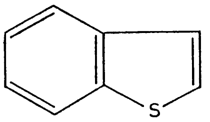

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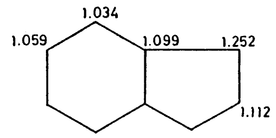

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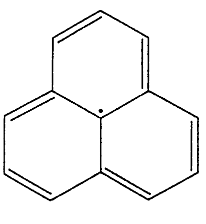
It is noteworthy that the indole (**18**) and benzo[*b*]furan (**19**) nuclei are much more common in nature than those of pyrrole and furan, respectively.[34] For example, a limited number of substituted pyrroles are known in nature, but a wide variety of indole alkaloids have been synthesized by plants.[35] This suggests that the cooperation of aromaticity and topological charge stabilization is highly desirable to stabilize the π-electron system although one of them is enough to stabilize organic molecules formed in nature. Alkyl-substituted thiophenes and benzo[*b*]thiophenes (**20**) are the most abundant organic sulfur compounds in petroleum.[13] Indole, benzo[*b*]furan, and benzo[*b*]thiophene are not only highly aromatic but also consistent with the TCS rule. The common URF for **18**—**20** is given in **21**.

There are some researchers who suspect that antiaromatic species may exist in nature. The ESR signal of the perinaphthenyl radical (phenalenyl radical, **22**) or something like that is detectable in coal and heated flint.[36,37] Chandra and co-workers suggested that



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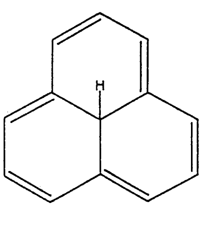

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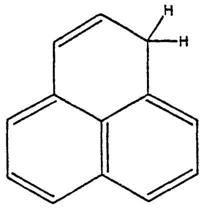
bridged [12]annulene (**23**) might be a precursor of this radical in heated flint.[37] However, nobody has succeeded in preparing this antiaromatic species in laboratories.[38] Note that the [12]annulene conjugated system is antiaromatic,[14,15] whereas the perinaphthenyl radical is aromatic with a TRE of $0.410|\beta|$.[39] Even if bridged [12]annulene (**23**) is formed in an isolated flint cavity, it will be converted into the aromatic isomer **24** immediately. We must say that there is no definite evidence at present for the existence of any molecule with a [12]annulene conjugated system in nature.



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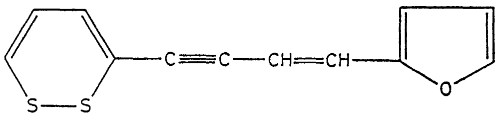

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Lam and co-workers proposed a molecular structure shown in **25** for a minor constituent of Santolina chamaecyparissus, a plant which grows in North Africa.[40] There is a six-membered heterocycle with eight π electrons in it, which is antiaromatic in character. If this proposed structure proved to be correct, it would be the first biomolecule with an antiaromatic ring. Unfortunately, their assignment is based solely on the pattern of the mass spectrum because the obtained sample was very scanty. There is no affirmative evidence for the existence of **25** or something like that in living organisms. In general, those who suggest the presence of antiaromatic species in nature appear to be rather indifferent to antiaromaticity.

Concluding Remarks

Two stabilizing mechanisms are operative in naturally occurring unsaturated molecules.[26] One is topological charge stabilization and the other is aromatic stabilization. We have seen that these two stabilizing mechanisms are equally important both in abiotic and biotic syntheses of organic molecules in nature. The TCS rule alone cannot differentiate between stabilities of aromatic and nonaromatic structures.[5] The TRE serves as a measure of aromaticity.[14,15]

Most cyclic conjugated systems formed in PES experiments and in living systems are more or less aromatic and conform to the TCS rule.[3,4] In this sense it is noteworthy that aromatic species are eligible to form in nature even if they do not conform to the TCS rule. In fact, antiaromatic molecules have not been detected in nature. It is clear that aromaticity is one of the determinant factors not only in chemical evolution but also in biosynthesis.

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