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Monocyclic Heterocyclic Biomolecules Conform to the Rule of Topological Charge Stabilization

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Some difficulty is felt in applying the rule of topological charge stabilization (TCS rule) to monocyclic heterocyclic biomolecules, such as substituted pyrroles, furans, thiophenes, imidazoles, and thiazoles. We found that the TCS rule can be reasonably extended to include such heterocycles. We propose that, if all carbon atoms in a hydrocarbon anion are charged uniformly, one or more of them can be replaced by eletronegative heteroatoms to stabilize the π-electron system. Thus, it is still true that the TCS rule dominates general biosynthesis and geochemistry. Coenzyme PQQ (pyrroloquinolinequinone) satisfies the TCS rule in both its oxidized and reduced states. Even apparently antiaromatic 1,2-dithiin seems to conform to the TCS rule.

The pattern of the π-electron densities in a molecule is determined primarily by the topology of the π-electron system.[1] In 1983, Gimarc noted that nature prefers to place heteroatoms of large electronegativity at those positions where a given neutral or charged hydrocarbon has larger charge densities.[1—6] This way of stabilizing a π-electron system has been referred to as the rule of topological charge stabilization (TCS rule).[1] A starting hydrocarbon or an isostructural, iso-π-electronic reference hydrocarbon is called a uniform reference frame (URF).[1—6]

In 1988 we pointed out that most organic molecules generated not only in the course of chemical evolution, but also in living organisms, satisfy the TCS rule.[3,4] In particular, heteroatoms that are the source of two π electrons obey the rule faithfully. Among them are amine-type nitrogen, ether- or phenol-type oxygen, and thioether-type sulfur atoms. When a biomolecule has this type of heteroatoms, their positions always correspond to those of larger π-electron density in the URF.[3,4] In general, a molecule that satisfies the TCS rule is thermodynamically more stable than the isomers that violate it.[1]

It seemed to us in 1990 that many aromatic biomolecules containing pyrrole (**1**), furan (**2**), thiophene (**3**), imidazole (**4**), and thiazole (**5**) rings do not satisfy the TCS rule (Fig. 1).[5] Since their common URF (the cyclopentadienide ion, **1a**) has a uniform charge distribution, there are no positions on which the charge densities are greater in it. There is no bias in the π-electron distribution of **1a**. Therefore, we could not use the TCS rule to explain the stability of such five-membered heterocycles.[5] We had to postulate a priori that monocyclic aromatic molecules are easy to form simply because they are thermodynamically stable due to cyclic conjugation.[5]

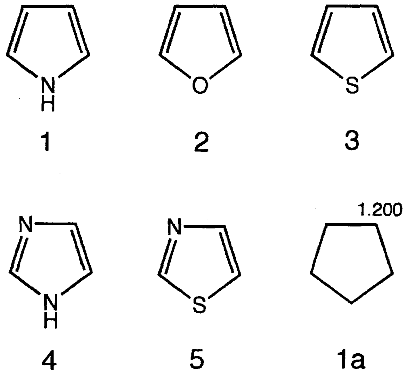
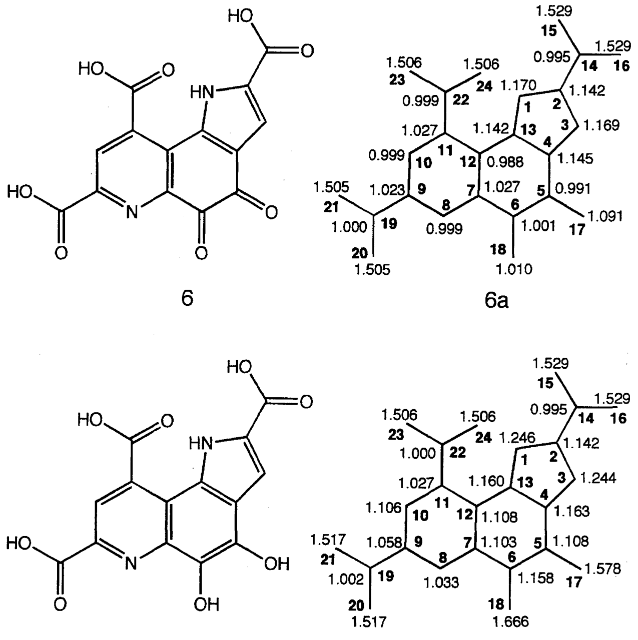


Fig. 1. Naturally occurring monocyclic heterocycles: Pyrrole (**1**), furan (**2**), thiophene (**3**), imidazole (**4**), and thiazole (**5**). Hydrocarbon anion **1a** is their common URF with π-electron densities.

We recently had an opportunity to examinie the electronic properties of so-called pyrroloquinolinequinone (PQQ, 4,5-dihydro-4,5-dioxo-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylic acid) (**6**) and its reduced form **7**, and obtained an important clue to the further understanding of the TCS rule and monocyclic heterocycles (Fig. 2). After an analysis of the stability of PQQ, we attempt to explain the occurrence in nature of monocyclic heterocyclic biomolecules in terms of the TCS rule.

Theory

The stability of some particular biomolecules was analyzed using the TCS rule[1] as well as the topological resonance energy (TRE)[7,8] and bond resonance energy (BRE) methods.[9,10] TRE is a measure of aromatic stabilization,[7,8] whereas BRE represents the contribution of each π bond to TRE of the molecule.[9,10] Hückel parameters determined by Van-Catledge were used to evaluate TREs and BREs.[11] Some



6 6a

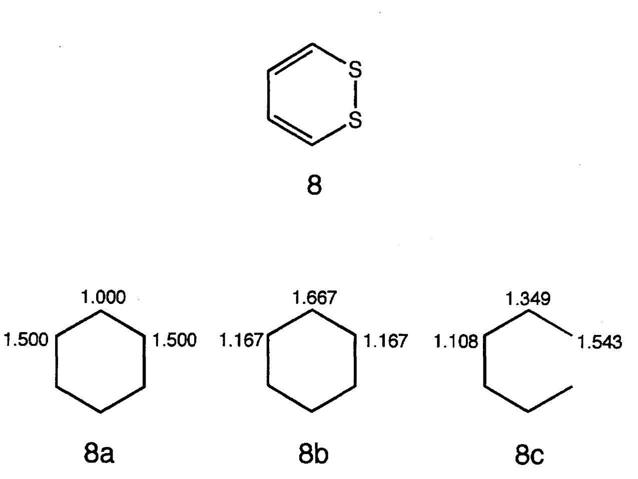
7 7a

Fig. 2. The oxidized (**6**) and reduced (**7**) forms of PQQ. Hydrocarbon anions **6a** and **7a** are the URFs with π-electron desnities for **6** and **7**, respectively.

electronic and geometric features of 1,2-dithiin (**8**) (Fig. 3) were predicted by carrying out an ab initio molecular orbital (MO) calculation at the HF/6-31G** level.[12]

PQQ and the TCS Rule. Nature elaborately designed enzymatic cofactors or coenzymes, such as nicotinamide, flavins, and deazaflavin, in such a manner that they satisfy the TCS rule in both the oxidized and reduced forms.[4] PQQ (**6**) was found to play the role of a redox coenzyme and a growth regulator in different bacteria.[13,14] Hydroquinone **7** is a reduced form of **6**. There are many enzymes for which PQQ has been demonstrated to be an essential cofactor.[13,14] We can show that both the oxidized and reduced forms of PQQ satisfy the TCS rule.

Hydrocarbon tetraanion **6a** is a URF for the oxidized form of PQQ (**6**). This URF has appreciably larger π-electron densities at all sites in the five-membered ring. Therefore, any carbon atom in this ring can in principle be replaced by an amine-type nitrogen atom, a source of two π electrons. Hydrocarbon hexaanion **7a** is a URF for the reduced form of PQQ (**7**), in which the 1- and 3-positions have larger π-electron densities. It is then unfavorable for an amine-type nitrogen atom to occupy the 2-, 4-, or 13-position in the five-membered ring. In reality, the nitrogen atoms is placed at the 1-position. Three carboxyl groups in PQQ are fully stabilized by locating oxygen atoms at the positions where the π-electron densities are very high both in **6a** and **7a**.



8

8a 8b 8c

Fig. 3. 1,2-Dithiin (**8**) and three types of URFs with π-electron densities for **8** (**8a**, **8b**, and **8c**).

The positions of one imine-type nitrogen and two ketone-type oxygen atoms in **6** do not reflect the π-electron distribution of **6a**. However, these exceptions are acceptable, because they are the sources of one π electron.[3,4] When **6** is reduced to **7**, ketone-type oxygen atoms are converted into phenol-type ones, the positions of which now correspond to those of higher π-electron density in the URF. Thus, these oxygen atoms are placed so as to stabilize the reduced form. An imine-type nitrogen atom at the 8-position in **6** and **7** can in principle be replaced by a carbon atom, since it is never converted into an amine-type nitrogen atom. It is clear that the electronegativity patterns in **6** and **7** are in harmony with the π-electron distributions in URFs **6a** and **7a**, respectively.

Hydrocarbon anion **9a** and trianion **10a** are the URFs for unsubstituted PQQ in the oxidized (**9**) and reduced (**10**) forms (Fig. 4), respectively, which is a PQQ molecule deprived of three carboxyl groups. The π-electron distribution in **9a** and **10a** appears to be insensitive to the presence of the carboxyl groups. Both **9a** and the rings in **6a** have quite similar π-electron distributions. Likewise, **10a** and the rings in **7a**. In all of these cases, an amine-type nitrogen atom is located at the site that corresponds to the 1-position in the URF.

BREs calculated for all π bonds in **9** and **10** are added in chemical formulae **9** and **10**, respectively. These BREs indicate that the aromaticity of **9** arises mainly from the two edge rings. The central *o*-quinonoid ring is non-aromatic. The π bonds located around the quinonoid ring, but not shared by other rings, have small negative BREs. In contrast, the BREs for the π bonds located around the edge rings are much larger. When **9** is reduced to **10**, the central ring is fully aromatized. Consequently, all π bonds in **10** are aromatic with large positive BREs, indicating that the three rings greatly contribute to aromaticity.

As has been seen, the PQQ molecule and its cyclic portion satisfy the TCS rule regardless of their oxidation state. The oxidized (**6**) and reduced (**7**) forms of PQQ are aromatic with TREs of 0.292 and 0.421 $|\beta|$, respectively, where β is the resonance integral for the CC bond. The oxidized (**9**) and reduced (**10**) forms of unsubstituted PQQ are also aromatic with TREs of 0.301 and 0.503 $|\beta|$, respectively. Note that the reduced form is more aromatic than the oxidized form. For reference, the TRE of benzene is 0.273 $|\beta|$.[7,8]

Reinterpretation of the TCS Rule. Next, the applicability of the TCS rule to monocyclic heterocyles is considered. Unsubstituted PQQ (**9**), 3-(2-pyrryl)pyridine (**11**), and 2-vinylpyrrole (**12**) are partial structures of PQQ (**6**). It

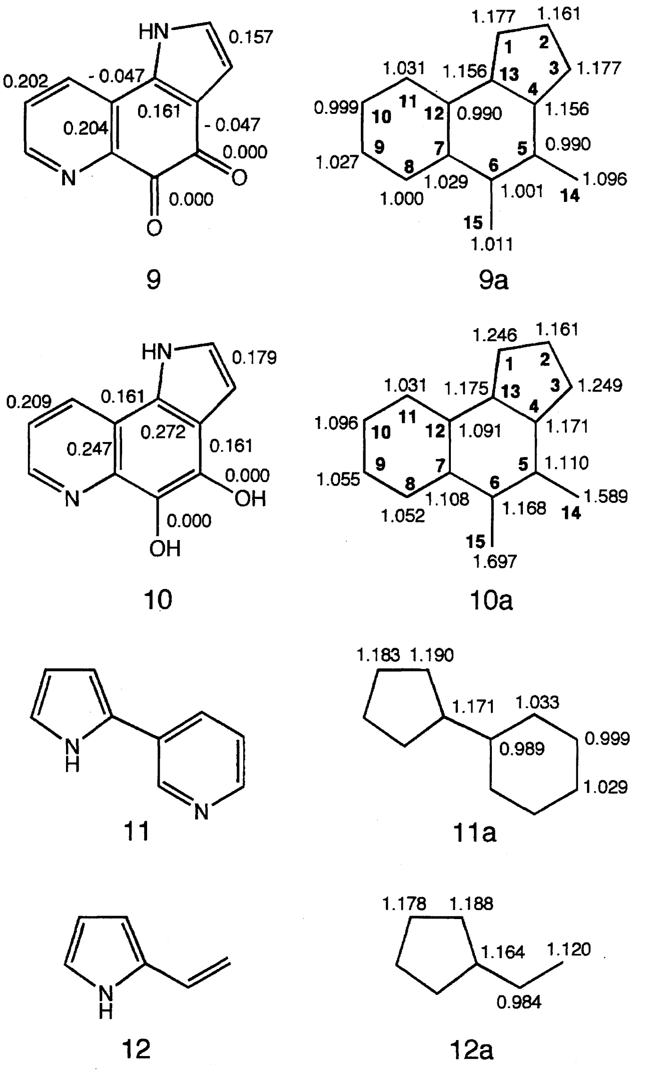


Fig. 4. Partial structures of PQQ (**6**): the oxidized (**9**) and reduced (**10**) forms of unsubstituted PQQ, 3-(2-pyrryl) pyridine (**11**), and 2-vinylpyrrole (**11**). BREs are added in **9** and **10**. Hydrocarbon anions **9a**, **10a**, **11a**, and **12a** are the URFs with π-electron desnities for **9**, **10**, **11**, and **12**, respectively.

is instructive to compare the π-electron distributions in the URFs for **1**, **6**, **9**, **11**, and **12**. In the URFs for all these molecules (**1a**, **6a**, **9a**, **11a**, and **12a**), ca. six π electrons are distributed rather uniformly over the five-membered ring. In general, a five-membered ring in a polycyclic system tend to attract ca. six π electrons to it. It is noteworthy that the π-electron density is relatively high at all carbon atoms in the five-membered ring of **6a**, **9a**, **11a**, and **12a**, whereas the π-electron density is absolutely high at all carbon atoms in **1a**.

What we want to stress in this context is that when heteroatoms are introduced into these URFs, the five-membered URF (**1a**) should not be distinguished from the five-membered rings in **6a**, **9a**, **11a**, and **12a**. When one formally designs the PQQ molecule (**6**), an amine-type nitrogen atom is placed at one of the five vertices in the almost uniformly charged five-membered ring of the URF (**6a**). Amine-type nitrogen atoms can also be introduced into the five-membered rings in its partial structures **9a**, **11a**, and **12a** to form **9**, **11**, and **12**, respectively. Likewise, when one designs the pyrrole molecule (**1**), an amine-type nitrogen atom can be placed at one of the five vertices in the uniformly charged five-membered hydrocarbon anion (**1a**). There are essentially no differences between these procedures. In all cases, one nitrogen atom is placed at one of the vertices in the uniformly charged five-membered ring. Heterocycles **6**, **9**, **11**, and **12** obviously satisfy the TCS rule, so must be **1**—**5**.

We are then led to the following interpretation of the TCS rule: A stable molecule often has heteroatoms of large electronegativity at the positions that correspond to those of relatively and/or absolutely high π-electron density in the corresponding URF. If we accept this interpretation, the stability of all monocyclic aromatic biomolecules can be readily justified using the TCS rule. Since all carbon atoms in the common URF for **1**—**5** (**1a**) bear 1.200 π electrons each, any heteroatom that is an origin of two π electrons can be safely placed at any site in the URF. We can say without difficulty that the resulting five-membered heterocycles are stabilized by cyclic conjugation and topological charge stabilization.

1,2-Dithiins and the TCS Rule. In 1990 we predicted that there must be no antiaromatic biomolecules, since they are thermodynamically destabilized by cyclic conjugation.[5)] We later learned that red-colored compounds, such as thiarubrines A (**13**) and B (**14**) (Fig. 5), are isolable from several composite plants.[15—18)] The systematic names of **13** and **14** are 3-(hex-5-ene-1,3-diynyl)-6-(prop-1-ynyl)-1,2-dithiin and 6-(3-buten-1-ynyl)-3-(1,3-pentadiynyl)-1,2-dithiin, respectively. These compounds contain a 1,2-dithiin (**8**) ring, which is apparently antiaromatic with eight π electrons. We recently noticed that the molecular structure of **8** is heavily deviated from planarity[19,20)] and that the Dewar resonance energy is close to zero.[20)] Therefore, there is no reason to withdraw our previous presumption that there must be no antiaromatic biomolecules.[5)] No antiaromatic species have been isolated by primitive-Earth-simulation experiments.[3,5)]

The URF for 1,2-dithiin (**8**) is nothing other than the benzene dianion. There are two singlet-state electronic configurations (**8a** and **8b**) for this dianion since the lowest vacant MOs of benzene are doubly degenerate. The positions of two sulfur atoms in **8** match the π-electron distribution in **8a**. However, the positions of two sulfur atoms in thiarubrines A (**13**) and B (**14**) cannot be explained in the same manner. The positions of the sulfur atoms in **13** and **14** do not correspond to the positions of high π-electron density in **13a** and **14a**, respectively. Do **13** and **14** violate the TCS rule?

This problem can be solved by taking into account the fact that the SS bond has a very weak π-bond character. VanCatledge estimated the Hückel resonance integral for the SS bond to be 0.63 β,[1)] assuming the CSSC dihedral angle to be 0° or 180°. However, the actual CSSC dihedral angle in 1,2-dithiin (**8**) is far from being 0° or 180°. According to the an ab initio MO calculation at the HF/6-31G** level, the CSSC dihedral angle is as large as 49.6°.[19,20)] As a result, the Hückel resonance integral for the SS bond must become much smaller. Then, the URF for **8** must be close in π-

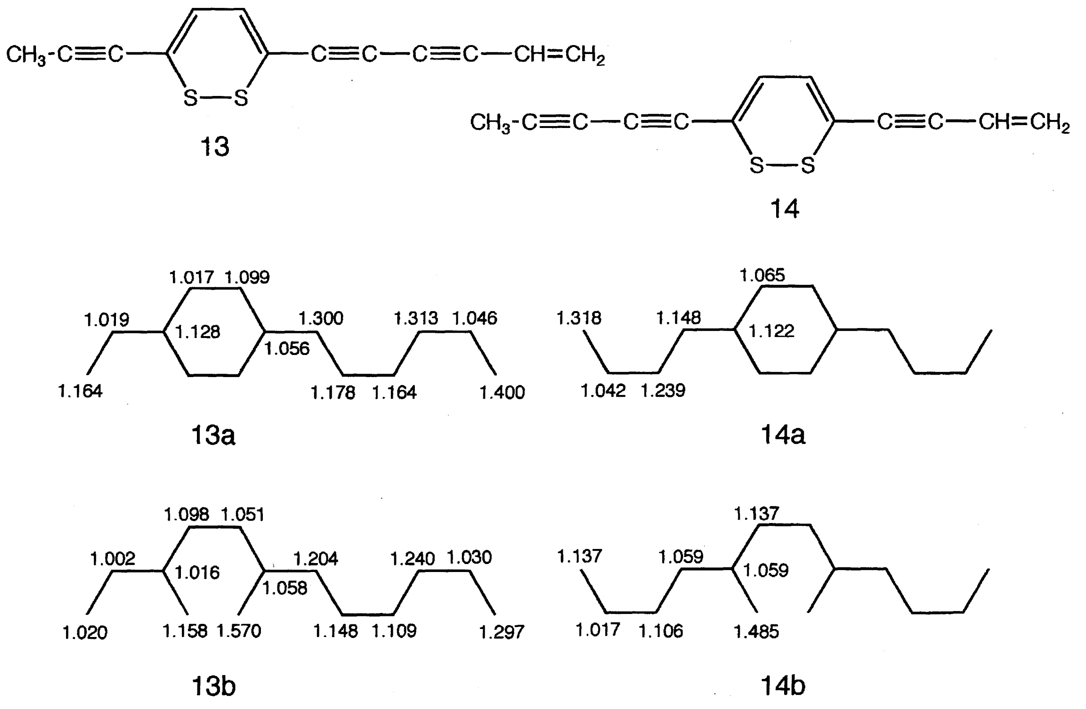


Fig. 5. Thiarubrine A (**13**), thiarubrine B (**14**), and two types of URFs with π-electron densities for **13** (**13a** and **13b**) and **14** (**14a** and **14b**).

bond character to the hexatriene dianion (**8c**). This idea is consistent with essentially no Dewar resonance energy[20] and is supported by the three-dimensional distribution of the four π-MOs in **8**. The overlaps between AOs of two sulfur atoms relevant to π-MOs were found to be very small although, it is not easy to evaluate quantitatively.

In the open-chain URF (**8c**), two end carbon atoms have the largest π-electron densities, which correspond exactly to the positions of sulfur atoms in **8**. Just in the same sense, the URFs for **13** and **14** should not be **13a** and **14a**, but must be more or less similar in π-bond character to **13b** and **14b**, respectively. Thus, there is little doubt that apparently antiaromatic, but in fact nonaromatic, 1,2-dithiins **8**, **13**, and **14** satisfy the TCS rule. Conversely, the TCS rule can still be used to explain fairly well why 1,2-dithiins are formed in some plants. However, since the 1,2-dithiin ring is never aromatic, it tends to be converted into the thiophene (**3**) ring.[15,16]

Concluding Remarks

As shown in previous papers,[3—6] most acyclic and polycyclic biomolecules satisfy the TCS rule. For some reason or another, nature is very reluctant to generate molecules that violate the TCS rule although it often generates highly strained molecules, such as substituted cyclopropanes.[20] Both the oxidized and reduced forms of coenzyme PQQ proved to be not only aromatic, but also consistent with the TCS rule.

There are many monocyclic aromatic biomolecules.[5] Coal and petroleum contain unsubstituted and substituted thiophenes.[5] All of these monocyclic heterocycles, including 1,2-dithiin, were again found to satisfy the TCS rule. Therefore, it is still very true that TCS dominates general biosynthesis and organic geochemistry.[3,4] For these molecules, the TCS rule is compatible with aromaticity, but not with antiaromaticity. Nature is very reluctant to generate antiaromatic molecules.

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