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Prebiotic Synthesis Obeys the Rule of Topological Charge Stabilization

Jun-ichi Aihara
Department of Chemistry, Faculty of Science, Shizuoka University,
Oya, Shizuoka 422

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Most organic molecules synthesized in primitive-Earth-simulation experiments conform to the rule of topological charge stabilization. Heteroatoms in these molecules are all located at the best sites to stabilize the conjugated systems. The situation must be the same for organic molecules formed under prebiotic conditions on primitive Earth.

Chemical evolution may be defined as prebiotic chemical processes leading to the origin of life on Earth.[1–7] It must have occurred in the presence of water and minerals, utilizing the components of the primitive atmosphere, such as carbon dioxide, carbon monoxide, methane, and hydrogen.[1–7] Small amounts of ammonia, hydrogen cyanide (HCN), and hydrogen sulfide were presumably dissolved in the primitive lakes and oceans. Chemical processes must have been driven principally by solar energy in the form of light, lightning, and heat. Some thermal energy was provided by volcanoes, meteoritic impact and radioactive decay.

Many laboratory experiments have been designed to model the prebiotic formation of amino acids, nucleoside bases, and many other biologically important molecules.[1–7] A variety of organic molecules can indeed be synthesized in primitive-Earth-simulation (PES) experiments. Most organic molecules synthesized in PES experiments have one or more heteroatoms in their π-electron systems. It might be a very important matter to seek for the reason why these molecules are produced under prebiotic conditions. Of course, it is never easy to answer this question. Even a partial answer will mark an important progress in the study of chemical evolution and the origin of life.

In 1983 Gimarc pointed out that the pattern of charge densities in a molecule is determined primarily by the connectivity or the topology of the molecule.[8–11] Many examples indicate that nature prefers to place heteroatoms of great electronegativity in those positions where the isostructural, iso-π-eleccronic hydrocarbon has large charge densities. Gimarc called the effect the rule of topological charge stabilization or the TCS rule.[8] This paper aims at explaining the stability of organic molecules formed in PES experiments in terms of Gimarc's TCS rule. We will show below that all these molecules are thermodynamically stable owing to the heteroatoms located at the right sites.

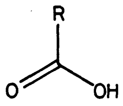
Theory

Charge densities calculated for a molecule containing heteroatoms depend on the choice of semiempirical parameters, but in the isostructural, iso-π-electronic hydrocarbon charge densities are determined only by the topology of the molecule and the number of π electrons. Gimarc referred to the isostructural, iso-π-electronic hydrocarbon as the uniform reference frame (URF).[8–10] The URF is nothing other than a conjugated hydrocarbon obtained by replacing all heteroatoms in a given molecule by sp^2 carbons and then by donating the same number of π electrons to the resulting system. The TCS rule utilizes such URF's to estimate the stability of organic molecules of abiotic origin. First-order perturbation theory has given a justification for the rule.[8]

All charge densities given below will be those calculated for the π-electron systems of the URF's. We used the Hückel molecular orbital (HMO) model in its simplest form. The HMO model is best suited for the present purpose which requires only a qualitative pattern of charge distributions.[8,11] All alkyl substituents will be disregarded for simplicity because they are scarcely conjugated with the parent π-electron framework.

Results and Discussion

Amino acids are crucial building blocks of life. Since the Miller-Urey experiment reported in 1953,[12] a great number of amino acid syntheses have been accomplished using a variety of gas mixtures subjcted to different energy sources.[1–4,7] Various amino acids can also be obtained by heating solutions of hydrogen cyanide.[1–6] All amino acids have one or more isolated carboxylic π-electron systems. A general formula for amino acids is shown in **1**. Here and hereafter, R, R_1, and R_2 represent the substituents not conjugated with a π-electron system in question. Not only amino acids but also carboxylic acids have been detected in many PES experiments.[1,4,6] Carboxylic acids can also be



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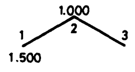

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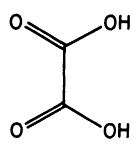
expressed as **1**.

The allyl anion $C_3H_5^-$ (**2**, four π electrons) represents the URF of a carboxyl group **1** not conjugated with the remainder of the molecule (R in **1**). The calculated charge densities in the URF are greater at the edge carbons than at the central carbon. Topological charge stabilization says that electronegative heteroatoms prefer to occupy the sites where electron density is already very great in the iso-π-electronic URF.[8–11] Oxygen is much more electronegative than carbon.[13] Stability of amino acids and carboxylic acids is attributable to the two constituent oxygens. These atoms occupy the two sites of greatest charge density in the URF. Oxalic acid (**3**) has also been formed in some PES experiments.[6] This acid again conforms to the TCS rule. Four oxygens in oxalic acid or oxalates occupy the sites of high charge density in the URF (**4**).



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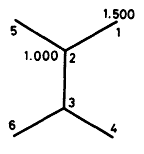

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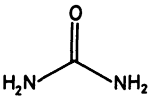
Urea (**5**) was produced in many PES experiments.[1–4,6] The trimethylenemethane dianion (**6**, six π electrons) constitutes the URF of urea. The calculated charge densities are greater at the peripheral carbons than at the central carbon. Nature puts electronegative atoms, oxygen and nitrogen, in the peripheral positions of the URF.[8] A molecule which is iso-π-electronic with **6** has been referred to as a Y-aromatic species, i.e., an exceptionally Y-shaped aromatic molecule, since it is of great stability.[14] Urea is a stable aromatic species in this sense, conforming to the TCS rule.



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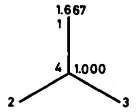

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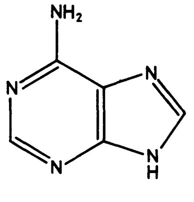
The purine and pyrimidine bases are key components of nucleic acids. Adenime (**7**), guanine (**8**) cytosine (**9**), thymine (**10**), and uracil (**11**) are formed under various prebiotic conditions.[1–7] These bases can be synthesized all at once in the electric-discharge experiment with methane–nitrogen–water mixtures.[15] Senarios can be developed for the prebiotic synthesis of aino acids, purines, and pyrimidines, using HCN as the sole source of carbon.[6] The occurrence of HCN on primitive Earth is supported by its facile formation under a variety of conditions.[6] HCN oligomerizes easily in laboratory experiments. HCN oligomers then hydrolyze to amino acids, purines, and pyrimidines. This synthetic scheme is very attractive, in that all three types may have been produced at the same time and place on primitive Earth.[6]



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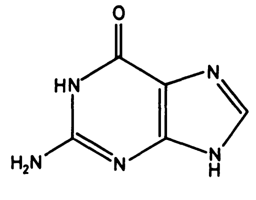

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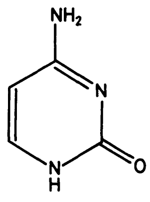

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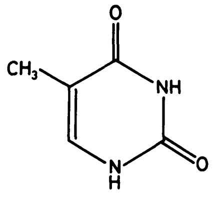

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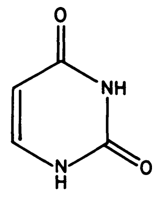

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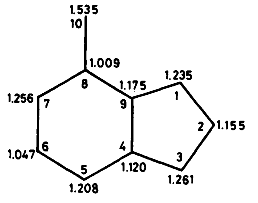
The URF's of two purine bases **7** and **8** are shown in **12** and **13**, respectively. Heteroatoms in these bases, without exception, are situated at the sites of large charge density in their respective URF's. All positions of high charge density in the URF's are occupied by heteroatoms in the corresponding purine bases. Three pyrimdine bases **9**, **10**, and **11** happen to have the same URF (**14**) with ten π electrons. Heteroatoms in these bases occupy the sites of high charge density in their common URF. Thus, nucleoside bases are not only stable but also easy to form on primordial Earth.



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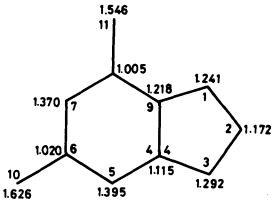

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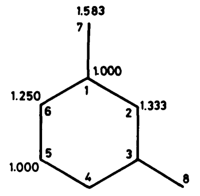

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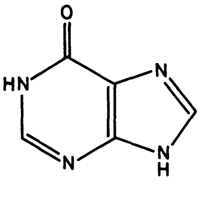
Similar PES experiments yield some more molecules which have either a purine or pyrimidine nucleus.[5,6] Among them are hypoxanthine (**15**), xanthine (**16**), 4,5-dihydroxypyrimidine (**17**), 5-hydroxyuracil (**18**), and orotic acid (**19**). The URF's of hypoxanthine and xanthine are the same as those of adenine (**12**) and guanine (**13**), respectively. The URF's of 4,5-dihydroxypyrimidine, 5-hydroxyuracil, and orotic acid are shown in **20**, **21**, and **22**, respectively. All these molecules conform to the TCS rule.



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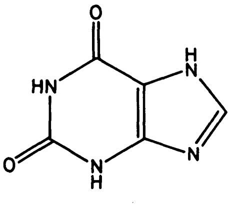

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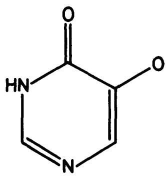

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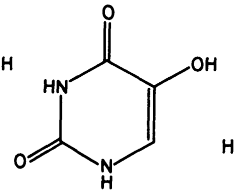

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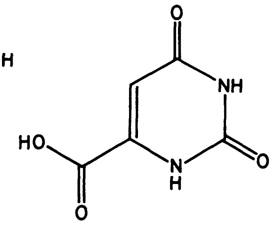

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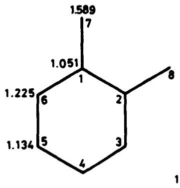

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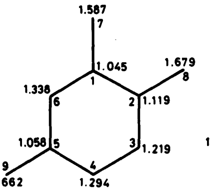

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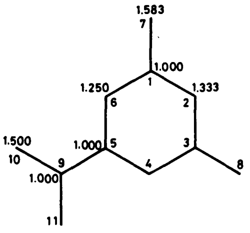

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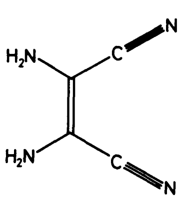
According to the original TCS rule,[8] one does not need to place heteroatoms at all sites of high charge density in the URF to construct a stable molecule. Position 6 in the URF of pyrimidine bases (**14**) has high charge density, but these bases has no heteroatom there. In contrast, heteroatoms in **2**, **3**, **5**, **7**, **8**, **15**, and **16** occupy all sites of high charge density in their respective URF's. We might say that these molecules are extremely faithful to the TCS rule.

The tetramerization of HCN to form diaminomaleonitrile (DAMN, **23**) is a key step for the synthesis of nucleoside bases from HCN.[2-6] 5-Amino-4-imidazolecarbonitrile (AICN, **24**), 5-amino-4-imidazolecarboxamide (AICA, **25**), and 5-amino-4-imidazolecarboxamidine (AICAI, **26**) are formed during the origomerization of HCN. These molecules are plausibly prebiotic since they are produced by the reaction of DAMN with some appropriate simple molecules.[2-6] Then, purine bases are synthesized from AICA and AICAI. Therefore, it is instructive to see if these three molecules conform to the TCS rule. The URF's of **23**, **24**, and **25** are shown in **27**, **28**, and **29**, respectively. The URF of **26** is identical with that of **25**. It is clear from these URF's that **23**–**26** obey the TCS rule. This implies that the TCS rule operates in almost every step of prebiotic chemistry.



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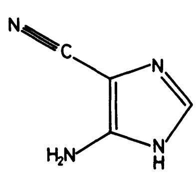

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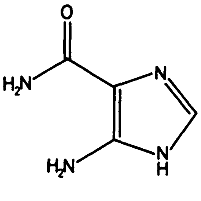

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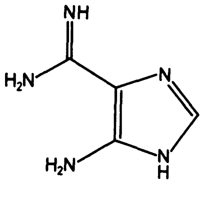

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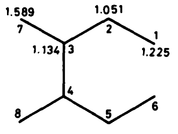

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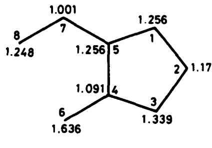

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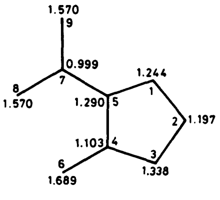

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Cyanamide (**30**) can be formed under prebiotic conditions from ammonium cyanide by a photochemical reaction.[1,2,6] This molecule undergoes self-addition to form a dimer, cyanoguanidine (**31**).[2,6]

$H_2N—C\equiv N$

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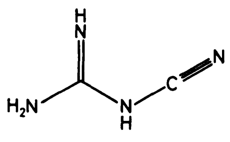

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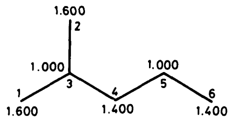
These two compounds may funtion as condensing agents in phosphorylation and peptide formation. The URF of cyanamide is identical with that of carboxylic acid **2**. The URF of cyanoguanidine is shown in **32**, which may be regarded as a cyano derivative of a Y-aromatic compound (guanidine). Heteroatoms in both molecules are placed at the sites of high charge density in the URF's. Individual peptide bonds **33** in polypeptide are iso-π-electronic with the allyl anion **1**. Peptide bonds also confrom to the TCS rule.



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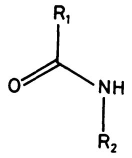

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Concluding Remarks

Gimarc pointed out that the TCS rule has potential value as a guide for synthetic efforts to be made by organic chemists.[8] We have shown above that many candidates for prebiotic organic molecules conform to the TCS rule. All heteroatoms in every molecule investigated are placed at the sites of large charge density in its URF. Amino acids, nucleoside bases, and related molecules are fully consistent with the TCS rule. This may imply that a chemical reaction with simple molecules, driven by a primitive energy source, yields molecules conforming to the TCS rule.

It seems very likely that real prebiotic chemical evolution[1,2] occurred in harmony with the TCS rule on primitive Earth. Then, nature presumably picked up these molecules to construct living organisms. Some of the molecules must have exerted important functions incidentally in cellular systems. Conversely, nature has been so skillful as to choose biologically important molecules from the products of chemical evolution on primitive Earth.

As noted by Gimarc,[8] a molecule conforming to the TCS rule is relatively stable in a thermodynamic sense. In general, a stable molecule is associated with low activation energy of formation.[16] Thus, nature has utilized energetically very accessible ways of organic synthesis. Living organisms must have chosen useful molecules from organic molecules readily available on primitive Earth. These molecules necessarily conform to the TCS rule. Thus, topological charge stabilization[8,11] serves as a unifying principle for the systematization of chemical evolution.

We thank Prof. Kensei Kobayashi (Yokohama National University) for familializing us with the concept of chemical evolution.

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