Stability of Naturally Occurring Pyrazines and Construction Route of Pyrazine Rings

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Naturally occurring pyrazines fit well the theory that conformity to the TCS rule gives a stable molecular system. Thus, many pyrazines so far synthesized and those in nature which are energetically very stable molecules can be synthetically quite accessible. The TCS rule applies very well to the construction route of pyrazine rings.

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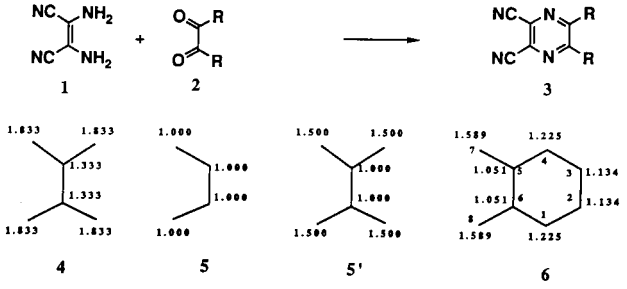
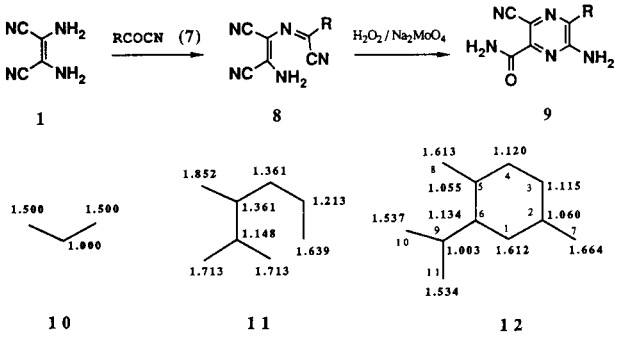
The substitution of 1,2-diaminoethenes with substituted α-dicarbonyl compounds leads to pyrazines and this method is the most widely used for pyrazine synthesis [1]. A number of pyrazine derivatives has been found to occur naturally. Recently, certain hydroxypyrazines such as septorine [2] and emeheterone [3], carrying a methoxy group on their pyrazine ring, have been found in nature. The structure and oxidation of 2-hydroxy-5-methoxy-3,6-diisobutylpyrazines were discussed in our previous paper [4]. In 1983, Gimarc [5] pointed out that the pattern of charge density in a molecule is primarily determined by its connectivity or topology. Many examples indicate that nature prefers to place heteroatoms of great electronegativity [6] in positions where the isostructural, iso-π-electronic hydrocarbon has a large charge density. Gimarc [5] refers to the isostructural, iso-π-electronic hydrocarbon as a uniform reference frame (URF) and calls the effect, "the rule of topological charge stabilization", or the TCS rule. Aihara [6] reported unsaturated organic molecules produced in nature tend to obey this rule. We recently reported [8] that the fundamental skeleton of tropones possessing a unique heptagonal structure may be predicted to be aromatic with a positive resonance energy [9] conforming to the TCS rule and that naturally occurring tropolones nicely fit the theory that conformity to this rule provides a stable molecular system. To obtain useful data on very complex reactions leading to the formation of tropylium compounds having triannulated heterocycles, the stability of the starting materials, intermediates, and products were also studied in relation to Gimarc's TCS rule. In this present study, examination was made on the stability of naturally occurring pyrazines and the construction route of pyrazine rings with regard to the TCS rule. The HMO theory [10] is assumed in its simplest form. Ketone oxygen and imine nitrogen contribute one π-electron to conjugated system, whereas the amine nitrogen and alcohol (or ether) oxygen contribute two π-electrons.

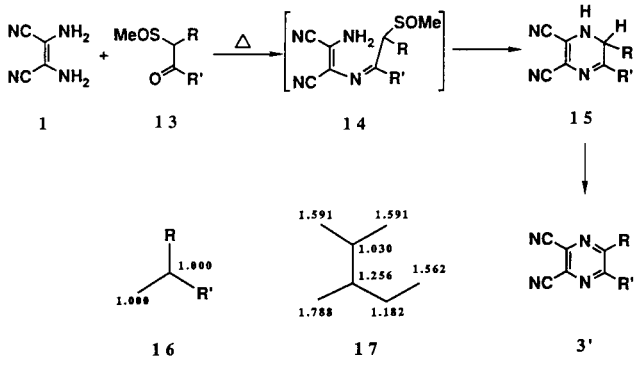
The uniform reference frames (URF's) for diaminomaleonitrile (**1**), diketone **2**, and pyrazine **3** are shown in **4**, **5**, and **6**, respectively. URF for **1** has a high charge density



at the exo-methylene carbons. Compound **1** can be designed by replacing the exo-methylene carbons by iso-π-electronic substituents. Butadiene is a URF for **2**. When R is a methyl group, the corresponding URF (**5'**) has a large charge density at the exo-methylene carbons. The corresponding positions in **5'** are all occupied by iso-π-electronic substituents. This reaction [11] probably proceeds in a stepwise manner, and when acyl cyanides **7** are used, the intermediate Schiff's bases **8** may be isolated and selectively hydrolyzed to amides which subsequently undergo ring closure to produce the pyrazine derivatives (**9**). URF's for **7**, **8**, and **9** are shown in **10-12**, respectively. In each case the heteroatoms and substituents are located at



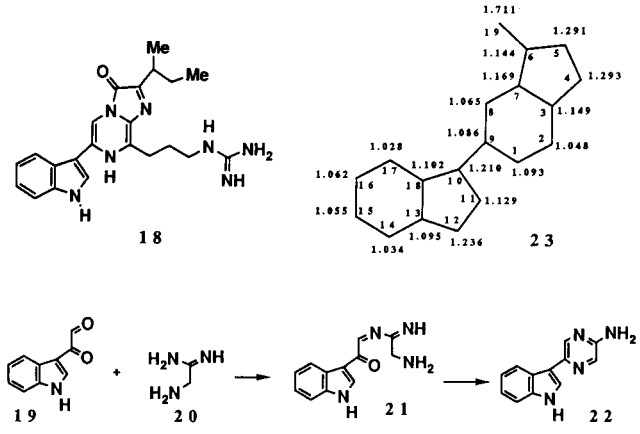
sites of large charge density in the corresponding URF's. Kano *et al.* [12] carried out the condensation of β-ketosulfoxides **13** with **1**. The URF for **15** is the same as that of



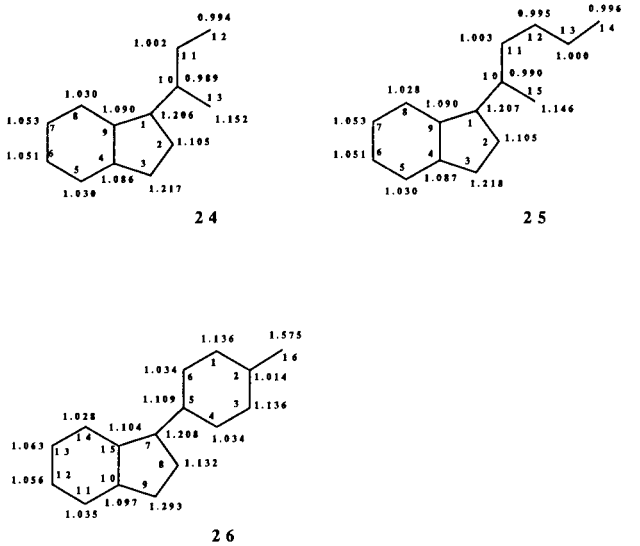
1 **13** **14** **15**

16 **17** **3'**

17. For the synthesis of the bioluminescent substance Cypridina luciferin (**18**), Kishi *et al.* [13] carried out the condensation of 3-indolylglyoxal (**19**) with aminoacetamidine (**20**) to obtain the 2-amino-5-(3-indoloyl)pyrazine (**22**)



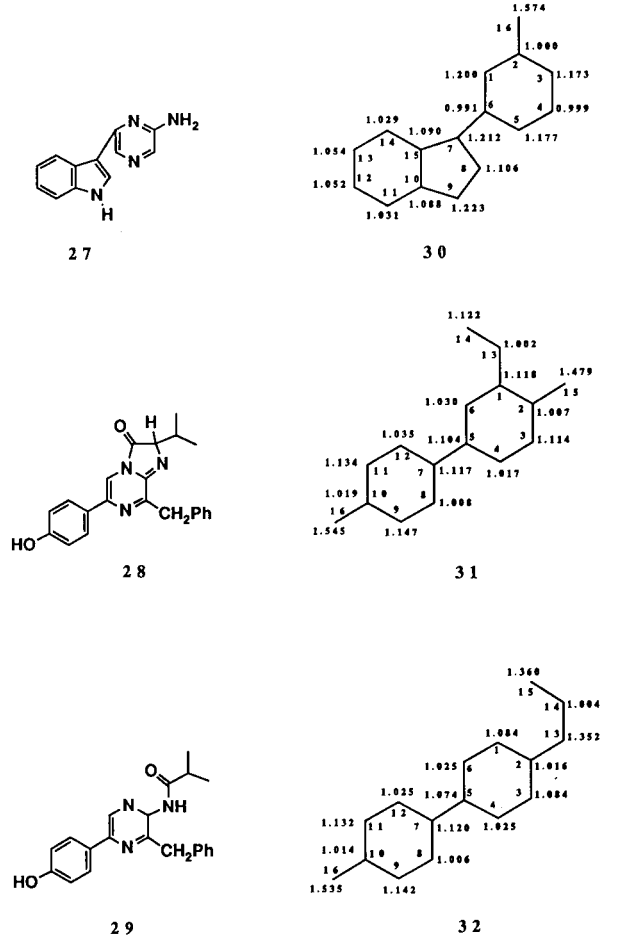
18 **23** **19** **20** **21** **22**



24 **25** **26**

which subsequently became **18**. The URF (**23**) of **18** has a large charge density at positions 1, 4, 7, 12, and 19. The heteroatoms and ketone oxygen are thus situated at the site of a large charge density in the corresponding URF. URF's for **19** and **21** are shown in **24** and **15**, respectively. The URF for **20** is the same as that of **10**. The URF for **19** has a high charge density at positions 3 and 13. The imine nitrogen and ketone oxygen atom are situated in the corresponding positions. However, the charge density at position 12 is not high in the URF. Thus, this position for the ketone oxygen does not conform to the TCS rule. Actually compound **19** is rather unstable. Kishi *et al.* [13] confirmed the indolyl group in **22** to be substituted at the 5 and not at the 6 position of the pyrazine ring based on a comparison of the nmr spectra of 2-amino-5-phenylpyrazine [13].

We consider the URF (**30**) of 2-amino-6-(3-indoloyl)pyrazine (**27**) and the indolyl group in **22** to be likely substituted at 6 position of the pyrazine ring. The URF for **22**

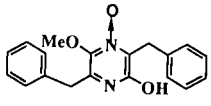


27 **30** **28** **31** **29** **32**

has a large charge density at exactly those positions where heteroatoms occur in the corresponding URF. However, the URF for **27** has a large charge density at positions 1, 9, and 16. The charge density at position 4 is not high in the

URF. The indolyl group in **22** is thus substituted at 5 and not the 6 position of the pyrazine ring, according to Gimarc's TCS rule. It is now generally recognized that simple pyrazines such as **28** are responsible for bioluminescence during enzyme-catalyzed oxidation, *viz.* **28**→**29** [14]. The URF's for **31** and **32** have a large charge density at just those positions where the heteroatoms are situated in the corresponding pyrazines. As above, the starting materials, intermediates, and products in the reactions are fully consistent with the TCS rule. The construction route presented for pyrazine rings appears in conformity with that which proceeds enegetically in the direction of the most favorable route.

Next to be considered is the stability of the naturally occurring pyrazines. The URF's for emeheterone (**33**) [3], septorine (**34**) [2], and astechrome (**35**) [15] are shown in



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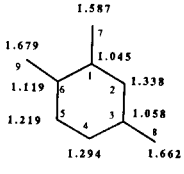

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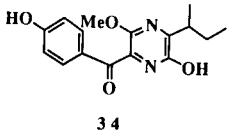

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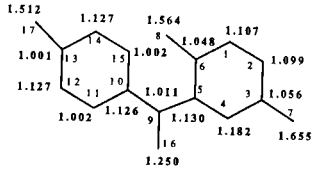

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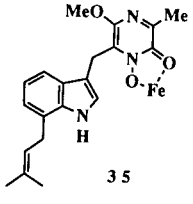

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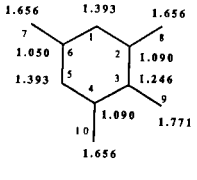

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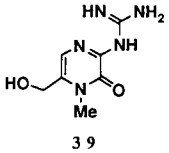
36-38, respectively. All positions of high charge density in URF's for naturally occurring pyrazines are occupied by heteroatoms in the corresponding natural products. The URF's for other naturally occurring pyrazines **39** [16], **40-42** [17] are shown in **43-46**, respectively. According to the original TCS rule [5], it is not necessary to place heteroatoms at all of the sites of high charge density in URF



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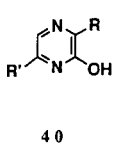

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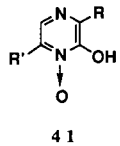

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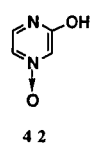

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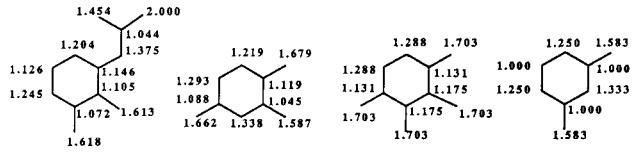
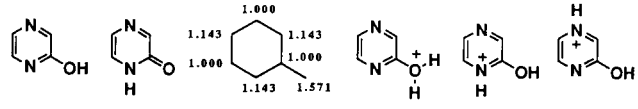


43 44 45 46

to stabilize molecules. URF's **39-42** have a large charge density at just those positions where heteroatoms and/or iso-π-electronic subsituents are found in the natural products. Naturally occurring pyrazines are thus shown to well fit the theory that conformity to the TCS rule gives a stable molecular system. Molecules that do not conform to this rule can, in principle, be designed using an infinite number of molecules. Consequently, many pyrazines so far synthesized were chosen from energetically very stable and synthetically very accessible molecules.

2-Hydroxypyrazines have two possible tautomers such as amido (pyrazinone type) and iminol (pyrazinol type) forms, as in the case of 2-hydroxypyridine [18]. The heats of formation for the amido and iminol forms of **47** and **48** were found to be 0.86 and 0.41 kcal/mol, respectively, by the AM1 method [19]. URF's for **47** and **48** are the same as that of **49**. The TCS rule thus can not be distinguished



47 48 49 50 51 52

between **47** and **48**. Proton affinities [20] of nitrogen and oxygen bases are about 200-400 and 150-250 kcal/mol, respectively. Those of **50**, **51**, and **52** were calculated to be 164, 202, and 204 kcal/mol, respectively, by the AM1 method [19]. The proton affinity of the nitrogen atom is much larger than that of the oxygen atom. The heats of formation and proton affinities thus indicate the pyrazinone form to be more stable than the pyrazinol form.

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