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Electronic Structure of β-Carboline Anhydro-Bases

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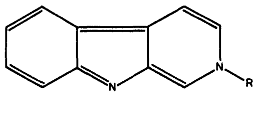
β-Carboline anhydro-bases generally have a large positive topological resonance energy although they apparently disobey the rule of topological charge stabilization (TCS rule). π-Electron densities and molecular geometries calculated at the STO-3G$^+$ level support the view that the dipolar aromatic structure contributes appreciably to the stability of β-carboline anhydro-bases. However, these molecules are still worse in energy than the isomeric β-carbolines. Protonated anhydro-bases or β-carbolinium ions conform to the TCS rule. All biogenic β-carboline anhydro-bases must be protonated in living organisms.

Although there is a lengthy list of alkaloids with an indole skeleton, those having a β-carboline anhydro-base ring system are rather scanty.[1] Here, the term "β-carboline anhydro-base" represents 2*H*-pyrido[3,4-*b*]indoles **1** and related species **2**—**6**.[2] Ring systems **4**, **5**, and **6** are the dihydro derivatives of **1**, **2**, and **3**, respectively. Among this kind of alkaloids are alstonine (**7**), sempervirine (**8**), euxylophorine B (**9**), nitramidine (**10**), 6,7-dihydroflavopereirine (**11**), and dehydroevodiamine (**12**).[1] These compounds constitute a group of biomolecules with a rather odd conjugated system.



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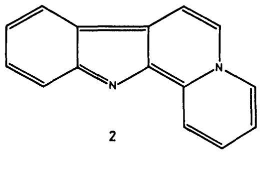

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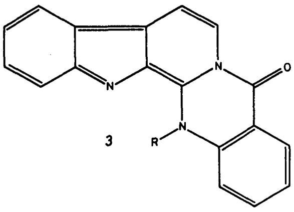

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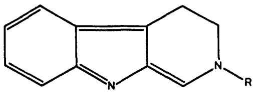

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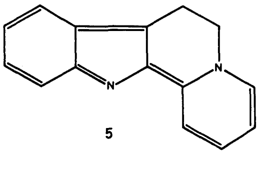

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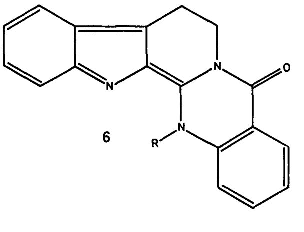

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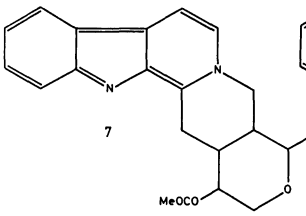

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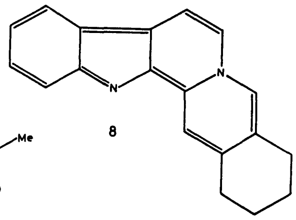

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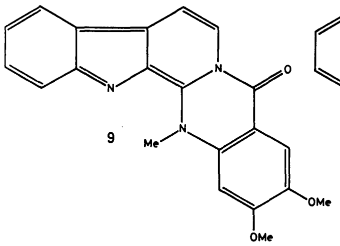

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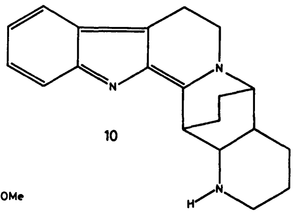

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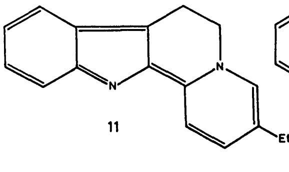

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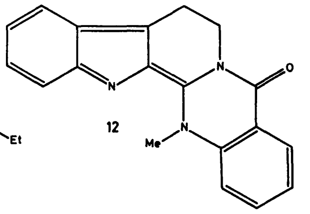

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All β-carboline anhydro-bases have an *o*-quinonoid substructure in the conjugated system.[2] Therefore, the number of possible covalent canonical structures is limited. For example, only one covalent structure can be written for **1**, **2**, **4**, and **5**. In general, substantial stabilization due to cyclic conjugation or a high degree of aromaticity cannot be expected from such molecular structures. Unfortunately, little has so far been learned about the quantum-chemical features of this kind of compounds. It is the purpose of this paper to examine the electronic structure and aromaticity of these rather unfamiliar conjugated systems in some detail.

Theory

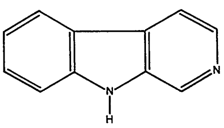
Aromaticity is one of the most important properties which are inherent in cyclic π-electron systems. Topological resonance energy (TRE) has served as an excellent measure of aromatic stabilization.[3,4] TREs of β-carboline anhydro-bases and related species were calculated using Hückel molecular orbital (HMO) theory. Two sets of Hückel parameters (one compiled by Streitwieser[5] and one determined by Hess, Schaad, and Holyoke[6,7]) were adopted.

Gimarc's rule of topological charge stabilization (TCS rule) provides another theoretical basis for predicting the stability of heterocyclic systems.[8—10] When one applies this rule to a given heteroconjugated molecule, one must obtain the π-electron distribution in the uniform reference frame (URF, i.e., the isostructural, iso-π-electronic hydrocarbon).[8] π-Electron densities in all URFs were calculated using simple HMO theory. Substituent R, if any, was omitted from the URF since it scarcely affects the gross π-electron distribution in the ring system.

Ab initio molecular orbital calculations were carried out to estimate realistic π-electron densities in two fundamental ring systems β-carboline anhydro-base **1** and β-carboline **13**. β-Carboline is a trivial name for 9*H*-pyrido[3,4-*b*]indole and its derivatives. The GAUSSIAN-82 program package[11] combined with the STO-3G+ basis set[12,13] was utilized. Since the STO-3G basis set[12] is not suited to atoms with excessive electrons, diffuse functions with $\alpha_{SP}(N)=0.0639$[13] were added to imine nitrogens. Geometry optimization procedures allowed bond angles and lengths to vary.

Results and Discussion

β-Carboline anhydro-bases **1**—**6** possess TREs listed in Table 1. TREs for the isomeric β-carbolines **13**—**16** are also given in this table. These TRE values are slightly dependent on the choice of Hückel parameters. The TRE of **1** is much larger than expected from its quinonoid conjugated system, i.e., about 0.8 time as large as that of its structural isomer **13**. This is somewhat surprising because aromatic sextets[14,15] or six-membered conjugated circuits cannot be chosen from **1**. The only conjugated circuit available in this molecule[16] is a peripheral fourteen-π-electron circuit. However, the heteroannulene having the same conjugated circuit (**17**) possesses a much less TRE than **1**. Therefore, individual rings or circuits in **1** must contribute much to aromaticity.



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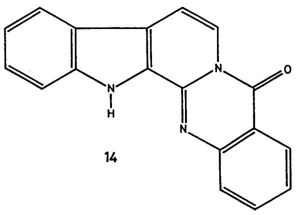

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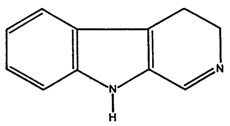

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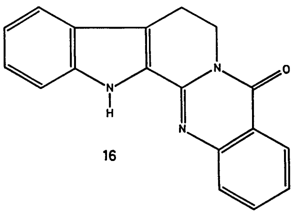

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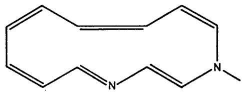
Table 1. TREs of β-Carboline Anhydro-Bases and Related Compounds

Species	TRE/|β|	
	Hess-Schaad parameters[a]	Streitwieser's parameters[b]
1	0.444	0.417
2	0.580	0.554
3	0.680	0.660
4	0.286	0.282
5	0.486	0.474
6	0.564	0.569
13	0.509	0.543
14	0.695	0.675
15	0.331	0.334
16	0.591	0.593
17	0.083	0.083

a) Refs. 6 and 7. b) Ref. 5.



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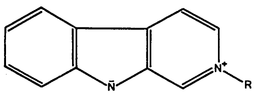
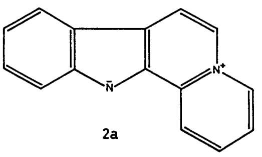
β-Carboline anhydro-bases other than **1** have essentially the same aromatic character as **1**. TREs of **2**—**6** are very large although they are likewise quinonoid with a limited number of covalent canonical structures. We might say that all these anhydro-bases are resonance-stabilized aromatic species. TREs of **3** and **6** are comparable in magnitude to those of the corresponding β-carbolines **14** and **16**, respectively. There are no isomeric β-carbolines for **2** and **5**.

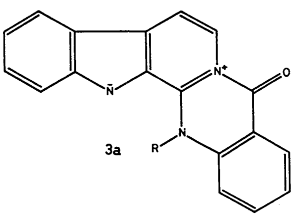
Large TREs of **1**—**6** tempt us to write dipolar aromatic structures for these molecules.[2,17—19] This can be done by converting the constituent amine and imine nitrogens into iminium and amide nitrogens, respectively. Dipolar aromatic structures thus written for **1**—**6** are shown in **1a**—**6a**. β-Carbolines are formally iso-π-electronic with these dipolar structures, in which iminium and amide nitrogens are the sources of one and two π electrons, respectively. The



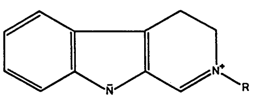
1a



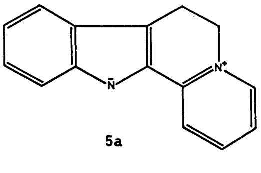
2a



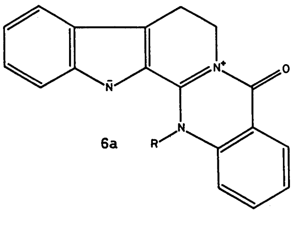
3a



4a



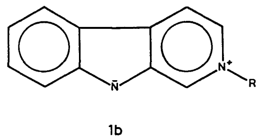
5a



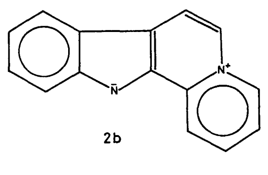
6a

coexistence and cooperation of an amine and an imine nitrogen is obviously required to write such aromatic charge-separated structures. It was Armit and Robinson who first proposed this type of aromatized structures.[17] In 1925 they depicted the conjugated system of a carboline anhydro-base as a compromise between a quinonoid and a dipolar aromatic structure.

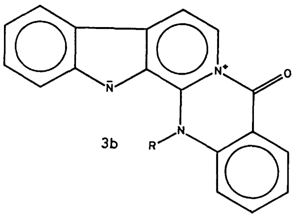
Aromaticity of every β-carboline anhydro-base can further be visualized by writing a Clar structure[14,15] in harmony with the arrangement of double bonds in the dipolar aromatic structure. Clar structures for **1**—**6** are shown in **1b**—**6b**, where the circles represent the aromatic sextets. It is noteworthy that one or more aromatic sextets[14,15] are created by replacing the quinonoid by the corresponding dipolar structure. Considering that every aromatic sextet in Clar structures must be as aromatic as substituted benzenes (TRE≈0.25|β|), Clar structures **1b**—**6b** are in quantitative agreement with large TREs for **1**—**6**.



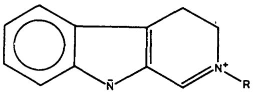
1b



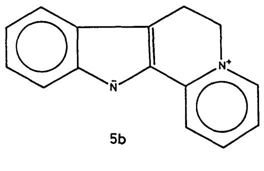
2b



3b



4b



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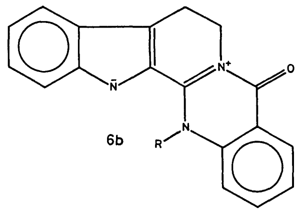


6b

The pattern of the π-electron distribution in a given anhydro-base reflects the weight of the dipolar aromatic structure. The molecular geometries of **1** and **13** optimized at the STO-3G$^+$ level are shown in Fig. 1, and the charge distributions obtained for them in Fig. 2. One may anticipate that an amide-type nitrogen attracts more π electrons than an imine-type nitrogen. In fact, the π-electron density at the imine nitrogen in **1** is larger by 0.239 than that at the imine nitrogen in **13**. This indicates decisively that the imine nitrogen in **1** takes an intermediate position between an imine and an amide nitrogen. On the other hand, the π-electron density at the amine nitrogen in **1** is smaller by 0.168 than that at the amine nitrogen in **13**. Diffuse functions added to imine nitrogens[13] were very effective for increasing the mobility of π electrons in the anhydro-bases.

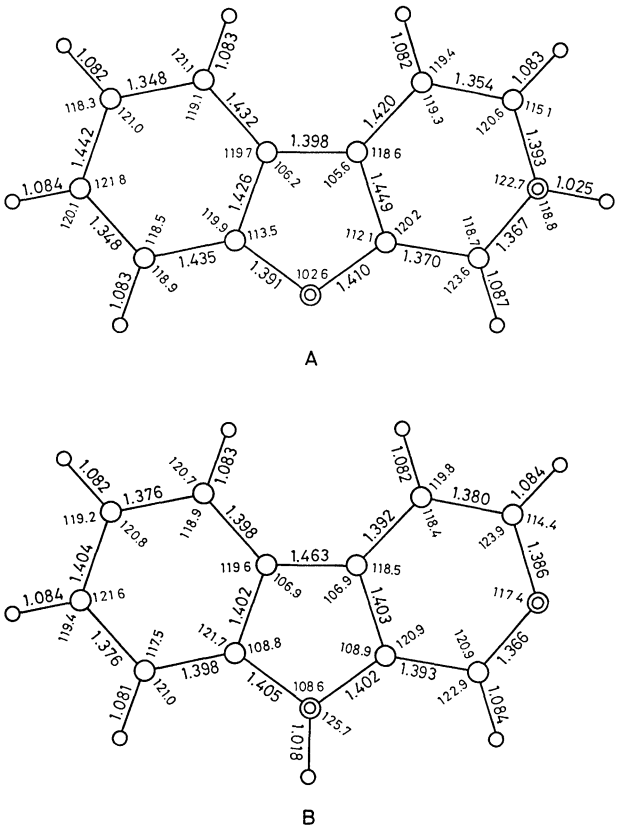


Fig. 1. Molecular geometries optimized at the STO-3G$^+$ level: (A) β-carboline anhydro-base and (B) β-carboline. Bond angles and lengths are given in units of degrees and Å, respectively, Double circles signify nitrogen atoms.

It should be emphasized that not only π-electron densities but also optimized molecular geometries of **1** and **13** support the view that the dipolar structure contributes appreciably to the resonance hybrid of **1**. The optimized geometry of **1** in Fig. 1 is fairly consistent with the dipolar aromatic structure **1a**. The lengths of two CN bonds in the central ring of **1** are almost equalized as in the case of **13**. This is not expectable from the covalent quinonoid structure.

As has been seen above, it is mobile π electrons that create aromatic sextets. Such a propensity of π electrons must be balanced by that of σ electrons to effect charge neutralization. σ Electrons displace to some extent so as to compensate the imbalance of π-electron densities at all conjugated atoms. It necessarily follows that overall electron density at every atom is determined primarily by the electronegativity of the atom. Ab initio overall electron densities in **1** and **13** are also given in Fig. 2.

However, even if a dipolar structure contributes appreciably to **13**, we can never say that **1** is lower in energy than **13**. At the STO-3G$^+$ level, unsubstitued β-carboline anhydro-base (**1**, R=H) is less stable by

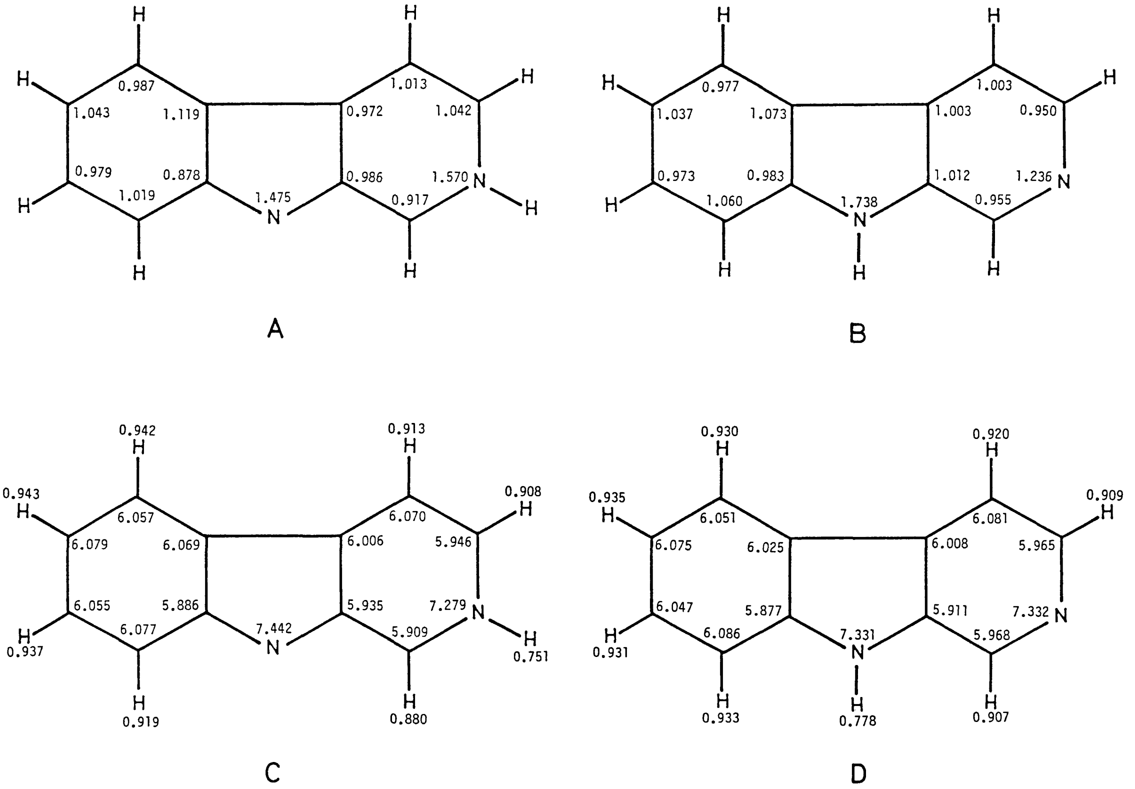


Fig. 2. Charge densities calculated at the STO-3G$^+$ level for β-carboline anhydro-base (**1**) and β-carboline (**13**): (A) π-electron densities in **1**; (B) π-electron densities in **13**; (C) overall electron densities in **1**; (D) overall electron densities in **13**.

28 kcal mol^{-1} than its structural isomer β-carboline (**13**). As this energy differences is far from being negligible, β-carboline would never isomerize to the anhydro-base.[2)] If substituent R in such anhydro-bases as **1**, **3**, **4**, and **6** were replaced by a hydrogen, the molecule would no longer retain the anhydro-base conjugated system, and would be converted to the corresponding β-carboline immediately. As shown in Fig. 1, the degree of bond-length alternation along the periphery is somewhat higher in **1** than in **13**. This reflects the arrangement of double bonds in the covalent canonical structure (**1**).

In a previous paper,[10)] we demonstrated that biomolecules conform to the TCS rule.[8)] Most heteroatoms in biomolecules occupy the positions which already have large charge density in the URFs. Above all, amine nitrogens and ether (or alcohol) oxygens were found to obey the TCS rule without exceptions.[10)] As these atoms contribute two π electrons to the conjugated system, they behave like dications which can attract about two π electrons. This is the primary reason why amine nitrogens and ether oxygens in biomolecules strictly obey the TCS rule.

The URFs for β-carboline anhydro-bases **1**—**6** are presented in Fig. 3. URF A in this figure is nothing other than the fluorenide ion with fourteen π electrons. The location of the imine nitrogen in **1** corresponds to the site of high charge density in this URF. However, the amine nitrogen in **1** occupies the wrong position. Charge density is not high at the corresponding position in URF A. Thus, **1** does not obey the TCS rule as a whole. Other anhydro-bases **2**, **4**, and **5** again disobey the TCS rule. The situation with many derivatives of these anhydro-bases is very similar. An amine nitrogen in these species does not occupy the position of high charge density in the URFs.

Ring systems **3** and **6** are different from others, in that their covalent canonical structures are fairly consistent with the TCS rule. This coincides with the fact that **3** and **6** have as large TREs as their structural isomers **14** and **16**, respectively. There is an *o*- or *p*-pyridone ring in all these ring systems. These substructures usually obeys the TCS rule.

The URF for every β-carboline anhydro-base is the same as that for its structural isomer β-carboline. Both URFs have the same number of π electrons in the same hydrocarbon framework. In case that all species concerned share the same URF, the most stable molecule(s) can be chosen from them on the basis of the TCS rule.[8)] For example, β-carboline anhydro-base **1** does not conform to the TCS rule, whereas β-carboline **13** does. This again shows that **13** must be

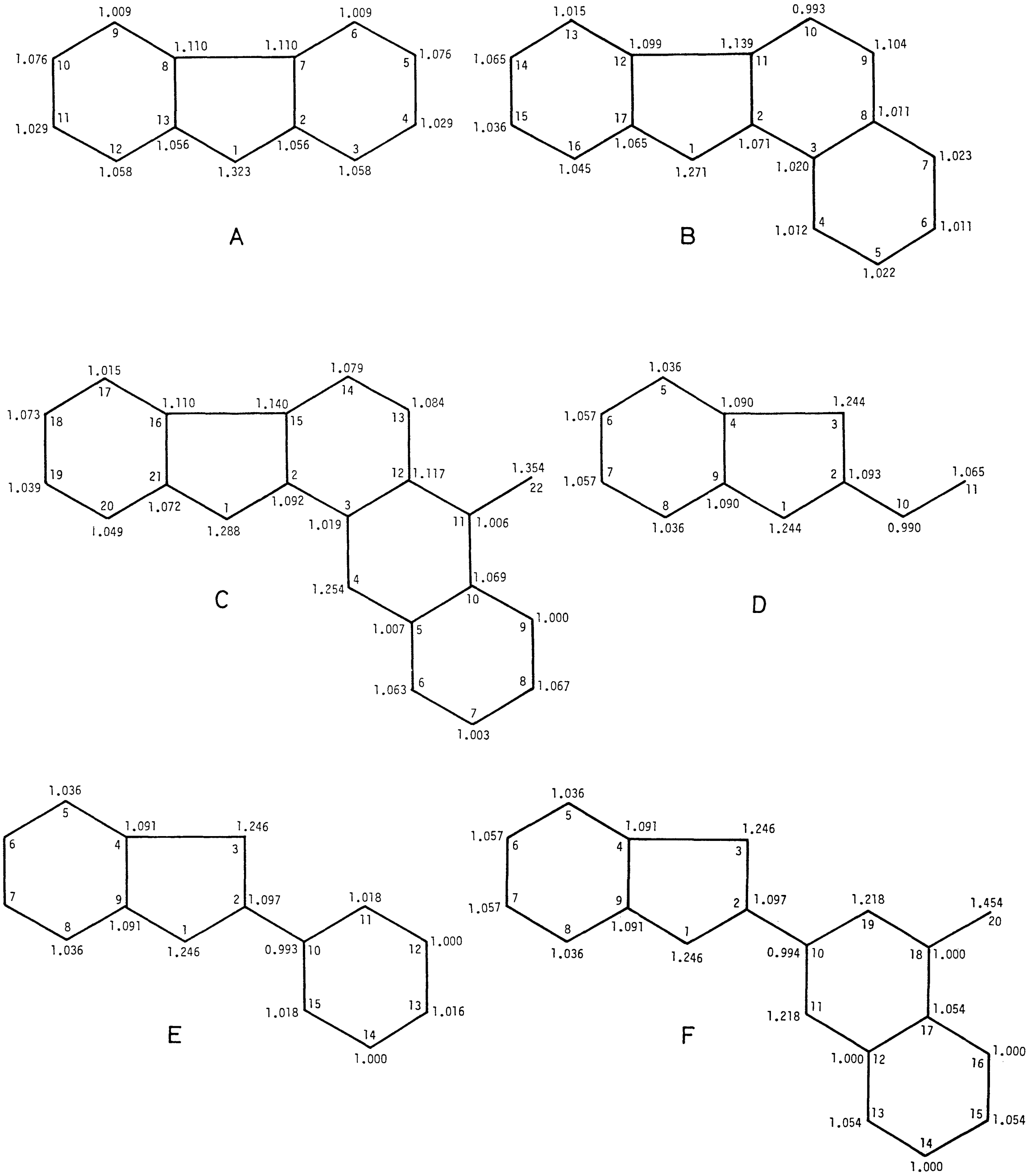


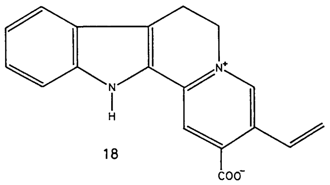
Fig. 3. Uniform reference frames (URFs) for β-carboline anhydro-bases: (A) **1**; (B) **2**; (C) **3**; (D) **4**; (E) **5**; and (F) **6**.

thermodynamically much more stable than **1**.

In this context, it is interesting to see that the dipolar aromatic structures for all anhydro-bases are consistent with the TCS rule. Electron-rich amide nitrogens occupy the positions of high charge density in the URFs. However, as can be seen from the relative energies of **1** and **13**, the contribution of a dipolar aromatic structure is not large enough to make a given anhydro-base comparable in energy to the corresponding β-carboline. The one-electron approximation in HMO theory may be responsible in part for large TREs of the anhydro-bases.

Another problem arises when aromaticity is attributed to a dipolar aromatic structure. The contribution of the dipolar structure intensifies the basicity of an imine or an amide nitrogen in the β-carboline anhydro-bases to a considerable extent. Accordingly, the anhydro-bases must be much more basic than the corresponding carbolines.[2,18,19] In fact, pK_a values between 10.5 and 10.7 were reported for alstonine (**7**), sempervirine (**8**), and related alkaloids.[2] Protonation and alkylation of **1** take place preferentially at the imine nitrogen.[2]

It is now clear that protonation is an important way to stabilize the anhydro-base conjugated systems. Vincarpine (**18**) indicates that if a dissociable proton is available in an anhydro-base molecule, it moves readily to the imine nitrogen to form a zwitterion.[20]



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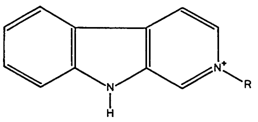
Particularly intriguing is the fact that the anhydro-bases are protonated even in neutral water.[19] Even if an anhydro-base molecule has no dissociable proton, the electronic absorption spectrum of the aqueous solution is identical with that given by the β-carbolinium ion.[19] The pH value of the solvent must be higher than 11.5 if one wants to obtain the absorption of the anhydro-base itself. Therefore, there is no doubt whether biomolecules such as **7**—**12** are stabilized in plants by forming protonated species.

β-Carbolinium ions or β-carboline anhydro-bases protonated at the imine nitrogen **19**—**24** are iso-π-electronic with the corresponding β-carbolines, so naturally conform to the TCS rule. The stability of the anhydro-bases enhanced by the contribution of the dipolar aromatic structure is further enhanced in water by protonation. It seems quite likely that without a tendency toward protonation, this kind of compounds would not have been synthesized in living organisms. The fact that the anhydro-bases can easily be isolated from plant extracts never means that they exist as free bases in plants.[1] The β-carboline anhydro-bases themselves are not biomolecules although they are often given as such in the list of alkaloids. The β-carbolinium ions instead are biomolecules.



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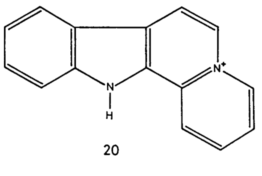

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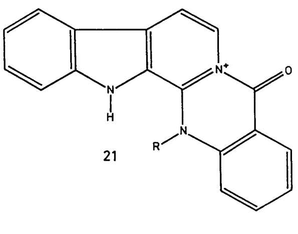

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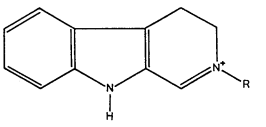

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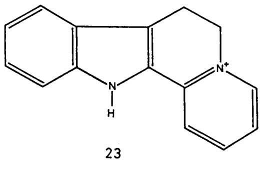

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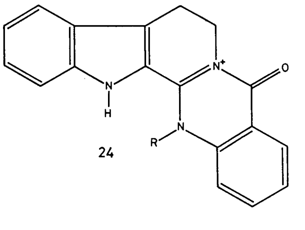

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Concluding Remarks

β-Carboline anhydro-bases have been isolated from plants although their quinonoid structures are not consistent with the TCS rule.[1] Aromaticity of these compounds can be rationalized by assuming that a dipolar aromatic structure contributes more or less to the resonance hybrid. The dipolar structure conforms to the TCS rule. β-Carboline anhydro-bases are highly basic and readily protonated in water to form β-carboline-like conjugated systems, which obey the TCS rule. Therefore, these compounds must be protonated in the tissues of plants. We can still say that biomolecules obey the TCS rule.[10]

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