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On the Ground State Energy Hypersurface of Blepharismins and Oxyblepharismins

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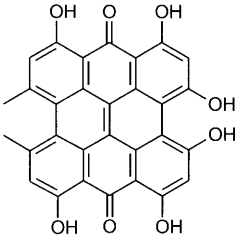
Summary. AM1 calculations on blepharismins and oxyblepharismins, which are related photosensory pigments of certain protists, revealed that the accessory substituents of the natural pigments do not lead to a change of the tautomerism and conformational states of the fundamental systems. The valence tautomerism possible in principle for the blepharismins yielding a cycloheptatriene–norcaradiene system was found to reside completely on the side of the cycloheptatriene. With respect to proton tautomerism, the strong predominance of the *meso*-type 7,15- and 7,14-dioxo tautomers was established in both series. Whereas the conformation of the fundamental condensed aromatic ring system of the oxyblepharismins remains comparable to that of hypericin, the conformational situation of the blepharismins was found to be unique with the phenyl group in an *endo*-position and dihedral twisting at the unperturbed *bay*-site only.

Keywords. Valence tautomerism; Tautomerism; Conformational analysis; AM1 semiempirical calculations.

Introduction

Whereas the chemistry of the photodynamic pigments of phenanthroperylene quinone natural products like hypericin (**1**) has been vividly investigated in the last decade, the photosensory pigments of this group, like the blepharismins or the stentorins, have attracted less attention [1]. This situation might be due to the rather small amounts of material accessible from natural sources on the one hand or the tedious (stentorin [2]) and even not yet achieved (blepharismins) chemical syntheses on the other hand.



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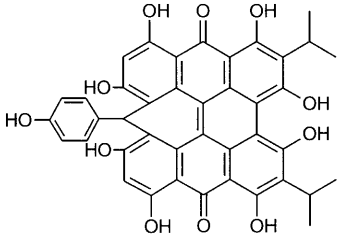

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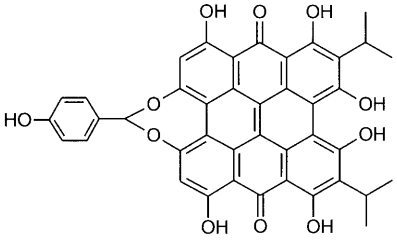

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Only recently an account describing the photochemical conversion of benzylhypericin into the blepharismin type chromophore and further into the oxyblepharismin type chromophore was given [3]. Within this work, considerable problems were encountered with respect to the rather highly complex structural situation involving dissociation, tautomerism, and stereoisomeric equilibria. Because they could not yet be adequately addressed by experimental methods, the present paper will try to draw a picture of the structurally intertwined net of species in the two series of the blepharismins (blepharismin C: **2**) and oxyblepharismins (oxyblepharismin C: **3**) using semiempirical calculations.

Results and Discussions

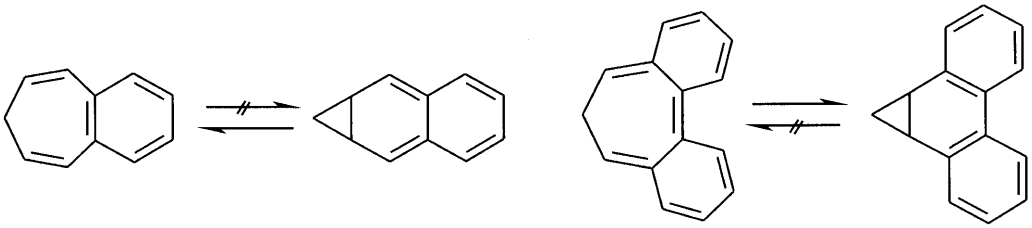
Calculations on the geometry and energy of phenanthroperylene pigments have been executed in recent years using a variety of methods of different degree of sophistication covering the entire palette from force field or HMO estimates to *ab initio* calculations [4–15]. In particular, for calculations of energy and geometry the AM1 method [16] proved to yield meaningful and reliable results, favourably comparing with the available experimental data [7, 10, 13–15].

The blepharismin system

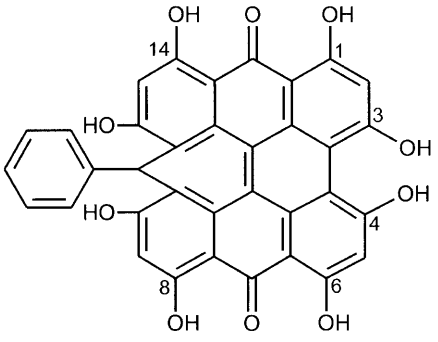
First of all, it has to be noted that the formula of blepharismin C (**2**) is just a more or less arbitrary way to express the structural details of the system. Thus, it should be kept in mind that similar to the situation of hypericin (**1**) [1, 11], **2** will be involved in a highly complex system consisting of the tautomeric equilibrium with respect to the positions of the two carbonyl groups (**2** may be denoted the $\mathbf{Q}^{7,15}$ tautomer), conformational enantiomerism, protonation and deprotonation equilibria, homoassociation equilibria, and, in addition, the cycloheptatriene – norcaradiene equilibrium and the diastereomerism arising from the homologated phenyl-substituted ring system.

As the first step in the investigation of the blepharismin system, the heats of formation (ΔH_f) of typical members of the cycloheptatriene – norcaradiene system were investigated and compared to experimental evidence to assess the reliability of AM1 calculations for such compounds. Thus, the condensed cycloheptatriene system **4** was calculated to be more stable than the norcaradiene **5** by $118\,kJ \cdot mol^{-1}$. From experiments it has been found that whereas **4** cannot be converted to **5**, the latter spontaneously isomerizes to **4** [17]. Similarly, **6** was calculated to be less stable than **7** by $109\,kJ \cdot mol^{-1}$. Actually, only **7** has been found to be rather stable – it does not isomerize to **6**, but stabilizes as 9-methylphenanthrene [18]. According to these introductory calculations, the AM1 method seemed to be well suited also to reliably reproduce the main features of the cycloheptatriene – norcaradiene valence tautomerism of blepharismins.

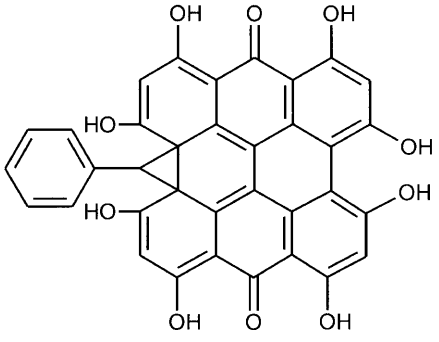
In continuation, the most stable conformers of all possible canonically structured tautomers of the cycloheptatriene **8** and the norcaradiene species **9** were minimized. They were derived by stripping of the natural product blepharismin C (**2**) from the 4-hydroxy group of the phenyl moiety and the two isopropyl groups in positions 2 and 5. Because a phenyl ring is attached to position 11 of the chromophore, *endo*- and *exo*-diastereomers had to be regarded. The results of these calculations are displayed in Fig. 1. Accordingly, the *endo*-phenyl-7,15-tautomer ($\mathbf{Q}^{7,15}$) of the cycloheptatriene valence tautomer **8** was found to be the most stable



4 **5** **6** **7**



8 (**Q**^{7,15})



9 (**Q**^{7,15})

one with its *exo*-isomer destabilized slightly but significantly by 19 kJ · mol^{-1}. The most stable norcaradiene system *exo*-phenyl-**Q**^{8,14}-**9** was found to be strongly destabilized compared with the cycloheptatriene **8** minimum by about 180 kJ · mol^{-1}. This finding is in agreement with experimental evidence for the exclusive presence of the cycloheptatriene valence tautomer in the natural product [19] and in a hypericin-derived model compound [3]. A similar order in the relative stabilities of the tautomers was found for the 3- and 10-phenolate ions as well as for the 3,10- and 3,12-diphenolate ions of *endo*- and *exo*-phenyl-**8** and *endo*- and *exo*-phenyl-**9**. Interestingly enough, the calculations also nicely reproduced the relative acidities of the two different *bay*-regions found experimentally [21]: the 3-phenolate of *endo*-**Q**^{7,15}-**8** was found to be stabilized over the corresponding 10-phenolate by 232 kJ · mol^{-1}. Efficient intramolecular hydrogen bonding stabilization of the anion is only possible in the 3-phenolate. Of the diphenolates the 3,10-dianion was calculated to be most stable.

With respect to the conformational details it turned out that in contrast to the propeller and double-butterfly conformer family found for hypericin (**1**), the tautomers of **8** and **9** and in particular the global minimum *endo*-**Q**^{7,15}-**8** adopt a more or less planar ($\theta_{7b,7c,14c,14b} \approx \pm 2°$) C_{2v} symmetrical envelope/saddle form within the cycloheptatriene fragment. The molecule is dihedrally twisted only at the opposite biaryl moiety (about 25°) as illustrated in the three orthogonal views of the molecule in Fig. 2. The interconversion barrier between the *endo*- and the *exo*-phenyl isomer was calculated to amount to more than 180 kJ · mol^{-1}. It should be noted that this high barrier is due to the fact that in this process the seven membered ring has to undergo a space-demanding *pseudo*-rotation, and in addition the phenyl

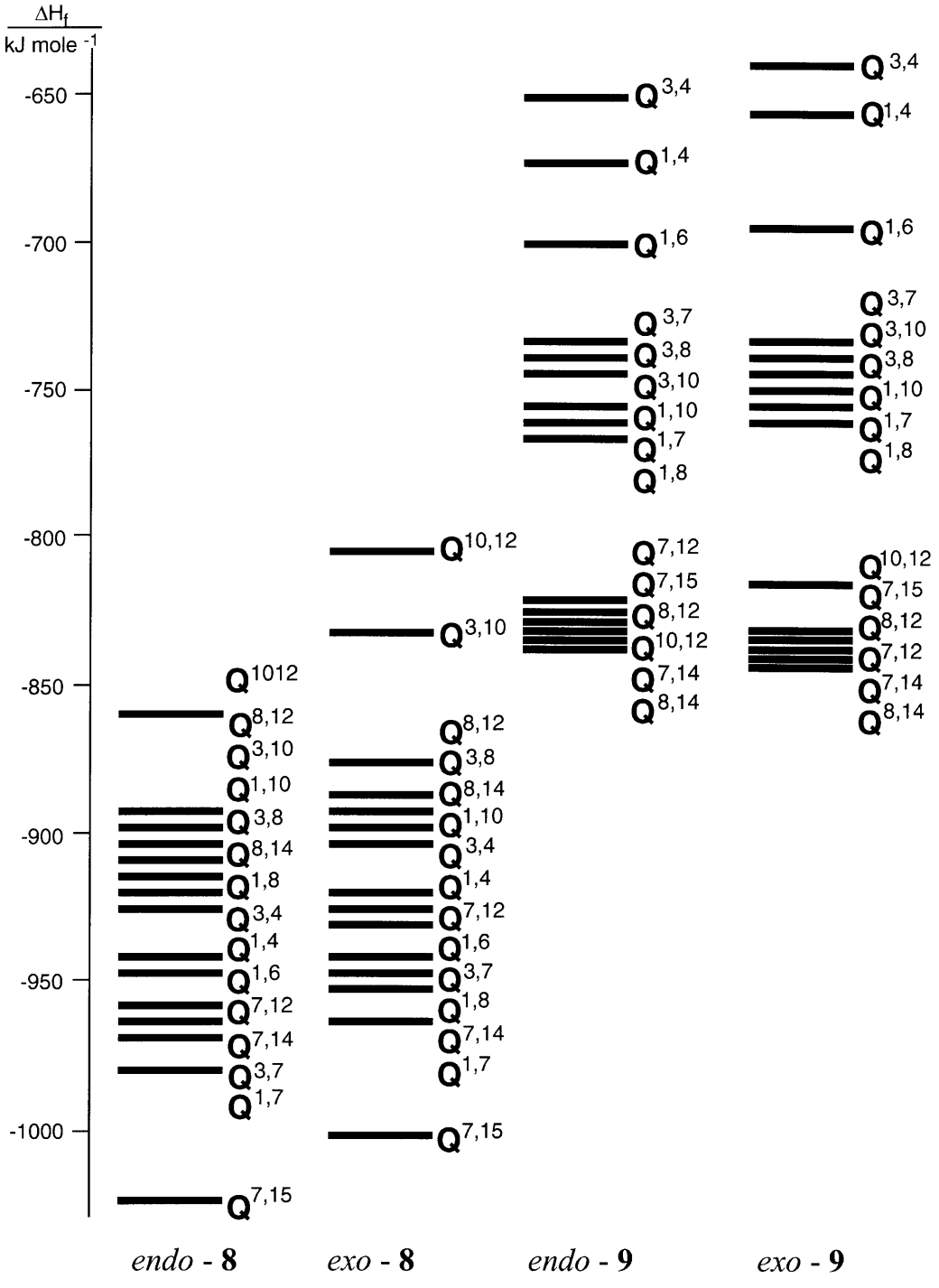


Fig. 1. Heats of formation (ΔH_f) of the various tautomers of the *endo*- and *exo*-isomers of the cycloheptatriene and norcaradiene valence tautomers **8** and **9**

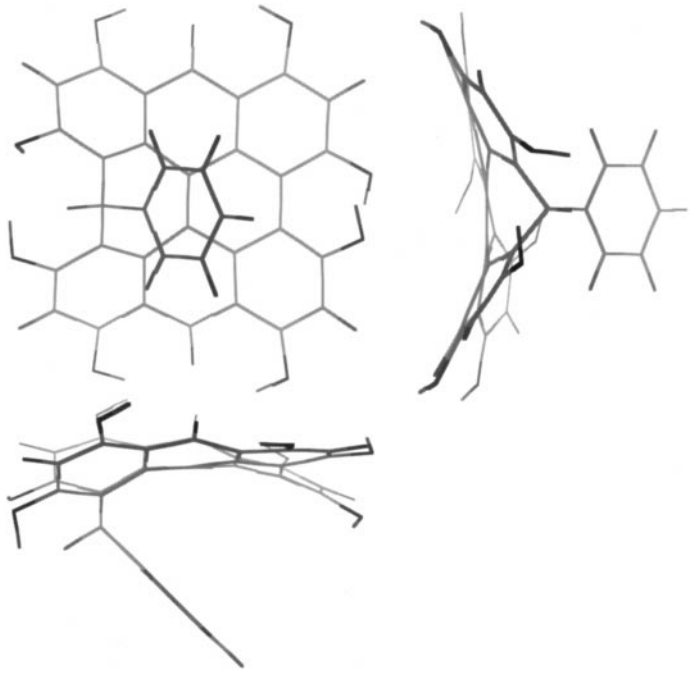


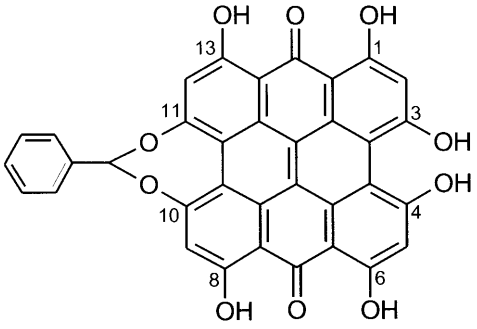
Fig. 2. Wireframe Ball&Stick orthogonal view drawings [20] of the most stable cycloheptatriene conformer *endo*-$\mathbf{Q}^{7,15}$-**8**

ring has to pass between the then sterically severely congested hydroxyl groups. However, the enantiomerization barrier at the biaryl site amounted only to $30\,\mathrm{kJ \cdot mol^{-1}}$. This is considerably lower than the enantiomerization barrier of hypericin (**1**) which has been calculated and experimentally determined to be in the order of $80\,\mathrm{kJ \cdot mol^{-1}}$ [8].

Calculations for the most stable forms of the natural product **2** revealed that the additional natural accessory substituents hydroxyl and isopropyl did not substantially change the picture advanced for the model system **8/9**.

The oxyblepharismin system

Oxyblepharismin C (**3**), which is biosynthetically related to blepharismin C (**2**) [19], is arbitrarily drawn as its $\mathbf{Q}^{7,14}$ tautomer in the formula scheme. It should also to be thought of being involved in a highly complex system consisting of the tautomeric equilibrium with respect to the positions of the two carbonyl groups, conformational enantiomerism, protonation and deprotonation equilibria, homoassociation equilibria, and, in addition, the conformational situation arising from the additional phenyl-substituted acetal ring system and the diastereomerism of unsymmetrical tautomers derived from the then chiral benzal carbon center. To reduce the rather high number of side minima making assignment of the global minimum troublesome, **3** was stripped of the 4-hydroxyl group of the phenyl ring and the two isopropyl groups to yield **10**. The latter can be regarded as a benzaldehyde acetal of fringelite D.



10

Calculations of all canonically structured dioxo tautomers of **10** resulted in the scheme of heats of formation displayed in Fig. 3. Thus, the 7,14-dioxo tautomer ($\mathbf{Q}^{7,14}$) was found to be extensively stabilized over all others, the most stable of them ranging about $43\,\mathrm{kJ \cdot mol^{-1}}$ above the global minimum. It should be emphasized that due to the unsymmetrical placement of the carbonyl groups, *e.g.* in the $\mathbf{Q}^{1,7}$ tautomer the benzal carbon atom becomes an asymmetric center. Therefore, taking into account the dihedral torsion at the opposite *bay*-region, diastereomers are generated in this case which in contrast to hypericin (**1**) render the $\mathbf{Q}^{1,7}$ and $\mathbf{Q}^{6,14}$ tautomers non-identical. However, it turned out that the heats of formation of these tautomers only differed insignificantly ($< 1\,\mathrm{kJ \cdot mol^{-1}}$, Fig. 3). In contrast to **8/9** the fundamental conformational states of the hypericin skeleton [1]

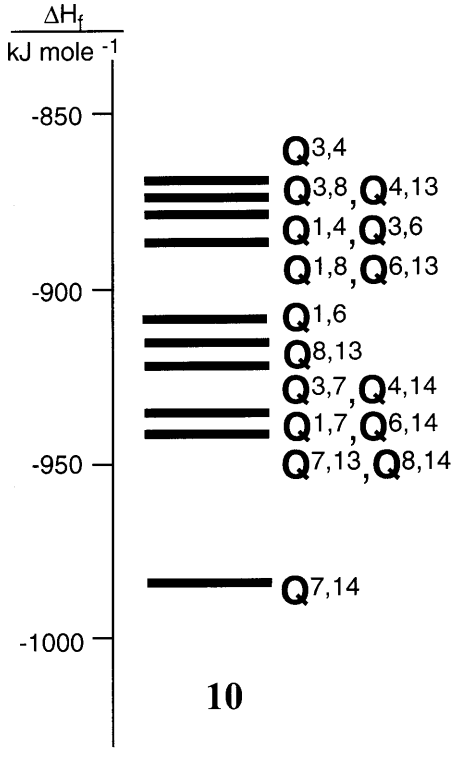


Fig. 3. Heats of formation (ΔH_f) of the various tautomers of the oxyblepharismin skeleton **10**

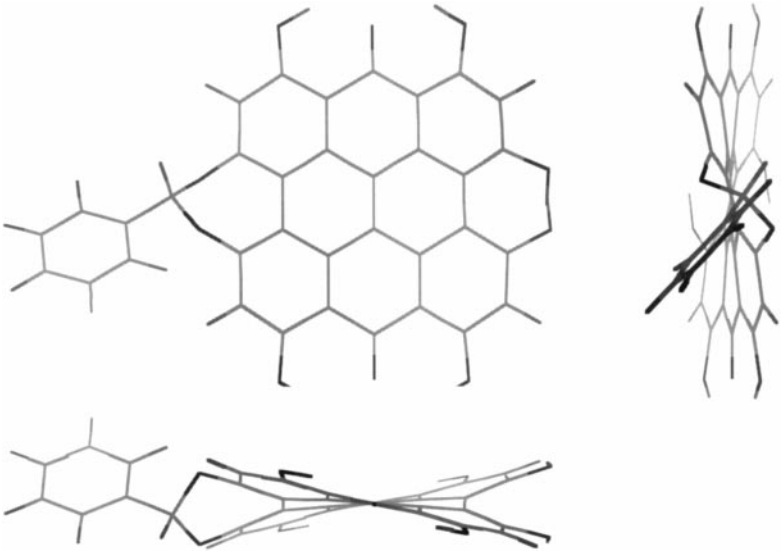


Fig. 4. Wireframe Ball&Stick orthogonal view drawings [20] of the most stable conformer of $\mathbf{Q}^{7,14}$-**10**

remain more or less unperturbed in **10**. This is due to the rather large additional ring in one of the *bay*-regions which modifies the conformational geometry of the fundamental condensed ring system only slightly. Propeller and double-butterfly conformations of $\mathbf{Q}^{7,14}$-**10** were calculated to possess similar heats of formation with the double-butterfly conformer being insignificantly more stable ($< 2\,\mathrm{kJ \cdot mol^{-1}}$) than the propeller conformer. The latter conformer is illustrated in Fig. 4. The acetal ring adopts a twisted conformation which was found to complement that of the fundamental skeleton. Although the influence of the acetal ring upon the geometry of the fundamental skeleton is only marginal it turned out that the enantiomerization barrier was considerably enhanced. Thus, for the inversion at the undisturbed 3,4-*bay*-region a barrier of about $30\,\mathrm{kJ \cdot mol^{-1}}$ was found. This value is similar to that obtained for the undisturbed *bay*-region of blepharismin and smaller than the experimental enantiomerization barrier of about $80\,\mathrm{kJ \cdot mol^{-1}}$ of hypericin (**1**) [8]. For the acetal-*bay*-region only an estimate could be obtained, the necessary sterically congested pseudorotatory movement of the acetal ring posing severe problems with respect to the minimization process. Nevertheless, a very high enantiomerization barrier of $> 200\,\mathrm{kJ \cdot mol^{-1}}$ seemed to emerge from this study.

Deprotonation of **10** at the *bay*-position 3 did not appreciably change the results obtained for undissociated **10** concerning tautomerism and conformation. Addition of the 4-hydroxyl group at the phenyl ring and the two isopropyl groups to yield the natural product **3** also did not change the fundamental picture obtained in the AM1 calculations of **10**. Accordingly, dissociation and the natural accessory substituents do not considerably change the conformational and tautomeric situation.

In conclusion, the AM1 calculations on blepharismins and oxyblepharismins revealed that the accessory substituents of the natural pigments do not change the tautomeric and conformational states of the fundamental systems. The valence

tautomerism possible in principle for the blepharismins yielding a cycloheptatriene *vs*. norcaradiene system was found to reside completely on the side of the cycloheptatriene. With respect to tautomerism, a strong predominance of the *meso*-type tautomers $\mathbf{Q}^{7,15}$ and $\mathbf{Q}^{7,14}$ was established in both series. Whereas the conformation of the fundamental condensed ring system of the oxyblepharismins remains comparable to that of hypericin (**1**), the conformational situation of the blepharismins was found to be unique.

Methods

For the calculations the AM1 method contained in the MOPAC package was used on the Origin computer of the LIZENS [16]. Starting geometries were obtained by means of force field calculations using the tinker package [22].

Acknowledgments

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