

Tautomerism and Stereochemistry of Isohypericin, Bromohypericines, and Gymnochromes: Force Field Investigations

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Summary. Using an MM2 derived force field the stereochemistry and tautomerism of isohypericin and several bromohypericines, including gymnochrome D and isogymnochrome D, were investigated. The geometries of the “propeller” and “double butterfly” conformers of isohypericin were similar to those of hypericin. However, an interconversion barrier between the enantiomeric “propeller” conformers was found, which was 53 kJ/mol lower in isohypericin. From the ten tautomers of isohypericin the 7,14-dioxo tautomer was calculated to be the most stable one by about 50 kJ/mol. In the bromo derivatives and the gymnochromes the bromine substituents caused a ruffling of the biaryl fragments. The buttressing effect of the bromine led to an enhancement of the interconversion barriers between enantiomeric conformers. The “double butterfly” conformer was found to be more stable than the “propeller” conformer for tetrabromohypericin and the gymnochromes.

Keywords. Isohypericin; Bromohypericines; Gymnochromes; Force field calculations; Tautomerism; Interconversion barrier.

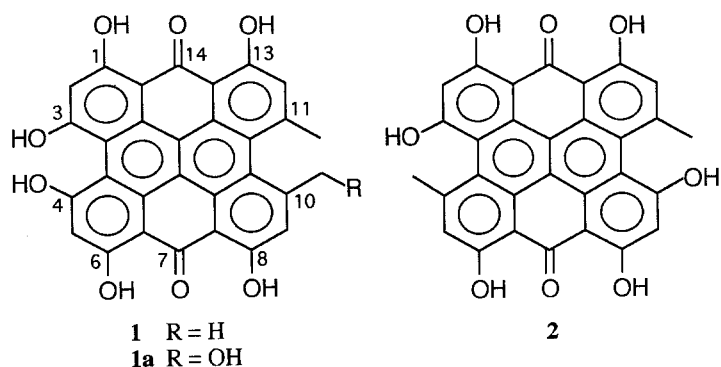
Tautomerie und Stereochemie von Isohypericin und Bromhypericinen: Untersuchungen mit Hilfe der Kraftfeld-Methodik

Zusammenfassung. Die Stereochemie von Isohypericin und einiger Bromhypericine sowie von Gymnochrom D und Isogymnochrom D wurden mit Hilfe eines von MM2 abgeleiteten Kraftfeldes untersucht. Die Geometrien der „Propeller“- und „Doppelschmetterlings“-Konformeren sind vergleichbar mit jenen des Hypericins. Die Interkonversionsbarriere zwischen den enantiomeren „Propeller“-Konformeren ist jedoch um etwa 53 kJ/mol niedriger als im Hypericin. Von den zehn Isohypericin-Tautomeren ist das 7,14-Dioxotautomere das um etwa 50 kJ/mol stabilste. In den Bromderivaten und den Gymnochromen bewirken die Bromsubstituenten eine Wellung der Biarylfragmente, wobei der Buttressing-Effekt der Bromsubstituenten zu einer Erhöhung der Interkonversionsbarrieren zwischen enantiomeren Konformeren führt. Das „Doppelschmetterlings“-Konformere ist beim Tetrabromhypericin und bei den Gymnochromen stabiler als das „Propeller“-Konformere.

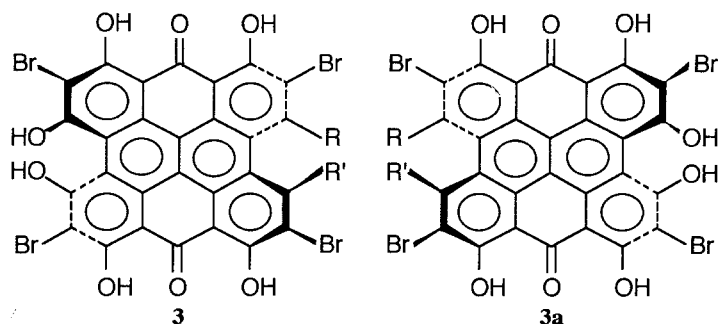
Introduction

Recently, stereochemistry and tautomerism of hypericin (**1**) have been investigated using force field calculations, spectroscopic measurements, and X-ray crystal-

lography [1]. Besides the most stable “propeller” type conformer the complicated energy hypersurface has been shown to contain a novel “double-butterfly” conformer of only slightly lower stability. These conformers were also comparable to those found for cercosporin derivatives [2]. The upper limit interconversion barrier between these conformers and their corresponding enantiomers has been found to be in the order of 115 kJ/mol. From the temperature dependence of the $^1\text{H-NMR}$ spectrum of **1** and pseudohypericin (**1a**) a lower limit interconversion barrier of at least 80 kJ/mol was deduced. This obviously rather low barrier did not yet allow to isolate optically stable enantiomers of **1** or **1a**. From the ten tautomers of **1** and **1a** possible in principle, the 7,14-dioxo tautomer has been derived to be the most stable one by 48 kJ/mol [1].



At this point it seemed to be interesting, to expand our knowledge of the stereochemistry and tautomerism of hypericin to the recently synthesized constitutional isomer of **1**, isohypericin (**2**) [3] on the one hand, and to brominated derivatives of **1** on the other hand. The latter have been investigated [4] with respect to the so-called gymnochromes, which occur in the marine deep-water stalked crinoid *Gymnocrinus richeri* [5]. In the gymnochrome series it has been shown with gymnochrome D [**3**, R = R' = (*R*)-CH₂CHOSO₃H(CH₂)₂CH₃] and isogymnochrome D [**3a**, R = R' = (*R*)-CH₂CHOSO₃H(CH₂)₂CH₃] that enantiomers with respect to the atropisomeric source of chirality can be isolated and are thermally stable [5]. The formulae of **3** and **3a** as given in Ref. [5] and in this section represent “propeller” conformers.



Methods

The force field calculations were performed using the MM2+ program which is based on the QCPE program 395 and the MM2(77) force field [6]. Minor modifications and the basic parametrization have been described in a preceding paper [2]. The parameters of the bromine atoms were taken from [7]. To allow for dipole-dipole and electrostatic interactions involving bromine, partial charges were estimated from the charge distribution obtained by means of a MNDO+ [8] calculation of 2-bromoresorcinol. Accordingly, charges of $-0.10e^-$ and $-0.03e^-$ were assigned to the bromine substituent and to the carbon atom bonded to it. To compensate for them, partial charges of $+0.035e^-$ and $+0.030e^-$ were attributed to the adjacent carbon and oxygen atoms in addition to the partial charges already assigned to the phenanthroperylene or hypericin skeleton [2]. The side chain partial charges in the gymnochromes were approximated by means of a MNDO+ calculation of isopropanol. Molecular models were drawn using the Ball & Stick program [9].

Results and Discussion

Isohypericin

Conformational analysis of isohypericin (**2**) proved to be simpler than for hypericin (**1**). This was due to the C_{2h} symmetry of the substitution pattern of **2**, which is only C_{2v} for **1**. As for **1** [1] force field calculations on **2** revealed the “propeller” conformer of **2** to be the most stable one. Its geometry (Fig. 1) was found to be characterized by dihedral angles of $\Theta_{3,3a,3b,4} = \Theta_{10,10a,10b,11} = 35^\circ$ at the two main torsional sites. Compared with the corresponding values of **1** ($\Theta_{3,3a,3b,4} = 33.3^\circ$, $\Theta_{10,10a,10b,11} = 38.7^\circ$ [1]), **2** was thus found to be torsionally less deformed. This somewhat smaller deformation clearly resulted from the two smaller $\text{OH} \leftrightarrow \text{CH}_3$ interactions in **2** as compared to the small $\text{OH} \leftrightarrow \text{OH}$ plus the large $\text{CH}_3 \leftrightarrow \text{CH}_3$ interactions in **1**. Such a smaller deformation of **2** has been also experimentally deduced by comparison of the UV-Vis spectra of **1** and **2**; the absorption bands of the latter have been found to be hypsochromically shifted by 12 nm [3].

The diastereomeric “double butterfly” conformer of **2** (Fig. 1) was found to be characterized by torsional angles of $\Theta_{3,3a,3b,4} = -\Theta_{10,10a,10b,11} = 35.7^\circ$, which are

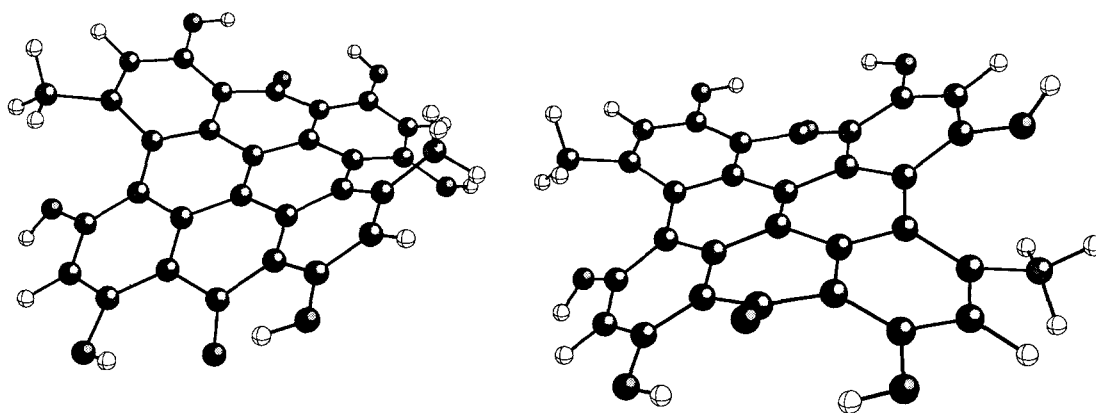


Fig. 1. Ball & Stick models of the “propeller” (left) and the “double butterfly” (right) conformers of **2** as deduced from force field calculations

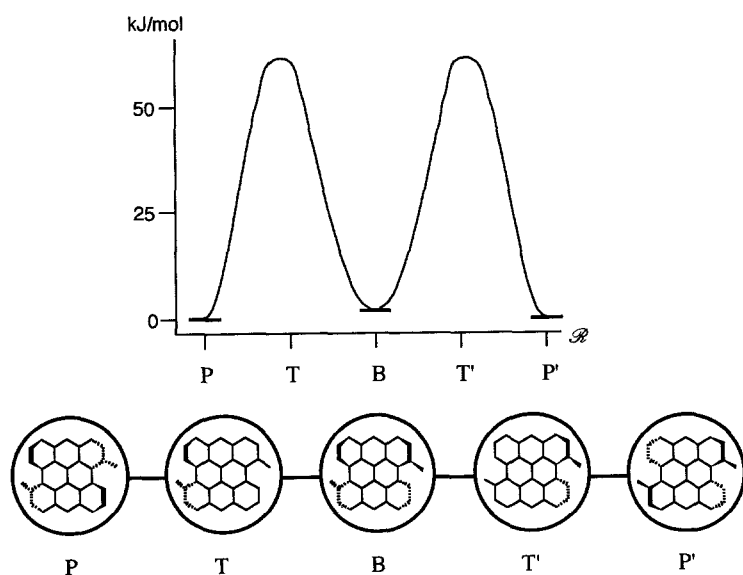
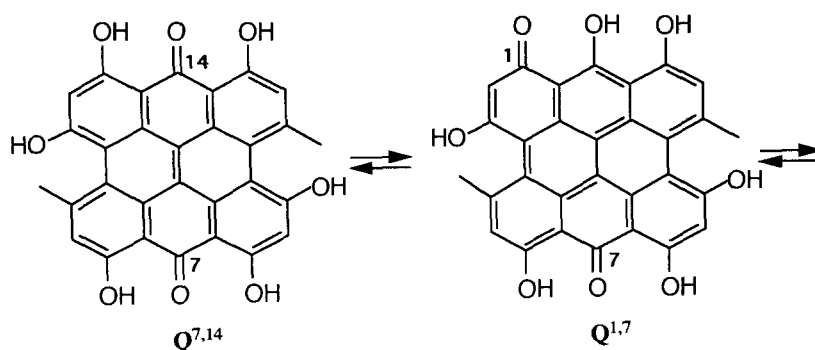


Fig. 2. Interconversion graph and energy scheme of **2** as deduced from force field calculations

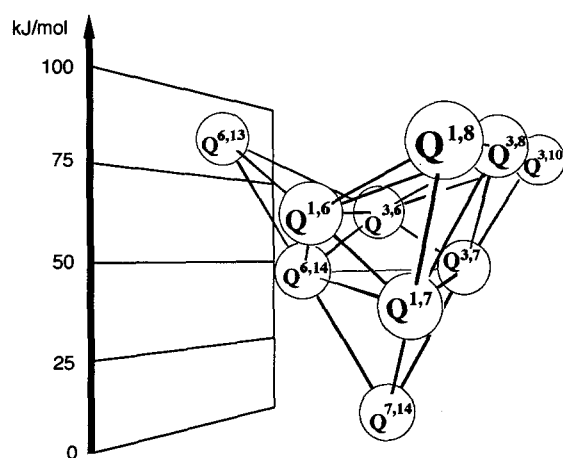
only marginally larger than those found for the “propeller” conformer. It was calculated to be 1.7 kJ/mol less stable than the “propeller” conformer, which has to be compared with the somewhat smaller value of 1.2 kJ/mol [1] for the enthalpy difference between the corresponding conformers of **1**.

The interconversion between the “propeller” (P) and the “double butterfly” (B) conformers, and eventually the enantiomer of P, P' of **2**, along the reaction coordinate \mathcal{R} was deduced to occur *via* the enantiomeric transition conformations T and T'. In contrast to **1**, where the existence of an enantiomer of the “double butterfly” conformer has been deduced [1], the mirror image of B was found to be identical with its image. Hence, B was shown to be a *meso* form in the case of **2**, which of course, was due to the C_2 symmetry of the conformers of this compound. The corresponding interconversion graph (Fig. 2) is a linear one as compared to the cyclic topology which has been found in the case of **1** [1]. The upper limit height of the interconversion barrier was calculated to amount 60.0 kJ/mol. This value was about twice the one derived for the enantiomerization of **1** at the C3–C3a–C3b–C4 fragment (28.3 kJ/mol [1]), however, it was considerably smaller than the one found for enantiomerization at the C10–C10a–C10b–C11 fragment of **1** (113.4 kJ/mol [1]). Bearing in mind that due to the rather low rate determining enantiomerization barrier for simple derivatives, like **1** and **1a**, optical isomers could not be isolated so far [1], the preparation of thermally stable enantiomers of **2** should not be feasible at all.

As with **1** [1], ten tautomers, ($Q^{7,14}$, $Q^{1,7}$, etc.; Scheme 1 – the superscripts indicate the position of the two carbonyl groups) were found to be possible in principle for **2**. The topological details of the interconversion graph of these tautomers of **2** (Fig. 3) are similar to those derived for **1** [1]. However, the tautomers were found to have a different order in enthalpy as calculated by means of the force field method. All tautomers were derived to exhibit a most stable “propeller”



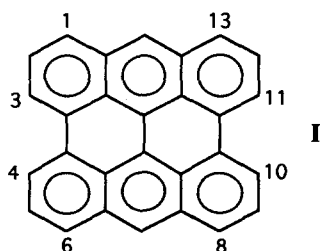
Scheme 1

Fig. 3. Enthalpy difference scaled inter-conversion graph of the ten tautomers of **2**

conformation with dihedral angles $\Theta_{3,3a,3b,4}$ and $\Theta_{10,10a,10b,11}$ ranging between 26° and 35° . However, one should be aware that due to the different symmetries of **1** (C_1) and **2** (C_2), tautomers labeled the same way in **1** and **2** are indeed different species in most cases. The $Q^{7,14}$ tautomer of **2** was calculated to be stabilized by 49.7 kJ/mol (as compared to 47.9 kJ/mol for **1** [1]), thus making experimental detection of other tautomers extremely unlikely in an equilibrium system of **2**.

The heats of formation of the most stable “propeller” conformers of the $Q^{7,14}$ tautomers of **1** and **2** differed by 0.8 kJ/mol, with **2** being the more stable one.

The Bromohypericines



To investigate the influence of bromine substituents on the conformation of bromohypericines and the gymnochromes, simple substituted phenanthroperylene (**I**) were considered first. It was found that bromine substitution in positions 2,5, 2,5,9, and 2,5,9,12 of the phenanthroperylene skeleton **I** did not affect its planarity. This situation did not change significantly upon further formal oxidation to yield carbonyl groups in positions 7 and 14, and substitution with hydroxyl groups in positions 1, 6, 8, and 13. Deformations of the dihedral angles $\Theta_{3,3a,3b,4}$ and $\Theta_{10,10a,10b,11}$ by a few degrees only were calculated. Starting from the 3,4-dihydroxyphenanthroperylene, substitution of bromine in positions 2 and 5 did not change the torsional deformation at the $\Theta_{3,3a,3b,4}$ angle (33.6° versus 32.2°). However, the steric strain introduced by the interaction of bromine and the hydroxyl group was partly relieved by a ruffling of the two benzene rings. This was indicated by the dihedral angle $\Theta_{1,2,3,3a}$, which was found to be about 1° in the 2,5-dibromo derivative, but about 10° in the dibromo-dihydroxy system. The upper limit interconversion barrier between the two enantiomeric states was calculated to be higher by 45 kJ/mol for the dibromo substituted compound. Thus, a significant buttressing effect of the bromine substituents was derived. An effect of this kind has also been deduced in the case of the cercosporins [2].

For the 10,11-dimethyl-phenanthroperylene, bromine substitution in positions 9 and 12 resulted in a similar deformation of the $\Theta_{3,3a,3b,4}$ dihedral angle. Again, it was accompanied by a ruffling of the aryl system as characterized by the dihedral angle $\Theta_{1,2,3,3a}$, which was found to be about 1° in the dimethyl derivative and about 10° in the dibromo-dimethyl product. A model of this molecule is provided in Fig. 4 to illustrate this kind of ruffling. However, the two enantiomer interconversion barriers were similar, which pointed to a higher flexibility of the Br-C-C-CH₃ fragment as compared to the Br-C-C-OH fragment.

Upon bromination of **1** in positions 2 and 5, the corresponding biaryl system of the "propeller" conformer was found to be ruffled as indicated by dihedral angles $\Theta_{1,2,3,3a}$ and $\Theta_{3,3a,3b,4}$ of -13° and 29° . In contrast to **1**, the "propeller" and the "double butterfly" conformer of the 2,3-dibromohypericin were calculated to be of the same enthalpy of formation. Whereas the interconversion barrier at the

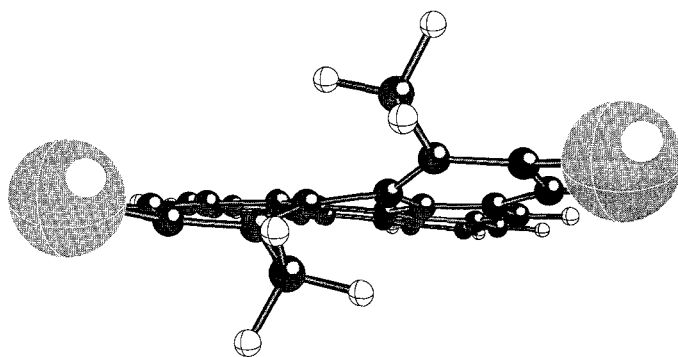
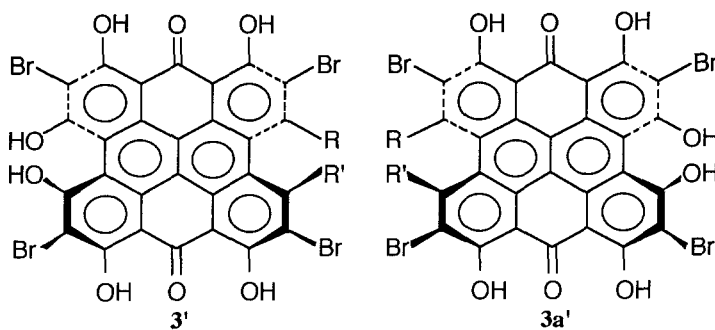


Fig. 4. Ball & stick model of 9,12-dibromo-10,11-dimethyl-**I** viewed from within an averaged molecular plane

C10–C10a–C10b–C11 fragment (112 kJ/mol) was similar to the one found in **1** (113.4 kJ/mol [1]), the one at the C3–C3a–C3b–C4 fragment was enhanced by 12 kJ/mol. Nevertheless, this 40 kJ/mol of the upper limit interconversion barrier did not allow for an experimental identification of these two conformers [4].

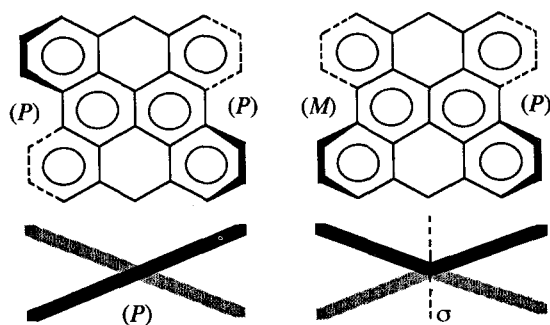
In 2,5,9,12-tetrabromohypericin the “double butterfly” conformer was found to be stabilized over the “propeller” conformer by 2.9 kJ/mol. This was contrary to the conformational situation of **1**, where the “propeller” conformer has been shown to be the most stable one [1]. The geometrical features of the “double butterfly” conformer of this tetrabromohypericin were characterized by ruffling at the C1–C6 fragment, and of the C8–C13 fragment of the molecule. The corresponding dihedral angles were calculated as $\Theta_{1,2,3,3a} = 11^\circ$, $\Theta_{3,3a,3b,4} = -29^\circ$, $\Theta_{10b,11,12,13} = 34^\circ$, and $\Theta_{10,10a,10b,11} = -10^\circ$. The “propeller” conformer was found to be ruffled significantly at both sides of the molecule as indicated by dihedral angles $\Theta_{1,2,3,3a}$ and $\Theta_{3,3a,3b,4}$ of -13° and 29° , and $\Theta_{10b,11,12,13}$ and $\Theta_{10,10a,10b,11}$ of -10° and 32° . The interconversion barriers between the “propeller” conformer and the “double butterfly” conformer, and from the latter to the enantiomeric “propeller” conformer, in analogy to the path derived for **1** [1], were found to be 46 and 127 kJ/mol. Thus, compared to **1** and its dibromo derivative, the tetrabromo derivative was found to be more rigid. It was also interesting to note, that judged from these results the hydroxyl groups in positions 8 and 13 seemed to exert an additional buttressing effect on the bromine substituents in positions 9 and 12, which on their part exerted a buttressing effect on the methyl groups in positions 10 and 11.



For force field calculations of gymnochrome D and isogymnochrome D (**3** and **3a**: “propeller” conformations; **3'** and **3a'**: “double butterfly” conformations; $R = R' = (R)\text{-CH}_2\text{CHOSO}_3\text{H}(\text{CH}_2)_2\text{CH}_3$) the $-\text{OSO}_3\text{H}$ groups were approximated by $-\text{OH}$ groups. This simplification seemed to be justified as it turned out that these groups of the molecule were not involved in interactions other than within the side chains. Of course, due to the flexibility of the side chains in positions 10 and 11, a vast variety of side minima in the conformational energy hypersurface were encountered. Thus, we could not be certain that the global minimum actually was found. Nevertheless, by choosing comparable side chain conformations for all skeleton conformers calculated, the possible error introduced by this arbitrary approximation seemed to be of minor relevance.

As in the case of tetrabromohypericin, the “propeller” conformations **3** and **3a** were found to be less stable than the “double butterfly” conformers **3'** and **3a'** by

5.4 kJ/mol. The “double butterfly” conformers **3'** and **3a'** were characterized by dihedral angles $\Theta_{1,2,3,3a}$ and $\Theta_{3,3a,3b,4}$ of -14° and 24° , and $\Theta_{10b,11,12,13}$ and $\Theta_{10,10a,10b,11}$ of 18° and -32° . In contrast to the corresponding conformer of tetrabromohypericin as discussed above, both biaryl fragments are significantly ruffled. The “propeller” conformers **3** and **3a** were found to be characterized by dihedral angles $\Theta_{1,2,3,3a}$ and $\Theta_{3,3a,3b,4}$ of -11° and 26° , and $\Theta_{10b,11,12,13}$ and $\Theta_{10,10a,10b,11}$ of -19° and 30° . They were similar to the tetrabromohypericin “propeller” geometry, but with a more pronounced ruffling at the C8–C13 fragment of the molecule. The side chain of the gymnochromes led also to an enhanced rigidity of the system. Thus, the upper limit interconversion barriers on a route similar to the one derived for **1** [1] from the “propeller” conformer **3** via the “double butterfly” conformer **3'** into the diastereomeric “propeller” conformer **3a** amounted to 47 and 147 kJ/mol. The latter barrier was high enough to account for the observed thermal stabilities of gymnochrome D and isogymnochrome D [5]. However, the barrier between “propeller” and “double butterfly” conformers was still too low to allow an experimental characterization of the two conformers so far.



Scheme 2

Nevertheless, from the results of these force field calculations on the gymnochromes their structural formulae given in Ref. [5] should be reconsidered as they are drawn as “propeller” conformers. The presence of the “double butterfly” conformers **3'** and **3a'** is of the same probability as that of the “propeller” conformers **3** and **3a** at least. As shown in Scheme 2, the “propeller” conformers constitute *like* (*threo*) forms, as both helical biaryl fragments are of the same configuration (*P*). These add up to an overall helicity of the molecule, which is of configuration (*P*). Such an inherently chiral chromophore should exhibit high chiroptical signals. This has been observed with the cercosporin type systems ($\Delta\epsilon > 10$), which are “propeller” conformers [10]. The “double butterfly” conformers constitute *unlike* (*erythro*) forms, as the configurations of the two biaryl fragments are opposite (*M, P*) as shown in Scheme 2. Accordingly, the resulting inherently symmetric chromophore (σ) should exhibit low chiroptical signals. Thus, the assignment of “double butterfly” conformers **3'** and **3a'** to the gymnochromes would nicely account for the rather low $\Delta\epsilon$ values (< 10), which have been observed for the gymnochromes [5]. The

tautomers of **3**, **3'**, **3a**, and **3a'** are similar in both, energy and geometry, to the ones derived for **1** [2].

Acknowledgements

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