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Stereochemistry and Tautomerism of Stentorin, Isostentorin, and Fringelit D: Force Field Investigations

C. Etzlstorfer and **H. Falk***

Institut für Chemie, Johannes Kepler Universität Linz, A-4040 Linz, Austria

Summary. Stereochemistry and tautomerism of stentorin, isostentorin, and fringelit D were investigated using an MM2 derived force field method. For these pigments, the 7,14-dioxo tautomers were derived to be the most stable ones, with a gap of about 50 kJ/mol separating them from the less stable species. The three quinones display propeller and double butterfly conformers. The double butterfly conformers were found to be slightly more stable than the propeller conformers. Compared to hypericin the interconversion barriers between these conformers and between enantiomeric conformers of the same type are lower. They were estimated to be in the order of 40 kJ/mol; thus an isolation of enantiomers is improbable.

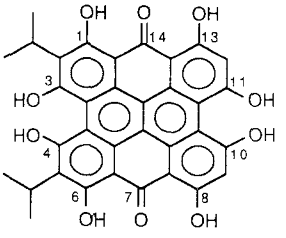
Keywords. Fringelit D; Stentorin; Isostentorin; Force Field Calculations; Tautomerism; Interconversion Barrier.

Stereochemie und Tautomerie von Stentorin, Isostentorin und Fringelit D: Untersuchungen mit Hilfe der Kraftfeld-Methodik

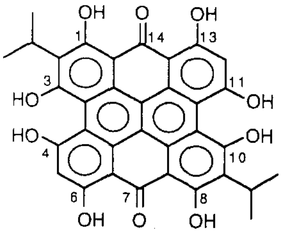
Zusammenfassung. Die Stereochemie und Tautomerie von Stentorin, Isostentorin und Fringelit D wurden mit Hilfe einer von MM2 abgeleiteten Kraftfeldmethodik untersucht. Für diese Pigmente wurde abgeleitet, daß die 7,14-Dioxotautomeren am stabilsten sind und daß sie durch eine Energielücke von etwa 50 kJ/Mol von den weniger stabilen Tautomeren getrennt sind. Diese drei Chinone liegen jeweils als Propeller- und Doppelschmetterlings-Konfomere vor, wobei letztere geringfügig stabiler als erstere sind. Verglichen mit Hypericin sind die Interkonversionsbarrieren zwischen diesen Konformeren, wie auch zwischen enantiomeren Konformeren desselben Typs, niederer. Sie wurden zu etwa 40 kJ/Mol abgeschätzt und lassen damit eine Isolierung von Enantiomeren unwahrscheinlich werden.

Introduction

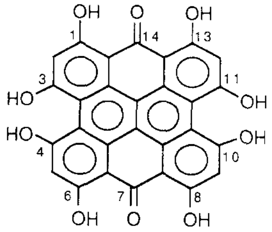
The chromophore constitution of the photo taxis photoreceptor of *Stentor coeruleus* has been elucidated recently by Song [1]. This pigment has been called stentorin. The isomerism of the pigment, **1a** or **1b**, could not yet be specified for this natural product [1]. As **1a** and **1b** are symmetry related constitutional isomers, we propose to use the names stentorin and isostentorin in analogy to the symmetry related constitutional isomers hypericin (**3**) and isohypericin [2]. The chromophores of **1a** and **1b** are structurally closely related (by loss of the two isopropyl groups) to fringelit D (**2**), a pigment which has been extracted from Jurassic crinoids [3]. The chromophoric system of **1a** and **1b** also resembles the one of the photosensitizing plant pigment hypericin (**3**) [2].



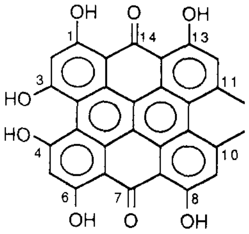
1a



1b



2



3

Tautomerism and stereochemistry of **3** have been throughly investigated recently by means of force field calculations and experimental methods. These studies revealed exceptional geometric and energetic features of its chromophoric system that are also of fundamental interest for its photochemistry [4]. Therefore **1** was clearly an interesting candidate for an extension of these studies. As **2** represented a higher symmetrical fundamental partial structure of **1** it was also included in the present force field investigations.

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 [5]. Minor modifications and parametrization have been described in a preceding paper [6]. Molecular models were drawn using the Ball & Stick program [7].

Results and Discussion

Stereochemistry

With respect to the conformation of **1** and **2** it was first of all established by means of an orientational calculation, that the $Q^{7,14}$ tautomers of both systems were by far the thermodynamically most stable ones, as has been derived for **3** earlier [4]. Starting with the most symmetrical (substitution pattern of D_{2h} symmetry) system **2**, a "propeller" and "double-butterfly" conformer were obtained as energy minima. The "double-butterfly" conformer of **3** has been found to be *less* stable than the "propeller" conformer by 1.2 kJ/mol [4]. The "double butterfly" conformer of **2** was found to be *more* stable than the "propeller" conformer by 0.3 kJ/mol. However, this difference was rather small and thought not to be significant. The deformations of the symmetry related phenanthrene moieties of the "double butterfly" conformer of **2** with dihedral angles $\Theta_{3,3a,3b,4} = 32.3$ and $\Theta_{10,10a,10b,11} = -32.3°$ were identical to the ones found for the "hydroxyl bearing side" of the "double-butterfly" conformer of **3** [4]. These deformations were similar for the "propeller" conformer of **2** where dihedral angles $\Theta_{3,3a,3b,4} = \Theta_{10,10a,10b,11} = 32.0°$ were found. The force field derived geometries of the two conformers are illustrated in Fig. 1.

For an interconversion between these two conformers of **2** an upper limit interconversion barrier was estimated to amount to 27.9 kJ/mol. Whereas there was only one "double-butterfly" conformer due to symmetry reasons (C_{2h}), there were two enantiomeric "propeller" conformers of symmetry D_2. As illustrated in Fig. 2, the barrier to interconvert between these two enantiomers P and P′ *via* the enantiomeric transition states T and T′ (symmetry C_2) was equal to the one between the "double butterfly" B and these "propeller" conformers. Due to this rather low barrier and the destabilization of the enantiomeric "propeller" conformers compared to the "double-butterfly" conformer, isolation of the enantiomers of fringelit D (**2**) at room temperature appears to be very improbable.

The formal substitution of fringelit D (**2**) with two isopropyl groups to yield stentorin (**1a**) and isostentorin (**1b**) reduced the C_{2h} symmetry of its substitution pattern to C_{2v} and C_{2h}. Accordingly, the stereochemical situation became more complex. For **1a** the "double butterfly" conformer was found to be more stable than the "propeller conformer" by 3.0 kJ/mol. The deformation of the side bearing the alkyl residues was slightly larger than on the side without them ($\Theta_{3,3a,3b,4} = 32.8°$, $\Theta_{10,10a,10b,11} = -31.1°$). However, contrary to the results for **2**, a significant out of plane deformation of the aromatic rings ($\Theta_{1,2,3,3a} = 7.0°$) on the alkyl substituted part of the molecule was calculated. The unsubstituted part remained more or less planar ($\Theta_{8,9,10,10a} = 1.5°$) as was found for **2**. These results were similar to those

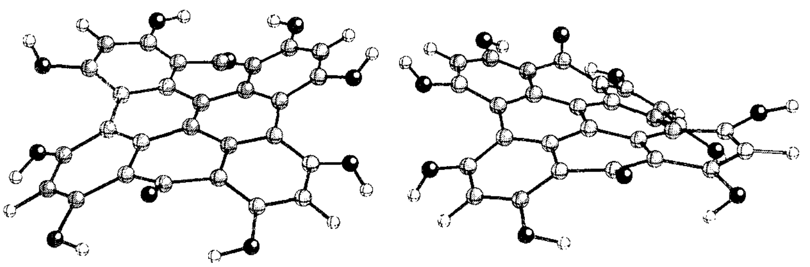


Fig. 1. "Ball & Stick" models [7] of the "double-butterfly" and "propeller" conformers of fringelit D (**2**)

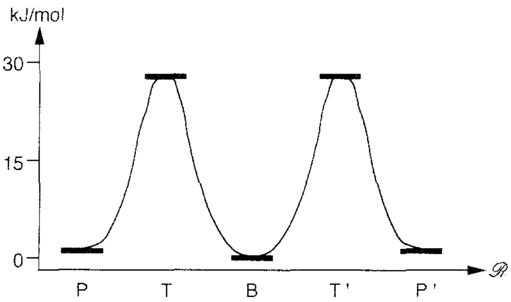


Fig. 2. Enthalpy diagram for the interconversion between the "double-butterfly" (B) and the enantiomeric "propeller" conformers (P, P′) *via* the transitions states (T, T′) of fringelit D (**2**)

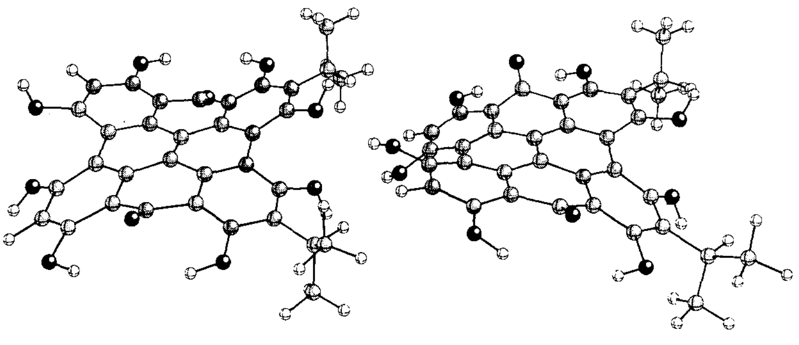


Fig. 3. "Ball & Stick" models [7] of the "double-butterfly" and "propeller" conformers of stentorin (**1a**)

which have been calculated for certain bromohypericines [8]. The "propeller" conformer of **1a** exhibited geometrical features ($\Theta_{3,3a,3b,4} = 33.3°$, $\Theta_{10,10a,10b,11} = 31.3°$, $\Theta_{1,2,3,3a} = 6.2°$, $\Theta_{8,9,10,10a} = 1.5°$) which were analogous to the "double butterfly" one. Fig. 3 illustrates the geometrical features of the two stentorin conformers.

Due to symmetry reasons (C_2) all species of stentorin are chiral. The interconversion paths between the enantiomeric "double butterfly" conformers (B, B′) *via* the "propeller" conformer (P) and the respective transition states (T_1, T_2) according to an interconversion scheme similar to the one of hypericin (**3**) [4] is shown in Fig. 4. Due to the buttressing effect of the isopropyl groups, the inversion barrier at the alkyl substituted side ($\Theta_{3,3a,3b,4} = 0°$, T_2) of the molecule was found to be higher than at the unsubstituted part ($\Theta_{10,10a,10b,11} = 0°$, T_1) by 27.6 kJ/mol. Compared to hypericin (**3**), the barrier of enantiomerization of **1a** (upper limit 58 kJ/mol) was estimated to be only about half as high [4], but significantly higher than for **2**. Thus, isolation of the stentorin enantiomers at room temperature seems rather improbable.

With isostentorin **1b**, the "double butterfly" conformer was found to be more stable than the "propeller" conformer even by 5.3 kJ/mol. The deformations on both sides of the "double butterfly" conformer ($\Theta_{3,3a,3b,4} = 32.6$, $\Theta_{10,10a,10b,11} = -32.6°$) were about the same as the one at the alkyl substituted side of the comparable conformer of **1a**. Due to the steric strain of the alkyl residues both aromatic systems of the left and right side became distorted ($\Theta_{1,2,3,3a} = \Theta_{8,9,10,10a} = 6.7°$). This value was comparable to the one observed for the alkyl substituted part of **1a**. In the "propeller" conformer, the deformations at the biarylic fragments ($\Theta_{3,3a,3b,4} =$

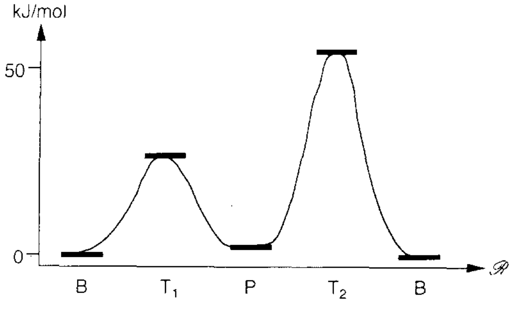


Fig. 4. Enthalpy diagram for the interconversion between the enantiomeric "double-butterfly" (B, B′) and the "propeller" conformers (P) *via* the transitions states (T_1, T_2) of stentorin (**1a**)

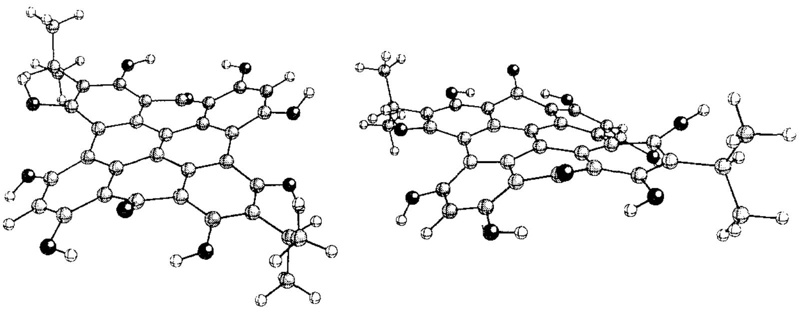


Fig. 5. "Ball & Stick" models [7] of the "double-butterfly" and "propeller" conformers of isostentorin (**1b**)

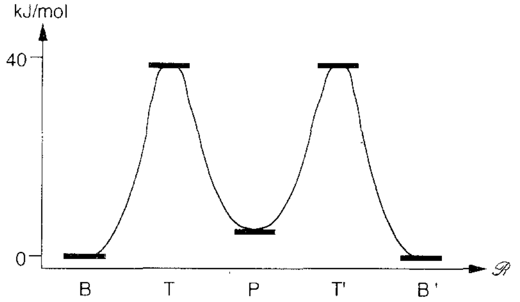


Fig. 6. Enthalpy diagram for the interconversion between the enantiomeric "double-butterfly" (B, B′) and the "propeller" conformers (P) *via* the transitions states (T, T′) of isostentorin (**1b**)

$\Theta_{10,10a,10b,11} = 29.4°$) were significantly smaller than in the "double butterfly" conformer. To compensate partly for this lesser strain, the aromatic systems became more distorted ($\Theta_{1,2,3,3a} = \Theta_{8,9,10,10a} = 11.4°$). Figure 5 displays ball and stick models of the two conformers of **1b**.

The interconversion between the "double butterfly" and "propeller" conformers of **1b** was found to be hindered by at least 39.0 kJ/mol. This value was intermediate between the two barriers of **1a**. Whereas in **1b** on both sides of the molecule a hydroxyl group and a hydroxyl group buttressed by an alkyl residue had to slide past each other, there are two different sides in **1a**. On the one side of this molecule two hydroxyl groups had to slide past each other, which was easier than in **1b**. On the other side two hydroxyl groups buttressed by isopropyl groups had to slide past each other, which is sterically more demanding than for **1b**. Of course, according to symmetry considerations all species of **1b** are chiral. However, compared to the dynamic situation of **1a** (Fig. 4) the transition barriers (T, T′) for the interconversion between the enantiomeric conformers B and B′ of **1b** became equal (Fig. 6). This is due to the two equivalent "sides" of the molecule.

Tautomerism

The principal tautomeric situation of **1**–**3** could be described in form of the permutational systems of Scheme 1, where $Q^{m,n}$ denote the type of tautomer by indicating the carbonyl positions m and n in superscript (compare [4]). In order to avoid construction of rather complicated interconversion graphs as accomplished

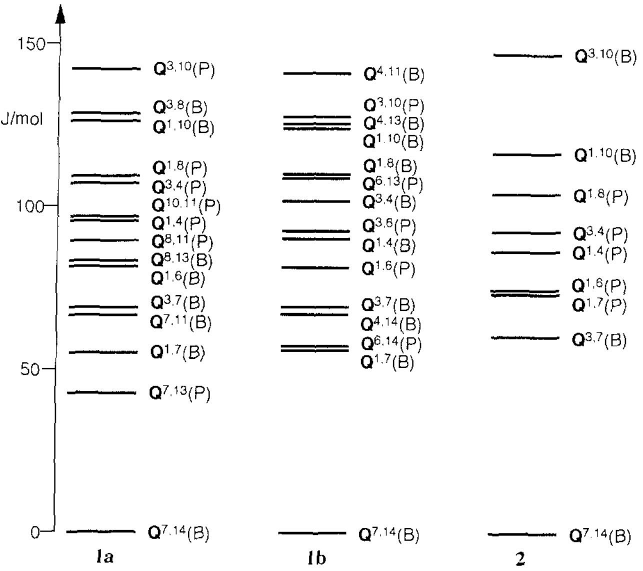


Fig. 7. Energy levels (heats of formation) of the tautomers of **1a**, **1b**, and **2**

for **3** in Ref. [4], numbers in parentheses were used to indicate one-proton tautomerization paths. Thus, *e.g.* for **2**, $Q^{7,14}(2)$ meant that this tautomer could be tautomerized by a one-proton transfer process into the two other tautomers which have the position numbers 7 or 14 in their superscript, *i.e.* $Q^{1,7}$ and $Q^{3,7}$. However, due care had to be exercised for paths which lead to tautomers which are identical due to symmetry. Thus, for example, for **3** four additional paths had to be considered, which resulted from this peculiarity ($Q^{1,4}$–$Q^{3,7}$, $Q^{1,4}$–$Q^{3,8}$, $Q^{1,8}$–$Q^{7,13}$, and $Q^{3,8}$–$Q^{7,13}$).

With respect to the energetic situation of the various tautomers, Fig. 7 displays the various tautomer levels for **1a**, **1b**, and **2** as obtained from the force field calculations. The most stable conformer (P or B) was indicated in parentheses. The enthalpy difference between these respective conformers was calculated to be in the order of a few kJ/mol. In contrast to the results for **3**, where the largest enthalpy difference between tautomers ($Q^{7,14}$–$Q^{3,8}$) has been found to amount to about 100 kJ/mol [4], these differences are much higher for the octahydroxy derivatives **1a**, **1b**, and **2**. This was due to the extremely unfavourable aromaticity situation of canonical structures, *e.g.* of the $Q^{3,10}$ tautomers. The general situation obtained for hypercin (**3**) was, however, similar for the octahydroxy derivatives. Thus an enthalpy gap of about 50 kJ/mol separated the most symmetrical $Q^{7,14}$ tautomers from the less stable tautomers.

1a	$Q^{1,4}(8)$	$Q^{1,6}(4)$	$Q^{1,7}(8)$	$Q^{1,8}(8)$	$Q^{1,10}(8)$
	$Q^{3,4}(4)$	$Q^{3,7}(8)$	$Q^{3,8}(8)$	$Q^{3,10}(8)$	
	$Q^{7,11}(8)$	$Q^{7,13}(8)$	$Q^{7,14}(4)$		
	$Q^{8,11}(8)$	$Q^{8,13}(4)$			
	$Q^{10,11}(4)$				
1b	$Q^{1,4}(8)$	$Q^{1,6}(8)$	$Q^{1,7}(8)$	$Q^{1,8}(4)$	$Q^{1,10}(8)$
	$Q^{3,4}(8)$	$Q^{3,6}(8)$	$Q^{3,7}(8)$	$Q^{3,10}(4)$	

	$Q^{4,11}(4)$	$Q^{4,13}(8)$	$Q^{4,14}(8)$		
	$Q^{6,13}(4)$	$Q^{6,14}(8)$			
	$Q^{7,14}(4)$				
2	$Q^{1,4}(7)$	$Q^{1,6}(4)$	$Q^{1,7}(6)$	$Q^{1,8}(4)$	$Q^{1,10}(7)$
	$Q^{3,4}(4)$	$Q^{3,7}(6)$	$Q^{3,10}(5)$		
	$Q^{7,14}(2)$				
3 [4]	$Q^{1,4}(6)$	$Q^{1,6}(3)$	$Q^{1,7}(6)$	$Q^{1,8}(6)$	
	$Q^{3,4}(3)$	$Q^{3,7}(6)$	$Q^{3,8}(6)$		
	$Q^{7,13}(6)$	$Q^{7,14}(3)$			
	$Q^{8,13}(3)$				

Scheme 1

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