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Tautomerism and Stereochemistry of Dihydroxyperylenequinones: Force Field Investigations

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Summary. Stereochemistry and tautomerism of cercosporin and several of its partial structure models were investigated using an MM2 derived force field method. Besides the "propeller" type conformer, which was found before by X-ray crystallography, the complicated energy hypersurface was shown to contain a novel "double-butterfly" conformer of similar stability. The interconversion barrier between these conformers and their enantiomers was found to be unusually high due to buttressing effects of neighbor substituents. Judged from the calculations, the 4,9-tautomer of cercosporin could also be present in favoring instances besides the 3,10-tautomer, whereas the 3,9-tautomer is strongly destabilized.

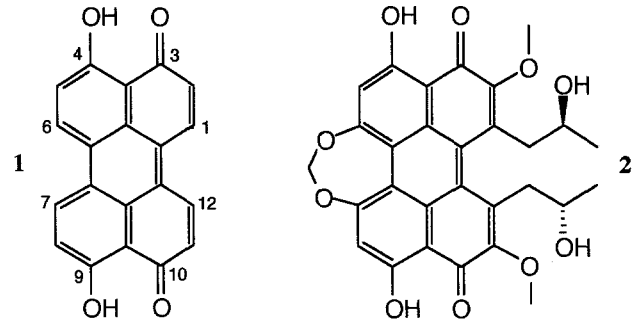
Keywords. Dihydroxyperylenequinones; Cercosporin; Force field calculations; Tautomerism; Interconversion barrier.

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

Zusammenfassung. Die Stereochemie von Cercosporin und einigen seiner Partialstrukturmodelle wurde Hilfe einer von MM2 abgeleiteten Kraftfeldmethodik untersucht. In der komplizierten Energiehyperfläche wurde neben dem aus der Röntgenstrukturanalyse bekannten „Propeller"-Konformeren auch ein neues „Doppelschmetterling"-Konformer ähnlicher Stabilität aufgefunden. Die Interkonversionsbarrieren zwischen diesen Konformeren und ihren Enantiomeren sind außergewöhnlich hoch, was auf einen Buttressing-Effekt der benachbarten Substituenten zurückgeführt wurde. Aus den Rechnungen folgte auch, daß neben dem 3,10-Tautomeren in günstigen Fällen auch das 4,9-Tautomere des Cercosporins vorliegen kann, wogegen das 3,9-Tautomere stark destabilisiert ist.

Introduction

4,9-Dihydroxyperylene-3,10-quinone (**1**) is the parent compound of a variety of natural perylenequinones including cercosporin (**2**) [1]. Interestingly enough **1** was prepared by Zinke in 1929 [2] long before it was shown to be also a natural product [3]. Recently, **2** has attracted considerable interest due to its photodynamic property and its phytotoxic activity [4].



There is a striking structural analogy of **1** and **2** to hypericin derivatives, which we are presently investigating with respect to their chemistry and stereochemistry [6]. The availability of X-ray crystallographic and spectroscopic data of a side chain derivative of **2** [5] together with several hitherto unanswered questions with respect to its tautomeric and stereochemical aspects prompted us to study **2** by means of semi empirical force field calculations as a first step before dealing with the even more complicated hypericin derivatives.

Method

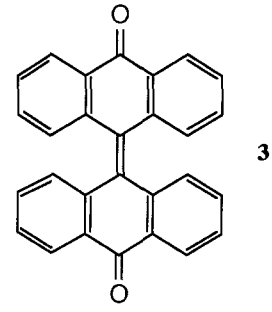
The calculations were performed using the MM2+ program which is based on the QCPE program 395 and the MM2 (77) force field [7]. It includes PI-SCF calculations for hydrocarbons [8]. Some modifications were introduced to suit the special needs of quinoid molecules: Parameters for potential functions in delocalized systems were added to the force field and the PI-SCF part of the program was modified to allow for hetero-atom parameters. The bond order dependent parameters were made linearly dependent on the π bond order p resulting from the PI-SCF calculations between the values for pure single and pure double bonds. The potential minimum for the C=O stretching function was thus varied between 1.407 Å ($p = 0$) and 1.208 Å ($p = 1$). Bonds between carbonyl carbon atoms and sp^2 carbon atoms (=C–C=O) were treated essentially like bonds between "normal" delocalized sp^2 carbon atoms with respect to stretching, bending, and torsion. The binding energy increment for the C=O group (855.7 kJ/mol) was parametrized to reproduce the enthalpy of formation of 121.2 kJ/mol found for quinone [9].

To account for the intramolecular hydrogen bonding between carbonyl and hydroxyl groups, point charges at these groups were estimated using the MNDO method [9, 10] with 5,7-dihydroxynaphthoquinone serving as a model system. These charges (Tab. 1) were equally distributed between the oxygen lone pairs in the force field calculations. A dielectric constant of 2.0 was used throughout. No changes were applied to the aliphatic carbon parameters. Minor adjustments were made for each molecule to preserve electro-neutrality.

To test the parametrization, the ground state structure of 10,10′-bi-anthrylidene (**3**) was calculated and compared with the X-ray crystallographic data [11]. Bond lengths agreed within ± 0.02 Å, bond angles within $\pm 0.7°$, and dihedral angles within $\pm 4.0°$. The superposition of the molecular mechanics and the crystallographic structures of **3** (Fig. 1) demonstrates that the out-of-plane distorsions in polycyclic

Table 1. Point charges (e) of atomic types calculated by the MNDO method for 5,7-dihydroxynaphthoquinone as a model system

Atom type	Charge	Atom type	Charge
C=**O**	−0.28	=**C**–O–H	0.12
C=O	−0.29	=**C**–O–H···O=	0.26
=C–O–**H**	0.20	O–C=**C**–C–O	−0.14
=C–**O**–H	−0.19	other –C=	−0.04
=C–**O**–H···O=	−0.30	=C–**H**	0.04



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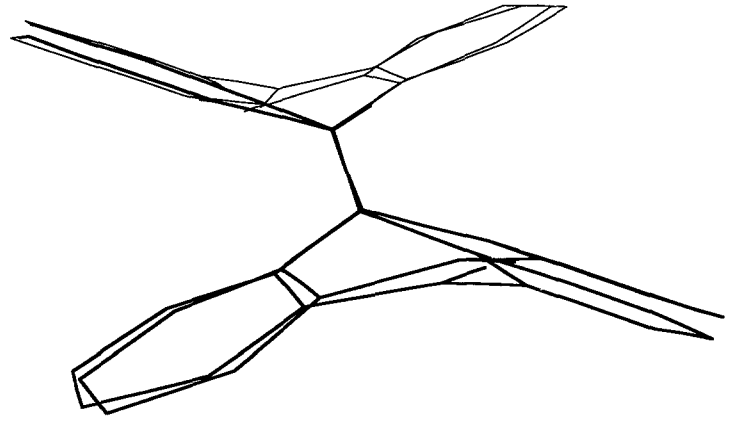


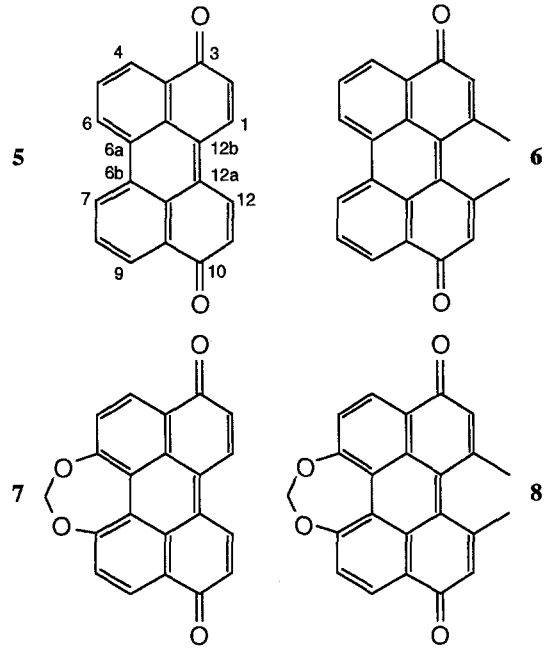
Fig. 1. "Ball & Stick" wire frame model [12] overlay of the results of the force field calculation and the X-ray crystallographic analysis [5] of **3**

aromatic sterically crowded molecules like **3** are adequately described by these parameters.

Results and Discussion

To provide data for comparison and analysis of the various structural details of **2** calculations of partial structures of this compound were performed. The first one investigated was perylene (**4**). The calculation yielded an essentially planar structure

(deviations of the dihedral angles 1–12b–12a–12 and 6–6a–6b–7 from 0° by only 0.3° as observed [13]) with bond lengths and bonding angles also in excellent agreement with experimental data [13]. With 3,10-perylenequinone (**5**) a small but significant twist of the dihedral angles 1–12b–12a–12 and 6–6a–6b–7 by 4.3° and 3.8° was obtained.



Substitution of two methyl groups in positions 1 and 12 of the quinone **5** to yield another partial structure of **2**, namely **6**, resulted in a pronounced increase of the dihedral angle 1–12b–12a–12 to 26.8°, but the dihedral angle 6–6a–6b–7 was also increased to 11.3°. Thus an overall helical "propeller" conformation of the molecule as shown in Fig. 2 was found. To approximate the transition state for the inversion of this conformation to its enantiomer, atoms 1, 12b, 12a, and 12 of **6** were constrained within a plane. The calculated energy of 144.1 kJ/mol serves as an upper limit of this inversion barrier. The strain in this transition state model was partially relieved by an increased torsion of the 6–6a–6b–7 angle, which then amounted 21.7°. Addition of hydroxyl groups in positions 4 and 9, and of methoxy groups in positions 2 and 11 to mimic the complete substitution pattern of **2**, slightly changed these results: The twisting angles were 30.2° and 7.6°, but the upper limit for the inversion barrier was found to be increased to 160.9 kJ/mol. This increase is obviously due to a buttressing effect exerted by the two adjacent methoxy groups.

Derivative **7**, another partial structure of **2** was constructed by adding a dioxymethylene bridge to positions 6 and 7 of the quinone **5**. As could be expected from the results given above, **7** was found to be twisted at 1–12b–12a–12 by only 7.1°, whereas the torsion angle 6–6a–6b–7 was 23.0°. The conformation of the heterocyclic ring of **7** was close to a twist form as shown in Fig. 2.

By constraining atoms 6–6a–6b–7 within a plane an upper limit for the inversion barrier of 33.4 kJ/mol was estimated. It is interesting to note that this

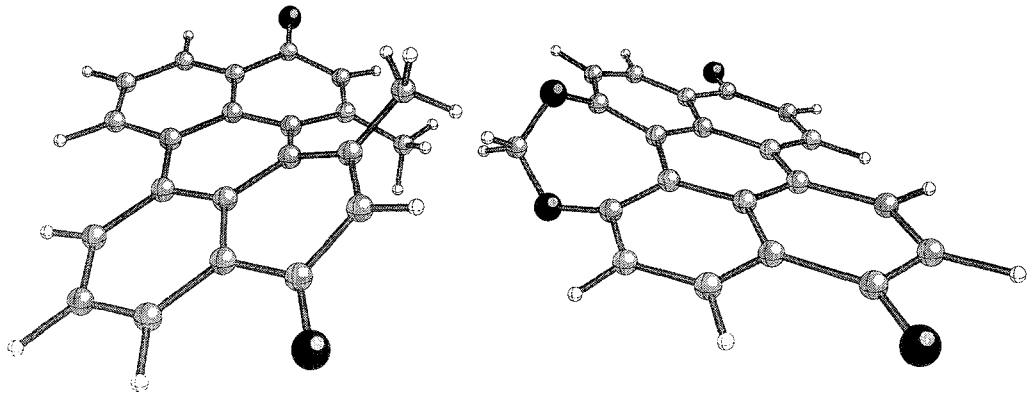


Fig. 2. "Ball & Stick" [12] model of **6** and **7** according to the force field calculation results

inversion barrier within the "left" half of the molecule is only about one quarter of the one within the "right" half in the methyl substituted derivative **6**. Addition of two hydroxy and two methoxy groups as described for **6** did not significantly change these results, i.e., 8.6° and 22.3° with an inversion barrier below 26.8 kJ/mol were calculated.

Merging the two partial structures **6** and **7** resulted in **8**, the fundamental skeleton of **2**. In this molecule both crucial dihedral angles were found to be twisted considerably. Values of 27.0° and 26.4° were found for 1–12b–12a–12 and 6–6a–6b–7. This most stable "propeller" conformer is shown in Fig. 3. An upper limit of the inversion barrier for the 1–12b–12a–12 side of the molecule was estimated to be 116.6 kJ/mol. Thus the upper limit of the inversion barrier obtained for **6** is somewhat lowered by the influence of the dioxymethylene bridge. Interestingly enough, by model calculations on this interconversion process a second, novel type of conformer was found. It was characterized by 1–12b–12a–12 and 6–6a–6b–7 torsion angles of −26.5° and 18.2°, and could be dubbed a "double-butterfly" conformer (Fig. 3). However, it is less stable than the "propeller" conformer by 18.8 kJ/mol (see Fig. 4).

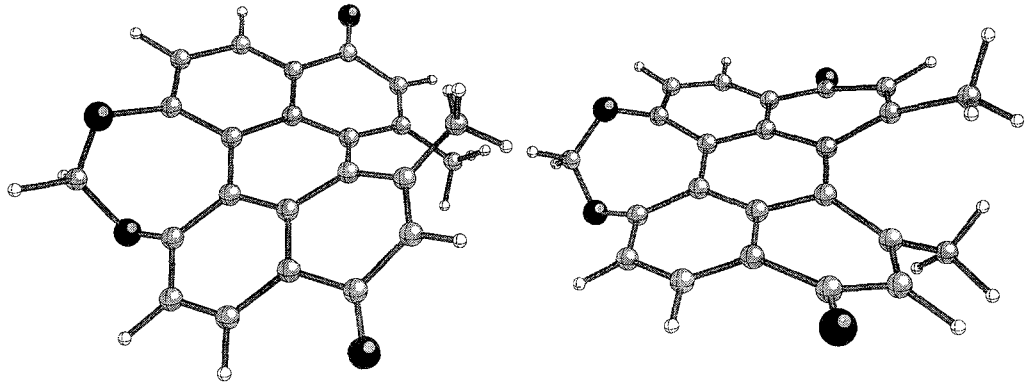
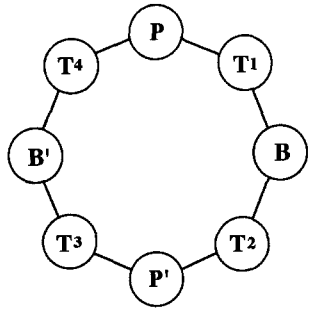


Fig. 3. "Ball & Stick" [12] model of the "propeller" and "double butterfly" conformations of **8** according to the force field calculation result

A more detailed stereochemical analysis revealed that the conformational space of compounds like **2** and **8** is considerably more complicated than assumed in a recent study [1, 5]. There are four possible stereo-isomers, two "propeller" conformers P and P′ which are enantiomers, and two "double-butterfly" conformers B and B′ which are also enantiomers. The interconversion between these atropisomers may be brought about *via* the transition state models T^1–T^4 as shown in the interconversion graph of Scheme 1. These states are characterized by dihedral angles of 0° at the 6–6a–6b–7 (T^1) and 1–12b–12a–12 (T^2) sites. T^1 and T^3, as well as T^2 and T^4 are enantiomers.



Scheme 1

The energy relation of the atropisomers of **8** and their interconversions are shown in Fig. 4. Whereas the upper limit of the interconversion barrier between the "propeller" and the "double-butterfly" conformers P and B, and P′ and B′ along the reaction coordinate $\mathscr{R}$ is as low as 33.0 kJ/mol, the interconversion between the enantiomers P and P′, which has to proceed via T^1, B, and T^2, is rather high, amounting to as much as 116.6 kJ/mol.

In accordance with the results for **6** and **7** given above, substitution of two hydroxyl and two methoxy groups in positions 4,9 and 2,11 of **8** to account for

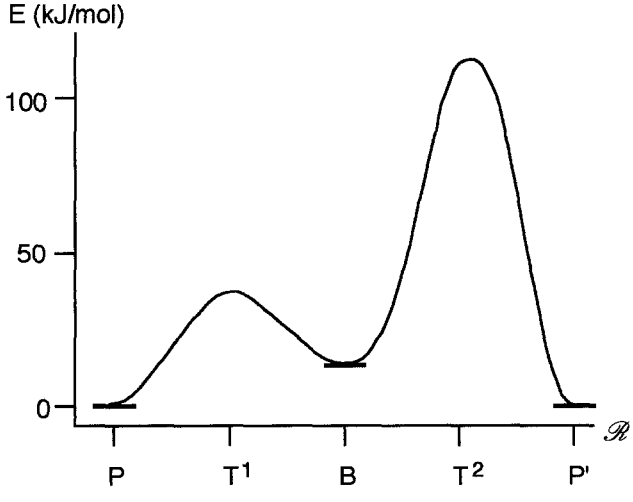


Fig. 4. Energetics of the conformational interconversions of **8**

the cercosporin substitution pattern, resulted in significant changes of the interconversion energy. Although the torsional deformation of the molecule remained similar in both conformers (P was characterized by dihedral angles 1–12b–12a–12 and 6–6a–6b–7 of 29.4° and 24.2°, and B by 28.7° and −19.3°), buttressing effects of the additional methoxy groups lead to enhanced interconversion barriers. The one from the P via T^1 to B conformer was found to be 22.6 kJ/mol and the one from P to P′ via B and T^2 was 155.5 kJ/mol. The "propeller" conformer P was found to be by 13.4 kJ more stable than the "double-butterfly" one.

Formal substitution of the hydroxyethyl fragments at the 1 and 12 methyl groups of the dihydroxy-dimethoxy derivative of **8** eventually lead to cercosporin (**2**). Again, the "propeller" conformer, as found for **8**, was the most stable one. It was characterized by 1–12b–12a–12 and 6–6a–6b–7 torsion angles of 30.6° and 25.9°. The first angle is slightly widened compared to the one of **8**, obviously this additional twisting is due to the steric strain introduced by the side chains. The geometry of the "propeller" conformer derived by the force field calculation compares favorably with the X-ray structural analysis of a derivative of **2** [5]: Deviations between the experimental and the force field calculation results of ±0.01 Å for the bond lengths, ±1.3° for the bonding angles, and ±4.8° for the dihedral angles of the cercosporin skeleton were observed.

The "double-butterfly" conformation of **2** was found to be characterized by 1–12b–12a–12 and 6–6a–6b–7 angles of 30.1° and −20.0°. It was 13.0 kJ/mol less stable than the "propeller" conformation. Fig. 5 displays model drawings of the two conformers. Interconversion between the P and P′ conformers (due to the chirality of the side chains the latter is a diastereomer called isocercosporin) of **2** *via* B and the transition state T^2 amounts to as much as 186.0 kJ/mol. In comparison to the corresponding value of the dihydroxydimethoxy derivative of **8** this value pointed to an additional influence of the sterically more crowded side chains. This upper limit was corroborated by the experimental finding, that a derivative of **2** is isomerized with $\Delta H^{\ddagger} = 83.6$ kJ/mol and $\Delta S^{\ddagger} = 86.9$ e.u. [5]. No significant energy difference was found between the two diastereomers P and P′ of **2**. The interconversion energy diagram thus resembled the one shown for **8** in Fig. 4.

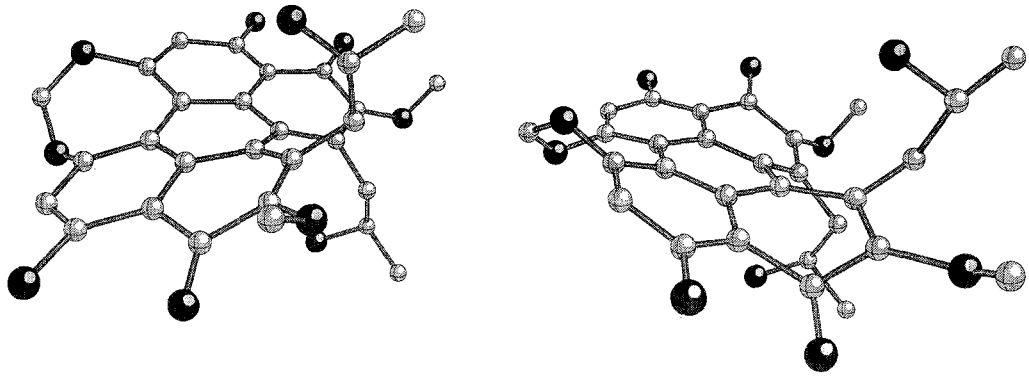
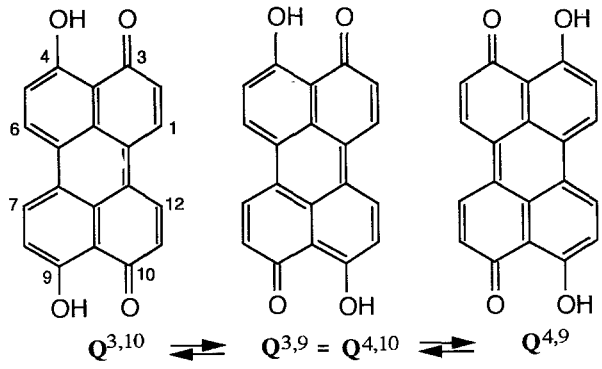


Fig. 5. "Ball & Stick" [12] model (non hydrogen atoms) of the "propeller" and "double butterfly" conformers of **2** according to the force field calculation result



Scheme 2

The two phenolic hydroxyl groups gave rise to an additional complication in the energy surface of molecules like **2**. Analysis of the tautomeric situation pointed to four possible tautomeric species $Q^{3,10}$, $Q^{3,9}$, $Q^{4,9}$, and $Q^{4,10}$ (see Scheme 2). In molecules with symmetric substitution patterns like **2**, $Q^{3,9}$ and $Q^{4,10}$ are, of course, identical.

Thus, three tautomers with four stereoisomers each makes up a total of twelve species possibly present! Fig. 6 displays the energy relations of the tautomers and their respective conformers of **2** as derived from the force field calculations. It turned out that in the case of **2** the $Q^{4,9}$ tautomer is favored by about 6 kJ/mol compared to the $Q^{3,10}$ tautomer, which is the species that is found in experiments. Of course, this calculated enthalpy difference is too small to allow a definite conclusion about which one of the two tautomers is actually favored in a certain state of matter. But it became clear from these results that one has to be very careful about tautomerism of these compounds. Experimental details for this aspect of cercosporin type molecules may also be found in literature [1]. Nevertheless, the $Q^{3,9}$ tautomer was found to be strongly destabilized. This destabilization was mostly due to the higher π-energy resulting from loosing the aromaticity of one of the two aromatic rings of $Q^{3,10}$ or $Q^{4,9}$.

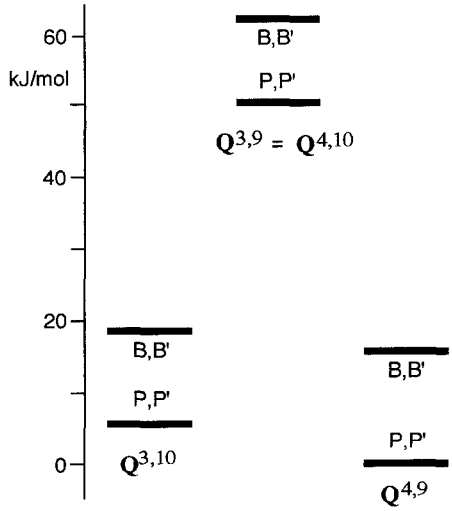


Fig. 6. Energy relations of the tautomers and conformers of **2** as derived from force field calculations

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