

# Concerning the Acidity and Hydrogen Bonding of Hydroxyphenanthroperylene Quinones like Fringelite D, Hypericin, and Stentorin

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**Summary.** The strongly enhanced acidity of the bay hydroxyl group as compared to the respective *peri* hydroxyl groups of fringelite D, hypericin, and stentorin could be rationalized on the basis of a vinylogous carboxylic acid and was nicely corroborated by semiempirical calculations of the AM1 type. Experimental data obtained from several independent experimental methods, like polarized absorption spectroscopy, hole burning, and isotope effects, as well as from semiempirical AM1 and 6-31G level *ab initio* calculations conclusively pointed to dissymmetrical hydrogen bonding systems in both the *peri* and *bay* regions of the corresponding *bay* phenolate ions.

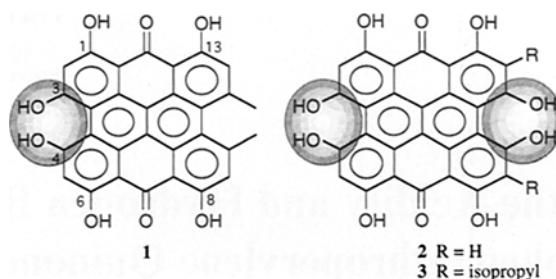
**Keywords.** Hypericin; Fringelite; Stentorin; Phenolate ions; Hydrogen bonding; *Ab initio* calculations; Acidity; Isotope effects.

## Zu Acidität und Wasserstoffbrückenbindung von Hydroxyphenanthroperylenchinonen wie Fringelit D, Hypericin und Stentorin

**Zusammenfassung.** Die stark erhöhte Acidität der bay-Hydroxylgruppen gegenüber jener der *peri*-Hydroxylgruppen von Fringelit D, Hypericin und Stentorin läßt sich auf der Basis einer vinylogenen Carbonsäure verstehen und wurde auch durch semiempirische Rechnungen vom AM1-Typ erhärtet. Daten aus unabhängigen Experimenten wie Polarisationspektroskopie, Lochbrennen und Isotopeneffekte sowie semiempirische AM1- und *ab initio*-Rechnungen auf 6-31G Niveau belegen ein unsymmetrisches Wasserstoffbrückenbindungssystem sowohl für den *peri*- als auch den *bay*-Bereich der entsprechenden *bay*-Phenolationen.

## Introduction

Hydroxyphenanthroperylene quinones, of which hypericin (**1**) [1], fringelite D (**2**) [2], and stentorin (**3**) [3] are examples, possess a unique *bay* region (shaded region). The two hydroxyl groups placed in this region are severely sterically congested, with an exceptionally short O...O distance of about 2.4 Å [4]. The first deprotonation step in the *bay* region is characterized by an acidity of  $pK_a \approx 1.5$  [5], which is about ten orders of magnitude stronger than those observed for the *peri* hydroxyl groups displaying the acidity of common phenols. The corresponding phenolate ions are characterized by a dramatic shift of the hydrogen bonded *bay* hydroxyl proton in



their  $^1\text{H}$  NMR spectra to about 17 ppm [5], indicating a rather strong hydrogen bond.

Several questions are still open with respect to this unique deprotonation and hydrogen bonding properties of the hydroxyphenanthroperylene quinones. In the present paper we wanted to address the reasons for the difference in acidity between *bay* and *peri* hydroxyl groups and to inquire the structural details of the deprotonated species of type **1–3** using experimental and quantum chemical methods.

## Methods

$^1\text{H}$ ,  $^2\text{H}$ , and  $^{13}\text{C}$  NMR spectra were recorded using a Bruker WM 360 instrument at 360, 55.3, and 90.5 MHz.  $\text{DMSO-d}_6$  was used as the solvent, and the spectra were referenced to the  $\text{DMSO}$  signal at 2.49 ppm. For the  $^2\text{H}$  NMR measurements, the lock channel of the instrument was used. FT-IR spectra were measured on a Biorad FTIR-45 instrument on solutions of  $\mathbf{1}^{(-)}$  and  $\mathbf{1}^{(-)}\text{-d}_{6(\text{O})}$  in  $\text{CHCl}_3$ , which was percolated over  $\text{Al}_2\text{O}_3$  immediately before use (1 mm pathlength, NaCl windows).

Per-O-deuterated hypericin bay phenolate ( $\mathbf{1}^{(-)}\text{-d}_{6(\text{O})}$ ) was prepared by suspending  $\mathbf{1}^{(-)}$  (**1** obtained according to Ref. [12] and deprotonated by means of N-ethyl-N, N-diisopropyl amine) in  $\text{CD}_3\text{OD}$  (Ueticon, 99.5%), equilibrating by heating to reflux temperature, stirring for 2 h at room temperature, and evaporating to dryness. This procedure was repeated three times. Deuteration was found to be >95%. Partial deuteration was obtained *in situ* by means of an addition of  $\text{CD}_3\text{OD}$  equivalents. It is interesting to note that upon prolonged standing (2 days) of these solutions with  $\text{CD}_3\text{OD}$ ,  $\mathbf{1}^{(-)}$  was also regioselectively deuterated at the two aromatic positions 2 and 5. Emodin anthrone was isolated according to Ref. [12], and the deuteration experiments were executed as described above.

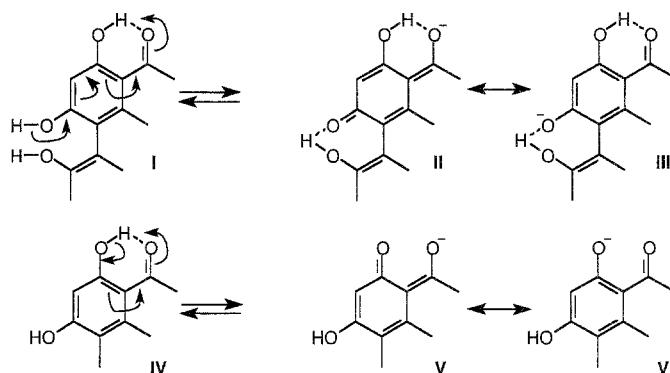
The *ab initio* calculations with a 6-31G basis set were performed using the Gaussian 94 program [6] on the DEC AlphaServer 2100 4/275 of the Vienna University Computer Center. Because the CNDO, MINDO/3, and MNDO semiempirical methods are known to show deficiencies with respect to a proper description of hydrogen bonds [7–9], the AM1 method [10] from the MOPAC package was used, having proven to be suited best for this purpose [11]. These calculations were performed at the Convex C3440 of the LIZENS (*Linzer Zentrum für Numerische Simulation*). For input geometries, the results of MM2+ calculations or X-ray structural data were used.

## Results and Discussion

### *Deprotonation Equilibria*

Qualitatively, the acidities of the *bay* and *peri* hydroxyl groups of compounds like **1–3** may be rationalized from the vinylogous carboxylic acid nature of the hydroxyl groups of hydroxyphenanthroperylenequinones as indicated in Scheme 1 (**I** and **IV**).

However, hydroxyl groups situated in the *peri* region of these molecules are characterized by  $pK_a$  values close to those of phenols, whereas those of the *bay* region exhibit extremely strong acidities [5]. Obviously, the stabilization of the phenol (**IV**) by hydrogen bonding as compared to the strongly destabilized phenolate ion (**V** ↔ **VI**) compensates the effect originating from the vinylogous carboxylic acid. For the *bay* region hydroxyl groups two effects add up: the stabilization of the phenolate ion (**II** ↔ **III**) by hydrogen bonding to the second closely spaced hydroxylic group on the one hand, and the vinylogous carboxylic acid nature of the system on the other hand.



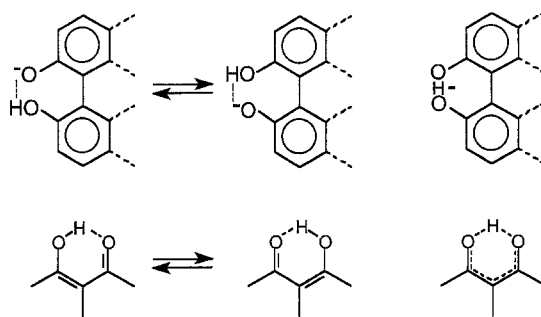
Scheme 1

This qualitative picture could be readily quantified on the basis of the semiempirical AM1 method. The phenolate ion formed by deprotonation of **1** at the *bay* region hydroxyl group (position “3”) was found to be stabilized over the two possible *peri* phenolate ions (deprotonation in position “1” or “8”) by 59 kJ/mol. This correlated with a  $pK_a$  difference of 10.1 units, which agreed nicely with the experimental *bay/peri*  $pK_a$  gaps of **1–3** [5, 13].

For compounds characterized by two *bay* hydroxyl regions (**2, 3**), two closely spaced deprotonation steps have been experimentally observed [5, 13]. From AM1 calculations it was concluded that from the three possible species the 3/10 dideprotonated one was more probable than the 3/11 (by 5.6 kJ/mol) and 3/4 ones (by 17.0 kJ/mol).

### Structural Aspects

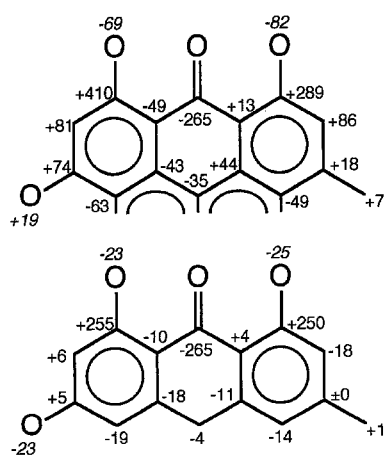
With respect to the structural details of the *bay* phenolate and the *peri* hydroxyl-oxo hydrogen bonding systems, two extreme situations are possible in principle (Scheme 2). The first one would be characterized by a two-well potential involving proton tautomerism. The other one would display a symmetrical single potential and thus an at least locally  $C_2$  symmetrical hydrogen bonding system. Examples for such systems have been investigated in a variety of molecules ranging from hydrogen phthalates to  $\beta$ -diketone enolates [14].



Scheme 2

From the experimental point of view, a variety of data on **1–3** has been made available. With respect to the *bay* phenolates of **1–3**,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the dissolved species point to systems of effective  $C_2$  symmetry [5, 13, 15] – of course this conclusion holds only within the limits of the methods time windows. On the other hand, the results of hole burning and *Stark* effect studies of the *bay* phenolate of **1** complexed to human serum albumin (*i.e.*, within the time window of electronic excitation) have been found to be in accordance with an unsymmetrical hydrogen bonding system in the *bay* region [16]. Moreover, polarized absorption spectra of the *bay* phenolate of a long chain derivative of **1** dissolved in an oriented polyethylene matrix led to the conclusion of the presence of an asymmetric hydrogen bonding system [17]. Concerning the *peri* regions, the chemical shifts of the 7,14-carbon atoms of **1–3** clearly identify them as hydrogen bonded carbonyl centers as compared to the 1/6, 8/13 carbon atoms which bear hydrogen bonded hydroxyl groups [5, 13, 15]. Thus, an intrinsically unsymmetrical hydrogen bonding system involving tautomerism seemed to be well documented.

Additional data were advanced in the present study by means of NMR investigations of the *bay* phenolate of **1** deuterated at the various hydroxyl groups. Unfortunately, we were not able to observe the otherwise highly conclusive [18] primary isotope effect. This was due to a fast deuterium exchange process rendering the spectral lines too broad to be detected. This process could not be slowed down sufficiently by temperature variation to provide proper detection of the deuterium signals. However, secondary isotope effects on both carbon and hydrogen nuclei (Fig. 1) could be nicely resolved.



**Fig. 1.** Secondary isotopic shifts of carbon atoms ( $\Delta C(\text{OD}) = \delta_{(\text{H})} - \delta_{(\text{D})}$ ; ppb) measured using **1**<sup>(-)</sup> and **1**<sup>(-)</sup>-d<sub>6(O)</sub> and of hydroxyl protons ( $\Delta H(\text{OD}) = \delta_{(\text{H})} - \delta_{(\text{H/D})}$ ; ppb) using partially (2/3 and 1/3) O-deuterated **1**<sup>(-)</sup> (top formula), and corresponding data for emodin anthrone and its partially and fully deuterated derivative

The  $^2\Delta\text{C(OD)}$  values of the *peri* oxygen bearing carbon atoms are at an intermediate level [19], and remarkably, these values even differ considerably from each other. This was in contrast to the two nearly equal values found for the rather similar emodin anthrone (Fig. 1). Obviously, the nearly doubled effect on C1 of  $\mathbf{1}^{(-)}$  was due to the isotope effect exerted by the *bay* region. The strongly negative  $^4\Delta(\text{OD})$  value of C7/C14 was found to be comparable to the corresponding data of hydroxyphenalenones and 1,8-dihydroxyanthrone [20–22] and to be identical with that of emodin anthrone. With respect to the *bay* region, a much smaller  $^2\Delta\text{C(OD)}$  value of +74 ppb was observed, pointing to a sterically strained hydrogen bonding system.

With the distinctly negative  $\Delta\text{H(OD)}$  values of the two *peri* hydroxyl groups a pronounced long range effect came into play, which has been related to the torsional deformations of systems [21]. The small but positive  $\Delta\text{H(OD)}$  value of the 3/4 hydroxyl group was found to be in contrast to the negative value observed for emodin anthrone. It was thought to stem from the  $\text{O}^3\text{--O}^{14}$  vinylogous interaction (Scheme 1:  $\mathbf{II}\leftrightarrow\mathbf{III}$ ), which is influenced by the change from  $\text{O}^1\text{--H}$  to  $\text{O}^1\text{--D}$ . However, this interaction made sense only in the case of an asymmetric hydrogen bonding situation in the *bay* region of  $\mathbf{1}^{(-)}$ .

A comparison of the FTIR spectra of  $\mathbf{1}$  and  $\mathbf{1-d}_{6(\text{O})}$  did not allow to assign the various absorption bands to characteristic deuterated and non-deuterated functional groups with any degree of certainty. Thus, we were not able to correlate vibrational isotopic shifts with hydrogen bonding potentials.

With respect to these structural details in the crystalline state of  $\mathbf{1}^{(-)}$ , we have been unable to locate the H atoms at the two O atoms in the *bay* region and at the pyridine nucleus of a crystal consisting of  $\mathbf{1}$  and one molecule of pyridine [4]. Accordingly, we have not been able to decide between the pyridinium hypericinate and the pyridine solvated non-deprotonated hypericin – in our first interpretation we favoured the latter in spite of the orientation and rather large distance of the pyridine with respect to the *bay* region (the distance between  $\text{O}^3$  and  $\text{N}^{\text{pyridine}}$  has been found to amount 10.5 Å [4]). However, a later X-ray analysis of a pyridinium hypericinate-pyridine-water crystal, which allowed to locate all hydrogen atoms, resulted in practically superimposable geometrical details with respect to the hypericin carbon and oxygen atoms [23]. Thus, it seemed to be highly probable that  $\mathbf{1}$  was also present as the *bay* phenolate ion in the first case. In both cases, a rather short  $\text{O}^3\cdots\text{O}^4$  distance of 2.34 and 2.36 Å has been obtained [4, 23]. A dissymmetrical  $\text{O}^3\text{--H}\cdots\text{O}^4$  hydrogen bridge with 1.17 and 1.20 Å distances has been advanced [23], although, due to a mean deviation of 0.05 Å, it has not been possible to decide definitely between a dissymmetrical and a symmetrical hydrogen bridge. However, a rather distinct dissymmetric distribution of the skeleton C–C and C=O (1.281 and 1.293 Å) distances, which could be anticipated from the mesomeric stabilization of the phenolate according to Scheme 1 ( $\mathbf{II}\leftrightarrow\mathbf{III}$ ), together with nonequal dihedral angles  $\theta_{\text{O}3\text{C}3\text{C}3\text{aC}3\text{b}}$  and  $\theta_{\text{O}4\text{C}4\text{C}3\text{bC}3\text{a}}$  of 1 and 6° and a dissymmetrical arrangement of the pyridine and water molecules with respect to the hypericinate molecule would strongly favour the presence of a dissymmetrical hydrogen bridge. Although the hydrogen atoms could not be localized in the first mentioned X-ray analysis [4], the dissymmetrical arrangement of the accessory pyridine molecule pointed to the same argument. Nevertheless, a  $C_2$  symmetrical structure has been favoured recently [23], mainly on account of the ESR spectrum of the *bay* phenolate radical of  $\mathbf{1}$  [24]. However, this latter result is, of course, also related to the time window of the method.

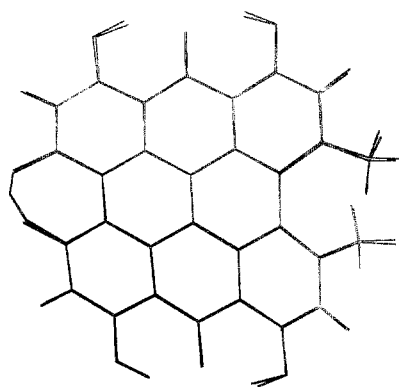
It has been shown that force field calculations of the MM2+ type were able to reproduce geometrical details of  $\mathbf{1}$ – $\mathbf{3}$  in general [4]. However, due to their semi-empirical parametrization they are not suited to achieve detailed conclusions about

the hydrogen bonding situation. Although the AM1 calculations were shown to yield reliable energy data about hydrogen bonding systems [11], we found that they overestimated the geometrical consequences of non bonded repulsion when compared with diffraction data. Thus, orienting AM1 calculations on salicylic acid and the hydrogenphthalate ion resulted in rather high O...O distances of 2.84 and 2.75 Å and O-H...O distances of 0.98 and 2.03, and 0.98 and 1.86 Å. The respective values from neutron diffraction studies on salicylic acid are 2.603–2.608, 0.916–0.954, and 1.788 and 1.766 Å [25]. For the hydrogenphthalate ion with two slightly different crystallographically independent molecules per unit cell the values are 2.404, 1.122, 1.294, and 2.394, 1.195, 1.205 Å [26].

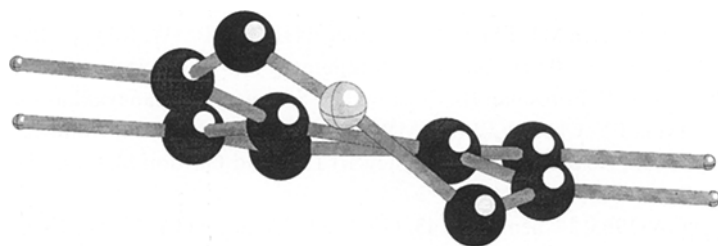
Indeed, the AM1 calculation of the hypericinate ion ( $\mathbf{1}^{(-)}$ ) propeller conformer resulted in an overall geometry consistent with the features of the X-ray data. However, the deformations of the molecule were somewhat overestimated. Thus, the dihedral angles  $\theta_{3,3a,3b,4}$  and  $\theta_{10,10a,10b,11}$  were calculated to amount to 26 and 36° with an O<sup>3</sup>...O<sup>4</sup> distance of 2.58 Å and O-H...O distances of 0.97 and 1.97 Å. Accordingly, the *bay* region hydrogen bonding system was found to be asymmetrically structured. The corresponding X-ray data were found to be 19.6 and 31.8°, and 2.36 Å [4, 23]. Due to the somewhat larger overall distortions of the molecule, the *peri* hydrogen bonding systems were also calculated to be more strongly dilated than has been found in the X-ray crystallographic studies [4, 23]. Accordingly, both experimental data and the result of the AM1 calculation corroborated a dissymmetrical hydrogen bonding in the *peri* regions.

The energetic and geometric aspects of hydrogen bonding is presently thought to be best described by extended basis set *ab initio* calculations [28]. To test for the suitability of the 6-31G level, orienting calculations on salicylic acid and hydrogenphthalate were executed first. In the first case O...O and O-H...O distances of 2.663, and 0.958 and 1.898 Å, and for the second case 2.402, and 1.029 and 1.388 Å were obtained – values which were in accordance with the experimental data mentioned above [25, 26]. Thus, it was interesting to note that the hydrogenphthalate ion, which has been repeatedly used as the working horse for a symmetrical hydrogen bond, has been definitely found to exhibit a dissymmetrical hydrogen bridge in the crystalline state as well as in water solutions [26, 27].

The *ab initio* calculation on  $\mathbf{1}^{(-)}$  using the same basis set resulted in an overall geometry which proved to be superimposable on the X-ray crystallographic structure [23] as shown in Fig. 2. Interestingly enough, this similarity between the X-ray structural data and the results calculated for the isolated molecule pointed to the fact that the highly strained and thus conformationally rather rigid hypericinate molecule is left unperturbed from the lattice interactions in the crystal. The dihedral angles  $\theta_{3,3a,3b,4}$  and  $\theta_{10,10a,10b,11}$  were calculated to amount 19.70 and 34.4° with an O<sup>3</sup>...O<sup>4</sup> distance of 2.40 Å (experimental values 19.65 and 31.8°, and 2.36 Å [23]), and O-H...O distances of 1.00 and 1.45 Å. Accordingly, the hydrogen bonding system of the *bay* region of  $\mathbf{1}^{(-)}$  was calculated to be definitely dissymmetrical. This dissymmetry was, on the one hand, due to the dihedral deformation of the *bay* region (Fig. 3), which did not allow for a planar arrangement of the hydrogen bonding system. On the other hand, the hydrogen bond was not found to be a linear one, but displayed an O<sup>3</sup>-H...O<sup>4</sup> bond angle of 157°. Both planarity and linearity of the system are thought to be of paramount importance for the formation of symmetrical



**Fig. 2.** Superposition of the 6-31G basis set *ab initio* and X-ray [23] propeller conformations of  $\mathbf{1}^{(-)}$  using the wire frame option of the 'ball & stick' program [29]



**Fig. 3.** *Ab initio* calculated bay region geometry of  $\mathbf{1}^{(-)}$  (ball & stick model [29]; clipped from the remainder of the molecule to enhance clarity)

hydrogen bonding systems [14, 28]. The hydrogen bonding system in the *peri* regions of the molecule was described by the *ab initio* calculation essentially as it has been found in the experimental structure determination [23] (Fig. 2).

Because the extended basis set *ab initio* calculation of  $\mathbf{1}^{(-)}$  consumed about 150 hours supercomputer cpu time, it seemed to be prohibitive to study its tautomerization potential by means of this method. Therefore, the height of this potential is presently unknown. However, from the short experimental and calculated  $\text{O}^3 \cdots \text{O}^4$  distance in  $\mathbf{1}^{(-)}$  one might anticipate a rather low tautomerization barrier.

### Conclusions

Experimental data obtained from several independent experimental methods, like polarized absorption spectroscopy, hole burning, and isotope effects, as well as semiempirical and *ab initio* calculations conclusively pointed to dissymmetric hydrogen bonding systems in both the *peri* and *bay* regions of the *bay* phenolate ions of  $\mathbf{1}$ – $\mathbf{3}$ . These data seemed also to corroborate the presence of an asymmetric hydrogen bonding system in the *bay* region of  $\mathbf{1}^{(-)}$  in the crystalline state, where the overall asymmetry of the molecule [4, 23] pointed indirectly to this feature. The strongly enhanced acidity of the *bay* hydroxyl group as compared to their respective *peri* hydroxyl groups could be rationalized on the basis of a vinylogous carboxylic acid and was nicely corroborated by semiempirical calculations of the AM1 type.

## Acknowledgements

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