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On the Relative Stability of Dioxo Derivatives of Phenanthro[1,10,9,8-*opqra*]perylene Related to the Tautomers of Hypericin

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Summary. In order to simplify the problems encountered in the study of the stability order of the tautomers of hypericin, we examined the structural factors influencing the stability of the respective dioxo derivatives of the parent benzenoid hydrocarbon phenanthro[1,10,9,8-*opqra*]perylene. It is shown that the stability order of these dioxo derivatives is essentially the same as that of the corresponding tautomers of hypericin. This corroborates the earlier opinion that the relative stability of the tautomers of hypericin is primarily determined by differences in π-electron conjugation and only to a lesser extent by steric effects of the oxo groups in positions 3 and/or 4.

Keywords. Hypericin; Tautomerism (in hypericin); Phenanthro[1,10,9,8-*opqra*]perylene; dioxo derivatives of phenanthro[1,10,9,8-*opqra*]perylene

Über die relativen Stabilitäten von mit den Tautomeren des Hypericins verwandten Dioxoderivaten von Phenanthro[1,10,9,8-*opqra*]perylen

Zusammenfassung. Um einen besseren Einblick in die Probleme im Zusammenhang mit der Stabilitätsreihenfolge der Tautomeren des Hypericins zu erhalten, haben wir die strukturellen Parameter untersucht, die die Stabilität der entsprechenden Dioxoderivate der Stammverbindung Phenanthro[1,10,9,8-*opqra*]perylen determinieren. Es wird gezeigt, daß die Stabilitätsreihenfolge dieser Verbindungen exakt jener der entsprechenden Tautomeren des Hypericins entspricht. Das bestätigt frühere Annahmen, daß die relativen Stabilitäten der Tautomeren des Hypericins vorwiegend durch Unterschiede in der π-Elektronen-Konjugation und weniger durch sterische Effekte der Oxogruppen in den Positionen 3 und/oder 4 bestimmt werden.

Introduction

Hypericin (**1**) is a naturally occurring and pharmacologically very interesting compound, a dimethyl-hexahydroxy-dioxo derivative of the benzenoid hydrocarbon phenanthro[1,10,9,8-*opqra*]perylene. Its properties have been extensively studied, both experimentally and theoretically (see, for instance, Refs. [1–5] and the references cited therein). The structural formula of hypericin is known for a long

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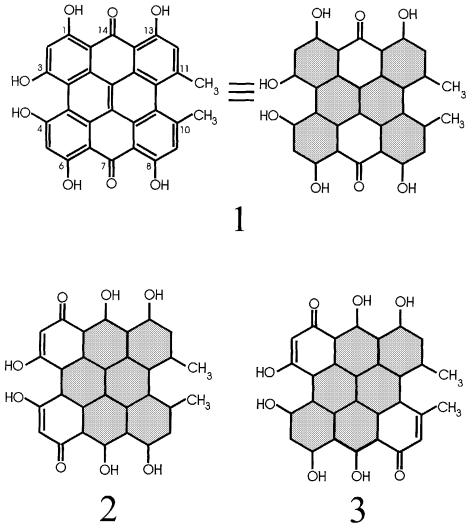

Fig. 1. Three tautomers of hypericin; in the text **1**, **2** and **3** are denoted by $Q(7,14)$, $Q(1,6)$, and $Q(1,8)$, respectively; the conjugated benzenoid domains in these molecules are indicated by shading

time [6]. On the other hand, hypericin may exist – at least in principle – in quite a few different tautomeric forms (for instance, in Fig. 1 the 7,14-, 1,6- and 1,8-dioxo tautomers (**1**–**3**) are presented; the 7,14-tautomer is considered to be the most stable one).

The problem of determining the stability order of the tautomers of hypericin and, thus, the identification of its dominant tautomeric form, attracted some attention [5, 7–9]. Interest in this direction has additionally increased after the preparation of the energetically less favorable 1,6-dioxo tautomer [10]. Tautomerism in a number of related naturally occurring polyoxy derivatives of benzenoid hydrocarbons (isohypericin, stentorin, isostentorin, fringelit D, *etc*.) has also been studied [11–13].

The main conclusion of the researches [7–13] was that the dominant factors influencing the stability order of the tautomers are the conjugation modes of the π-electrons which, in turn, are determined by the position of the two oxo groups. The effects of the hydroxy and methyl groups (including the effect of the intermolecular hydrogen bonding) were believed to be much less important since these are believed to be roughly the same in all tautomers.

On the other hand, when determining the geometries of the tautomers (by means of quantum-chemical calculations that include geometry optimization based on locating minima on the energy hypersurface, see below), the methyl and hydroxy groups cause serious problems. It turns out that slight changes in the initial guess of the position of the hydrogen atoms in the OH and CH_3 groups may lead the calculation towards significantly different ''optimized'' geometries with significantly different energies. In addition, the quantum-chemical methods employed for determining the energies and geometries of the tautomers [7, 8, 11–13] are known to poorly reproduce intramolecular hydrogen bonding, whereas intermolecular hydrogen bonding is certainly beyond the scope of these methods.

Especially awkward happens to be the determination of the geometry of the two *bay*-oxygen atoms (those in position 3 and 4), for which AM1 and *ab initio* calculations give completely different results [9, 14].

In view of all this, we decided to approach the problem of the stability of the tautomers of hypericin and related compounds by using a drastic simplification, considering the respective dioxo isomers of the parent benzenoid hydrocarbon phenanthro[1,10,9,8-*opqra*]perylene, thus fully eliminating the effects caused by hydroxy and methyl groups. These dioxo derivatives may, but need not, be a satisfactory model for the tautomers of hypericin. As the calculations reported in this work show, the model happens to be quite well chosen.

Following Refs. [7–10], the tautomer of hypericin in which the oxo groups are in positions x and y will be denoted by $Q(x, y)$. The respective dioxo derivative of phenanthro[1,10,9,8-*opqra*]perylene is denoted by $D(x, y)$. There are 10 distinct tautomers $Q(x, y)$ with and 6 tautomers without *Kekulé* structures. Because the parent benzenoid hydrocarbon has higher symmetry than hypericin, there are only 8 *Kekuléan* and 5 *non-Kekuléan* $D(x, y)$ isomers. Their structures are shown in Fig. 2.

The correspondencies between tautomers and isomers are as follows: $D(1,3)$/$Q(1,3)$; $D(1,4)$/$Q(1,4)$; $D(1,6)$/$Q(1,6)$, $Q(8,13)$; $D(1,7)$/$Q(1,7)$, $Q(7,13)$; $D(1,8)$/

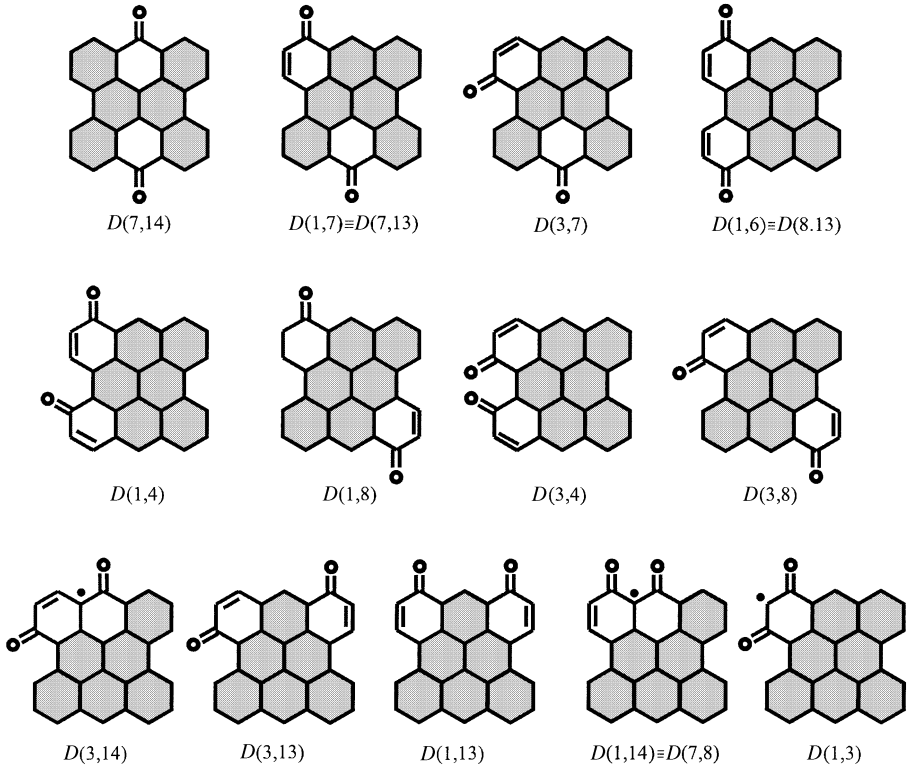

Fig. 2. Dioxo derivatives of phenanthro[1,10,9,8-*opqra*]perylene corresponding to the tautomers of hypericin (for details see text); the conjugated benzenoid domains in these molecules are indicated by shading

$Q(1,8)$; $D(1,13)/Q(1,13)$; $D(1,14)/Q(1,14)$, $Q(7,8)$; $D(3,4)/Q(3,4)$; $D(1,7)/Q(3,7)$; $D(3,8)/Q(3,8)$; $D(3,13)/Q(3,13)$; $D(3,14)/Q(3,14)$; $D(7,14)/Q(7,14)$.

Results and Discussion

In Table 1, the calculated energies of the dioxo isomers of phenanthro[1,10,9,8-*opqra*]perylene are given. In the same Table we present the energies of the corresponding tautomers of hypericin in both the (most stable) *propeller* and the (less stable) *double-butterfly* conformation [7, 10, 18]. Note that the present energies of the $Q(x, y)$ species differ somewhat from those previously reported by us [8]. This is due to the fact that in the meantime we managed to locate some deeper-lying minima on the energy hypersurface of hypericin. Our energies also slightly differ from what recently has been found by *Etzlstorfer* and *Falk* [9]. We fully agree with their opinion [9] that these small discrepancies are caused by ''the rather dense population of side minima around the global minimum'' which makes the pinpointing of the global energy minimum a very tricky task.

The results shown in Table 1 reveal that the stability order of the dioxo derivatives of phenanthro[1,10,9,8-*opqra*]perylene is precisely the same as the stability order of the tautomers of hypericin. A minor violation is observed only in the case of the least stable *non-Kekuléan* species, which are of no relevance for our consideration.

Among the *Kekuléan* isomers $D(x, y)$, the rules determining stability are precisely the same as in the case of the tautomers $Q(x, y)$ [8] and read as follows:

1. The stability of the *Kekuléan* isomers $D(x, y)$ decreases with decreasing extent of cyclic conjugation of the π-electrons; in Fig. 2, the respective conjugated

Table 1. Energies (kJ/mol) of the dioxo isomers $D(x, y)$ of phenanthro[1,10,9,8-*opqra*]perylene and of the corresponding tautomers $Q(x, y)$ of hypericin (in propeller and double-butterfly conformations); x and y indicate the position of the two oxo groups (cf. Fig. 1)

			Propeller	Butterfly
$D(7, 14)$	0.0	$Q(7, 14)$	0.0	0.0
$D(1, 7) \equiv D(7, 13)$	41.5	$Q(7, 13)$	43.1	43.8
		$Q(1, 7)$	44.0	45.1
$D(3, 7)$	52.4	$Q(3, 7)$	63.1	63.0
$D(1, 6) \equiv D(8, 13)$	56.8	$Q(8, 13)$	69.4	71.7
		$Q(1, 6)$	73.5	75.2
$D(1, 4)$	65.9	$Q(1, 4)$	88.7	90.0
$D(1, 8)$	89.6	$Q(1, 8)$	93.3	92.8
$D(3, 4)$	92.2	$Q(3, 4)$	100.0	110.9
$D(3, 8)$	100.6	$Q(3, 8)$	114.8	111.7
$D(3, 14)$	202.3	$Q(3, 14)$	151.2	149.3
$D(3, 13)$	220.3	$Q(3, 13)$	178.3	177.4
$D(1, 13)$	222.8	$Q(1, 13)$	203.2	203.2
$D(1, 14) \equiv D(7, 8)$	229.4	$Q(1, 14)$	202.4	201.2
		$Q(7, 8)$	210.2	209.7
$D(1, 3)$	257.9	$Q(1, 3)$	209.5	213.0

domains are indicated by shading. A rough, yet reliable, measure of the extent of this conjugation is the number of *Kekulé* structures (K) [19]. Thus, $K\{D(7,14)\} = 24$, $K\{D(1,7)\} = K\{D(3,7)\} = 16$, $K\{D(1,6)\} = K\{D(1,4)\} = K\{D(3,4)\} = 14$, and $K\{D(1,8)\} = K\{D(3,8)\} = 10$.

2. Among the isomers $D(x,y)$ with coinciding modes of cyclic conjugation (and, in particular, with equal K values), the stability decreases if one oxo group is in position 3 or 4. In all the cases considered *i.e.* $D(1,7)$ *vs.* $D(3,7)$, $D(1,6)$ *vs.* $D(1,4)$, and $D(1,8)$ *vs.* $D(3,8)$, this decrease is about 10 kJ/mol. In the single case when the oxo groups are in positions 3 and 4 ($D(3,4)$), the decrease of stability is much more pronounced (over 25 kJ/mol relative to the $D(1,4)$-isomer). Because of this, the position of the $D(3,4)$ isomer in the stability order is somewhat anomalous; it comes after $D(1,8)$ instead before $D(1,8)$ as would be expected on the basis of the *Kekulé* structure counts.

The analogy between the stability of the dioxo derivatives of phenanthro[1,10,9,8-*opqra*]perylene and of the tautomers of hypericin is remarkable. First of all, as in the case of hypericin, the far most stable isomer is $D(7,14)$. Its energy is by more than 40 kJ/mol below the energy of the next stable isomer $D(1,7)$.

As in the case of hypericin [8], the stability order of the $D(x,y)$ isomers is just what could be anticipated on the basis of their conjugated benzenoid domains and *Kekulé* structure counts; details have been given above. In addition, the energies of the *non-Kekuléan* isomers are by 200–250 kJ/mol higher than those of $D(7,14)$ and, consequently, these should be extremely unstable moieties, deserving no further attention.

The second important factor influencing the stability of the $D(x,y)$ isomers is the steric repulsion caused by the oxo group(s) in position(s) 3 and/or 4. Indeed, all isomers in which the oxo groups are not in positions 3 or 4 ($D(7,14)$, $D(1,7)$, $D(1,6)$, $D(1,8)$, $D(1,13)$, and $D(1,14)$) were found to be perfectly planar. The isomers with one oxo group in position 3 or 4 are slightly non-planar: whereas all the carbon atoms lie practically in one plane, the oxo group in position 3 or 4 is out of plane by about 8°. The angles pertaining to $D(3,7)$, $D(1,4)$, $D(3,8)$, $D(3,14)$, $D(3,13)$, and $D(1,3)$ are 8.3, 8.6, 8.0, 7.5, 5.3, and 9.3°, respectively. A similar value (8.35°) is found for the angle between each oxo group of $D(3,4)$ and the plane determined by the carbon atom skeleton. The two oxo groups lie on opposite sides of this plane, and thus the angle between them is 16.7°. Consequently, in the vicinity of the carbon atoms 3 and 4 the molecule $D(3,4)$ is highly non-planar.

The above mentioned increase of energy when one or two groups are put into positions 3 and/or 4 is an evident consequence of the steric strain caused by them. In the case of the hypericin tautomers, a similar effect takes place, but envisaging it is less easy because of the simultaneous presence of other steric repulsions (of the two methyl groups *etc.*) and because of the pronounced non-planarity of the central part of the molecule.

In summary, our results indicate that the structural/electronic factors determining the stability of the $D(x,y)$ isomers are essentially the same as those determining the stability of the $Q(x,y)$ tautomers. Therefore, the dioxo derivatives of phenanthro[1,10,9,8-*opqra*]perylene provide a plausible model for rationalizing

the complex structural/electronic effects occurring in the tautomers of hypericin and causing the drastic differences in their stabilities.

Materials and Methods

The energies and geometries of the $D(x, y)$ isomers were calculated by the same procedure as in the case of the earlier reported $Q(x, y)$ tautomers of hypericin [8]. This is the AM1 (Austin Model 1) semiempirical molecular orbital approximation at the restricted *Hartree-Fock* (RHF) level [15]. A MOPAC package has been used [16, 17], and full geometry optimization has been done in all cases.

In order to be able to make a complete comparison with the previous results [8], RHF calculations were performed also on the *non-Kekuléan* species $D(1, 3)$, $D(1, 13)$, $D(1, 14)$, $D(3, 13)$, and $D(3, 14)$. For these, the assumption of a closed-shell electronic configuration is doubtful. Therefore, the results obtained for the *non-Kekuléan* isomers should be taken with some caution. They certainly are less accurate than those for *Kekuléan* systems. Anyway, as anticipated, *non-Kekuléan* isomers have much higher energies (by 100–150 kJ/mol) than the *Kekuléan* isomers, and their real existence is as elusive as the existence of the *non-Kekuléan* tautomers of hypericin.

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