Ivan Gutman, Zoran Marković and Johan P. Engelbrecht, *S. Afr. J. Chem.*, 2000, **53** (3), 169-178,
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<http://ejour.sabinet.co.za/images/ejour/chem/chem_v53_n3_a1.pdf>.
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RESEARCH ARTICLE

On the Relative Stability of Tetraoxo-bisanthrenes Related to the Radical Anions of Hypericin

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Abstract

In recent experimental and theoretical studies of the photochemical proton transfer from hypericin, it was conjectured that the relative stability of the various hypericin radical anions parallels the relative stability of the corresponding tetraoxo derivatives of the parent hydrocarbon (bisanthrene). In order to test this hypothesis, we determined the energies and geometries of the respective tetraoxo-bisanthrenes by quantum-chemical methods and analyzed their dependence on molecular structure. The stability order of tetraoxo-bisanthrenes was indeed found to match that of the hypericin radical anions.

1. Introduction

Hypericin **1** (Fig. 1), a dimethylhexahydroxydioxo derivative of the benzenoid hydrocarbon bisanthrene **2** (Fig. 1), has been known for a long time for its interesting (photo)physiological and pharmacological properties. This compound is found in various plants, in particular in St. John's wort. Since antiquity this plant has been used in medicine for the healing of wounds and, in recent times, against alcohol craving. Details on the chemistry of hypericin and its various roles and applications in physiology and pharmacology, as well as an exhaustive bibliography, may be found in a recent review by Falk, whose research team has been responsible for most of the recent physico-chemical studies on hypericin.[1] It was recently discovered that, under the influence of light, hypericin shows virucidal and antiproliferative activity as well as cytotoxic effects on tumour cells.[1] Because of these properties, the study of the photochemistry of hypericin has gained much in importance.

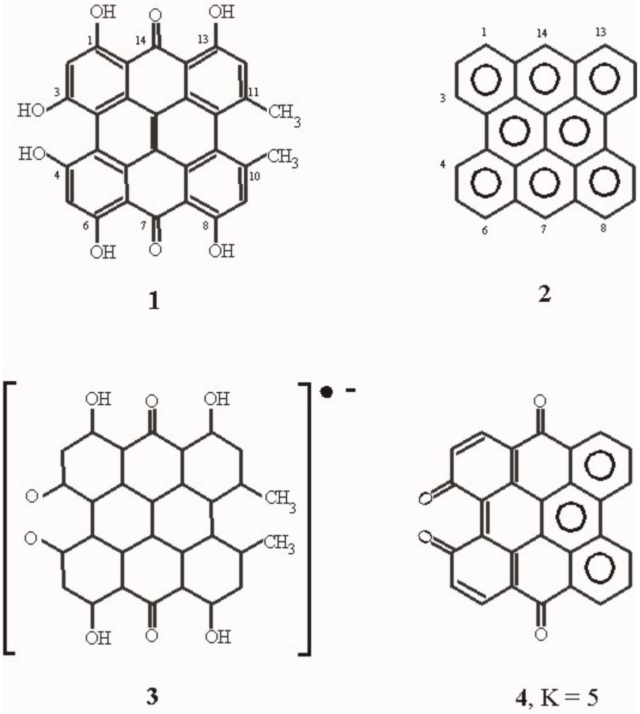

Figure 1 Hypericin **1** and its parent hydrocarbon bisanthrene or phenanthro[1,10,9,8-*o,p,q,r,a*]perylene **2**, and the numbering of their carbon atoms. Species **3** is the most stable radical anion of hypericin; **4** is the corresponding tetraoxo bisanthrene.

Under physiological conditions hypericin is in its 7,14-dioxo tautomeric form (as shown in **1**), although other tautomers may also exist.[2] Since compound **1** is a strong acid, it is present almost exclusively as the 3-hypericinate anion (that is, the anion in which the proton is missing from the OH-group at position 3). A remarkable property of hypericin is that upon irradiation it becomes a much stronger acid and loses one more proton.[3-5] Based on both experimental[5] and theoretical[6] examinations, it was concluded that the 3-hypericinate anion is first oxidized to an uncharged radical, which is then deprotonated for the second time, forming a radical anion.

In order to establish the position from which the second proton originates, quantum chemical studies (using the AM1 calculation scheme) of the possible doubly-deprotonated radical anions of hypericin have been undertaken.[6] [In what follows, the species in which protons are missing from the OH groups at positions x and y will be referred to as the (x,y)-species.] It was shown[6] that the two most stable radical anions are the (3,4)- and (3,6)-species (heats of formation –975.0 and –963.6 kJ mol^{-1}, respectively). The (3,1)-, (3,8)- and (3,13)-radical anions are significantly less stable (heats of formation –931.4, –925.1 and –914.4 kJ mol^{-1}, respectively). This implies that the second proton originates from the OH groups in positions 4 and/or 6, and not from the OH groups in positions 1, 8 and 13.

The five possible radical anions of hypericin are formally related to certain tetraoxo-derivatives of the parent hydrocarbon **2**. Thus:

- the (3,4)-radical anion of hypericin (formula **3** in Fig. 1) corresponds to 3,4,7,14-tetraoxo bisanthrene (formula **4** in Fig. 1), a conjugated molecule possessing five Kekulé structural formulas (K = 5);
- the (3,6)-radical anion of hypericin corresponds to 3,6,7,14-tetraoxo bisanthrene (K = 5), which by symmetry is identical to the 1,4,7,14-tetraoxo species;
- the (3,8)-radical anion of hypericin corresponds to 3,7,8,14-tetraoxo bisanthrene (K = 1);
- the (3,1)-radical anion of hypericin corresponds to 1,3,7,14-tetraoxo bisanthrene (K = 0);
- the (3,13)-radical anion of hypericin corresponds to 3,7,13,14-tetraoxo bisanthrene (K = 0).

Within a series of isomeric benzenoid molecules, the thermodynamic stability is known to be a monotonically (almost linearly) increasing function of the number of Kekulé structures K.[7] Applying this rule to the tetraoxo derivatives of bisanthrene, one arrives at a surprising conclusion:[6] the stability order of the radical anions of hypericin matches the stability order of the corresponding tetraoxo bisanthrenes.

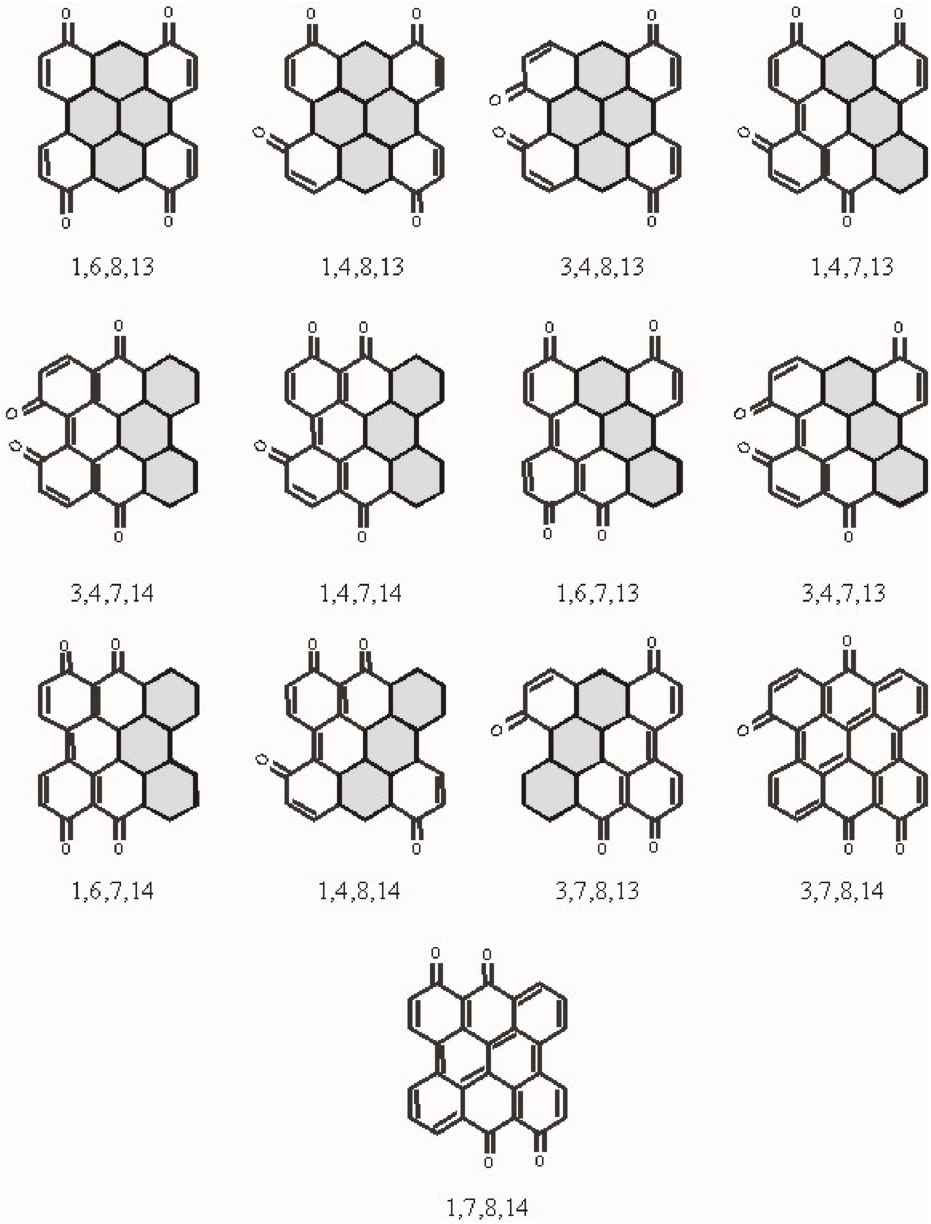

Figure 2 The 13 possible Kekuléan isomers of tetraoxo bisanthrene that correspond to (possible) radical anions of hypericin, in order of decreasing stability.

In the abovementioned work,[6] the relative stabilities of the tetraoxo bisanthrenes were estimated only on the basis of their K-values. In view of the anticipated electrostatic repulsion and other steric and electronic effects of the four oxo groups, such an estimate cannot be considered as fully satisfactory. In order to fill this gap we have undertaken further quantum chemical examinations. Thus, the purpose of this work is to gain more detailed and more reliable information on the properties of tetraoxo bisanthrenes (in particular, their energies and geometries). We believe that such a study will contribute to the better understanding of the fine details of the photooxidation of hypericin and, less directly, of its physiological activity.

In this work we report the results of quantum chemical studies (obtained by means of the AM1 method) of the tetraoxo derivatives of bisanthrene that are related to the radical anions of hypericin, as specified above. We have considered only Kekuléan species, that is molecules for which the K-value is greater than zero. There are 13 possible isomers of this kind, the structures of which are depicted in Fig. 2.

2. Method

The results reported in this work were obtained by using the AM1 (Austin Model 1) semiempirical molecular-orbital calculation scheme at the restricted Hartree–Fock (RHF) level.[8] A MOPAC computer software package was employed.[9, 10] The geometries were fully optimized. In some cases the molecules considered possess two stable conformations, which is analogous to what has previously been observed in the case of hypericin.[11, 12] In view of the earlier proposed terminology[11, 12] we refer to these conformations as "propeller" and "double-butterfly".

Earlier RHF calculations performed on non-Kekuléan tautomers of hypericin[13] and the corresponding dioxo derivatives of bisanthrene[14] showed that the energies of these species are more than 100 kJ mol^{-1} below the energy of the least stable Kekuléan isomer. Therefore such hypothetical moieties are of little or no chemical relevance. Bearing in mind these findings, the tetraoxo isomers of bisanthrene for which K = 0 were excluded from the present study.

3. Results

The energies of the tetraoxo bisanthrenes are given in Table 1. In Fig. 3, 4 and 5 are shown the geometries of three isomers of tetraoxo bisanthrene. Of all the 13 tetraoxo bisanthrene isomers studied, only the 1,6,8,13-species is planar (Fig. 3).

In what follows we examine the violations of some carbon atoms from the molecular plane. These are caused by the oxygen atoms attached to the respective carbon atoms, and their mutual repulsion. The out-of-plane deformations of the oxygen atoms are usually much larger.

Table 1 The energies of the tetraoxo bisanthrenes (from Fig. 2), relative to the most stable 1,6,8,13-isomer[a]

Isomer	K	Energy / kJ mol^{-1}	
1,6,8,13-	6	0	
1,4,8,13-	6	3.16	
3,4,8,13-	6	23.69	
1,4,7,13-	4	40.76	
3,4,7,14-	5	41.51	
1,4,7,14-	5	42.39	
1,6,7,13-	4	59.24	
3,4,7,13-	4	60.02	
1,6,7,14-	5	60.85 (p)	62.75 (db)
1,4,8,14-	4	60.9	
3,7,8,13-	4	64.77	
3,7,8,14-	1	157.2	
1,7,8,14-	1	174.63 (p)	178.81 (db)

[a] K = number of Kekulé structures, (p) = "propeller" conformation, (db) = "double butterfly" conformation; for details see text.

As mentioned above, all tetraoxo bisanthrenes except the 1,6,8,13-isomer (Fig. 3) are non-planar. For example, the C4 atom of the 1,4,8,13-isomer is out of the plane by approximately 8.5° while the analogous deformation in the 1,4,7,13-species is almost identical (9°). The isomer 1,4,7,14- has an analogous deformation at the C4 atom of 10.2°; an additional deformation of 11.2° is caused by the repulsion between the two oxygen atoms in positions 1 and 14. The isomers 1,4,8,14-, 3,7,8,14- and 3,7,8,13- have similar deformations of the carbon skeleton (9–10°) as a consequence of the repulsion between the bay-oxygen and hydrogen atoms (those in positions 3 and/or 4). Each of these molecules has an additional deformation by 4–8°, the first one in position 1,4 whereas the second and third ones have deformations in position 7,8. These deformations are caused by the repulsion between the adjacent O-atoms.

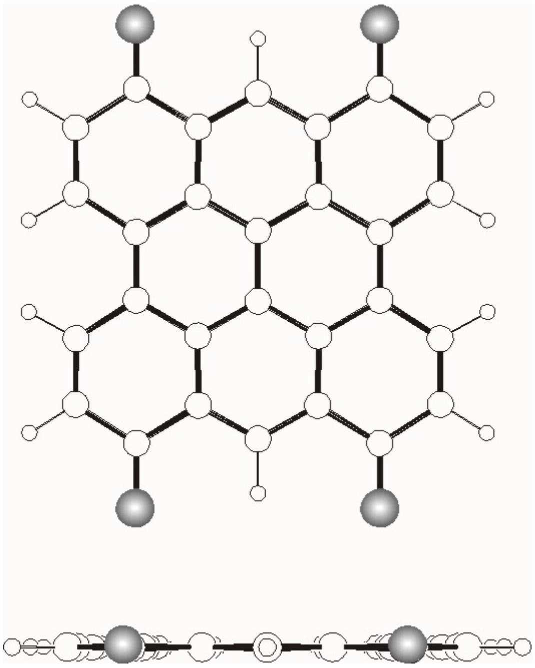

Figure 3 1,6,8,13-Tetraoxo bisanthrene, the most stable of the tetraoxo bisanthrene isomers, is perfectly planar.

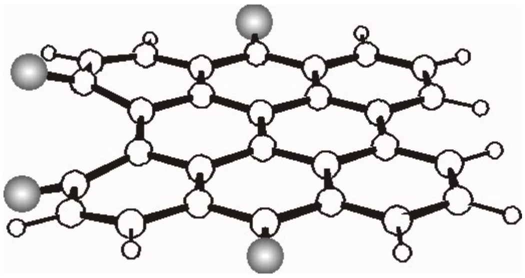

Figure 4 3,4,7,14-Tetraoxo bisanthrene, which corresponds to the most stable radical anion of hypericin.

Compounds 3,4,8,13-, 3,4,7,14- and 3,4,7,13- comprise a group of isomers that have only one noticeable deformation of the carbon atom skeleton, which is caused by the repulsion between two bay-region oxygen atoms. The deformation in all cases is about 16°. The geometry of the 3,4,7,14-isomer is depicted in Fig. 4. The 1,6,7,13-tetraoxo derivative has a slight deformation (8°) of the carbon-atom skeleton, mainly localized at the position 1,6.

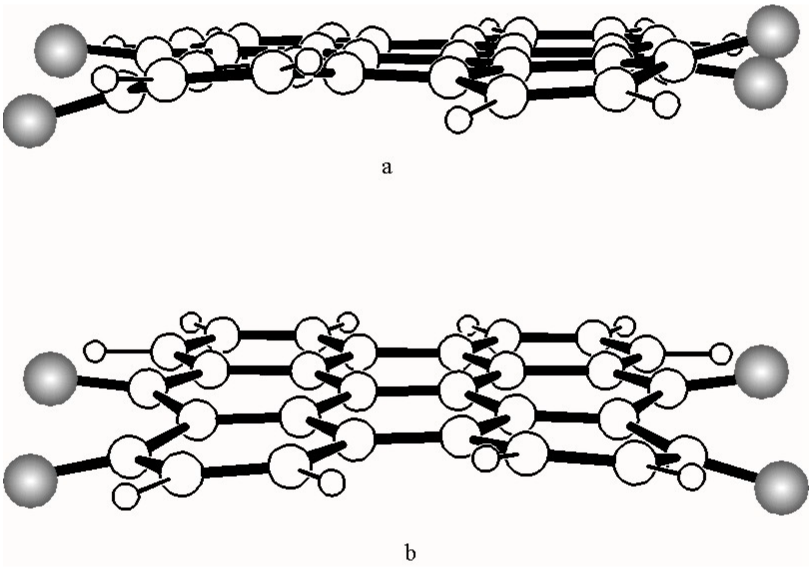

Figure 5 1,6,7,14-Tetraoxo bisanthrene occurs in two conformations of nearly equal energy. In the "propeller" conformation (a), the oxygen atoms in positions 1 and 6 as well as those in positions 7 and 14 lie on the opposite sides of the molecular plane; in the "double-butterfly" conformation (b), the oxygen atoms in positions 1 and 6 as well as those in positions 7 and 14 lie on the same side of the molecular plane.

In the case of the 1,6,7,14-isomer there is a pronounced repulsion between the oxo groups in positions 1 and 14, as well as between those in positions 6 and 7. This causes deformations of two types, resulting in two distinct conformations (Fig. 5). In the "propeller" conformation the deformations are 9.4° and 8.2°, respectively. In the "double butterfly" conformation the analogous deformations are 9.4° and 8.5°. The "propeller" is somewhat more stable than the "double butterfly" (Table 1). The situation is similar also in the case of the 1,7,8,14-tetraoxo compound, where two repulsions between the oxo groups at C1-C14 and C7-C8 cause nearly isoenergetic conformers.[15]

4. Discussion

Our results are in good agreement with the expected[6] stability order of the tetraoxo bisanthrenes corresponding to the radical anions of hypericin. Indeed, the 3,4,7,14-tetraoxo and 1,4,7,14-tetraoxo species have practically equal energies, and are much more stable than the 3,7,8,14-isomer. The energies of the non-Kekuléan 1,3,7,14- and 1,7,13,14-tetraoxo isomers have not been calculated, but they certainly significantly exceed the energies of the Kekuléan isomers.

Comparing the data given in Table 1 and the structures given in Fig. 2, we arrive at the following conclusions.

The most favourable arrangement of the four oxo groups is in positions 1,6,8,13, when they are as far apart as possible, and when no steric repulsions in positions 3 and/or 4 are present. The same arrangement enables a planar geometry and a maximum Kekulé structure count, K = 6.

The 1,4,8,13-isomer also possesses six Kekulé structures and has only a slightly higher energy caused by the (weak) repulsion between the H atom in position 3 and the O atom in position 4. When O atoms are present in both positions 3 and 4 (as in the 3,4,8,13-isomer), the repulsion is significantly greater, causing an increase in energy of over 20 kJ mol^{-1}.

In general, the stability of the tetraoxo bisanthrenes diminishes with the decreasing number of Kekulé structures (see Table 1), but a few exceptions exist. Another major destabilizing effect is the presence of close-lying oxo groups, such as in positions 1-14, 3-4, 6-7, 7-8 and/or 13-14. Each such O–O repulsion increases the energy by approximately 20 kJ mol^{-1}. Compare, for instance the 1,4,7,13- and 3,4,7,13-isomer pairs, or the 3,7,8,14- and 1,7,8,14-derivatives. In some cases, species with smaller Kekulé structure counts but without O–O repulsion (*e.g.*, the 1,4,7,13-isomer, K = 4) may be more stable than species with a greater number of Kekulé structures but with O–O repulsion (*e.g.*, the 1,4,7,14-isomer, K = 5).

The isomers with a single Kekulé structure, namely the 3,7,8,14- and 1,7,8,14-species, are found to have energies that are lower than those of the other tetraoxo bisanthrenes by some 100 kJ mol^{-1}. This confirms once again that cyclic conjugation (or, in old-fashioned wording, "resonance") is the dominant -electron effect influencing the stability order of isomeric benzenoid compounds.[7, 16]

References and Notes

1 H. Falk, *Angew. Chem.*, 1999, **111**, 3307; *Angew. Chem. Int. Ed.,* 1999, **38**, 3134.

2 T. G. Dax, H. Falk and E. I. Kapinus, *Monatsh. Chem.*, 1999, **130**, 827.

3 M. J. Fehr, M. A. McCloskey and J. W. Petrich, *J. Am. Chem. Soc.*, 1995, **117**, 1883.

4 T. A. Wells, A. Losi, R. Dai, P. Scott, S. M. Park, J. Golbeck and P. S. Song, *J. Phys. Chem.*, 1997, **101**, 366.

5 R. A. Obermüller, G. J. Schütz, H. J. Gruber and H. Falk, Monatsh. Chem., 1999, **130**, 275.

6 C. Etzlstorfer, I. Gutman and H. Falk, Monatsh. Chem., 1999, **130**, 1333.

7 I. Gutman and S. J. Cyvin, *Introduction to the Theory of Benzenoid Hydrocarbons*, Springer-Verlag, Berlin, 1989.

8 M. J. S. Dewar, E. G. Zoebish, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.

9 J. J. P. Stewart, *J. Comput.-Aided Molec. Des.*, 1990, **4**, 1.

10 J. J. P. Stewart, QCPE No. **455**.

11 C. Etzlstorfer, H. Falk, N. Müller, W. Schmitzberger and U. G. Wagner, *Monatsh. Chem.*, 1993, **124**, 751.

12 R. Altmann, C. Etzlstorfer and H. Falk, *Monatsh. Chem.*, 1997, **128**, 361.

13 I. Gutman, Z. Marković, S. Solujic and S. Sukdolak, *Monatsh. Chem.*, 1998, **129**, 481.

14 I. Gutman and Z. Marković, *Monatsh. Chem.*, 1998, **129**, 1019.

15 Further data relating to the geometries of Kekuléan isomers can be obtained from the authors upon request.

16 I. Gutman, *Topics Curr. Chem.*, 1992, **162**, 29.