Crystal Structures of Sulochrin Derivatives

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The crystal structures of sulochrin derivatives, sulochrin triacetate (2) and sulochrin 4-(4′-bromobenzoate) (3), were determined. Triacetyl derivative 2 was in a conformation where the planes of two aromatic rings and the central carbonyl plane were all oblique to each other. Compound 3 was in a conformation where ring B and the central carbonyl planes were co-planar and crossed at a right angle to the ring A plane, suggesting the effect of substituents at *ortho* positions on conformation of tetra *ortho* substituted benzophenones.

Key words   sulochrin; crystal structure; benzophenone; sulochrin oxidase; phenol oxidative coupling

Sulochrin (1) has an unique benzophenone scaffold, in which the four *ortho* positions are all substituted (Fig. 1). Sulochrin was isolated from fungi (*Aspergillus terreus var. aureus.*) as an antibacterial[1] and antifungal metabolite.[2] We recently have reported the inhibitory action on eosinophil degranulation by sulochrin.[3] During the course of our study on the structure–activity relationship, it was found that the modification of those *ortho* positions affects the biological activity. The purpose of this study was to examine the effect of substituents on the conformation of tetra *ortho* substituted benzophenones. There has been only one report on the three dimensional structure of such tetra *ortho* substituted benzophenone derivatives (4) as far as we know[4] (Fig. 2).

Results and Discussion

The crystallization of sulochrin itself was first attempted, however no crystal suitable for X-ray measurement was obtained. Fortunately, sulochrin triacetate (2), in which three hydroxyl groups were protected by acetyl groups, gave good crystals. The data for 2 with bond lengths and bond angles are given in Table 1, where the selected torsion angles of 2 are also shown. All the bond lengths and bond angles were within the range of standard values. The crystal structure of 2 (Fig. 3a) was in a conformation with the two torsion angles, RB1=63.0° and RB2=33.0° (the plane angles of ring A and
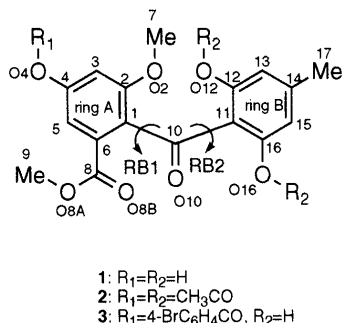

1: R₁=R₂=H
2: R₁=R₂=CH₃CO
3: R₁=4-BrC₆H₄CO, R₂=H

Fig. 1.   Sulochrin and Its Derivatives

As ring B is symmetric, O12 is defined for the oxygen atom that is closer to C10 and O16 is the oxygen atom closer to O10. The torsional angles, RB1 and RB2, were defined as C2–C1–C10–C11 and C1–C10–C11–C12, respectively. The planes of ring A and ring B were defined by the aromatic carbons. The central carbonyl plane was defined by atoms C1, C10, O10 and C11.
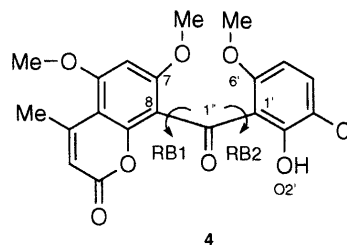

Fig. 2.   8-(3′-Chloro-2′-hydroxy-6′-methoxybenzoyl)-5,7-dimethoxy-4-methylcoumarin

An intramolecular hydrogen bond between O2′ and center carbonyl oxygen atom was observed. The planes of two aromatic rings were twisted (RB1=49°, RB2=24°; RB1 is defined as the torsional angle C7–C8–C1″–C1′ and RB2 as C8–C1″–C1′–C6′).
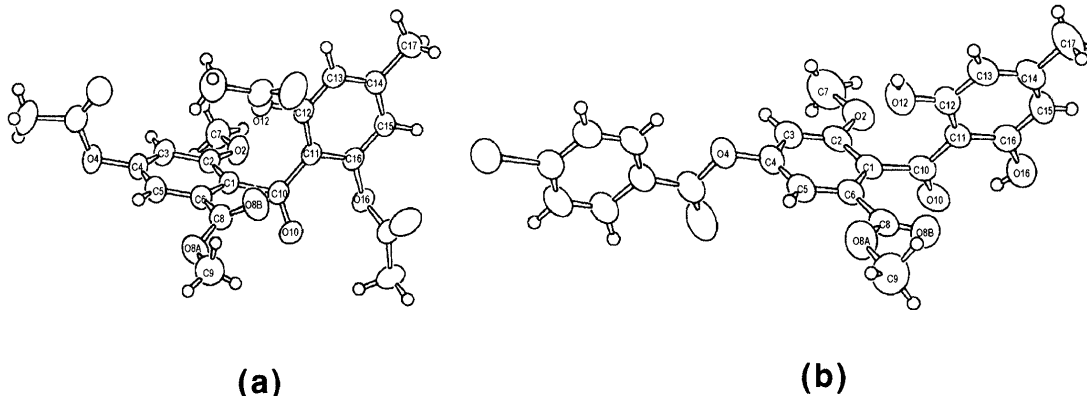

(a)   (b)

Fig. 3.   Ortep Drawing of 2 and 3

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Table 1. Topology of Sulochrin Derivatives

Bond length (Å)		2	3
C1	C2	1.401 (3)	1.395 (5)
C2	C3	1.388 (3)	1.381 (6)
C3	C4	1.370 (3)	1.371 (6)
C4	C5	1.360 (3)	1.358 (6)
C5	C6	1.389 (3)	1.394 (6)
C6	C1	1.394 (3)	1.389 (5)
C2	O2	1.365 (2)	1.367 (4)
C4	O4	1.402 (2)	1.402 (5)
C6	C8	1.485 (3)	1.494 (5)
C8	O8A	1.325 (2)	1.332 (5)
C8	O8B	1.204 (2)	1.188 (5)
C1	C10	1.509 (3)	1.505 (5)
C10	O10	1.213 (2)	1.239 (4)
C10	C11	1.495 (3)	1.452 (5)
C11	C12	1.396 (3)	1.404 (5)
C12	C13	1.371 (3)	1.381 (5)
C13	C14	1.378 (3)	1.375 (6)
C14	C15	1.392 (3)	1.356 (6)
C15	C16	1.371 (3)	1.388 (6)
C16	C11	1.396 (3)	1.404 (5)
C12	O12	1.402 (2)	1.346 (5)
C14	C17	1.503 (4)	1.522 (7)
C16	O16	1.404 (2)	1.363 (5)

Bond angle (°)			2	3
C1	C2	C3	120.2 (2)	121.3 (4)
C2	C3	C4	119.1 (2)	118.6 (4)
C3	C4	C5	122.3 (2)	122.0 (4)
C4	C5	C6	119.0 (2)	119.6 (4)
C5	C6	C1	120.6 (2)	120.1 (4)
C1	C2	O2	116.1 (2)	114.6 (4)
O2	C2	C3	123.7 (2)	124.1 (4)
C3	C4	O4	118.7 (2)	119.0 (4)
O4	C4	C5	118.8 (2)	118.8 (4)
C5	C6	C8	119.1 (2)	120.6 (4)
C8	C6	C1	119.9 (2)	119.3 (4)
C6	C8	O8A	111.7 (2)	111.0 (4)
C6	C8	O8B	123.7 (2)	124.9 (4)
O8A	C8	O8B	124.5 (2)	124.1 (4)
C10	C1	C2	120.6 (2)	118.1 (3)
C6	C1	C2	118.6 (2)	118.5 (4)
C6	C1	C10	120.7 (2)	123.4 (4)
C1	C10	C11	119.7 (2)	122.2 (3)
C1	C10	O10	119.5 (2)	116.8 (3)
O10	C10	C11	120.8 (2)	121.0 (4)
C10	C11	C12	123.6 (2)	123.8 (4)
C10	C11	C16	121.5 (2)	120.1 (4)
C16	C11	C12	114.9 (2)	116.1 (4)
C11	C12	C13	122.6 (2)	121.1 (4)
C12	C13	C14	121.0 (2)	121.3 (4)
C13	C14	C15	118.1 (2)	119.1 (4)
C14	C15	C16	119.9 (2)	120.8 (4)
C15	C16	C11	123.4 (2)	121.7 (4)
C11	C12	O12	118.1 (2)	117.0 (4)
O12	C12	C13	119.2 (2)	121.9 (4)
C13	C14	C17	121.4 (2)	119.1 (6)
C17	C14	C15	120.4 (2)	121.8 (6)
C15	C16	O16	117.7 (2)	117.3 (4)
O16	C16	C11	118.7 (2)	121.0 (4)

Torsion angle (°)					2	3
C2	C1	C10	C11	(RB1)	60.3 (3)	95.1 (5)
C6	C1	C10	C11		−121.8 (2)	−85.1 (5)
C2	C1	C10	O10		−115.6 (2)	−82.1 (5)
C6	C1	C10	O10		59.6 (3)	97.6 (5)
C1	C10	C11	C12	(RB2)	33.0 (3)	1.0 (6)
C1	C10	C11	C16		−148.4 (2)	−179.9 (4)
O10	C10	C11	C12		−148.4 (2)	178.2 (4)
O10	C10	C11	C16		30.2 (3)	−2.8 (6)

ring B relative to the central carbonyl plane are 61.0° and 31.2°). This conformation is comparable to the previous report,[4] suggesting that the conformation is restricted by the steric hindrance caused by the tetra *ortho* substituents of the benzophenone scaffold.

Replacement of acetyl groups of **2** to generate sulochrin 4-(4′-bromobenzoate) (**3**) led to a significant conformational change in the crystal structure. All the bond lengths and bond angles were again in the range of standard values (Table 1). Planes of ring B and center carbonyl group were nearly co-planar (the plane angle was 0.7°; RB2=1.0°). The 16-OH of ring B and O10 formed a hydrogen bond (Fig. 3b). In contrast, the central carbonyl plane and ring A were oriented orthogonal each other (the plane angle 96.3°; RB1=95.1°). An intermolecular hydrogen bond between O12 and the carbonyl oxygen atom of a crystal solvent molecule (ethyl acetate) was observed. The atomic distance between O12 and C1 was 2.60 Å, suggesting that these two atoms were in tight atomic van der Waals contact. This conformation is not assumed very stable in a mono-molecular state. It is believed that the lattice-dependent intermolecular force and the intramolecular hydrogen bond may stabilize this conformation.

It is known in fungal cells that sulochrin is oxidized to bisdechlorogeodin by a phenol oxidative coupling enzyme, sulochrin oxidase[5] (Fig. 4). It had been suggested that a conformation in which ring A orients orthogonal to the central carbonyl plane and ring B is co-planar to the carbonyl plane would be necessary for the regio-specific bond formation between O12 and C1.[5] The crystal structure of **3** is nearly in the expected conformation for this hypothetical transition-state (Fig. 4). Such conformation could be available to sulochrin when stabilized by the enzyme–ligand interaction in analogy of the crystal lattice force.

In conclusion, two different conformations were observed for *ortho*-substituted benzophenones. Benzophenones with large substituents at four *ortho* positions prefer a conformation that is twisted while, when the substituents of ring B are hydroxyl groups, a conformation where ring A orients orthogonal to both ring B and the central carbonyl plane is available to the benzophenone scaffold.

Experimental

X-Ray Crystallography All measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated $CuK\alpha$ radiation and a 12 kW rotating anode generator.

Sulochrin Triacetate (2) Compound **1** was converted to **2** using anhydroacetic acid and pyridine. MS *m/z* 548 (FD). ^{1}H-NMR (CDCl$_3$) 2.00 (6H, s), 2.32 (3H, s), 2.38 (3H, s), 3.67 (3H, s), 3.73 (3H, s), 6.81 (2H, s), 6.82 (1H, d, *J*=2 Hz), 7.26 (1H, d, *J*=2 Hz). Crystallized from ethyl acetate–hexane. A colorless prismatic crystal having approximate dimensions of 0.20×0.20×0.20 mm was used. Crystal data: triclinic, $P\bar{1}$, *a*=10.264(2) Å, *b*=13.572(3) Å, *c*=8.1552(8) Å, α=90.28(1)°, β=97.51(1)°, γ=97.85(2)°, Z=2. The final R value was 0.040.

Sulochrin 4-(4′ Bromobenzoate) (3) Compound **1** was converted to **3** using 4-BrC$_6$H$_4$COCl and pyridine. MS *m/z* 516 (FD), ^{1}H-NMR (CDCl$_3$) 2.25 (3H, s), 3.67 (3H, s), 3.77 (3H, s), 6.22 (2H, br s), 7.03 (1H, d, *J*=2 Hz), 7.49 (1H, d, *J*=2 Hz), 7.86 (2H, d, *J*=9 Hz), 8.05 (2H, d, *J*=9 Hz). Crystallized from ethyl acetate–hexane. A colorless prismatic crystal having approximate dimensions of 0.20×0.20×0.10 mm was used. Crystal data: monoclinic, $P2_1/n$, *a*=12.640(4) Å, *b*=13.883(2) Å, *c*=16.208(2) Å, β=94.75(2)°, Z=4. The final R value was 0.045.
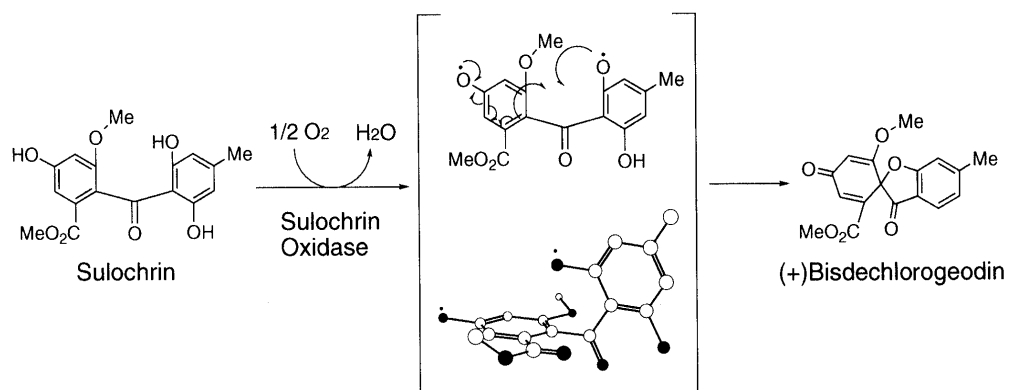
Fig. 4. The Biosynthesis of Bisdechlorogeodin

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