Monatshefte für Chemie 133, 707–716 (2002)

Monatshefte für Chemie
Chemical Monthly

Crystal Structure and Conformation of a 10-Thiabilirubin

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Summary. A crystal structure determination of a bilirubin analog with a sulfur instead of a C(10)–CH_2 linking the two dipyrrinones is reported. Conformation-determining torsion angles and key hydrogen bond distances and angles are compared to those obtained from molecular dynamics calculations as well as to the corresponding data from X-ray determinations and molecular dynamics calculations of bilirubin. Like other bilirubins, the component dipyrrinones of the analog are present in the *bis*-lactam form with (*Z*)-configurated double bonds at C(4) and C(15). Despite the large differences in bond lengths and angles at –S– *vs.* –CH_2–, the crystal structure shows considerable similarity to bilirubin: both pigments adopt a folded, intramolecularly hydrogen-bonded ridge-tile conformation stabilized by six hydrogen bonds – although the interplanar angle of the ridge-tile conformation of the title compound is smaller ($\sim 86°$) than that of bilirubin ($\sim 98°$). The collective data indicate that even with long C–S bond lengths and a smaller C–S–C bond angle at the pivot point on the ridge-tile seam, intramolecular hydrogen bonding persists.

Keywords. Bile pigments; Stereochemistry; Hydrogen bonding.

Introduction

Bilirubin (Fig. 1), the yellow pigment of jaundice [1, 2], is an important and conformationally interesting member of the linear tetrapyrrole class [3]. Bilirubin is composed of two dipyrrinones conjoined by a CH_2 group (Fig. 1A), and it is the relative orientation of these dipyrrinones about the (C10)–CH_2 group that determines the shape of the pigment, which is neither linear (Fig. 1A) nor porphyrin-like (Fig. 1B), but adopts a shape similar to the ridge-tile of a roof (Fig. 1C). The ridge-tile conformation minimizes intramolecular nonbonded steric interactions and is thus intrinsicially favored over all others [4, 5]. Dipyrrinones are known to be avid participants in hydrogen bonding, self-associating strongly to form hydrogen-bonded dimers [6], but engaging carboxylic acids in hydrogen bonding even more strongly [7, 8]. Thus, the two dipyrrinones of bilirubin cling to the two carboxylic acids, which adds considerable additional stabilization to the ridge-tile conformation through a network of six intramolecular hydrogen bonds [4, 9–11]. The ridge-tile conformation is of course not rigid, and it is the only conformation of bilirubin observed in crystals [10, 12, 13] of bilirubin by X-ray crystallography and by solid

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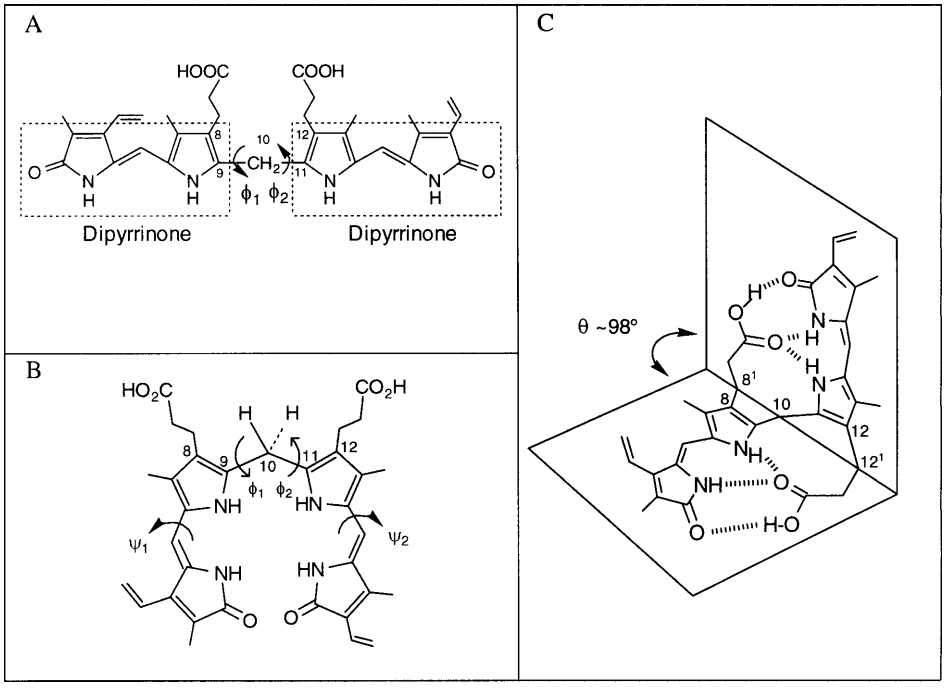

Fig. 1. A: Bilirubin in a high-energy linear conformational representation with angles of rotation about the C(9)–C(10) and C(10)–C(11) bonds, ϕ_1 and ϕ_2, of about 180°; B: high energy, porphyrin-like conformation, $\phi_1 = \phi_2 \approx 0°$; rotations about ψ_1 and ψ_2 within the two dipyrrinones distort the chromophores from planarity; C: energy-minimized conformation shaped like a ridge-tile, with $\phi_1 = \phi_2 \sim 60°$ and an interplanar angle of $\sim 98°$; the ridge-tile seam lies approximately along the line connecting carbons 8^1, 10, and 12^1; this conformation achieves considerable stabilization from intramolecular hydrogen bonds (hatched lines); bilirubin has two dipyrrinone chromophores; rotations about torsion angles ϕ_1 and ϕ_2 interconvert the porphyrin-like, ridge-tile, and linear conformations

state NMR [14]. Solution NMR studies [11, 15] and circular dichroism spectroscopy [4, 16] confirm its dominance in solution, even when the carboxyl groups are ionized, and molecular mechanics energy calculations [3, 17, 18] support the general notion that this conformation is very strongly stabilized.

Only a few crystal structures have been obtained for bilirubins [3, 9, 10, 12, 13], which is largely due to the considerable difficulty encountered in growing suitable crystals. From earlier work on the crystal structure of a 10-substituted bilirubin, 10-isopropyl-3,17-*bis*-nor-mesobilirubin-XIIIα, we learned that the presence of the isopropyl group caused the dihedral angle (θ of Fig. 1C) to open slightly while maintaining full intramolecular hydrogen bonding [12]. Our continued interest in bilirubin stereochemistry and its stabilization by intramolecular hydrogen bonds between propionic acid and dipyrrinone groups led us to consider whether such hydrogen bonding might be retained in a bilirubin analog with the C(10)–CH_2 at the 'hinge' of the ridge-tile replaced by sulfur. Given the long C–S bond lengths, this would be expected to extend the dipyrrinones away from the hinge; and with the small C–S–C bond angle, the ridge-tile ought to have a steeper pitch than in bilirubin. In an earlier study [19] we reported on the synthesis, solution properties,

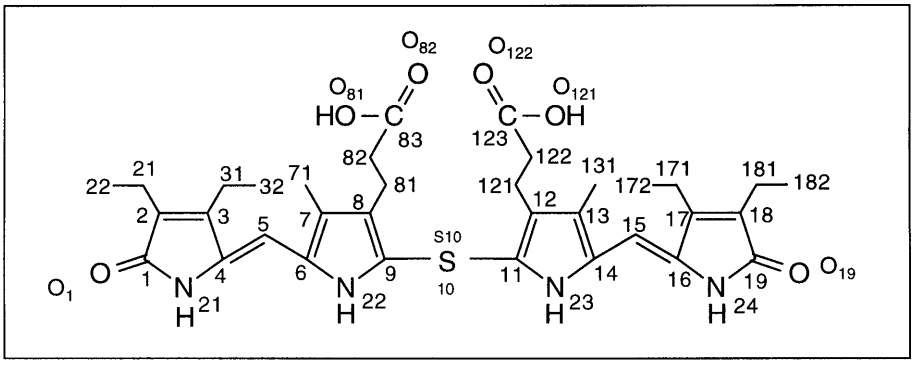

Fig. 2. Numbering system for carbon, nitrogen, oxygen, and sulfur atoms of 10-thiarubin **1** used in its crystal structure determination

and excretion of **1** (Fig. 2), an S(10) analog of bilirubin. This thia analog was found to be more lipophilic than either its parent rubin (with CH_2 replacing S) or bilirubin while still being constrained to adopt a ridge-tile shape. Solution spectroscopic studies showed that (*i*) even when a sulfur atom replaces the C(10)–CH_2, intramolecular hydrogen bonding persists in non-polar solvents, (*ii*) the pigment adopts a more peaked ridge-tile conformation in non-polar solvents, and (*iii*) the changes do not affect its metabolism in rats: it is excreted only after glucuronidation of the propionic acids.

In the present communication, we describe stereochemical investigations of **1** based on its X-ray crystal structure and molecular mechanics calculations. The results are compared to bilirubin X-ray crystal determinations [9, 10a, b, 13] and molecular dynamics calculations [3, 4, 16] and indicate an intramolecularly hydrogen bonded ridge-tile conformation for **1**.

Results and Discussion

Configuration and overall conformation

An examination of the ORTEP drawing of the X-ray structure of **1** clearly indicates that the molecule is folded into a ridge-tile conformation (Fig. 3) consistent with that found in crystals of bilirubin [9, 10a, b], mesobilirubin-IXα [10d], bilirubin-IXα *bis*-isopropyl ammonium salt [13], and 10-isopropylglaucorubin [12]. The seam of the ridge-tile lies approximately along the line connecting C(8^1), C(10), and C(12^1) (Fig. 1) (or C(81)–C(10)–C(121) of **1** in Fig. 3), where the two planes containing the two dipyrrinones intersect at an interplanar angle (θ) of about 85°. This dihedral angle is considerably smaller than that found in bilirubin [10a, b] ($\theta \sim 98°$) and even smaller than that reported for mesobilirubin ($\theta \sim 104°$) [10c]. The pyrrole and lactam nitrogens of **1** lie in close proximity to the propionic carboxyl oxygens, making hydrogen bonding possible and likely. Although we were unable to locate the protons in **1**, the calculated carboxylic acid and pyrrole/lactam hydrogens have an average hydrogen bond distance of about 1.9 Å which is longer than that found in bilirubin (1.7 Å) whose hydrogens have been located in the X-ray structure [10a, b].

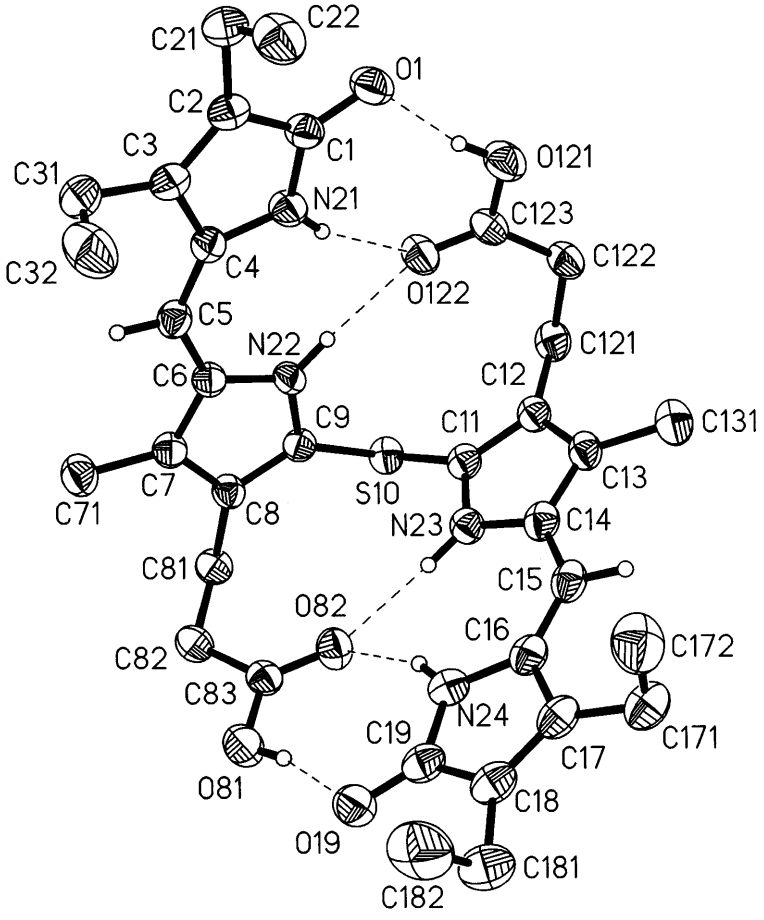

Fig. 3. ORTEP drawing [25] of **1** as observed in its crystal structure with NH and OH hydrogens located; librational ellipsoids have been drawn with 50% probability

The crystal structure conformation of **1** correlates reasonably well with that predicted earlier from solution NMR studies [19] and is similar to that of bilirubin [10]. The dipyrrinones adopt a *syn*-(*Z*) configuration of the C=C double bond at C(4) and C(15). The observed bond lengths suggest that delocalization over an individual conjugated system of two pyrrole rings is rather limited, since C(4)=C(5) and C(15)=C(16) seem to be essentially full double bonds (average bond length of 1.35 Å). The same bond lengths are found in the crystal structure of 10-isopropylglaucorubin [12]; however, they are slightly longer than in bilirubin (average bond length: 1.30 Å). As suggested earlier for bilirubin [10a, b], mesobilirubin [10c], and its isopropyl analog [12], thiarubin **1** can be regarded as a 2,2′-dipyrrylmethane with conjugating substituents at the α positions.

It has been demonstrated that when the possibility of lactam/lactim tautomerism exists, the lactam form predominates [20] by about 4–10 orders of magnitude over the lactim form for bile pigments in solution [10c] and in all known rubin X-ray structures [9, 10, 12, 13, 20]. Consistent with this, 10-thiarubin **1** is found to prefer the *bis*-lactam tautomeric form, as confirmed by lactam C=O bond lengths that are comparable to C=O distances in ordinary lactams. The

C(1)=O(1) and C(19)=O(19) bond lengths of **1** are 1.25 Å, which compare favorably with those of 10-isopropylglaucorubin (1.25, 1.26 Å) [12] and bilirubin [9, 10a, b] where the corresponding bond lengths are 1.25 and 1.28 Å, respectively. Furthermore, the lactam C–N bond distances are consistent with a carbon nitrogen single bond: C(1)–N(21) ∼ 1.35 Å, C(19)–N(24) ∼ 1.36 Å – again identical to those of 10-isopropylglaucorubin [12] and very similar to those found in bilirubin [10a–c] (1.41 and 1.35 Å, respectively). In the bilirubin structure, the lactam tautomer is known to be present since the NHs were found in the X-ray structure determination. In contrast, C=N and C–O(Et) bond distances of 1.28 and 1.33 Å were observed for the lactim (ether) bonds in 5-ethoxy-5′-ethoxycarbonyl-3′,4′-dihydro-3,4-dimethyl-2,2′-pyrromethane [21].

Comparison of conformation from molecular dynamics calculations and X-ray analysis

Insight into the preferred conformations of bilirubin and its C(10) thia analog **1** and the influence of the C(10) sulfur substituent may be obtained from molecular dynamics computations as well as by crystallography. Torsion angles (C–C) about the carbon–carbon bonds linking the four rings are largely responsible for determining the pigment's conformation and helicity. Such torsion angles and helical pitch can be extracted from atomic coordinates of the minimum energy conformation determined by molecular dynamics calculations [3, 4, 12] and by crystallography [3, 9, 10]. Comparison of the torsion angles obtained from both techniques for bilirubin and its 10-thia analog **1** is shown in Table 1.

Significantly, molecular dynamics calculations, which do not take into account crystal packing forces, reproduce the experimental data reasonably well, predicting slightly smaller torsion angles (ϕ_1 and ϕ_2) about C(9)–C(10) and C(10)–C(11) and a smaller dihedral angle (θ) between the two planes (Table 1). It can be seen from these parameters that the global minimum energy conformations of **1** and bilirubin are very similar, with slight differences arising from the smaller C–S–C bond angle (91.5° computed; 101° from X-ray) and long C–S bond lengths (1.77 Å computed; 1.75 Å X-ray) imposed by the C(10) sulfur. Although the torsion angles (ϕ_1 and ϕ_2)

Table 1. Comparison of conformation determining torsion angles (°) and distances (*d*) from X-ray crystallography and molecular dynamics (MD)[a] calculations for 10-thiarubin **1** and bilirubin (*BR*)

Method		ϕ_1 (11-10-9-22)[c]	ϕ_2 (9-10-11-23)[c]	Ψ_1 (4-5-6-22)[d]	Ψ_2 (16-15-14-23)[c]	(N21-4-5-6)[e]	(14-15-16-24)[e]	θ (dipyrrinone)[f]	θ (pyrrole)[f]
1	X-ray	61	61.5	7.1	1.0	2.6	−0.9	85.5	90.3
	MD	60	60	4.8	4.8	−0.1	−0.8	77.3	77.0
BR[b]	X-ray	60	64	17.5	−2.7	10.7	5.8	95.4	99.3
	MD	59	58	16.1	16.1	1.0	−0.2	88.0	94.2

[a] Using Sybyl ver. 6.0 for the SGI workstation [17]; [b] data taken from X-ray diffraction coordinates given in Ref. [10a]; [c] values would be ∼0° for the porphyrin conformation, ∼60° for the ridge-tile conformation, and ∼180° for the linear conformation; [d] indicates distortion from a planar dipyrrinone, where $\psi \sim 0$; [e] indicates twist from 0° of C=C; [f] interplanar dihedral angle using the average plane of each dipyrrinone or the dihedral angle of the two pyrroles adjacent to C(10)

of **1** are quite similar to those of bilirubin (Table 1), the dihedral angle θ in **1** is clearly smaller ($\sim 77^\circ$ computed; $\sim 86^\circ$ X-ray). This means that the ridge-tile of **1** is more closed than that in its (C10)–CH_2 parent or bilirubin ($\theta \sim 98^\circ$) and adapted to a roof of much steeper pitch [12]. Within the dipyrrinones there is less distortion from planarity in **1** than in bilirubin (cf. ψ_1 and ψ_2 of Table 1) [3]. In the dipyrrinone component of **1**, the slight distortion from planarity appears to come mainly from twisting of the C(5)–C(6) and C(14)–C(15) single bonds, as there is very little distortion or twist in the C(4)=C(5) and C(15)=C(16) double bonds. In bilirubin, there is more twist in both of the corresponding single and double bonds and therefore slightly less effective π-conjugation within a given dipyrrinone unit. Somewhat greater π-delocalization or conjugation in **1** relative to bilirubin may be assumed from the slightly longer C(4)=C(5) and C(15)=C(16) bond lengths found by X-ray analysis, averaging ~ 1.35 Å, compared to bilirubin where the corresponding average bond length is *ca*. 1.30 Å, indicating more delocalization in the former relative to the latter.

A comparison of hydrogen bond distances and hydrogen bond angles in **1** and bilirubin from their crystal structures and their global minimum energy structures determined by molecular dynamics calculations is given in Table 2. The hydrogen bond distances are distinctly longer in crystalline **1** than in the computed energy-minimized structure, differences which were not observed in bilirubin. Apparently, the somewhat flatter ridge-tile of the crystal (flatter due to crystal packing forces) causes the N–H $\cdots$ O=C hydrogen bonds to become extended by $\sim 30\%$ and the O–H $\cdots$ O=C hydrogen bond to lengthen by $\sim 10\%$ – all relative to the computed energy-minimum structure seen in the hydrogen bond angles. All computed and 'observed' (X-ray) hydrogen bond angles of **1** lie within 20° of the optimium angle of 180°. The O–H $\cdots$ O angles are nearly identical in the computed and observed structure, but the computed N–H $\cdots$ O angles differ from one another by as much as 15°, with the greatest differences coming for the pyrrole N–H $\cdots$ O angles. In addition, crystals of **1** show lactam N–H $\cdots$ O angles very similar to those found in

Table 2. Comparison of hydrogen bond distances (*d*) and hydrogen bond angles (°) from X-ray crystallography and molecular dynamics (MD)[a]; calculations for lactam (*L*) NH, pyrrole (*P*) NH, and acid (OH) for 10-thiarubin **1** and bilirubin (*BR*)

Method		Hydrogen bond distance (Å)			Hydrogen bond angle (°)		
		*L*N–H $\cdots$ O	*P*N–H $\cdots$ O	O–H $\cdots$ O	*L*N–H $\cdots$ O	*P*N–H $\cdots$ O	O–H $\cdots$ O
1	X-ray	1.98	2.05	1.76	161.4	162.6	166.9
		1.96	2.06	1.81	160.4	164.0	167.2
	MD	1.54	1.57	1.54	168.7	171.5	167.7
		1.54	1.58	1.53	164.4	178.3	167.6
BR[b]	X-ray	1.8	1.8	1.5	160.3	157.3	179.9
					162.3	157.4	179.9
	MD	1.6	1.6	1.5	152.7	164.1	169.3
					152.4	165.2	169.0

[a] Using Sybyl ver. 6.0 for the SGI workstation [12]; [b] data taken from X-ray diffraction coordinates given in Ref. [10a]

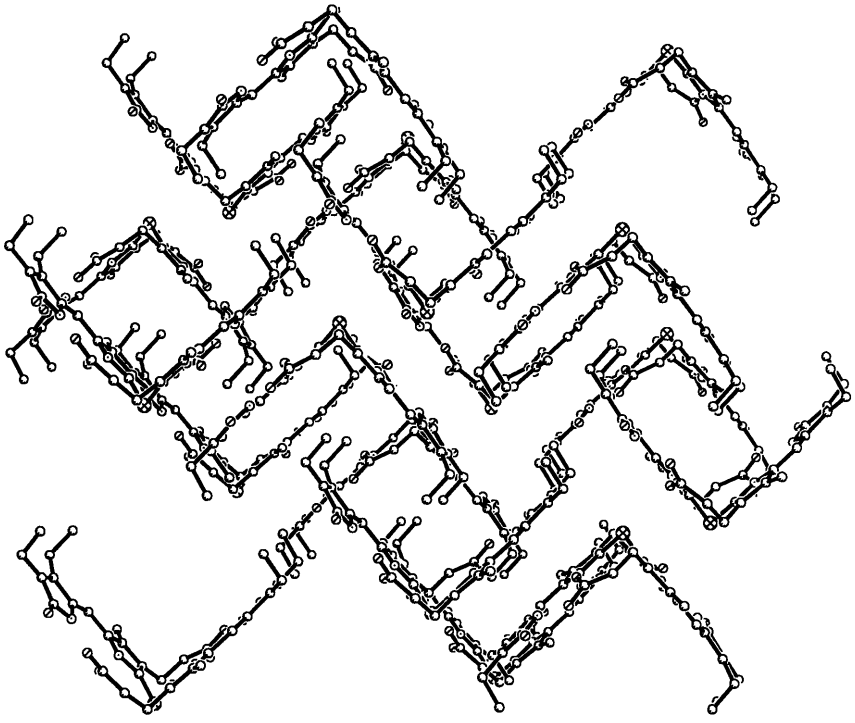

Fig. 4. Molecular packing of molecules of **1** in a projection showing its ridge-tile conformation

bilirubin, but the pyrrole N–H $\cdots$ O angles of **1** are by $\sim 5^\circ$ larger, and the O–H $\cdots$ O angles are even larger ($\sim 12^\circ$). The differences seem to be related to the smaller dihedral angle (θ) in **1** than in bilirubin and the longer C–S bonds that extend the planar dipyrrinones farther from the central atom at position 10.

Crystal packing

The stacking pattern in the 10-thiarubin **1** is very similar to that found in bilirubin and mesobilirubin (Fig. 4) [10]. The ridge-tiles are stacked with their dipyrrinone systems parallel to one another (at the *van der Waals* distance), thereby giving rise to channels in the crystal lattice in which disordered solvent molecules reside. Stacks of ridge-tile shaped molecules of **1** interleave with similar but inverted stacks. There is little evidence for intermolecular association as the hydrogen bond pattern is almost exclusively intramolecular. The stacking pattern described here is very characteristic of intramolecularly hydrogen-bonded ridge-tile conformers of bilirubins [9, 13] but it is very different than the stacking pattern of those bilirubins which cannot or do not attain ridge-tile conformations in the solid state [9, 21].

Experimental

Crystals of thiarubin **1** [19] were grown by slow diffusion of di-*n*-butyl ether into a solution of CH_2Cl_2. A crystal (approximate dimensions $0.40 \times 0.25 \times 0.08\,mm^3$) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Bruker SMART system for data collection at 173(2) K. A preliminary set of cell constants was calculated from reflections harvested from three

sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 120 reflections. The data collection was carried out using MoK_α radiation (0.71073 Å graphite monochromator) with a frame time of 30 seconds and a detector distance of 4.0 cm. A randomly oriented region of reciprocal space was surveyed to the extent of 1.3 hemispheres and to a resolution of 0.84 Å. Three major sections of frames were collected with 0.30° steps in ω at 3 different ϕ settings and a detector position of −28° in 2θ. The intensity data were corrected for absorption and decay (SADABS) [22]. Final cell constants were calculated from the *xyz* centroids of strong reflections from the actual data collection after integration (SAINT 6.01, 1999) [23]. Crystal data and refinement information may be found in Table 3.

The structure was solved using SHELXS-86 [23] and refined using SHELXL-97 [24]. The space group P-1 was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the *E*-map. Full-matrix least squares/difference *Fourier* cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms (Table 4) were refined with anisotropic displacement parameters unless stated otherwise. The data were corrected for absorption using an empirical model derived from ψ scans. Hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement paramenters (a C–H distance fixed at 0.96 Å and a thermal parameter of 1.2

Table 3. Crystal data and structure refinement for 10-thiarubin **1**

Formula weight	634.78
Crystallized from	CH_2Cl_2/*n*-hexane
Temperature	173(2) K
Formula	$C_{34}H_{42}N_4O_6S$
Crystal size	$0.40 \times 0.25 \times 0.08\,mm^3$
Crystal system	Triclinic
Space group	P-1
Z	2
Unit cell dimensions	$a = 11.524(2)$ Å $\alpha = 64.332(3)°$
	$b = 12.622(2)$ Å $\beta = 82.750(3)°$
	$c = 13.155(2)$ Å $\gamma = 68.294(3)°$
Volume	1601.0(5) Å^3
Density (calculated)	$1.317\,Mg/m^3$
Absorption coefficient	$0.153\,mm^{-1}$
F(000)	676
Crystal habit and color	Plate, Yellow
Theta range for data collection	1.72 to 25.08°
Index ranges	$-13 \le h \le 13,\ -13 \le k \le 15,\ 0 \le l \le 15$
Reflections collected	5635
Independent reflections	5635 (R(int) = 0.0398)
Observed reflections	3966
Completeness to $\theta = 25.08°$	99.2%
Absorption correction	Multiscan
Max. and min. transmission	1.000000 and 0.758859
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5635/0/414
Goodness-of-fit on F^2	0.996
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0475$, $wR_2 = 0.1193$
R indices (all data)	$R_1 = 0.0701$, $wR_2 = 0.1326$
Largest diff. peak and hole	0.345 and -0.283 e.Å^{-3}

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) for **1**; U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

	x	y	z	U_{eq}
S10	−157(1)	5382(1)	3396(1)	35(1)
O1	5832(2)	2213(2)	5952(1)	46(1)
C1	5213(2)	1500(2)	6276(2)	35(1)
C2	5624(2)	153(2)	7004(2)	36(1)
C3	4637(2)	−222(2)	7117(2)	34(1)
C4	3555(2)	876(2)	6463(2)	33(1)
C5	2401(2)	913(2)	6330(2)	34(1)
C6	1338(2)	1930(2)	5658(2)	31(1)
C7	146(2)	1919(2)	5598(2)	32(1)
C8	−573(2)	3093(2)	4747(2)	31(1)
C9	193(2)	3802(2)	4343(2)	31(1)
C11	958(2)	5255(2)	2377(2)	33(1)
C12	1853(2)	5808(2)	1984(2)	33(1)
C13	2416(2)	5490(2)	1083(2)	34(1)
C14	1872(2)	4724(2)	973(2)	35(1)
C15	2162(2)	4157(2)	189(2)	37(1)
C16	1650(2)	3429(2)	34(2)	35(1)
C17	2043(2)	2804(2)	−734(2)	38(1)
C18	1324(2)	2112(2)	−574(2)	41(1)
O19	−407(2)	1825(2)	672(1)	45(1)
C19	431(2)	2282(2)	286(2)	38(1)
N21	3993(2)	1880(2)	5985(2)	36(1)
N22	1340(2)	3104(2)	4889(2)	31(1)
C21	6952(2)	−596(2)	7446(2)	45(1)
N23	970(2)	4606(2)	1770(2)	33(1)
C22	7788(2)	−996(2)	6593(2)	53(1)
N24	669(2)	3065(2)	621(2)	36(1)
C31	4622(2)	−1533(2)	7723(2)	44(1)
C32	4982(3)	−2243(2)	6995(3)	65(1)
C71	−310(2)	872(2)	6319(2)	45(1)
O81	−1669(2)	2050(2)	2379(2)	47(1)
C81	−1898(2)	3480(2)	4381(2)	37(1)
O82	−1011(2)	3561(2)	2238(1)	42(1)
C82	−2110(2)	2684(2)	3864(2)	41(1)
C83	−1538(2)	2813(2)	2756(2)	34(1)
O121	5016(2)	4373(2)	4171(2)	47(1)
C121	2139(2)	6609(2)	2421(2)	39(1)
O122	3047(2)	4445(1)	4475(1)	42(1)
C122	3473(2)	6111(2)	2877(2)	40(1)
C123	3809(2)	4891(2)	3916(2)	36(1)
C131	3394(2)	5940(2)	351(2)	46(1)
C171	3108(2)	2906(2)	−1508(2)	45(1)
C172	4356(3)	1935(3)	−968(3)	64(1)
C181	1342(3)	1275(2)	−1107(2)	52(1)
C182	2025(3)	−98(3)	−367(3)	74(1)

times that of the host carbon atom). The final full matrix least squares refinement converged to $R_1 = 0.0475$ and $wR_2 = 0.1326$ (F^2, all data). The structural data were deposited and can be obtained under CCDC 175788.

Acknowledgments

We thank the US National Institutes of Health (HD-17779) for generous support of this work. Special thanks are accorded to Dr. *Victor G. Young* of the University of Minnesota's X-ray Crystallographic Lab, Chemistry Department, for assistance with the X-ray crystallographic measurements.

References

[1] McDonagh AF (1979) Bile Pigments: Bilatrienes and 5,15-Biladienes. In: Dolphin D (ed) The Porphyrins, vol 6, Academic Press, New York, p 293
[2] Chowdhury JR, Wolkoff AW, Chowdury NR, Arias IM (1979) Hereditary Jaundice and Disorders of Bilirubin Metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The Metabolic and Molecular Basis of Inherited Disease, vol II. McGraw-Hill Inc., New York, pp 2161–2208
[3] Falk H (1989) The Chemistry of Linear Oligopyrroles and Bile Pigments. Springer, Wien
[4] Person RV, Peterson BR, Lightner DA (1994) J Am Chem Soc **116**: 42
[5] Boiadjiev SE, Pfeiffer WP, Lightner DA (1997) Tetrahedron **53**: 14547
[6] Nogales DF, Ma JS, Lightner DA (1993) Tetrahedron **49**: 2361
[7] Boiadjiev SE, Anstine DT, Lightner DA (1994) Tetrahedron Asymm **5**: 1945
[8] a) Huggins MT, Lightner DA (2000) J Org Chem **65**: 6001; b) Huggins MT, Lightner DA (2000) Tetrahedron **56**: 1797; c) Tipton AK, Lightner DA (1999) Monatsh Chem **130**: 425
[9] For a review of crystal structures of linear polypyrrolic compounds, see Sheldrick WS (1983) Israel J Chem **23**: 155
[10] a) Bonnett R, Davies JE, Hursthouse MB, Sheldrick GM (1978) Proc R Soc London Ser B **202**: 249; b) LeBas G, Allegret A, Mauguen Y, DeRango C, Bailly M (1980) Acta Crystallogr Sect B **B36**: 3007; c) Becker W, Sheldrick WS (1978) Acta Crystallogr Sect B **B34**: 1298
[11] a) Kaplan D, Navon G (1983) Israel J Chem **23**: 177; b) Kaplan D, Navon G (1983) Org Magn Res 198; c) Kaplan D, Navon G (1982) Biochem J **201**: 605; d) Navon G, Frank S, Kaplan D (1984) J Chem Soc Perkin Trans 2, 1145
[12] Kar AK, Tipton AK, Lightner DA (199) Monatsh Chem **130**: 833
[13] Mugnoli A, Manitto D, Monti D (1983) Acta Crystallogr Sect C **39**: 287
[14] Brown SP, Zhu XX, Saalwächter K, Spiess HW (2001) J Am Chem Soc **123**: 4275
[15] a) Doerner T, Knipp B, Lightner DA (1997) Tetrahedron **53**: 2697; b) Nogales D, Lightner DA (1995) J Biol Chem **270**: 73
[16] Boiadjiev SE, Person RV, Puzicha G, Knobler C, Maverick E, Trueblood KN, Lightner DA (1992) J Am Chem Soc **114**: 10123
[17] a) Falk H, Müller N (1982) Monatsh Chem **112**: 1325; b) Falk H, Müller N (1983) Tetrahedron **39**: 1875
[18] Shelver WL, Rosenberg H, Shelver WH (1992) Intl J Quantum Chem **44**: 141
[19] Tipton AK, Lightner DA, McDonagh AF (2001) J Org Chem **66**: 1832
[20] Kratky C, Jorde C, Falk H, Thirring K (1983) Tetrahedron **39**: 1859
[21] Sheldrick WS, Borkenstein A, Blacha-Puller M, Gossauer A (1977) Acta Crystallogr **B33**: 3625
[22] Blessing R (1995) Acta Cryst **A51**: 33
[23] SAINT V6.1, Bruker Analytical X-Ray Systems, Madison, WI, USA
[24] SHELXTL-Plus V5.10, Bruker Analytical X-Ray Systems, Madison, WI, USA

Received August 16, 2001. Accepted September 12, 2001