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Crystal Structure and Conformation of a 10-Isopropyl Bilirubin

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Summary. A crystal structure determination of a bilirubin analog (**1**) with an isopropyl group at C(10) is reported. Conformation determining torsion angles within the molecule and key hydrogen bond distances and angles are compared to those from molecular dynamics calculations and to the corresponding values from bilirubin X-ray determinations and molecular dynamics calculations. The crystal structure of **1** is very similar to that found by X-ray analysis of bilirubin and shows that **1** adopts a folded, intramolecularly hydrogen bonded ridge-tile conformation stabilized by six hydrogen bond. Taken collectively, the data indicate that even when a sterically demanding and potentially conformation distorting isopropyl group is located on the ridge-tile seam near the center of the molecule at C(10), intramolecular hydrogen bonding persists in the solid state. Like other bilirubins, the component dipyrrinones of **1** are present in the *bis*-lactam form with *Z*-configuration double bonds at C(4) and C(15).

Keywords. Bile pigments; Stereochemistry; Hydrogen bonding.

Kristallstruktur und Konformation eines 10-Isopropylbilirubins

Zusammenfassung. Die Kristallstrukturbestimmung eines Bilirubinanalogons (**1**) mit einer Isopropylgruppe in Position C(10) wird mitgeteilt. Die konformationsbestimmenden Torsionswinkel innerhalb des Moleküls und wesentliche Wasserstoffbrückenbindungsdistanzen werden mit Resultaten aus Moleküldynamikrechnungen und den entsprechenden Werten aus Röntgenstrukturanalyse und Molekulardynamikrechnungen von Bilirubin verglichen. Die Kristallstruktur von **1** ist sehr ähnlich zu jener des Bilirubins und zeigt, daß **1** eine gefaltete und intramolekular durch Wasserstoffbrückenbindungen vernetzte Firstziegelkonformation einnimmt, die durch sechs Wasserstoffbrücken stabilisiert wird. Insgesamt zeigen die Daten, daß trotz der sterisch anspruchsvollen und prinzipiell konformationsstörenden Isopropylgruppe, die an der Kante des Firstziegels nahe dem Molekülzentrum an C(10) angebracht ist, die intramolekulare Wasserstoffbrückenbindung im Festzustand erhalten bleibt. Wie in andern Bilirubinen liegen die Dipyrrinonkomponenten des Moleküls in der *bis*-Lactamform vor und weisen *Z*-konfigurierte Doppelbindungen an C(4) und C(5) auf.

Introduction

The important and structurally interesting mammalian natural product bilirubin (Fig. 1) is the yellow-orange pigment of jaundice and the end product of heme

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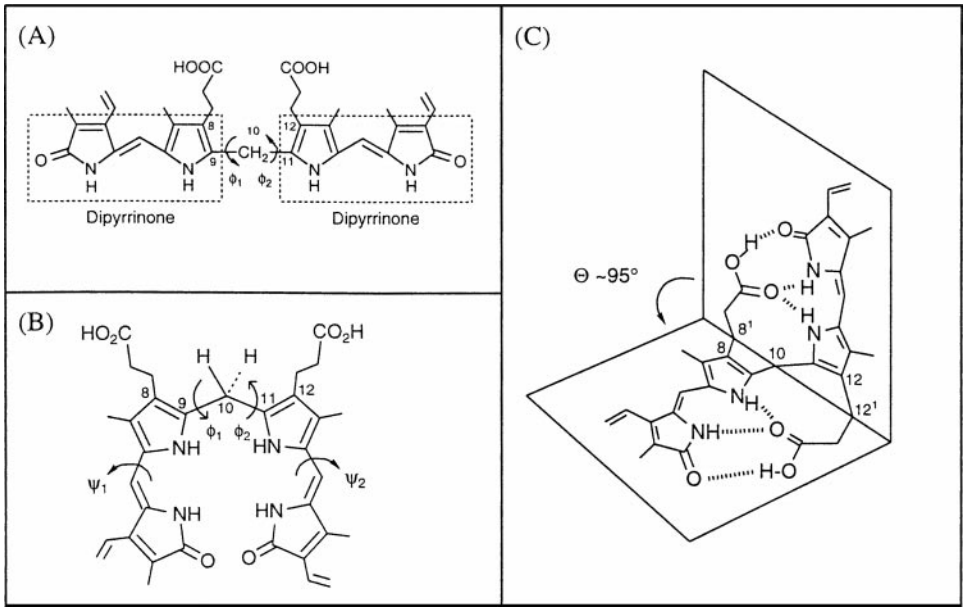

Fig. 1. Bilirubin in a (A) high energy linear conformational representation with angles of rotation about the C(9)–C(10) and C(10)–C(11) bonds (ϕ_1 and ϕ_2) of about 180°; (B) high energy, porphyrin-like conformation, $\phi_1 = \phi_2 \approx 0°$ rotations about ψ_1 and ψ_2 within the two dipyrrinones distorts the chromophores from planarity; and; (C) minimized energy conformation shaped like a ridge-tile with $\phi_1 = \phi_2 \approx 60°$ and an interplanar angle of $\sim 95°$. In (C) the dipyrrinones are planar, and the ridge-tile seam lies approximately along the line connecting 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

metabolism in mammals [1–3]. It is produced in the normal breakdown of red blood cells by degradation of hemoglobin and from other heme proteins, and in a healthy adult affords ~250–400 mg of bilirubin each day [1]. Considerable effort has been devoted to understanding the properties and metabolism of bilirubin, with particular attention being focussed on its unique ability to fold into a conformation shaped like a ridge-tile (Fig. 1C). The ridge-tile conformation is favoured over others for steric reasons [4, 5], and it is further strongly stabilized by a network of six intramolecular hydrogen bonds linking polar carboxylic acids to opposing dipyrrinones [4–8]. Such hydrogen bonding renders the native pigment lipophilic and unexcretable in normal metabolism, However, this is overcome by glucuronidation [1, 9], and it is the glucuronides of bilirubin that are excreted into bile.

The ridge-tile conformation is the only one observed in crystals [7, 10]. NMR [8, 11] and circular dichroism spectroscopy [4, 12] confirm its dominance in solution even when the carboxyl groups are ionized, and molecular mechanics energy calculations [2, 13, 14] support the generalized notion that this conformation is strongly preferred.

Very few crystal structures have been obtained for bilirubins [2, 6, 7, 10], largely due to the considerable difficulties in growing a suitable crystal, and no crystal structures have been available for a 10-substituted rubin. Our continued

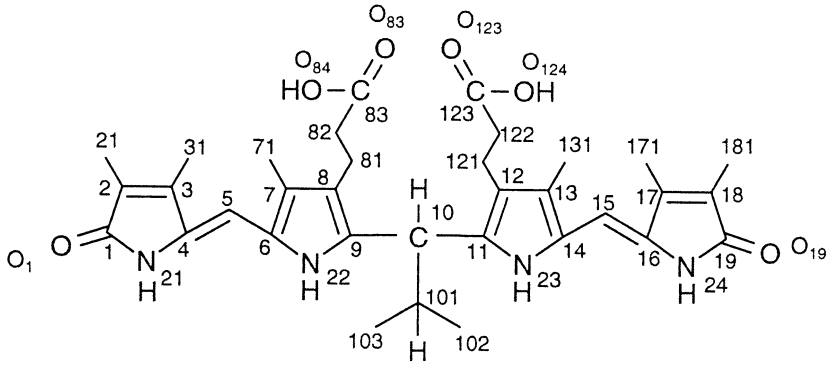

Fig. 2. Numbering system for carbon, nitrogen, and oxygen atoms of 10-isopropyl rubin **1** used in its crystal structure determination

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 bilirubin analogs with bulky substituents at C(10), *i.e.* at the ridge-tile seam (Fig. 1C). In an earlier study [15] we have reported on the synthesis and solution properties of **1** (Fig. 2), a C(10) isopropyl analog of bilirubin. The isopropyl analog was found to be much more amphiphilic than the parent rubin while still being constrained to adopt a ridge-tile shape. Solution spectroscopic studies showed that (*i*) even when an isopropyl group is located at C(10), intramolecular hydrogen bonding persists in non-polar solvents, (*ii*) the isopropyl group introduces a molecular dissymmetry with one half of the molecule accommodating less effective hydrogen bonding, and (*iii*) the pigment adopts a slightly flattened distorted ridge-tile conformation in non-polar solvents.

In the present communication, we describe stereochemical investigations of a 10-isopropyl bilirubin analog (**1**) based on its X-ray crystal structure and molecular mechanics calculations. The results are compared to bilirubin X-ray crystal determinations [6, 7a, b, 10] and molecular dynamics calculations [2, 4, 12]. The analyses 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). This conformation is consistent with that found in the X-ray structures of bilirubin [6, 7a, b], mesobilirubin-IXα [6d], and bilirubin-IXα *bis*-isopropyl ammonium salt [10]. 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 105°. This dihedral angle is slightly larger than that found in bilirubin [7a, b] ($\theta\sim95°$) and about the same as that reported for mesobilirubin [7c] ($\theta\sim104°$). The pyrrole and lactam nitrogens of **1** lie in close proximity to the propionic carboxyl

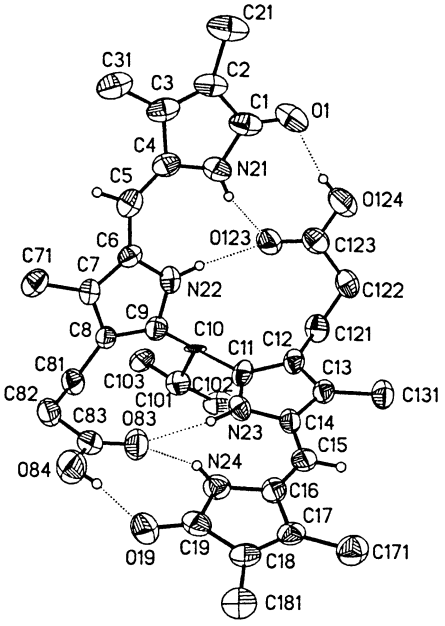

Fig. 3. ORTEP drawing [20] of **1** as observed in its crystal structure with NH and OH hydrogens located; vibrational ellipsoids have been drawn with 50% probability

groups, thus making hydrogen bonding possible and likely. Although it proved to be impossible to locate the protons in **1**, the calculated carboxylic acid and pyrrole/lactam hydrogens have an average hydrogen bond distance of about 1.7 Å which is about the same as that found in bilirubin whose hydrogens were located in the X-ray structure [7a, b]. Furthermore, it may be assumed from the O(1) to O(124) and O(19) to O(84) distances (2.50 and 2.71 Å, respectively) that the lactams and carboxylic acids are involved in strong C=O···H–O–C(=O) hydrogen bonds.

The crystal structure conformation of **1** correlates well with that predicted earlier for bilirubin from solution NMR studies and energy calculations [8, 15]. 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). However, they are slightly longer than in bilirubin (average bond length of 1.30 Å), possibly indicating that there may be slightly more delocalization in the isopropyl analog. As suggested earlier for bilirubin [7a, b] and mesobilirubin [7c], the isopropyl analog 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 [16] by about 4–10 orders magnitude over the lactim form for bile pigments in solution [7c] and in all known rubin X-ray structures [6, 7, 10, 16]. Consistent with this, the 10-isopropyl rubin **1** is found to prefer the *bis*-lactam tautomeric form, an 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 1.26 and 1.25 Å, respectively,

which compare favourably with those of bilirubin [6, 7a, 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)∼1.36 Å, C(19)–N(24)∼1.35 Å – again very similar to those found in bilirubin [6a–c] (1.41 and 1.35 Å, respectively). In the bilirubin structure, the lactam tautomer is known to be present since the N-Hs 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′-ethoxy-5′-ethoxy carbonyl-3′,4′-dihydro-3,4-dimethyl-2,2′-pyrromethane [17].

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

Insight into the preferred conformations of bilirubin and its C(10) isopropyl analog **1** and the influence of the C(10) isopropyl 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 [2, 4, 18] and by crystallography [2, 6, 7]. A comparison of the torsion angles obtained from both techniques for bilirubin and its 10-isopropyl analog **1** is shown in Table 1.

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

		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]	φ_1/° (22-4-5-6)[e]
1	X-ray	61	72	7.3	2.5	2.1
	MD	55	65	5.2	1.0	0.1
BR	X-ray	60	64	17.5	−2.7	10.7
	MD	59	58	16.1	16.1	1.0

		φ_2/° (14-15-16-24)[e]	θ/° (dipyrrinone)[f]	θ/° (pyrrole)[f]	d/Å (C=O···O=C)[g]	d/Å (vertical)[h]
1	X-ray	−0.2	104.7	104.3	11.3	5.8
	MD	−0.1	90.1	90.3	11.1	5.9
BR	X-ray	5.8	95.4	99.3	11.1	6.2
	MD	−0.2	88.0	94.2	11.5	5.4

[a] Sybyl package (version 6.0) for Evans & Sutherland ESV-10+ workstation [15]; [b] data taken from X-ray diffraction coordinates given in Ref. [7a]; [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 $\psi \approx 0°$; [e] indicates twist relative to 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); [g] dipyrrinone oxygen-oxygen nonbonded distance; [h] vertical distance determined from one dipyrrinone oxygen to the average plane of the second dipyrrinone

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 than found by X-ray crystallography (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 steric constraints imposed by the C(10) isopropyl group. The torsion angles (ϕ_1 and ϕ_2) and the dihedral angle (θ) in **1** would seem to indicate a more open, flattened ridge-tile conformation relative to bilirubin. However, within the dipyrrinones there seems to be less distortion from planarity in the isopropyl analog than in bilirubin (cf. ψ_1 and ψ_2) [2]. In the dipyrrinones of **1**, distortion from planarity appears to arise mainly from twisting of the C(5)–C(6) and C(14)–C(15) single bonds with 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 in the X-ray structure, averaging $\sim$1.35 Å, compared to bilirubin where the corresponding average bond length is $\sim$1.30 Å, indicating more delocalization in the former relative to the latter. Yet, differences in the torsion angles in Table 1 for both **1** and bilirubin appear to cancel, since the pitch of the helix (cf. non-bonded lactam C=O to O=C lactam distances) is very nearly the same for each.

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 using both techniques for the two pigments are very close, with the computed distances being slightly shorter. The three hydrogen bonds in either half of the ridge-tile molecule are of the same length as those in the other

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

		d/Å			∢/°		
		LN–H···O	*P*N–H···O	O–H···O	*L*N–H···O	*P*N–H···O	O–H···O
1	X-ray	1.6	1.7	1.9	159.6	172.8	165.3
					166.3	175.2	168.6
	MD	1.6	1.5	1.6	172.2	176.8	168.0
					167.6	176.2	168.2
BR	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] Sybyl package (version 6.0) for Evans & Sutherland ESV-10+ workstation [15]; [b]data taken from X-ray diffraction coordinates given in Ref. [7a]

half. Greater differences between the two pigments and the technique used are seen in the hydrogen bond angles. All hydrogen bond angles are within 30° of the optimium angle of 180°, but they differ from one another by as much as 20° depending on the pigment and the choice of method (X-ray or molecular dynamics). In addition, the pigments appear to be dissymmetric: the bond angles in one half of the molecular are slightly different from those in the other half. In bilirubin, the differences in hydrogen bond angles of the two halves are small (∼2° or less), whereas in **1** they differ by as much as 5° in both the calculated and experimental values. This suggests that the presence of the 10-isopropyl group is the cause of the mild conformational distortion, in accord with predictions from our NMR studies which found molecular dissymmetry of the ridge-tile non-polar solvents [15].

Crystal packing

The stacking pattern in the 10-isopropyl rubin **1** is very similar to that found in bilirubin and mesobilirubin (Fig. 4) [7]. The ridge-tiles are stacked with their dipyrrinone systems parallel to one another (at the *van der Waals* distances), 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 [6, 10], but it is very different from the stacking pattern of those bilirubins which cannot or do not attain ridge-tile conformations in the solid state [16, 17].

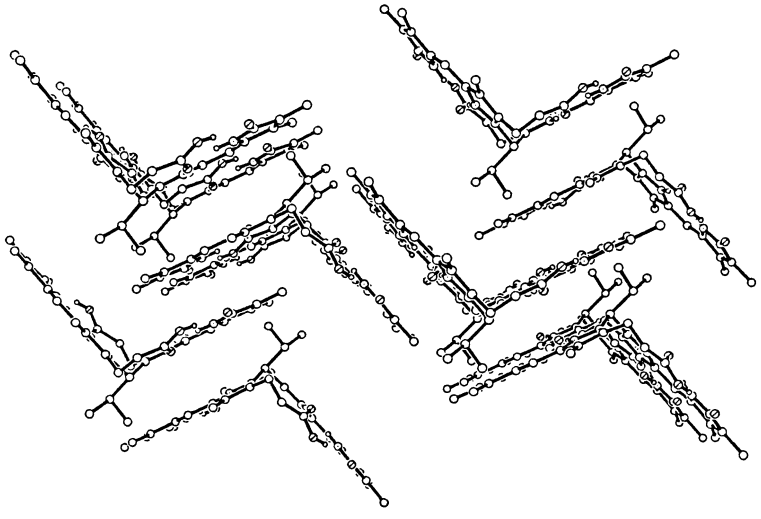

Fig. 4. Molecular packing of molecules of **1** in a projection showing its ridge-tile conformation

Experimental

X-Ray structure and solution

Crystals of **1** were grown by slow diffusion of di-*n*-butyl ether into a solution of **1** in dichloromethane. Suitable crystals were coated with epoxy cement, mounted on a glass fiber, and placed on a Siemens P4 diffractometer. Unit cell parameters were determined by least squares analysis of 20 reflections with $4.80 < \theta < 12.50^\circ$ using graphite monochromatized MoK_α radiation (0.7073 Å). 5236 reflections were collected between $0 < 2\theta < 50^\circ$ yielding 4350 unique reflections ($R_{\text{int}} = 0.0464$). The data were corrected for *Lorentz* and polarization effects. Crystal data are given in Table 3. Scattering factors and corrections for anomalous dispersion were taken from a standard source [19].

Calculations were performed using the Siemens SHELXTL PLUS system of programs refining on F^2 (version 5.03). The structure was solved by direct methods in the space group P_1. The unit cell

Table 3. Crystallographic data for 10-isopropyl rubin **1**

Formula weight	602.7
Crystallized from	CH_2Cl_2/*n*-butyl ether
Temperature (K)	298
Crystal size (mm)	$0.42 \times 0.60 \times 0.24$
Formula	$C_{34}H_{42}O_6N_4$
Space group	P_1
Z	4
Cell dimensions	$a = 10.183(3)$ Å
	$b = 10.646(3)$ Å
	$c = 16.503(5)$ Å
	$\alpha = 84.23(2)^\circ$
	$\beta = 80.62(2)^\circ$
	$\gamma = 71.00(2)^\circ$
	$V = 1666.9(8)$ Å^3
No. / ϑ range of Refs. used for cell refinement	$20/4.80^\circ < \theta < 12.50^\circ$
Calc. density d_x (g/cm^3)	1.257
Data collection range	$0^\circ < 2\theta < 50^\circ$
Scan type / scan range	w / 1.2°
No. of total data recorded	5236
No. of unique data	4350
Weighting scheme[a]	$a = 0.1288$, $b = 0$
No. obs. / no. parameters	3602/441
R_1^b, wR_2^c ($I = 2\sigma(I)$)	$R_1 = 0.0801$, $wR_2 = 0.1954$
e.s.d. of C–C bondlength	0.009
Highest peak in final ΔF map (e · Å^{-3})	0.416
Anisotropic non-H atoms	all
Isotropic non-H atoms	none
μ(MoK_α) (mm^{-1})	0.088
Radiation (λ, Å)	0.71073
Transmission factors	0.9071–0.9167

[a] $w^{-1} = (\sigma^2(F_0^2) + (aP)^2 + bP)$ where $P = (F_0^2 + 2F_c^2)/3$; Goodness of fit (GOOF): $(\sum(w(F_0^2 - F_c^2)^2)/(M - N))^{0.5}$ where M is the number of reflections and N is the number of parameters refined; [b] $R_1 = \sum \|F_0| - |F_c\| / \sum |F_0|$; [c] $wR_2 = (\sum(w(F_0^2 - F_c^2)^2)/\sigma(w(F_0^2)^2))^{0.5}$

Table 4. Atomic coordinates ($\times 10^4$) and equivalent 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)
C(1)	320(9)	7373(9)	−5089(4)	64(2)
C(2)	688(8)	6266(8)	−5623(4)	62(2)
C(3)	1821(8)	5323(8)	−5381(4)	60(2)
C(4)	2246(8)	5796(7)	−4694(4)	57(2)
C(5)	3288(7)	5161(6)	−4253(4)	56(2)
C(6)	3747(7)	5496(6)	−3555(4)	47(2)
C(7)	4829(6)	4724(6)	−3140(4)	46(2)
C(8)	4945(6)	5436(6)	−2490(4)	46(2)
C(9)	3902(7)	6671(6)	−2527(4)	51(2)
C(10)	3451(24)	8015(24)	−2199(10)	33(5)
C(11)	2033(7)	8248(6)	−1550(4)	50(2)
C(12)	801(7)	9320(6)	−1585(4)	49(2)
C(13)	−175(7)	9102(6)	−916(4)	50(2)
C(14)	456(7)	7908(6)	−499(4)	47(2)
C(15)	−143(7)	7318(6)	214(4)	51(2)
C(16)	305(7)	6130(6)	625(4)	51(2)
C(17)	−370(7)	5580(7)	1355(4)	50(2)
C(18)	449(8)	4344(7)	1548(4)	55(2)
C(19)	1696(8)	4054(7)	928(4)	54(2)
O(1)	−665(6)	8453(5)	−5101(3)	83(2)
O(19)	2719(5)	3008(5)	858(3)	69(1)
O(83)	4007(5)	4964(5)	−612(3)	76(2)
O(84)	4805(6)	2768(5)	−336(3)	83(2)
O(123)	982(6)	9080(4)	−3557(3)	69(1)
O(124)	−1247(5)	9906(5)	−3807(3)	85(2)
N(21)	1294(6)	7055(5)	−4562(3)	64(2)
N(22)	3204(5)	6694(5)	−3177(3)	52(2)
N(23)	1806(5)	7410(5)	−909(3)	48(1)
N(24)	1561(6)	5137(5)	406(4)	53(1)
C(21)	−126(9)	6239(9)	−6293(4)	89(3)
C(31)	2515(8)	3987(8)	−5721(4)	79(2)
C(71)	5758(7)	3333(6)	−3343(4)	64(2)
C(81)	6048(7)	4968(7)	−1942(4)	61(2)
C(82)	6103(7)	3690(7)	−1402(4)	66(2)
C(83)	4870(8)	3866(8)	−743(4)	63(2)
C(101)	4518(15)	8448(14)	−1838(9)	60(4)
C(102)	3942(27)	9766(21)	−1454(11)	67(6)
C(103)	5752(22)	8393(20)	−2442(8)	57(3)
C(104)[a]	4071(15)	8958(14)	−2363(9)	57(3)
C(105)[a]	3968(29)	10022(26)	−1768(12)	57(3)
C(106)[a]	5645(21)	8433(19)	−2789(9)	57(3)
C(121)	483(7)	10550(6)	−2157(4)	62(2)
C(122)	−674(7)	10689(6)	−2683(4)	64(2)
C(123)	−228(9)	9814(7)	−3393(4)	63(2)
C(131)	−1641(7)	10006(6)	−661(4)	64(2)
C(171)	−1792(7)	6301(7)	1788(4)	71(2)
C(181)	245(8)	3390(6)	2235(4)	68(2)
C(10A)[a]	3564(30)	7791(23)	−1853(10)	45(6)

[a] A refers to the enantiomeric molecule in which 104, 105, 106 correspond to 101, 102, 103

contains an ordered array of the molecule and a highly disordered methanol solvate molecule with no unusual contacts. The methanol is presumably residual solvent from chromatography. The structure contains a disordered isopropyl group with carbons C(10), C(101), C(102), and C(103) occupying one position fifty percent of the time and C(10a), C(104), C(105), and C(106) occupying another position fifty percent of the time.

All non-hydrogen atoms (Table 4) were refined with anisotropic thermal parameters. The data were corrected for absorption using an empirical model derived from ψ-scans. Hydrogen atom positions were calculated using a riding model with a C–H distance fixed at 0.96 Å and a thermal parameter of 1.2 times that of the host carbon atom. The largest peak in th final difference map corresponded to 0.497 $e^-/Å^3$ and was located 0.41 Å from the carbon of the methanol solvate. The structural data have been deposited at the Cambridge structural Data file (CDC No. 115871).

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