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Chiral Metal Complexes with the Biologically Active (+)-Pilocarpine Ligand: $[MCl_2(\kappa N\text{-}(+)\text{-pilocarpine})_2]$ (M = Co, Cu)

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Dedicated to Professor Alfonso Castiñeiras on the Occasion of his 65th Birthday

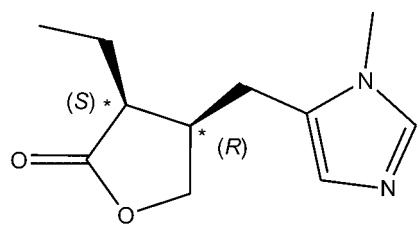
Abstract. The enantiopure ligand (+)-pilocarpine [(3*S*,4*R*)-3-ethyldihydro-4-((1-methyl-1*H*-imidazol-5-yl)methyl)furan-2(3*H*)-one] from the chiral pool coordinates with the imidazole nitrogen atom to transition metal atoms. Complexes $[MCl_2(\kappa N\text{-}(+)\text{-pilocarpine})_2]$ (M =Co, Cu) crystallize as pseudo-tetrahedral (M = Co) or distorted in-between tetrahedral and square-planar (M = Cu) molecules. Supramolecular C-H···Cl contacts are seen in the crystal packing. In aqueous solution the tetrahedral cobalt complex expands its coordination sphere to pseudo-octahedral through the addition of two water molecules as indicated by the reversible color change between blue (solid, non-aqueous solution) and pink.

Keywords: Pilocarpine; Chirality; Metal complexes; Coordination sphere; Reversible hydration; C-H···Cl Hydrogen bonding

Introduction

(+)-Pilocarpine is one of several alkaloids which can be found in leaves of the South American bush *Pilocarpus jaborandi* [1, 2]. Pilocarpine is used pharmaceutically to stimulate the parasympathetic part of the vegetative nervous system. (+)-Pilocarpine is effective against increased intraocular pressure by the discharge of the chamber water in medications like eye drops (Borocarpin®, Pilocarpin ankerpharm, Pilomann®, Pilopos®, Spersacarpin®) or eye ointment (Spersacarpin®) [3]. It is used to treat glaucoma diseases [4]. (+)-Pilocarpine is also in clinical use to improve the secretory function of impaired salivary glands after radiotherapy [5].

The synthesis of molecular chiral metal complexes is of continued interest [6, 7], including the metal coordination and supramolecular chemistry of (inexpensive) enantiomeric (enantiopure) ligands, like *S*-1,1′-bi-2-naphthol (*S*-BINOL) [8] and derivatives [9], (*R*)-(aryl)ethylamines [10], amino acids [11−13] and others [14]. Also, there is ongoing research in the metallation of ligands with biological activity [15]. With its imidazole nitrogen atom (+)-pilocarpine could act as a chiral ligand towards metal atoms. So far, no (+)-pilocarpine metal complexes appear to be structurally authenticated [16], despite some synthetic work [17]. Here we report the molecular and crystal structure of two (+)-pilocarpine metal complexes and the reversible hydration behavior of the cobalt-pilocarpine complex.



(+)-pilocarpine

Rote Liste: (3*S*,4*R*)-3-ethyl-dihydro-4-((1-methyl-1*H*-imidazol-5-yl)methyl)furan-2(3*H*)-one
Aldrich: (3*S*,4*R*)-4,5-dihydro-3-ethyl-4-(1-methyl-1*H*-imidazol-5-ylmethyl)-2(3*H*)-furanone
Beilstein: 3*S*-3*R*-ethyl-4*c*-(3-methyl-3*H*-imidazol-4-ylmethyl)-dihydro-furan-2-one

Results and Discussion

(+)-Pilocarpine coordinates to $CuCl_2$ and $CoCl_2$ in alcoholic solutions, in the case of copper with immediate formation of a precipitate. Crystals of $[CuCl_2(\kappa N\text{-}(+)\text{-pilocarpine})_2]$ (**1**) could be grown from acetone. Initially a yellow precipitate forms which appears to provide the seeding for

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the growth of green crystals. The structure elucidation shows the copper atom to be coordinated by two chloro and two (+)-pilocarpine ligands. The coordination polyhedron is in-between tetrahedral and square-planar as judged by the trans-angles around Cu atom between 139-150° [18] (for structures of related parent $CuCl_2$(imidazole)$_2$ compounds, see [19]).

The formation of a yellow phase followed by the green crystals appeared reminiscent of the thermochromic polymorphism in $[Et_2NH_2]_2[CuCl_4]$ between a green low-temperature (<45 °C) phase with more square-planar $CuCl_4^{2-}$ and a yellow high-temperature (>45 °C) phase with more tetrahedral $CuCl_4^{2-}$ [20]. The crystals of **1** remained green up to 190 °C, however.

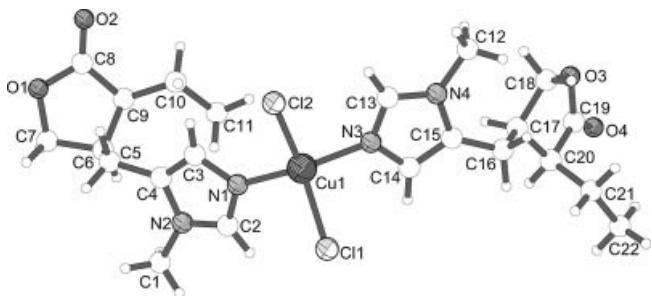

Fig. 1 Molecular structure of one of the two independent molecules in **1**. For distances and angles see Table 1.

The crystal packing in **1** is organized *inter alia* by (C−)H···Cl contacts between 2.72 and 2.83 Å and C−H···Cl angles between 139.1(2) and 158.9(1)° (Fig. 2) [18, 21, 22].

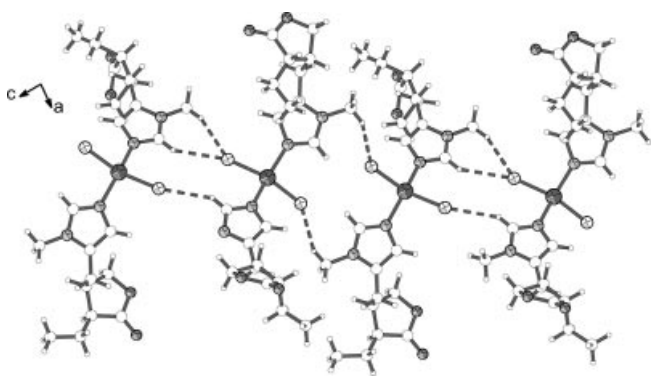

Fig. 2 Packing of **1** with C−H···Cl contacts as dashed lines.

Blue crystals of $[CoCl_2(\kappa N\text{-}(+)\text{-pilocarpine})_2]$ (**2**) could be grown from cobalt(II) chloride hexahydrate and (+)-pilocarpine in a mixture of ethanol and ethyl acetate. In **2** the cobalt atom is tetrahedrally coordinated by two (+)-pilocarpine ligands and two chloro ligands (Fig. 3) [23] (for structures of related parent $CoCl_2$(imidazole)$_2$ compounds, see [24]). The C_2-axis passes through the Co atom (special position 0 y 1/2, Wykoff letter *b*) so that the two chlorine and the two pilocarpine ligands, respectively, are symmetry related in this C_2-symmetrical molecule.

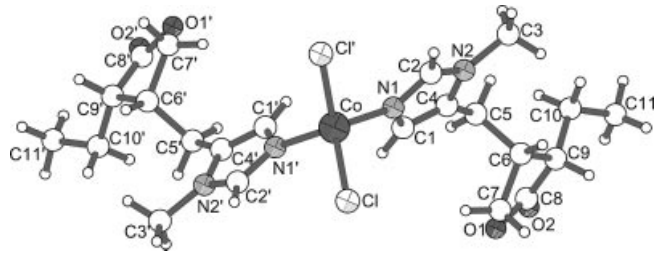

Fig. 3 Molecular structure of **2**. Symmetry relation ′ = −x, y, 1−z. For distances and angles see Table 1.

The crystal packing in **2** also features a (C−)H···Cl contact of 2.75 Å and 166.5(2)° (Fig. 4).

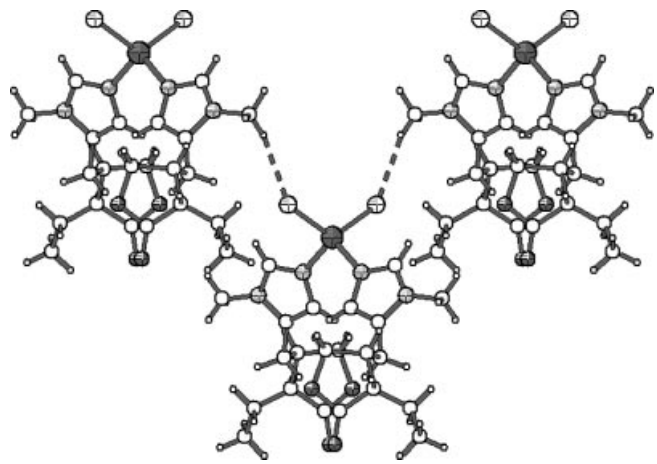

Fig. 4 Packing in **2** with C−H···Cl contacts as dashed lines.

Table 1 Selected distances/Å and angles/° in **1** and **2**

	1, M = Cu [a]		**2**, M = Co
	molecule 1	molecule 2	
M−Cl	−Cl1 2.261(1) −Cl2 2.255(1)	−Cl3 2.255(1) −Cl4 2.253(1)	2.2535(9)
M−N	−N1 1.945(3) −N3 1.972(3)	−N5 1.959(3) −N7 1.968(3)	2.017(3)
Cl−M−Cl	141.50(5)	138.68(5)	115.35(5)
Cl−M−N	Cl1/N1 94.8(1) Cl1/N3 93.7(1) Cl2/N1 95.8(1) Cl2/N3 95.2(1)	Cl3/N5 94.7(1) Cl3/N7 95.5(1) Cl4/N5 95.7(1) Cl4/N7 95.4(1)	Cl/N1 115.23(8) Cl/N1′ 103.60(8)
N−M−N	149.9(1)	149.5(1)	103.6(2)

[a] Two symmetry independent molecules in the unit cell.

The ESI mass spectrum of **2** in methylene chloride shows the molecular ion and mono- as well as dinuclear cobalt-containing ions with varying Co:Cl and Co:pilocarpine ratios from 1:1 over 1:1.5 (dinuclear) to 1:2. In methanol with addition of trifluoroacetic acid (TFA) the molecular ion peak of $[CoCl_2(\text{pilocarpine})_2]^+$ could not be seen, but methanol- and TFA-containing species like $[Co(TFA)(\text{pilocarpine})_3]^+$) or $[CoCl(\text{pilocarpine})_2(CH_3OH)]^+$ were abundant.

The blue crystals of **2** yield a blue solution in methylene chloride, absolute methanol or ethanol. The solubility in ethanol for **2** was low, however. In water or aqueous methanol a pink solution was obtained. The tetrahedral complex **2** expands its coordination sphere to octahedral with the addition of at least two aqua ligands. A residual water content in "dry" methanol (here 0.0069 weight-% according to a Karl-Fischer-Titration) also yields a pink solution at low concentrations of **2** (10^{-3} mol/l). In such a solution the water amount of the "dry" methanol corresponds to three H_2O equivalents for each molecule of **2**. The octahedral complex $[CoCl_2(H_2O)_2(pilocarpine)_2]$ can be obtained with two H_2O equivalents. (A complex $[CoCl_2(H_2O)_2(1H\text{-imidazole})_2]$ has been structurally authenticated [25].) A saturated solution of **2** in such "dry" methanol is then blue. Chloro and pilocarpine ligands may further be substituted through aqua ligands on the labile, high-spin Co^{2+}-d^7-ion (Eq. 1) [26]. This addition is reversible as blue crystals of **2** were formed again from such aqueous solutions through solvent evaporation.

$$\underset{\text{blue, tetrahedral}}{[CoCl_2(\text{pilocarpine})_2]\downarrow} \overset{2H_2O}{\rightleftharpoons} \underset{\text{pink, octahedral}}{[CoCl_2(H_2O)_2(\text{pilocarpine})_2]} \rightleftharpoons H_2O \rightarrow \begin{array}{c}[CoCl(H_2O)_3(\text{pilocarpine})_2]^+ \\ + \\ [CoCl_2(H_2O)_3(\text{pilocarpine})] \\ + \\ \ldots \\ + [Co(H_2O)_6]^{2+} \\ + 2\ Cl^- + 2\ \text{pilocarpine}\end{array} \quad (1)$$

The UV/VIS spectrum gives clear evidence for this change in coordination polyhedron. The broad split d-d-band at about 610 nm in CH_2Cl_2 or absolute methanol is typical in wavelength and in intensity for tetrahedral Co^{2+}, e.g. in $[CoCl_4]^{2-}$ ($^4A_2(F) \rightarrow {}^4T_1(P)$ transition) [27]. In aqueous methanol this band is no longer visible. Instead a much weaker transition is observed at 522 nm which is typical for high-spin octahedral Co^{2+} ($^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transition) [28]. This same band is also seen for $CoCl_2$ in aqueous methanol (Fig. 5). The color change from blue to pink when going from tetrahedral to octahedral cobalt(II) upon hydration is used as a humidity indication in silica gel with indicator („blue gel") [29].

Experimental Section

Elemental analyses were obtained on a VarioEL from Elementaranalysensysteme GmbH. IR spectra (2-4 mg compound/300 mg KBr pellet) were measured on a Bruker Optik IFS25. NMR spectra were collected on a Bruker ARX200 (200 MHz for ^1H) with calibration against the residual protonated solvent signal ($CDCl_3$ 7.25 ppm, CD_2Cl_2 5.47 ppm, D_2O 4.79 ppm). UV/VIS spectra were measured on a Jasco V-570 UV/VIS/NIR-Spectrophotometer. Optical activity was measured with a Perkin Elmer 241 polarimeter (Hg lamp 578 nm) at room temperature. ESI-MS measurements were carried out using a Finnigan MAT TSQ7000 spectrometer in CH_2Cl_2 or methanol/trifluoroacetic acid. Mass spectra were measured in positive mode in the range m/z = 160−2000. Chloride containing ions had a clearly visible isotope pattern, arising from the distribution ^{35}Cl 100 %, ^{37}Cl 32 %, accordingly copper containing ions from the distribution ^{63}Cu 100 %, ^{65}Cu 45 % [30]. Peaks were given for combinations with ^{63}Cu and ^{35}Cl.

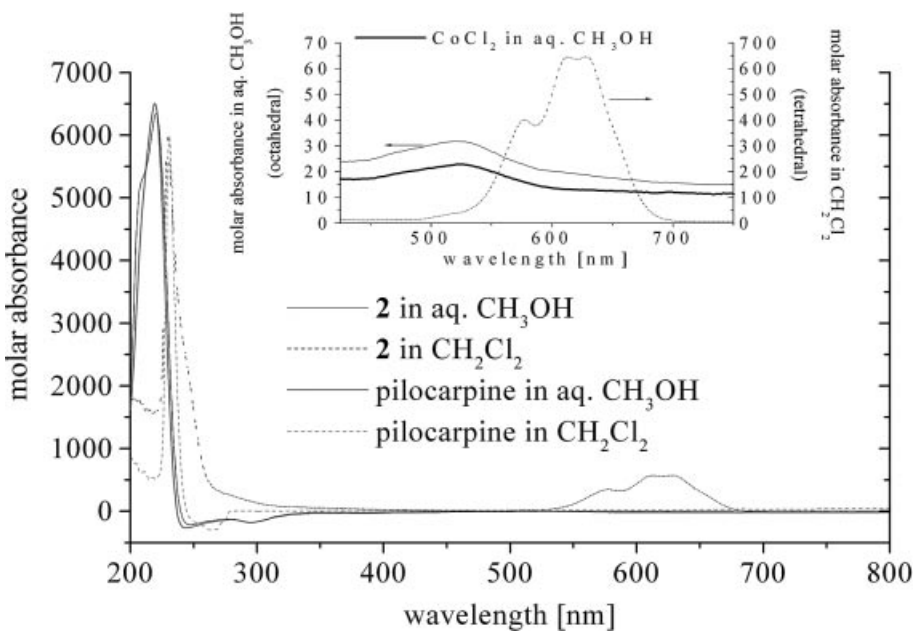

Fig. 5 UV/VIS spectra of **2** and pilocarpine in aqueous methanol (solid lines) and methylene chloride (dashed lines) with $c = 10^{-4}$ mol/l. Insert shows UV/VIS spectra of $CoCl_2$ and **2** in aqueous methanol (solid lines) and **2** in methylene chloride (dashed line) with $c = 10^{-3}$ mol/l.

Structure determination

Data Collection: Bruker APEX II with CCD area-detector for **1** and Bruker AXS with CCD area-detector for **2**, temperature 203(2) K, Mo-Kα radiation (λ = 0.71073 Å), graphite monochromator, ω-scans, Data collection and cell refinement with SMART [31], data reduction with SAINT [31], experimental absorption correction with SADABS [32]. *Structure Analysis and Refinement*: The structure was solved by direct methods (SHELXS-97) [33]; refinement was done by full-matrix least squares on F^2 using the SHELXL-97 program suite [33]. All non-hydrogen positions were found and refined with anisotropic temperature factors. Hydrogen atoms on the aromatic rings and the carbon atoms were placed at calculated positions with an appropriate riding model (AFIX 43 for CH, AFIX 23 for CH_2 and AFIX 137 for CH_3) and an isotropic temperature factor of Ueq(H) = 1.2 Ueq(CH, CH_2) and 1.5 Ueq(CH_3). Details of the X-ray structure determinations and refinements are provided in Table 2. Graphics were drawn with DIAMOND [34]. CCDC reference number 641681 for **1** and 641680 for **2**. The cif data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Preparation of the compounds

Dichloro-bis(κ*N*-(+)-pilocarpine)copper(II), [$CuCl_2$(κ*N*-(+)-pilocarpine)$_2$] (1).

A solution of (+)-pilocarpine hydrochloride (489.4 mg, 2.0 mmol) in distilled water (10 ml) (pH = 5-6) was alkalinized with sodium carbonate to pH = 9 and extracted with chloroform. The chloroform solvent was removed in vacuum and the residue was solved in 1-butanol (20 ml). The butanol solution was given to a hot solution of copper(II) chloride (170.5 mg, 1.0 mmol) in 1-butanol (20 ml). The mixture was heated for a few minutes and the green precipitate separated by filtration. Green crystals suitable for X-ray analysis could be grown from acetone (with co-precipitation of some initially formed yellow powder).

Yield 152.9 mg, 14 % based on pilocarpine. Calc for $C_{22}H_{32}Cl_2CuN_4O_4$ (550.96) C 47.96, H 5.85, N 10.17. Found C 47.60, H 5.87, N 10.06 %.

$\alpha^{21}{}_{Hg\ 578}$ (acetone): + 75° (c = 0.5 g/100 ml)

IR (cm^{-1}): 3443m, 3118m, 2964m, 2932m,2876m, 2360w, 1774s, 1636m, 1580w, 1524m, 1456m, 1424w, 1373m, 1243m, 1170m, 1102m, 1052w, 1021w, 976w, 960m, 945w, 896w, 655m.

ESI-MS (in MeOH/acetone, pilocarpine = $C_{11}H_{16}N_2O_2$ = 208 g/mol): 514 (23 %, $[CuCl(pilocarpine)_2]^+$), 479 (100 %, $[Cu(pilocarpine)_2]^+$), 303 (30 %, $[Cu(pilocarpine)(MeOH)]^+$), 289 (22 %, $[Cu(pilocarpine)(H_2O)]^+$), 209 (8 %, $[pilocarpine+H]^+$).

Dichloro-bis(κ*N*-(+)-pilocarpine)cobalt(II), [$CoCl_2$(κ*N*-(+)-pilocarpine)$_2$] (2).

A solution of (+)-pilocarpine hydrochloride (48.9 mg, 0.2 mmol) in distilled water (5 ml) (pH = 5-6) was alkalinized with sodium carbonate to pH = 9 and extracted with ethyl acetate (3 ml). The ethyl acetate solution was overlayered with a solution of cobalt(II) chloride hexahydrate (0.1 mmol, 23.8 mg) in ethanol (5 ml). The solvent was allowed to evaporate slowly at room temperature. After two days blue crystals formed which were suitable for single crystal X-ray analysis.

Yield 53.0 mg, 97 % based on pilocarpine. Calc for $C_{22}H_{32}Cl_2CoN_4O_4$ (546.36) C 48.36, H 5.90, N 10.25. Found C 47.99, H 6.06, N 10.19 %.

$\alpha^{21}{}_{Hg\ 578}$ (CH_2Cl_2 or MeOH or H_2O): + 75° (c = 0.2 g/100 ml)
[$\alpha^{20}{}_D$ (H_2O, (+)-pilocarpine hydrochloride): +80° (c = 5)]

^{1}H-NMR: δ(CD_2Cl_2) 11.83 (br. s, 1H, N=C*H*-N), 11.34 (br. s, 3H, N-CH_3), 10.25 (br. s, 1H, C=C*H*-N), 3.69 (br. s, 1H, C-C*H*-CH_2), 3.04 (br. s, 2H, O-CH_2-C), 2.66 (br. s, 2H, C-CH_2-C), 1.88 (br. s, 1H, C*H*-Et), 1.57 (br. s, 2H, CH_2CH$_3$), 1.08 (br. s, 3H, CH_2CH_3). − δ(D_2O) 8.77 (br. s, 3H, N-CH_3), 5.01 (br. s, 1H), 4.68 (br. s, 2H), 4.41 (br. s, 1H), 3.35 (br. s, 1H), 2.22 (br. s, 2H, CH_2CH$_3$), 1.20 (t, 3H, CH_2CH_3, ^3J = 6.3 Hz).

IR (cm^{-1})**:** 3441m, 3111m, 2925m, 2853w, 2360w, 1754s, 1636m, 1525m, 1458w, 1427w, 1372m, 1240m, 1171m, 1105m, 1051w, 1030w, 977w, 945w.

ESI-MS: (in CH_2Cl_2, pilocarpine = $C_{11}H_{16}N_2O_2$ = 208 g/mol): 961 (21 %, $[CoCl_2(pilocarpine)_4]^+$), 847 (8, $[Co_2Cl_3(pilocarpine)_3]^+$), 718 (44, $[CoCl(pilocarpine)_3]^+$), 639 (12, $[Co_2Cl_3(pilocarpine)_2]^+$), 545 (17, $[CoCl_2(pilocarpine)_2]^+$), 527 (45), 510 (100, $[CoCl(pilocarpine)_2]^+$), 320 (32, $[CoCl(H_2O)(pilocarpine)]^+$), 302 (37, $[CoCl(pilocarpine)]^+$), 267 (63, $[Co(pilocarpine)]^+$), 209 (100, $[pilocarpine+H]^+$). − (in MeOH, TFA anion = CF_3COO^- = 113 g/mol): 927 (8 %, $[CoCl(pilocarpine)_4]^+$), 828 (28, $[Co(TFA)(pilocarpine)_3(CH_3OH)]^+$), 796 (100, $[Co(TFA)(pilocarpine)_3]^+$), 718 (65, $[CoCl(pilocarpine)_3]^+$), 619 (69), 542 (81, $[CoCl(pilocarpine)_2(CH_3OH)]^+$), 334 (11, $[CoCl(pilocarpine)(CH_3OH)]$), 209 (47, $[pilocarpine+H]^+$),

UV/VIS: (in CH_2Cl_2, c = 10^{-4} or 10^{-3} mol/l, λ_{max} [nm] with ε [l·mol^{-1}·cm^{-1}]): 229 (6000), 577 (400), 613 (600), 628 (600). − (in MeOH, c = 10^{-4} or 10^{-3} mol/l): 220 (6300), 522 (30).

Table 2 Crystal data and structure refinement for **1** and **2**.

Compound	1	2
Empirical formula	2x $C_{22}H_{32}Cl_2CuN_4O_4$ [a]	$C_{22}H_{32}Cl_2CoN_4O_4$
M/g mol^{-1}	2 x 550.96 [a]	546.36
Crystal size/mm	0.19 x 0.14 x 0.02	0.31 x 0.05 x 0.02
θ range/°	1.00−25.15	0.99−27.25
h; k; l range	±9; ±14; ±15	±35; ±8; ±8
Crystal system	triclinic	monoclinic
Space group	$P\bar{1}$	$C2$
a/Å	8.1652(1)	27.4457(12)
b/Å	12.3356(2)	6.6281(3)
c/Å	13.3177(2)	6.9596(3)
α/°	72.991(1)	
β/°	82.325(1)	97.574(2)
γ/°	84.594(1)	
V/Å^3	1269.08(3)	1254.99(10)
Z	1	2
D_{calc}/g cm^{-3}	1.442	1.446
F (000)	574	570
μ/mm^{-1}	1.106	0.932
Max/min transmission	0.9782/0.8174	0.9816/0.7598
Reflections collected	40189	6814
Independent reflections	8860 (R_{int} = 0.1679)	2681 (R_{int} = 0.0467)
Obs. reflect. [$I > 2\sigma(I)$]	6813	2246
Parameters refined	581	152
Max./min. $\Delta\rho$ [b] /e Å^{-3}	0.597/−0.258	0.925/−0.267
R_1/wR_2 [$I > 2\sigma(I)$] [c]	0.0309/0.0706	0.0406/0.0756
R_1/wR_2 (all reflect.) [c]	0.0617/0.0748	0.0564/0.0804
Goodness-of-fit on F^2 [d]	0.938	1.057
Flack parameter [35]	−0.006(9)	0.07(2)
Weight. scheme w; a/b [e]	0.0000/0.0000	0.0240/0.4825

[a] Two symmetry independent molecules in the unit cell. − [b] Largest difference peak and hole. − [c] $R_1 = [\Sigma(||F_o| - |F_c||)/\Sigma|F_o|]$; $wR_2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$. − [d] Goodness-of-fit = $[\Sigma[w(F_o^2-F_c^2)^2] /(n-p)]^{1/2}$. − [e] $w = 1/[\sigma^2(F_o^2)+(aP)^2+bP]$ where $P = (\max(F_o^2 \text{ or } 0)+2F_c^2)/3$.

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