Bipodal benzoylthiocarbamic acid esters: crystal and molecular structures of $R = \text{Et}$ (a polymorph), and of a binuclear Cu(I) complex, $R = \text{iPr}$

Abstract: The crystal and molecular structure of a second polymorph ($P_{2_1}/n$) of [1,4-ROC(=S)N(H)C(=O)C$_6$H$_4$C(=O)N(H)C(=S)OR], $R = \text{Et}$, is shown to have inversion symmetry and to have a more twisted conformation than the previously reported $P4_22_2$ form which has 2-fold symmetry. Despite utilising equivalent atoms in forming intermolecular interactions, very distinct crystal packing patterns are observed. Crystal characteristics and theory (DFT) are consistent with the $P_{4_2}2_2$ form being more stable, a conclusion correlated with the observation that this form is the overwhelming majority of the sample (PXRD). An analysis of a binuclear copper(I) complex containing the $R = \text{iPr}$ analogue, reveals the neutral ligand to bind via the thione-S atom resulting in a distorted $\text{ClP}_2\text{S}$ tetrahedral geometry.

Keywords: benzoylthiocarbamic acid esters; copper(I) complex; crystal structure analysis; DFT; X-ray diffraction.

Introduction

Thiocarbamides are readily synthesised from the reaction of an alcohol with, e.g., an N-aryl isothiocyanate, to form acids [1, 2], Figure 1A, which are readily deprotonated and capable of binding metals, such as thiolates in the case of phosphanegold(I) complexes [3–5]. The facile synthesis and ready crystallisation have made these very useful systems for crystal engineering studies on the free thiocarbamide molecules themselves [1, 2], their phosphanegold(I) complexes [3–5] as well as their co-crystals [6] with bipyridine-type molecules [7]. In addition to their usefulness in crystal engineering, certain derivatives exhibit exciting biological activities. While the organic molecules show no biological effect, certain phosphanegold(I) derivatives, e.g., $\text{Ph}_3\text{PAu}[\text{SC(OR)}=\text{NPh}]$, show anti-cancer potential against HT-29 colon cancer cell lines with their activity related to the induction of apoptosis by extrinsic and intrinsic pathways and, crucially, dependent on the nature of the $R$ substituent [8]. Remarkably, another series of active complexes, $\text{Ph}_3\text{PAu}[\text{SC(OR)}=\text{N(p-tolyl)}]$, were found to be potent, particularly against Gram-positive bacteria over gram-negative bacteria [9]. While these results are exciting, a possible drawback for clinical applications is their general lack of aqueous solubility. During a course of recent studies designed to enhance the solubility of these types of molecules in polar solvents, we investigated benzoylthiocarbamic acid esters, Figure 1B. These molecules are related to thiocarbamides by having a carbonyl group inserted between the amide-N and aryl-C atoms. In the present study, crystal structures are described for polymorphic bipodal benzoylthiocarbamic acid esters, Figure 1C, along with a theoretical study. These molecules may potentially complex two metal centres, as demonstrated herein for a binuclear copper(I) complex. Crystal structure determinations for benzoylthiocarbamic acid esters are comparatively rare according to a search of the Cambridge Structural Database [10]. As discussed in more detail below, there are some mono-functional molecules [11–13], three bipodal derivatives of which one [14, 15], the tetragonal polymorph of [1,4-EtOC(=S)N(H)C(=O)C$_6$H$_4$C(=O)N(H)C(=S)OEt] [14] is re-investigated in the present report, as well a sole example of a metal complex [16].
Experimental

Instrumentation

$^1$H and $^{13}$C NMR data were measured on a Bruker Avance III 400 MHz instrument. Melting points were measured on an A. KRUSS OPTRONIC (Germany) KSPID automatic melting point apparatus. PXRD data were recorded with a PANalytical Empyrean XRD system with Cu-Kα radiation ($\lambda = 1.54056$ Å) in the 2θ range 5–40° with a slit size = 0.5°. The comparison between experimental and calculated (from CIF’s) PXRD patterns was performed with X’Pert HighScore Plus [17].

Synthesis and characterisation

O,O′-diethyl N,N′-(p-phenylenedicarbonyl)bis-(thiocarbamate) (I): Terephthaloyl chloride (Merck, 4.0604 g, 20 mmol) was dissolved in acetone (10 mL). Potassium thiocyanate (R&M Chemicals, 3.8878 g, 40 mmol) was added drop wise to the solution over 10 min and the precipitate turned yellow. The mixture was stirred for a further 2 h after which the yellow precipitate was filtered off and washed thoroughly with water and acetone. Yield: 79% (5.40 g, 16 mmol). The crystals are obtained from slow evaporation (ca 1 month) of the powder in chloroform. M.Pt: 482.2–483.6 K. Melting point (K): 482.2–483.6 K. $^1$H NMR (CDCl$_3$, ppm): δ 1.32 (t, CH$_3$, J = 7.08 Hz), 7.22 (t, m-PC$_6$H$_5$, J = 7.44 Hz), 7.32 (d, o-PC$_6$H$_5$, J = 7.2a), 7.37 (t, o-PC$_6$H$_5$, J = 9.04 Hz), 2.02 (s, o-H of central ring), 10.94 (s, NH). $^{13}$C NMR (CDCl$_3$, ppm): δ 189.4 (C=O), 162.5 (C=S), 136.4 (ipso-C of central ring), 133.7 (d, m-PC$_6$H$_5$, J$_{CH}$ = 16.5 Hz), 132.9 (d, i-PC$_6$H$_5$, J$_{CH}$ = 28.2 Hz), 129.7 (p-PC$_6$H$_5$), 128.9 (ortho-C of central ring), 128.5 (d, o-PC$_6$H$_5$, J$_{CH}$ = 8.8 Hz), 78.2 (CH$_2$), 21.2 (CH$_3$).

Crystal structure determination

Intensity data were measured at 100 K on an Agilent Technologies SuperNova Dual CCD with an Atlas detector fitted with Mo Kα radiation. Data processing and absorption correction were accomplished with CrysAlis PRO [18]. Details of cell data, X-ray data collection and structure refinement are given in Table 1. The structures were solved by direct methods [19]. Full-matrix least-squares refinement on F$^2$ with anisotropic displacement parameters for all non-hydrogen atoms was performed [19]. The C-bound H atoms were placed on stereochemical grounds and refined in the riding model approximation with U$^{	ext{iso}}$ = 1.2–1.5U$_c$ (carrier atom). The N-bound H atoms were located from difference maps and included in each refinement with the distance restraint N–H = 0.88 ± 0.01 Å, and with U$^{	ext{iso}} = 1.2U_{	ext{eq}}$(N). A weighting scheme of the form w = 1/[σ(F$_o$)$^2$ + (aP)$^2$ + bP] where P = (F$_o^2$ + 2F$_c^2$)/3 was introduced in each case. The final difference maps were featureless. The programs WinGX [20], PLATON [21], ORTEP-3 for Windows [20] [at the 70% probability level], DIAMOND [22] and QMol [23] were also used in the study.

Theoretical methods

Lattice energies and equilibrium geometries were calculated using density-functional theory (DFT) in the plane-waves/pseudopotentials approach as implemented in Quantum ESPRESSO [26]. We used the PW86 [25] exchange plus PBE [26] correlation functional coupled with the exchange-hole dipole moment (XDM) model of dispersion [27], which has been shown to predict accurate lattice energies [28–30] and geometries of molecular crystals [28]. The calculations were run using the projected augmented wave (PAW) formalism [31] with a 60 Ry cut-off energy for the plane-waves and a 600 Ry cut off energy for the density grid. A 2 × 2 × 2 k-point grid was used, which ensures a convergence in the total energy to <0.1 mRy for both polymorphs. The lattice energies were calculated by subtracting the energy for the relaxed crystal from that of the isolated molecule. The latter was calculated by relaxing the molecular geometry inside a cubic super-cell of side 45 Bohr, with a single k-point at Γ.
Results and discussion

Crystal structures of the polymorphs of O,O′-diethyl N,N′-(p-phenylenedicarbonyl) bis-(thiocarbamate)

[1,4-EtOC(S)=N(H)=O]C6H4C(S)=OEt] is dimorphic, crystallising concomitantly in monoclinic $P_2_1/n$ (1) and tetragonal $P_4_2_2_2$ (2) space groups. The molecular structures are shown in Figure 2 and selected geometric parameters collated in Table 2. The structure of 2 has been reported previously [14]. However, full details are included here to enable a comparison of the molecular and crystal structures obtained under identical conditions.

The molecule in 1 is located about a centre of inversion. The adjacent thione-S1 and ketone-O1 atoms are approximately syn and, owing to the presence of the centre of inversion, the two pairs of thione-S1 and ketone-O1 atoms lie to opposite side of the molecule, i.e., are orientated in an anti disposition. The S1–C1–N1–C2=O1 residue is non-planar as seen in the values of the S1–C1–N1–C2 and O1–C2–N1–C1 torsion angles of 18.6(2) and 4.8(2)$^\circ$, respectively, indicating a twist around the N1–C1 bond. The angles subtended at the C1 atom involving the larger S1 atom are systematically wider, by 19–20$^\circ$, than the O2–C1–N1 angle. Owing to the influence of the ketone-O1 atom, disparity in the angles around the C2 atom are also apparent, but the variation is angles is reduced, i.e., 6–8$^\circ$. The angle about the N1 is broad, at about 127$^\circ$. Overall, the molecule is non-planar with the carbamate residue inclined to the plane through the central benzene as seen in the N1–C2–C3–C4 torsion angle of –147.38(12)$^\circ$.

The molecular structure of 2 has to a first approximation the same features as just described for 1. The first important difference being that the molecule in 2 is situated about a 2-fold axis of symmetry with the axis of symmetry being perpendicular to the central ring. The key bond lengths are equal within experimental error but some variations are noted in bond angles. Thus, the S1–C1–O2 and S1–C1–N1 angles in 2 are narrower and wider by about 1$^\circ$ than the comparable angles in 1. The same trend is found for the O1–C2–C3 and N1–C2–C3 angles, Table 2.
More significant is the overall conformation which is somewhat flattened in 2 cf. 1, Table 2. This flattening is manifested in the N1–C2–C3–C4 torsion angle of 170.7(2)°.

**Tab. 2:** Summary of key geometric parameters (Å, °) for 1 and 2, as well as the minimum energy structure (gas phase).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(1)</th>
<th>(2)</th>
<th>Gas phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1=S1</td>
<td>1.6290(14)</td>
<td>1.634(3)</td>
<td>1.648</td>
</tr>
<tr>
<td>C1–O2</td>
<td>1.3353(16)</td>
<td>1.333(3)</td>
<td>1.362</td>
</tr>
<tr>
<td>C1–N1</td>
<td>1.3863(17)</td>
<td>1.379(4)</td>
<td>1.394</td>
</tr>
<tr>
<td>C2=O1</td>
<td>1.2144(16)</td>
<td>1.211(3)</td>
<td>1.226</td>
</tr>
<tr>
<td>C1–N1–C2</td>
<td>126.67(11)</td>
<td>127.3(2)</td>
<td>129.5</td>
</tr>
<tr>
<td>S1–C1–N1</td>
<td>125.72(10)</td>
<td>124.4(2)</td>
<td>126.4</td>
</tr>
<tr>
<td>O2–C1–N1</td>
<td>127.08(10)</td>
<td>128.7(2)</td>
<td>127.8</td>
</tr>
<tr>
<td>O1–C2–N1</td>
<td>123.39(12)</td>
<td>123.2(2)</td>
<td>124.2</td>
</tr>
<tr>
<td>O1–C2–C3</td>
<td>121.42(12)</td>
<td>120.4(2)</td>
<td>122.2</td>
</tr>
<tr>
<td>N1–C1–N1</td>
<td>115.17(11)</td>
<td>116.3(2)</td>
<td>113.7</td>
</tr>
<tr>
<td>S1–C1–N1–C2</td>
<td>18.6(2)</td>
<td>–3.3(4)</td>
<td>–10.2</td>
</tr>
<tr>
<td>O1–C2–N1–C1</td>
<td>4.8(2)</td>
<td>–5.3(5)</td>
<td>–5.3</td>
</tr>
<tr>
<td>O1–C2–C3–C4</td>
<td>30.78(19)</td>
<td>–9.2(4)</td>
<td>–25.8</td>
</tr>
<tr>
<td>N1–C2–C3–C4</td>
<td>–147.38(12)</td>
<td>170.7(2)</td>
<td>153.3</td>
</tr>
<tr>
<td>C1–N1–C2–C3</td>
<td>–177.06(12)</td>
<td>174.9(2)</td>
<td>175.6</td>
</tr>
</tbody>
</table>

The S1=C1–N1–C2=O1 residue is also comparatively planar as seen in the values of the S1–C1–N1–C2 and O1–C2–N1–C1 torsion angles of –3.3(4) and –5.3(5)°, respectively. As expected, the molecular structure of 2, matches the previously reported determination [14]. However, this report pays scant attention to the crystal packing which is crucial in the present study comparing this structure to the monoclinic form.

**Fig. 2:** Molecular structures of [1,4-EtOC(=S)N(H)C(=O)C6H4C(=O)N(H)C(=S)OEt]: (A) monoclinic polymorph (1), and (B) tetragonal polymorph (2). Unlabelled atoms are related by the symmetry operation –x, 1–y, 1–z for (1) and y, x, –z for (2). Displacement ellipsoids are drawn at the 70% probability level. (C) Overlay diagram of (1), red image, (2), blue, and (3) geometry optimised structure, green, having one S1,N1,O2 unit superimposed, as indicated by the arrow.

Geometric parameters associated with intermolecular interactions are collated in Table 3. The crystal packing of 1 features layers constructed about amine-N–H···O(ketone) hydrogen bonds with each molecule, from symmetry, forming two donor and two acceptor interactions, Figure 3A. Weak benzene-C–H···O(ketone) interactions provide additional stability to the framework and indicate that the ketone-O1 atom is bifurcated. Layers stack along (101) and the contacts between them are of the type S1···S1 with a separation of 3.4541(5) Å for symmetry operation i: –x, –y, –z, Figure 3B.

A distinct packing arrangement is found in 2 despite the participation of the equivalent atoms in the amine-N–H···O(ketone) and benzene-C–H···O(ketone) interactions,
Theoretical study of the polymorphs of O,O’-diethyl N,N’-(p-phenylendicarbonyl) bis-(thiocarbamate)

The minimum energy structure of \([1,4\text{-EtOC}(=\text{S})(\text{H})(\text{C}(=\text{O})\text{C}_5\text{H}_4\text{C}(=\text{O})\text{N}(\text{H})(\text{C}(=\text{S})\text{OEt}) = \text{S})\text{OiPr}] \) was determined and revealed a structure closer to 2 despite having overall \(C_i\) symmetry. The conformational differences are primarily seen in the relative orientations of the terminal ethyl groups. This can be seen in the overlay diagram, Figure 2C. Consistent with the molecule “breathing” or “relaxing” in the absence of the constraints of crystal packing effects, there are marginal elongations of the key bond lengths included in Table 2. Similarly, some small differences are noted in the bond angles. The key torsion angles differentiating 1 and 2, i.e., \(C_2\text{–}N_1\text{–}C_1\text{–}S_1\) and \(C_1\text{–}N_1\text{–}C_2\text{–}O_1\) torsion angles are -10.2 and -5.3\(^\circ\), respectively, in the optimised molecule. From the torsion angle data collected in Table 2, it is evident that the molecule in 2 most approximates a plane whereas the molecule in 1 is the most twisted.

As indicated in the Experimental section, crystals of the monoclinic (1) and tetragonal (2) polymorphs were obtained concomitantly from the same recrystallisation experiment suggesting that they may have similar energies of stabilisation. The calculated density for 1 at 1.430 g cm\(^{-3}\) is marginally less that 1.438 g cm\(^{-3}\) for 2. This trend is mirrored in the trend in the Kitaigorodskii packing indices, calculated with PLATON [21], of 69.8 and 70.0\%, respectively. The calculated lattice energies were indistinguishable at 49.49 and 49.58 kcal/mol per molecule for 1 and 2, respectively. The relaxation energies of 2.68 and 3.31 kcal/mol per molecule for 1 and 2, respectively, are not greatly different and are quite small indicating no significant perturbation in molecular geometry occurs upon optimisation, a conclusion consistent with the above. Despite the closeness of these parameters, a powder X-ray diffraction pattern measured on the bulk powder indicated the overwhelming majority of the sample to be the tetragonal polymorph. That the relaxation energy of 2 is greater than 1 is consistent with the increased planarity of 2 cf. 1. Table 2, a geometry which leads to a more efficient packing, at the cost of deforming the molecule into a planar arrangement. Still, the effect is quite subtle.

Copper(I) complex

The structure of \([[(\text{Ph,P})_2\text{CuCl}], [1,4\text{-iPrOC}(=\text{S})(\text{H})(\text{C}(=\text{O})\text{C}_5\text{H}_4\text{C}(=\text{O})\text{N}(\text{H})(\text{C}(=\text{S})\text{OEt}) = \text{S})\text{OiPr}] \) (3) has been crystallised as a tetra-chloroform solvate; see Figure 5 for the molecular structure and Table 4 for selected geometric parameters. The binuclear complex is located about a centre of inversion. The copper(I) centre is coordinated by the thione-S atom, two phosphane-P atoms and a chloride, the latter providing the charge balance. The coordination geometry is distorted tetrahedral with the deviations from the ideal geometry ascribed to the disparate Cl, S and P atoms comprising the ligand donor set and the wide angle subtended at the copper centre by the bulky phosphane ligands. That being stated, the range of tetrahedral angles, ca 107–118\(^\circ\), is relatively narrow. The amide-N–H atom is orientated to form an intramolecular N–H···Cl...
Related complexes, i.e., featuring the same donor set and quasi (CuCl···HNCS) chelate rings, have attracted attention recently as the ring was shown to participate in an attractive intramolecular interaction with an arene-H atom [32]. These interactions, termed arene-C–H···π(quasi-chelate ring) interactions, are analogous to the more familiar arene-C–H···π(arene) interactions. Of the approximately 90 copper(I) structures having the same donor set/N–H···Cl hydrogen bond included in the Cambridge Structural Database [10], approximately 1/6 featured this intramolecular interaction. An analysis of 3 shows that while there a close approach of the C16–H atom to the quasi-ring centroid, the separation of ca 2.92 Å, is long and does not fit all the criteria specified for such interactions [32].

In the bipodal ligand, the thione-S1 and ketone-O2 atoms are anti, an orientation that allows the simultaneous coordination of the S1 atom and the formation of the intramolecular N–H···Cl hydrogen bond. Overall, the ligand adopts a slightly twisted conformation with the twist being about the C2–C3 bond, connecting the carbamate residue to the plane through the central benzene ring, the N1–C1–N1–C2–C3 torsion angle is −23.5(2)°, and twists about the C1–N1 and C2–N1 bonds within the S1=Cl–N1–C2=O1 residue, as seen in the values of the C2–N1–C1–S1 and C1–N1–C2–O1 torsion angles of 169.19(14) and ~20.5(3)°, respectively. Thus, allowing for the anti disposition of the doubly bonded S1 and O1 atoms, the overall conformation for the bipodal ligand in 3 matches that found for the monoclinic polymorph of the R = Et ester (2) with the exception of the C1–N1–C2–O1 torsion angle which is about 15° wider, probably to minimise repulsion between the oxygen atoms.
In the absence of a crystal structure for the bipodal molecule with \( R = \text{iPr} \), the geometric parameters within the bipodal ligand in 3 are compared with those determined for the uncoordinated \( R = \text{Et} \) ester (1 and 2). This analysis reveals some general trends. Consistent with the coordination of the thione-S1 atom to copper, the \( C1=S1 \) bond length has significantly elongated in 3 cf. the non-coordinated thione bond in 1 and 2. Also, the reduced double bond character in the thione bond is manifested in a decrease in the angles subtended by the S1 atom at the C1 atom with a concomitant widening of the O2–C1–N1 angle, by over 5°. The angles about the N1 and C2 atoms remain largely unperturbed by coordination of the bipodal molecule in 3.

In the crystal packing both relatively strong C–H⋯O and C–H⋯Cl interactions are evident, Table 3. From symmetry, two chloroform–C–H⋯Cl(coordinated) and two
chloroform-C–H···O(ketone) interactions are formed for each binuclear molecule to generate a four-molecule aggregate. The coordinated Cl1 atom is bifurcated as it also forms an intramolecular N–H···Cl hydrogen bond. The ketone-O1 is also bifurcated, accepting an interaction from an arene-C65–H atom so that a supramolecular chain along the b-axis is generated, Figure 6A. The most significant contacts between the chains are of the type methyl-H···π(arene), Table 3 and Figure 6B.

**Discussion**

The new structures reported herein complement a relatively small number of literature precedents of benzoylthiocarbamide acid esters [11–16]. The compounds for which crystal structures have been determined are listed in Table 5. There are three monofunctional examples of benzoylthiocarbamide acid esters, akin to Figure 1B, and each of these features a syn disposition of the thione-S and ketone-O atoms. As described above, a similar arrangement is found in the original tetragonal polymorph of bipodal [1,4-EtOC(S)=N(H)C(O)C6H4C(O)N(H)C(S)OEt] (2) [14]. Two conformational polymorphs have been found for the 1,3 isomer of 1 and 2, but with R = Me [15]. In one of these, a syn arrangement of thione-S and ketone-O atoms is found for both residues, Figure 7A, but in the other polymorph, with crystallographically imposed 2-fold symmetry, the thione-S and ketone-O atoms are anti, Figure 7B. Finally, until the present report, only one metal complex of benzoylthiocarbamide acid esters had been crystallographically investigated. As shown in Figure 7C, the square planar nickel(II) centre in Ni[PhC(O)=N(C(S)OEt)]2 is bis chelated by the mono-anion derived from PhC(O)=N(H)C(S)OEt within a cis-S2O2 donor set [16].

Tab. 5: Literature precedents for crystal structures of benzoylthiocarbamate esters and derived anions.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-Ethyl benzoylthiocarbamate</td>
<td>PhC(O)=N(H)C(S)OEt</td>
<td>[11, 12]</td>
</tr>
<tr>
<td>O-Butyl benzoylthiocarbamate</td>
<td>PhC(O)=N(H)C(S)OBu</td>
<td>[13]</td>
</tr>
<tr>
<td>O-Ethyl (4-methylbenzoyl)thiocarbamate</td>
<td>4-MeC6H4C(O)=N(H)C(S)OEt</td>
<td>[12]</td>
</tr>
<tr>
<td>N,N′-bis(Ethoxythiocarbonyl)terephthalamide</td>
<td>[1,4-EtOC(S)=N(H)C(O)C6H4C(O)N(H)C(S)OEt]</td>
<td>[14]</td>
</tr>
<tr>
<td>anti-anti-O,O′-Dimethyl N,N′-(m-phenylendicarbonyl)bis(thiocarbamate)</td>
<td>[1,3-MeOC(S)=N(H)C(O)C6H4C(O)N(H)C(S)OEt]</td>
<td>[15]</td>
</tr>
<tr>
<td>syn-anti-O,O′-Dimethyl N,N′-(m-phenylendicarbonyl)bis(dithiocarbamate)</td>
<td>[1,3-MeOC(S)=N(H)C(O)C6H4C(O)N(H)C(S)OMe]</td>
<td>[15]</td>
</tr>
<tr>
<td>bis(O-Ethyl-N-benzoyl-thiocarbamate)nickel(II)</td>
<td>Ni[PhC(O)=N(C(S)OEt)]2</td>
<td>[16]</td>
</tr>
</tbody>
</table>
Conclusions

The structural chemistry of benzoylethiocarbamic acid esters is in its infancy. Despite this, evidence has already been found for polymorphism with significant differences in the orientation of the key thioamide groups [15]. In the present study, another system has been proven polymorphic but, the differences in molecular conformation are relatively minor and probably arise from the dictates of crystal packing. This is vindicated by a theoretical study showing that the minimum energy structure corresponds more closely to the high symmetry tetragonal polymorph. Only the second metal complex and first example of neutral coordination mode for this class of compound has been demonstrated in a binuclear copper(I) compound.

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