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Crystal and Molecular Structures of Benzyl-(2-chloro-6methylpyrimidin-4-yl)amine and Benzyl-(4-chloro-6methylpyrimidin-2-yl)amine: Confirmation of Computationally Predicted Restricted Rotation

Luke R. Odell · Adam McCluskey · Timothy W. Failes · Edward R. T. Tiekink

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Abstract Crystal structures for the isomeric compounds benzyl-(2-chloro-6-methylpyrimidin-4-yl)amine (1), as its hemi-hydrate, and benzyl-(4-chloro-6-methylpyrimidin-2-yl)amine (2) have been determined. Conformational differences lead to multiple molecules, i.e. two and three, in their respective structures. Layers feature in each of the crystal structures and are stabilized by substantial hydrogenbonding interactions. Compound (1) crystallizes as a hemihydrate in the triclinic space group *P*-1 with *a* = 8.667(5) Å, *b* = 11.421(7) Å, *c* = 12.954(8) Å, α = 78.330(10)°, β = 84.553(10)°, γ = 75.510(9)°, and *Z* = 4. Compound (2) crystallizes in the monoclinic space group *P*2₁/*c* with *a* = 10.740(3) Å, *b* = 21.487(6) Å, *c* = 14.914(4) Å, β = 95.014(5)°, and *Z* = 12.

Keywords Pyrimidine · Conformation · Crystal structure · Hydrogen-bonding

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L. R. Odell · A. McCluskey Department of Chemistry, School of Environmental and Life Sciences, University of Newcastle, University Drive, Callaghan, NSW 2308, Australia e-mail: Adam.McCluskey@newcastle.edu.au

T. W. Failes

School of Chemistry, University of Sydney, Sydney, NSW 2006, Australia

E. R. T. Tiekink (🖂)

Department of Chemistry, The University of Texas at San Antonio, One UTSA Circle, San Antonio, TX 78249-0698, USA e-mail: Edward.Tiekink@utsa.edu

Introduction

Multiply substituted pyrimidines have found considerable utility in medicinal chemistry, either being pivotal intermediates or the final product of an extensive structure activity relationship (SAR) study. As part of an on-going medicinal chemistry investigation into the structural requirements of corticotrophin releasing hormone type 1 receptor (CRH₁) antagonists, we synthesized a series of targeted libraries of small di-substituted pyrimidines [1]. During the course of these studies it became apparent that there was no facile methodology appropriate for the rapid assignment of substitution patterns on the pyrimidine ring. Analogs of the type shown in Scheme 1 were synthesized from the corresponding 2,4-dichloropyrimidine via a simple amminolysis reaction. Subsequent comprehensive NMR examinations revealed that key signals displayed significant line broadening. Moreover, the nature and extent of signal broadening was dependant upon the position of substitution. The most pronounced NMR broadening was observed in those instances where substitution occurred at the C4 position; with the signal at C5 broadened [2]. Typically this was evidenced in both the ¹H and ¹³C NMR spectra.

For our pyrimidines there was also a strong contribution to the rotamer equilibrium by a C-2 or C-6 methyl substituent. The energy difference of 20 kJ mol⁻¹ between the highest and lowest energy conformers represents a reasonable barrier to rotation at the temperatures over which line broadening is observed. The highest-energy conformers always oriented the amine N–H towards C–H(5) and usually were in the same plane as the aromatic ring. Most low-energy conformers oriented the amine N–H oriented away from C–H(5). However, it appears that hindered rotation gives rise to distinct populations of high- and



Scheme 1 Chemical structures for (1) and (2)



Fig. 1 Illustrative example of a high-energy conformer of (1), left, and (2), right

low-energy conformers; Fig. 1 highlights the high-energy conformer of 1 which is responsible for line broadening and also the high energy conformer of 2 which does not induce this effect. Aniline derivatives have been shown to prefer a stable orientation orthogonal to the plane of the pyrimidine residue and consequently no line broadening would be observed [3]. This is in keeping with our modeling data with conformational energy differences of the order of $\sim 2 \text{ kJ mol}^{-1}$ between the highest and lowest energy conformer. In order to confirm our experimental and theoretical observations, the crystal and molecular structures of the two representative compounds, benzyl-(2-chloro-6-methylpyrimidin-4-yl)amine (1), characterized as a hemihydrate, and benzyl-(4-chloro-6-methylpyrimidin-2-yl)amine (2) were determined.

Experimental

Synthesis

2-yl)amine (2) were prepared by adding a solution of 2,4dichloro-6-methylpyrimidine (0.65 g, 4.0 mmol) in THF (5 mL) to benzylamine (0.86 g, 8 mmol, 2 eq). The resulting solution was stirred at 30 °C for 18 h, filtered and concentrated in vacuo. The residue was purified by flash chromatography using 1:9 ethyl acetate–hexanes to yield the corresponding isomers. Slow evaporation of the eluting solvents allowed crystal formation.

(1) yield 340 mg, 49%, mp 78–81 °C; ¹H NMR (CDCl₃): δ 2.25 (s, 3H), 4.51 (d, 2H), 6.06 (s, 1H), 6.15 (br s, 1H), 7.29 (m, 5H) ppm; ¹³C NMR (CDCl₃): δ 23.1, 44.9, 99.9 (br), 126.7, 127.1, 128.3, 136.8, 159.6, 163.8, 171.1 (br) ppm.

(2) yield 142 mg, 19%, mp 136–138 °C; ¹H NMR (CDCl₃): δ 2.29 (s, 3H), 4.64 (s, 2H), 5.48 (br s, 1H), 6.48 (s, 1H), 7.31 (m, 5H) ppm; ¹³C NMR (CDCl₃): δ 23.2, 44.9, 109.0, 126.7, 126.9, 128.0, 139.2, 160.7, 161.6, 169.0 ppm.

X-ray Crystallography

Intensity data for colorless crystals of $(1) \cdot 0.5 H_2O$ and (2)were collected at 150 K on a Bruker SMART 1000 CCD fitted with Mo K α radiation. The data sets were corrected for absorption based on multiple scans [4] and reduced using standard methods [5]. The structures was solved by direct-methods [6] and refined by a full-matrix leastsquares procedure on F^2 with anisotropic displacement parameters for non-hydrogen atoms, carbon-and nitrogenbound hydrogen atoms in their calculated positions and a weighting scheme of the form $w = 1/[\sigma^2(F_0^2) + (aP)^2 + bP]$ where $P = (F_0^2 + 2F_c^2)/3$ [7]. Crystal data and refinement details are given in Table 1. Figures 2 and 5, showing the atom labeling schemes, were drawn with 50% displacement ellipsoids using ORTEP [8] and the remaining figures were drawn with DIAMOND [9] and Qmol (Figs. 2 and 5) [10]. Data manipulation and interpretation were accomplished using teXsan [11] and PLATON [12].

Results and Discussion

The crystallographic asymmetric unit of $(1) \cdot 0.5H_2O$ comprises two independent molecules of (1) and a solvent water molecule of crystallization. The molecular structures of (1) are illustrated in Fig. 2 and selected geometric parameters are collected in Table 2. Immediately apparent from Fig. 2 is that there are conformational differences between the two molecules in relation to the orientation of the benzyl residue with respect to the remaining part of the molecule so that in the first independent molecule, the

Table 1Crystal data andrefinement details for $(1) \cdot 0.5H_2O$ and (2)

| Structure | $(1) \cdot 0.5 H_2 O$ | (2) |
|--|----------------------------------|--|
| Empirical formula | $C_{12}H_{12}ClN_3\cdot 0.5H_2O$ | C ₁₂ H ₁₂ ClN ₃ |
| Formula weight | 242.70 | 233.70 |
| Crystal habit, color | block, colorless | block, colorless |
| Crystal system | Triclinic | Monoclinic |
| Space Group | <i>P</i> -1 | $P2_1/c$ |
| a (Å) | 8.667(5) | 10.740(3) |
| b (Å) | 11.421(7) | 21.487(6) |
| c (Å) | 12.954(8) | 14.914(4) |
| α (°) | 78.330(10) | 90 |
| β (°) | 84.553(10) | 95.014(5) |
| γ (°) | 75.510(9) | 90 |
| Volume (Å ³) | 1,214.5(13) | 3,428.5(16) |
| Z | 4 | 12 |
| Density (calculated) | 1.327 | 1.358 |
| Absorption coefficient (mm ⁻¹) | 0.296 | 0.309 |
| <i>F</i> (000) | 508 | 1464 |
| Crystal size (mm) | $0.13 \times 0.38 \times 0.72$ | $0.45\times0.50\times0.95$ |
| θ range for data collection (°) | 1.6–26.5 | 1.7-26.5 |
| Reflections collected | 10,957 | 30,825 |
| Independent reflections | 4,981 | 7,103 |
| R _{int} | 0.018 | 0.023 |
| Reflections with $I \ge 2\sigma(I)$ | 4,199 | 5,432 |
| Number of parameters | 312 | 445 |
| Goodness-of-fit on F^2 | 1.06 | 1.09 |
| a, b for weighting scheme | 0.055, 0.095 | 0.090, 0.365 |
| Final R indices $[I \ge 2\sigma(I)]$ | R1 = 0.033, wR2 = 0.090 | R1 = 0.042, wR2 = 0.139 |
| R indices [all data] | R1 = 0.039, wR2 = 0.093 | R1 = 0.055, wR2 = 0.146 |
| Largest difference | | |
| Peak and hole (\AA^{-3}) | 0.23, -0.24 | 0.56, -0.35 |
| CCDC deposition no. | 648,755 | 648,756 |

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benzyl group occupies a position opposite to the chloride substituent and the reverse is true for molecule a. This is highlighted in the overlap diagram shown in Fig. 2. Other differences are evident in the torsion angle data listed in Table 2. A common feature of the two molecules is that the two aromatic rings are effectively orthogonal to each other as seen in the dihedral angles between the pyrimidine and phenyl rings of 86.15(7)° and 85.95(7)°, respectively. Despite the different conformations, there are no systematic differences between comparable bond distances and angles describing the two molecules. As expected from the composition of $(1) \cdot 0.5 H_2 O$, there are significant hydrogenbonding interactions operating in the crystal structure and given that there is significant evidence of ¹H and ¹³C line broadening as judged from the NMR study, it is likely that the distinct conformations arise so as to optimize the stabilization of the crystal structure [2].

Geometric parameters describing the intermolecular forces are summarized in Table 3. The water molecule

plays a pivotal role in the crystal packing by forming a bridge between the two independent molecules of (1) via O-H···N hydrogen-bonds to the pyrimidine-N3 atoms. The water-O1 atom also accepts a proton from N1a-H. The first independent molecule associates with a centrosymmetrically related molecule via an eight-membered [N-C-N-H···]₂ synthon. The N2a atom forms a close intramolecular contact with a C7-H atom. A detailed view of the hydrogen-bonding in $(1) \cdot 0.5 H_2 O$ is shown in Fig. 2. Globally, the molecules pack into layers along the b-direction in the crystal structure. Stabilization in the layers is afforded by the aforementioned N-H…N hydrogen-bonding interactions, C-H··· π interactions and π ··· π stacking interactions; details in Table 3. Layers of molecules are capped on either side by the water molecules and the primary interlayer contacts are C-H...O interactions. From Fig. 3 it can be seen that the water molecules are proximate and at these junctures of the crystal structure there are $2 \times C-H\cdots O$ contacts of 2.88 Å and $2 \times C-H\cdots O$



Fig. 2 Molecular structures and crystallographic numbering schemes for the two independent molecules in $(1) \cdot H_2O$. Displacement ellipsoids are drawn at 50% probability level

contacts of 2.89 Å. So, while each C–H \cdots O contact must represent a weak interaction, the sum total of four weak interactions provides cohesion to the crystal packing (Fig. 4).

The crystal structure determination of (2) shows three independent molecules comprise the asymmetric unit,

Table 2 Selected bond lengths (Å) and angles (°) for $(1) \cdot 0.5H_2O$

| Atoms | Molecule | Molecule a | |
|-------------|-------------|------------|--|
| N1-C7 | 1.4526(19) | 1.4593(19) | |
| N1-C8 | 1.3405(18) | 1.3391(18) | |
| N2-C8 | 1.3609(18) | 1.3567(17) | |
| N2-C9 | 1.3195(18) | 1.3212(18) | |
| N3-C9 | 1.3170(18) | 1.3169(18) | |
| N3-C10 | 1.3645(19) | 1.3754(18) | |
| C8-C12 | 1.4132(19) | 1.420(2) | |
| C10-C12 | 1.370(2) | 1.359(2) | |
| C7-N1-C8 | 123.59(11) | 123.53(11) | |
| C8-N2-C9 | 114.71(12) | 114.50(12) | |
| C9-N3-C10 | 114.06(12) | 114.07(11) | |
| N1-C7-C6-C1 | -172.73(12) | 30.33(19) | |
| C8-N1-C7-C6 | 85.61(16) | -99.55(15) | |
| N2-C8-N1-C7 | -179.34(12) | 0.94(19) | |

Fig. 5 and Table 4. The first molecule and molecule a are virtually super-imposable but the orientation of the phenyl group in molecule b is in the opposite direction to these owing to a twist about the N1-C7 bond; see overlay plot in Fig. 5. As for the molecules of (1), the aromatic rings in (2)are orthogonal to each other as seen in the dihedral angles of 89.67(8)°, 84.82(8)° and 84.99(8)°, respectively. Again, as for (1), there are no significant differences between chemically equivalent bond distances and angles describing the independent molecules. Rearranging the heteroatoms in isomer (2) cf. (1) results in the expected changes in bond distances within the pyrimidine rings. Small differences are also observed in bond angles. Whereas the C-N2-C angles are the same in the two structures, there has been a small expansion in the C-N3-C angle by about 2° in (2) compared with (1). This arises as a result of the reorganization of π -electron density within the pyrimidine ring so that the disparity in the N3-C bond distances of about 0.05 Å in (1) is reduced to about 0.015 Å in (2). This means the N-lone pair/C = N repulsion is reduced somewhat in (2) and so there is an expansion in the C-N-C angle (Table 4).

The primary intermolecular contacts in the crystal structure of (2) are of the type N–H…N; see Table 5 for a summary of the geometric parameters for all discussed intermolecular interactions in (2). The most prominent synthon is the eight-membered [N–C–N–H…]₂ arrangements also seen in (1)·0.5H₂O. In (2), molecules *a* and *b* associate in this way and for the other molecule, centro-symmetrically related pairs are associated similarly. The global crystal packing again comprises layers and these stack along the *b*-direction. Stabilizing the layers are the

Table 3 Hydrogen bondingparameters (A–H···B; Å, °) for $(1) \cdot 0.5H_2O$

| A | Н | В | Н…В | А…В | А–Н…В | Symmetry operation |
|----------|------|--------------|------|----------|-------|----------------------------------|
| 01 | H1w | N3a | 2.09 | 2.934(2) | 178 | -1 + x, y, z |
| O1 | H2w | N3 | 2.04 | 2.880(2) | 173 | + <i>x</i> , <i>y</i> , <i>z</i> |
| N1a | H2n | 01 | 1.99 | 2.865(2) | 176 | <i>x</i> , <i>y</i> , <i>z</i> |
| N1 | H1n | N2 | 2.17 | 3.048(2) | 175 | 1 - x, 1 - y, -z |
| C7a | H7a2 | N2a | 2.40 | 2.791(3) | 103 | <i>x</i> , <i>y</i> , <i>z</i> |
| C4 | H4 | Cg(N2-ring) | 2.95 | 3.802(3) | 151 | -x, 1 - y, -z |
| C5a | H5a | Cg(C1-ring) | 2.88 | 3.713(3) | 147 | -x, 1 - y, 1 - z |
| Cg(N2-ri | ng) | Cg(C1a-ring) | - | 3.811(3) | 12 | 1 - x, 1 - y, 1 - z |

Cg = ring centroid

Fig. 3 View of the hydrogenbonding in the crystal structure of (1) \cdot H₂O. Color code: chloride, cyan; oxygen, red; nitrogen, blue; carbon, grey; and hydrogen, green. Orange-dashed lines represent O–H…N and N– H…O hydrogen-bonds and bluedashed lines represent N–H…N hydrogen-bonds

Fig. 4 Unit cell contents for $(1) \cdot H_2O$ viewed down the *c*-direction. Color codes as for Fig. 2





Fig. 5 Molecular structures and crystallographic numbering schemes for the three independent molecules in (2). Displacement ellipsoids are drawn at 50% probability level



Table 4 Selected bond lengths(Å) and angles (°) for (2)

| Atoms | Molecule | Molecule a | Molecule b | |
|---------------------|-------------|-------------|-------------|--|
| N1-C7 | 1.451(2) | 1.455(2) | 1.452(2) | |
| N1-C8 | 1.350(2) | 1.347(2) | 1.350(2) | |
| N2-C8 | 1.357(2) | 1.356(2) | 1.357(2) | |
| N2-C9 | 1.323(2) | 1.323(2) | 1.326(2) | |
| N3–C8 1.349(2) | | 1.350(2) | 1.349(2) | |
| N3–C11 1.334(2) | | 1.334(2) | 1.335(2) | |
| C9–C10 | 1.376(2) | 1.379(3) | 1.373(3) | |
| C10-C11 | 1.392(2) | 1.390(2) | 1.391(2) | |
| C7-N1-C8 | 122.07(14) | 122.43(14) | 121.84(15) | |
| C8–N2–C9 114.68(15) | | 114.75(15) | 114.47(15) | |
| C8-N3-C11 | 116.30(14) | 116.24(14) | 116.30(15) | |
| N1-C7-C6-C1 | -147.76(15) | -147.20(15) | 146.32(16) | |
| C8-N1-C7-C6 | 74.8(2) | 78.3(2) | -78.0(2) | |
| N2-C8-N1-C7 | -178.30(14) | -176.92(15) | -179.38(15) | |

N–H…N interactions reinforced by C–H… π contacts involving methyl–H atoms. In the absence of other intermolecular interactions, it appears that layers are held together by Cl… π interactions, involving the Cl1 and Cl1b atoms (Fig. 6).

Supplementary Material

CCDC-648755 and CCDC-648756 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by

Fig. 6 Unit cell contents for (2) viewed down the *a*-direction. Color code: chloride, cyan; nitrogen, blue; carbon, grey; and hydrogen, green. Orange-dashed lines represent N–H…N hydrogen-bonds



| Table 5 Hydrogen bonding |
|------------------------------|
| parameters (A-H…B; Å, °) for |
| (2) |

| А | Н | В | H…B | A…B | A–H…B | Symmetry operation |
|------|------|--------------|------|----------|-------|--|
| N1 | H1n | N2 | 2.17 | 3.049(2) | 176 | 1 - x, 1 - y, 1 - z |
| N1a | H2n | N2b | 2.17 | 3.043(2) | 174 | <i>x</i> , <i>y</i> , <i>z</i> |
| N1b | H3n | H2a | 2.18 | 3.062(2) | 178 | <i>x</i> , <i>y</i> , <i>z</i> |
| C12 | H12b | Cg(C1b-ring) | 2.93 | 3.880(2) | 164 | x, y, 1 + z |
| C12a | H12f | Cg(N2-ring) | 2.89 | 3.828(2) | 162 | x, y, z |
| C9 | Cl1 | Cg(C1b-ring) | 3.83 | 5.558(2) | 172 | $x, 1\frac{1}{2} - y, \frac{1}{2} + z$ |
| C9b | Cl1b | Cg(C1-ring) | 3.79 | 5.506(2) | 168 | $x, \frac{1}{2} - y, -\frac{1}{2} + z$ |

e-mailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44(0)1223-336033.

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