Research Article

Hydrogen Bonds between Acidic Protons from Alkynes (C–H ⋅⋅⋅ O) and Amides (N–H ⋅⋅⋅ O) and Carbonyl Oxygen Atoms as Acceptor Partners

Pierre Baillargeon, Tommy Lussier, and Yves L. Dory

1 Département de Chimie, Cégep de Sherbrooke, 475 Rue du Cégep, Sherbrooke, QC, Canada J1E 4K1
2 Laboratoire de Synthèse Supramoléculaire, Département de Chimie, Institut de Pharmacologie, Université de Sherbrooke, 3001 12e Avenue Nord, Sherbrooke, QC, Canada J1H 5N4

Correspondence should be addressed to Pierre Baillargeon; pierre.baillargeon@usherbrooke.ca and Yves L. Dory; yves.dory@usherbrooke.ca

Received 10 September 2013; Revised 21 November 2013; Accepted 10 December 2013; Published 12 January 2014

Academic Editor: Leonard MacGillivray

Copyright © 2014 Pierre Baillargeon et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Crystals of tert-butyl (2S)-2-(prop-2-yn-1-ylcarbamoyl)pyrrolidine-1-carboxylate (Boc-L-Pro-NHCH$_2$CCH) have been obtained. The title compound crystallizes easily as sharp needles in orthorhombic system, space group P 2$_1$2$_1$2$_1$, with a = 9.2890(2), b = 9.7292(2), c = 15.7918(4) Å, V = 1427.18(6) Å$^3$, and Z = 4. The main feature of the structure is the orientation of the carbamate and amide. Their dipoles add up and the molecule displays an electric dipole moment of 5.61 D from B3LYP/6-31G(d) calculations. The antiparallel H bonding of amides and the alignment of dipoles induce columnar stacking (the dipole moment along the columnar a axis is 4.46 D for each molecule). The other components across the other axes are, therefore weaker, (3.17 D and 1.23 D along the b and c axes, resp.). The resulting anisotropic columns pack side by side, in an antiparallel fashion mostly by (alkyne) CH ⋅⋅⋅ O=C (carbamate) interactions.

1. Introduction

The design of organic solid (crystal or supramolecular engineering) is still today challenging and of great importance [1, 2]. Understanding the details of weak intermolecular interactions plays definitely a major role in the rational design of ordered organic crystals. In our lab, we already achieved great molecular macroscopic order with specially designed peptides, macrocycles as precursors to organic nanotubes [3–5] or supramolecular walls [6]. Here, we present the crystal structure of the proline derivative 1 (Figure 1) which alkyne, amide, and carbamate functionalities are all involved in hydrogen bonding.

2. Materials and Methods

2.1. Synthesis. To Boc-L-proline N-hydroxysuccinimide ester (2.0 g, 6.4 mmol) in CH$_2$Cl$_2$ (40 mL) was added, at 0°C, propargylamine (0.46 g, 8.4 mmol) and K$_2$CO$_3$ (1.43 g, 10.3 mmol). The reaction mixture was allowed to warm up to RT and was stirred for 72 h. Water (30 mL) was added and the organic phase was isolated. The remaining aqueous layer was extracted again with CH$_2$Cl$_2$ (2 × 30 mL). The combined organic layers were filtered through a cotton plug and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel, eluted with Et$_2$O/Hexane (75:25), to yield the title product as a white solid (1.654 g, 78%).

Rf = 0.36 (Et$_2$O/Hexane 75:25); T$_{max}$ (108–111°C); IR (NaCl, v cm$^{-1}$): 3242, 3055, 2982, 2288, 2117, 1688, 1536, 1402, 1324, 1258, 919, 885, and 718. NMR$^1$H (300 MHz, CDCl$_3$, δ ppm): 6.20 (br, 1H), 4.30–3.90 (m, 3H), 3.50–3.30 (m, 2H), 2.40–2.00 (m, 2H), 2.20 (brs, 1H), 2.00–1.80 (m, 2H), and 1.45 (s, 9H); HRMS (m/z): calcld for C$_{13}$H$_{20}$N$_2$O$_3$Na [MNa$^+$]: 275.1366, found: 275.1367.
2.2. X-Ray Crystallography. A dilute CDCl$_3$ solution of 1 (Figure I) was left to stand in a small vial (partially screwed lid) at room temperature for several days. The alkyne I started crystalizing and the vial was kept until nearly complete evaporation of the solvent.

A colorless crystalline needle with approximate dimensions of $0.24 \times 0.25 \times 0.43$ mm$^3$ was mounted on a Bruker AXS P4/SMART 1000 CCD diffractometer. The determination of unit cell parameters and data collections were performed with Cu-K$_\alpha$ radiation ($\lambda = 1.54178$ Å). A total of 8432 frames were collected. The total exposure time was 4.68 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 25149 reflections to a maximum $\theta$ angle of 70.03$^\circ$ (0.82 Å resolution), of which 2670 were independent (average redundancy: 9.419, completeness = 98.4%, $R_{int} = 1.90$%, $R_{sig} = 0.96$%) and 2655 (99.44%) were greater than 2$\sigma(F^2)$. The final cell constants of $a = 9.2890(2)$ Å, $b = 9.7292(2)$ Å, $c = 15.7918(4)$ Å, volume = 142718(6) Å$^3$ and are based upon the refinement of the XYZ-centroids of 9807 reflections above 20 $\sigma(I)$ with 5.596$^\circ < \theta < 139.6^\circ$. Data were corrected for absorption effects using the multiscan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.909. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7575 and 0.8531. The structure was solved and refined using the Bruker SHELXTL software package, using the space group P 2$_1$ 2$_1$ 2$_1$, with $Z = 4$ for the formula unit, C$_{13}$H$_{20}$N$_2$O$_3$. The final anisotropic full-matrix least-squares, refinement on $F^2$ with 166 variables converged at $R_1 = 2.46$%, for the observed data and $wR_2 = 6.39$% for all data. The goodness of fit was 1.035. The largest peak in the final difference electron density synthesis was 0.196 $e$/$\AA^3$ and the largest hole was $-0.151 e$/$\AA^3$ with an RMS deviation of 0.028 $e$/$\AA^3$. On the basis of the final model, the calculated density was 1.174 g/cm$^3$ and $F(000)$, 544 $e$$. The crystal data, intensity collection conditions, and refinement parameters are presented in Table 1.

### Table 1: Crystal data, intensity collection conditions, and refinement parameters for I.

| CCDC No | 906056 |
|----------|--------|
| Empirical formula | C$_{13}$H$_{20}$N$_2$O$_3$ |
| Formula weight | 252.31 |
| Temperature | 100 K |
| Wavelength | 1.54178 Å Cu K\(\alpha\) |
| Crystal system, space group | Orthorhombic, P 2$_1$ 2$_1$ 2$_1$ |
| Unit cell dimensions | $a = 9.2890(2)$ Å $b = 9.7292(2)$ Å $c = 15.7918(4)$ Å $\alpha = \beta = \gamma = 90^\circ$ |
| Volume | 1427.18(6) Å$^3$ |
| Z, calculated density | 4.1174 Mg/m$^3$ |
| Absorption coefficient $\mu$ | 0.684 mm$^{-1}$ |
| Absorption correction | Multiscan |
| Max. and min. transmission | 0.85 and 0.77 |
| Crystal size | $0.24 \times 0.25 \times 0.43$ mm$^3$ |
| $F(000)$ | 544 |
| $\theta$ range for data collection | $5.53$ to 70.03$^\circ$ |
| Index ranges | $-11 \leq h \leq 11$, $-11 \leq k \leq 11$, $-19 \leq l \leq 19$ |
| Reflections collected/unique | 25149/2670 ($R_{int} = 0.0190$) |
| Refinement method | Full-matrix least squares on $F^2$ |
| Completeness to theta = 25.00$^\circ$ | 98.4% |
| Goodness of fit on $F^2$ | 1.035 |
| Data/restraints/parameters | 2670/0/166 |
| Final $R$ indices ($I > 2\sigma(I)$) | $R_1 = 0.0246$, $wR_2 = 0.0637$ |
| $R$ indices (all data) | $R_1 = 0.0247$, $wR_2 = 0.0639$ |
| Largest diff. peak and hole | 0.196 and $-0.151$ e$^-\AA^3$ |

1EZ, UK e-mail: deposit@ccdc.cam.ac.uk. See CIF file in Supplementary Material available online at http://dx.doi.org/10.1155/2014/371629.

3. Results and Discussion

The main feature of the crystal structure of the title compound Boc-L-Pro-NHCH$_2$CCH 1 is the columnar architecture and the orientation of the carbamate, amide, and alkyne groups (Figure 2). From B3LYP/6-31G(d) calculations, the electric dipole moment has a total theoretical value of 5.61 D, with a major contribution (4.46 D) along the $a$ axis (which is nearly the orientation of both carbonyl groups). The other components across the other axes are, therefore, weaker (3.17 D and 1.23 D along the $b$ and $c$ axes, resp.). As expected, both nearly parallel carbonyls act as hydrogen bond acceptors toward the same NH group of a neighboring molecule. Between two consecutive molecules, the NH⋯O=C (amide) and NH⋯O=C (carbamate) distances are 2.218 Å and 3.141 Å, respectively (corresponding to...
Along the a axis
From the 2 carbonyls

Figure 2: View along b axis of the columnar polar staking of 1, which emphasizes the orientation of the amide, carbamate, and alkyne groups. Amide H bond interactions are represented with green dotted lines.

Figure 3: Plot of seven columns viewed along a axis, showing all the hydrogen bonds as dotted lines (NH⋅⋅⋅O= C(amide) inside column and (alkyne) CH⋅⋅⋅ O=C (carbamate) between columns).

2.97 Å and 3.58 Å between N and O atoms). Therefore, the contribution of the carbamate carbonyl appears to be less important than that of the amide. This is also confirmed in the alignment of the corresponding carbonyls with the amide N–H groups. Thus, the C=O⋅⋅⋅H(N) angles assume values of 141° and 79° for the amide and the carbamate, respectively. The latter being very distorted is accordingly much weaker than the former [7]. Finally, the linear terminal alkyne groups are disposed nearly perpendicularly to the polar column.

Columns are directly linked to one another by (alkyne) CH⋅⋅⋅ O=C (carbamate) interactions (Figure 3) [8, 9]. Although the hydrogen bond character of the CH⋅⋅⋅ O interaction has been a subject of controversy [10, 11], CH⋅⋅⋅ O hydrogen bonds are now well accepted by the scientific community [12–15], especially hydrogen bonds formed by terminal acetylenes where the C–H groups can act as weak hydrogen bond donors owing to their relatively high acidity [8].

The preference for linearity is the main structural feature distinguishing hydrogen bonds from van der Waals interactions [7]. In our case, the θ angle (CH⋅⋅⋅ O angle) is near linearity with a value of 161.61° (Figure 4). This compares well with the known mean value for C(sp)H⋅⋅⋅ O angle of 152° [8, 13, 14]. Also, the distance D between the terminal alkyne C atom and the carbonyl O atom (3.100 Å) observed in the crystal of 1 is relatively short compared to the literature mean value (3.31 and 3.46 Å) obtained from crystallographic database studies [8, 12].

Finally, when we look along the c axis (Figure 5), the columns pile side by side through weak van der Waals noncovalent interactions. The closest distance between H atoms of the t-Bu group is 2.565 Å, which is slightly above the expected vdW radii.
4. Conclusions

In conclusion, the crystal structure of the proline alkyne derivative 1 is dominated by three different interactions of different strengths: (1) hydrogen bonds between amides partners and mostly oriented parallel to the $a$ axis, (2) hydrogen bonds between carbonyl oxygen atoms and slightly acidic alkyne hydrogen, whose orientation lies mainly in the $bc$ plane, and (3) van der Waals interactions involving aliphatic residues.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

Financial support by NSERC, FQRNT, QC, Canada, and "Programme de collaboration universités-collèges" as well as RQCHP (Réseau Québécois de Calcul de Haute Performance) is gratefully acknowledged for computational resources.

References

[1] K. Biradha, C. Su, and J. J. Vittal, "Recent developments in crystal engineering," Crystal Growth and Design, vol. 11, no. 4, pp. 875–886, 2011.
[2] G. R. Desiraju, "Crystal engineering: from molecule to crystal," Journal of the American Chemical Society, vol. 135, no. 27, pp. 9952–9967, 2013.
[3] D. Gauthier, P. Baillargeon, M. Drouin, and Y. L. Dory, "Self-Assembly of cyclic peptides into nanotubes and then into highly anisotropic crystalline materials," *Angewandte Chemie International Edition*, vol. 40, no. 24, pp. 4635–4638, 2001.

[4] D. Pasini and M. Ricci, "Macrocycles as precursors for organic nanotubes," *Current Organic Synthesis*, vol. 4, no. 1, pp. 59–80, 2007.

[5] P. Baillargeon, S. Bernard, D. Gauthier, R. Skouta, and Y. L. Dory, "Efficient synthesis and astonishing supramolecular architectures of several symmetric macro lactams," *Chemistry A*, vol. 13, no. 33, pp. 9223–9235, 2007.

[6] P. Baillargeon and Y. L. Dory, "Supramolecular walls from cyclic peptides: modulating nature and strength of weak interactions," *Crystal Growth and Design*, vol. 9, no. 8, pp. 3638–3645, 2009.

[7] T. Steiner, "The hydrogen bond in the solid state," *Angewandte Chemie International Edition*, vol. 41, no. 1, pp. 48–76, 2002.

[8] T. Steiner and G. R. Desiraju, "Distinction between the weak hydrogen bond and the van der Waals interaction," *Chemical Communications*, no. 8, pp. 891–892, 1998.

[9] G. R. Desiraju, "Strength and linearity of C–H⋯O bonds in molecular crystals: a database study of some terminal alkynes," *Journal of the Chemical Society, Chemical Communications*, pp. 454–455, 1990.

[10] C. H. Schwalbe, "June Sutor and the C–H⋯O hydrogen bonding controversy," *Crystallography Reviews*, vol. 18, no. 3, pp. 191–206, 2012.

[11] J. Bernstein, "It isn't," *Crystal Growth & Design*, vol. 13, no. 3, pp. 961–964, 2013.

[12] G. R. Desiraju, "The C–H⋯O hydrogen bond in crystals: what is it?" *Accounts of Chemical Research*, vol. 24, no. 10, pp. 290–296, 1991.

[13] G. R. Desiraju, "Hydrogen bridges in crystal engineering: interactions without borders," *Accounts of Chemical Research*, vol. 35, no. 7, pp. 565–573, 2002.

[14] G. R. Desiraju, "C–H⋯O and other weak hydrogen bonds. From crystal engineering to virtual screening," *Chemical Communications*, no. 24, pp. 2995–3001, 2005.

[15] C. R. Jones, P. K. Baruah, A. L. Thompson, S. Scheiner, and M. D. Smith, "Can a C–H⋯O interaction be a determinant of conformation?" *Journal of the American Chemical Society*, vol. 134, no. 29, pp. 12064–12071, 2012.
