The crystal structure of trandolapril, $C_{24}H_{34}N_2O_5$: an example of the utility of raw data deposition in the powder diffraction file

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The crystal structure of trandolapril has been solved by parallel tempering using the FOX software package with laboratory powder diffraction data submitted to and published in the Powder Diffraction File. Rietveld refinement was performed with the software package GSAS yielding orthorhombic lattice parameters of $a = 19.7685(4)$, $b = 15.0697(4)$, and $c = 7.6704(2)$ Å ($C_{24}H_{34}N_2O_5$, $Z = 4$, space group $P2_12_12_1$). The Rietveld refinement results were compared with density functional theory (DFT) calculations performed with CRYSTAL14. While the structures are similar, discrepancies are observed in the configuration of the octahydroindole ring between the Rietveld and DFT structures, suggesting the refined and calculated molecules are diastereomers. © *2016 International Centre for Diffraction Data*. [doi:10.1017/S0885715616000294]

Key words: trandolapril, powder diffraction, structure solution, density functional theory

I. INTRODUCTION

Trandolapril is a common angiotensin converting enzyme inhibitor used to treat hypertension or high blood pressure (Wiseman and McTavish, 1994; Guay, 2003), either by itself or in combination with verapamil (Reynolds *et al*., 2005). The systematic name is (2S,3aR,7aS)-1-[(2S)-2-[[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2-carboxylic acid, and the two-dimensional (2D) molecular structure is given in Figure 1. Despite widespread usage for over 20 years (Wiseman and McTavish, 1994), to the best of our knowledge the crystal structure of trandolapril has not been published in the open literature.

While the International Centre for Diffraction Data (ICDD) has collected raw powder diffraction data for many years, submitted both by Grant-in-Aid recipients and private contributors, in the 2008 release of Powder Diffraction File PDF-4 products the ICDD began publishing raw data as part of both new and legacy PDF entries. The powder diffraction data used here for the solution of the crystal structure of trandolapril were part of set of high-quality pharmaceutical patterns submitted to the PDF by Martin Vickers of the Department of Chemistry at the University College London (UCL). This work illustrates one of the advantages of including raw data in the PDF, the potential for collaborative work within the powder diffraction community to solve new structures. Raw powder diffraction data also provide significantly improved illustration of materials with anisotropic broadening features or poor crystallinity such as clays, polymers, and amorphous materials.

II. EXPERIMENTAL

Laboratory powder X-ray diffraction (PXRD) data were obtained at the UCL using a Stoe StadiP diffractometer in the transmission mode. The diffractometer was equipped with a copper anode operated at 40 kV and 30 mA, and an incident beam germanium monochromator ($\lambda = 1.540\,59$ Å). The sample was mounted in a 0.6 mm diameter glass capillary and using a 6° linear position-sensitive detector, data were

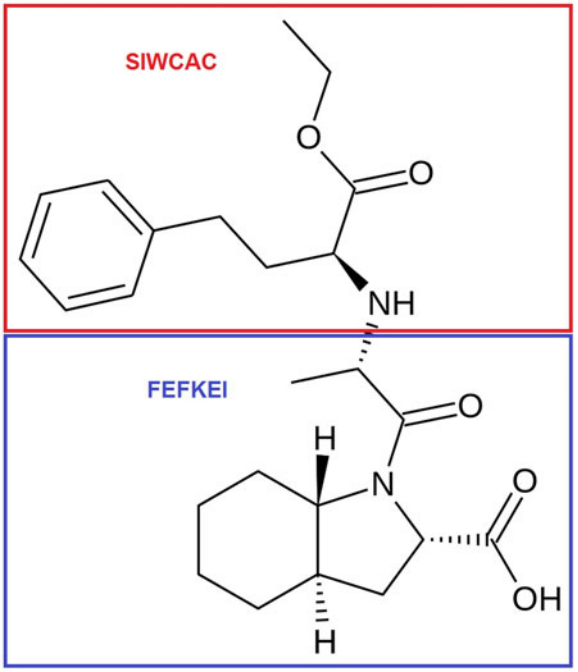

Figure 1. (Color online) The 2D molecular structure of trandolapril, illustrating the fragments of the molecule prepared from edited portions of the CSD entries SIWCAC and FEFKEI.

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collected between 2 and 40°2θ in 0.2° steps, and re-binned to give a data-step of 0.02°. The raw data were published online (Vickers, 2008) and in the PDF (ICDD, 2013) as part of PDF entry 00-060-1211.

Pattern indexing with DICVOL06 (Boultif and Louer, 2004) suggested an orthorhombic unit cell with lattice parameters $a = 19.7145$, $b = 15.0499$, $c = 7.6534$ Å, and a cell volume of 2270.8 Å^3 ($M_{20} = 33.1$, $F_{20} = 93.9$), in strong agreement with the initial assessment made at the UCL (Vickers, 2008) and tabulated in the PDF entry. Space-group determination with ChekCell (Laugier and Bochu, 2000) suggested space group $P2_12_12_1$ as the most plausible option (space group $Pmn2_1$ was also identified based on the observed reflections, but is incompatible with chiral molecules).

A trandolapril molecule was created using fragments of the Cambridge Structural Database (CSD, Allen, 2002) entries SIWCAC (Hausin and Codding, 1991) and FEFKEI (Bojarska *et al*., 2012), as illustrated in Figure 1. The molecule was prepared from the fragments using the molecular modelling software Avogadro (Hanwell *et al*., 2012). The molecule was converted to a Fenske–Hall *Z*-matrix with Open Babel (O'Boyle *et al*., 2011) and used to solve the structure with FOX (Favre-Nicolin and Černý, 2002), using 24 sets of parallel tempering with 2×10^6 trials set^{-1}. These sets yielded two solutions with cost functions of approximately 20 000 that were significantly lower than the other sets.

Initial refinement was performed using the Le Bail method with the program FullProf (Rodriguez-Carvajal, 2001) in order to determine the profile parameters, given the absence of an initial instrumental parameter file. The final profile parameters determined with FullProf were converted to their GSAS equivalents (Kaduk and Reid, 2011) for the Rietveld refinement.

Rietveld refinement of the crystal structure was performed with the GSAS/EXPGUI program (Toby, 2001; Larson and Von Dreele, 2004). Restraints on the bonds, angles, and planar restraints on the phenyl ring were applied using values determined by the Mogul 1.7 module of the CSD (Bruno *et al*., 2004). The background was refined using a Chebyshev polynomial with 14 terms. The positions of the C, N, and O atoms were refined, while the positions of the H atoms remained fixed but were periodically optimized using Avogadro. An overall isotropic displacement parameter was refined for the C, N, and O atoms, with the H atoms constrained to 1.3 times this value. A fourth-order spherical harmonic correction (Von Dreele, 1997) was used to model preferred orientation, which yielded a small texture index (1.023).

The crystal data, data collection, and refinement details are summarized in Table I.

A density functional geometry optimization (using fixed experimental unit cell) was carried out using CRYSTAL14 (Dovesi *et al*., 2014). The basis sets for the H, C, N, and O

TABLE I. The crystal data, data collection, and refinement parameters obtained for trandolapril.

Crystal data, data collection and refinement parameters	
Formula, Z	$C_{24}H_{34}N_2O_5$, $Z = 4$
Molecular mass (M_r)	430.545 g mol^{-1}
Symmetry, space group	Orthorhombic, $P2_12_12_1$
Unit-cell parameters	$a = 19.7685(4)$, $b = 15.0697(4)$, $c = 7.6704(2)$ Å
Volume	2285.0 (1) Å^3
Density (ρ_{calc})	1.251 g cm^{-3}
Diffractometer	Stoe StadiP (40 kV, 30 mA), germanium monochromator
Specimen mounting	0.6 mm capillary
Collection mode	Transmission
Anode, wavelength	Cu$K\alpha$1, $\lambda = 1.540\,59$ Å
Collection range, step size	2°–40° (2θ), 0.02° step^{-1}
Number of data points	1900
Distance restraints	33 (weight factor 25)
Angle restraints	44 (weight factor 25)
Planar restraints	1 (weight factor 50)
Background correction	14-term Chebyshev polynomial
Number of refined parameters	121
R_p	0.0184
R_{wp}	0.0236
R_{exp}	0.0157
χ^2	2.75

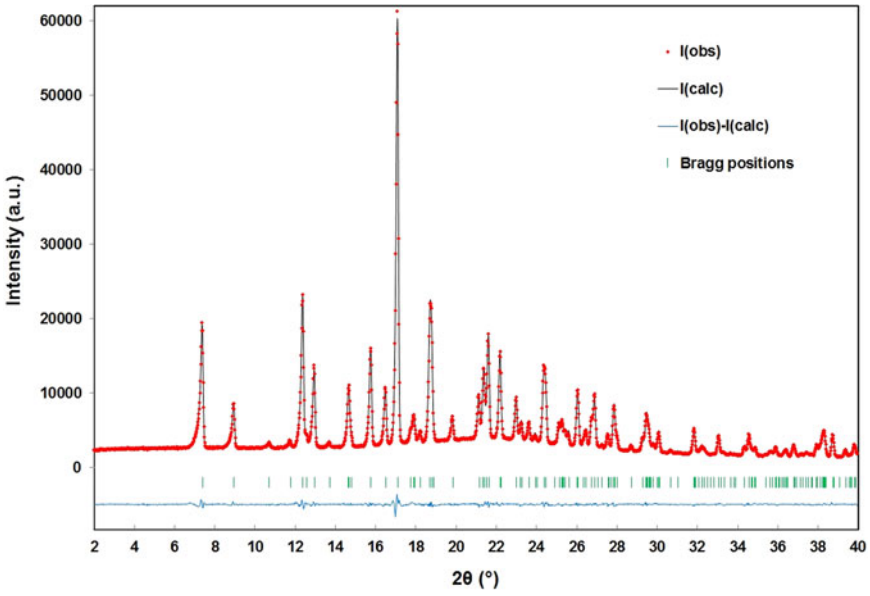

Figure 2. (Color online) A plot illustrating the final Rietveld refinement of trandolapril obtained with GSAS.

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atoms were those of Gatti *et al*. (1994). The calculation was run on eight 2.1 GHz Xeon cores (each with 6 Gb RAM) of a 304-core Dell Linux cluster at the Illinois Institute of Technology (IIT), used eight *k*-points and the B3LYP functional, and took approximately 7 days.

III. RESULTS AND DISCUSSION

The final Rietveld refinement obtained for trandolapril is illustrated in Figure 2, while the refined atomic coordinates and density functional theory (DFT)-optimized coordinates are presented in Tables II and III, respectively. The atomic labelling used for both models is illustrated in Figure 3. The root-mean-square (RMS) difference between the Rietveld and DFT coordinates for the non-hydrogen atoms is 0.332 Å, which is towards the upper end of the range expected for correct powder structures from laboratory PXRD data (Van de Streek and Neumann, 2014). The DFT-optimized and Rietveld refined structures are overlaid for comparison in Figure 4. The largest source of discrepancy in the heavy atoms relates to atoms C15, C18, and C19, which suggest different configurations of the octahydroindole ring, with the two molecules being diastereomers. The H53 (C18) and H56 (C20) atoms exhibit a *syn* configuration in the DFT-calculated molecule and an *anti*-configuration in the Rietveld refined molecule. To confirm the refinement results were consistent independent of the starting model, separate Rietveld refinements were performed starting with both the model obtained from FOX and the DFT solution. The Rietveld refinements obtained from both starting models yielded identical results.

The discrepancy between the DFT and Rietveld results may be due to the relatively low amount of powder data, with an upper 2θ limit of 40°. The pattern contains 144 reflections, and after accounting for reflection overlap (Altomare *et al.*, 1995), the effective number of reflections varies between 123.8 (optimistic estimate) and 80.5 (pessimistic estimate). Using either estimate, the model is significantly underdetermined, emphasizing the importance of the restraints in the refinement and the use of DFT modelling for comparison. Given the low observation-to-parameter ratio, it is possible that the DFT model is more accurate than the Rietveld refined model. However, it has been observed by crystal energy landscape calculations (Price, 2008, 2009) that many thermodynamically plausible structures can fall within a narrow energy band of possible polymorphs (a few kJ mol^{-1}), including numerous structures, which are not observed experimentally. Different plausible structures are a trade-off between factors, including hydrogen bonding and close packing. Observed polymorphs are often metastable local energy minima that do not necessarily correspond to the most thermodynamically stable structure, due to kinetic barriers associated with crystal nucleation or growth.

The Rietveld refined structure is illustrated in Figure 5. Visually, the Rietveld fit looks excellent (Figure 2) with slight residuals in the difference plot due to the strong reflection asymmetry observed at low angles. Examination of the Rietveld refined structure with Mogul yields three angles which are unusual (*z*-scores greater than 3) including two angles through atom C18 (C15–C18–C19 and C15–C18–C20 with *z*-scores of 4.04 and 3.03, respectively). One angle is

TABLE II. The refined crystal structure of trandolapril with lattice parameters $a = 19.7685(4)$, $b = 15.0697(4)$, and $c = 7.6704(2)$ Å.

Atom	*x/a*	*y/b*	*z/c*	U_{iso} (Å^2)
C1	0.2159(5)	0.6687(6)	0.5952(15)	0.0335(23)
C2	0.1463(4)	0.7061(7)	0.5618(18)	0.0335(23)
O3	0.1344(4)	0.7727(7)	0.4797(14)	0.0335(23)
O4	0.0991(5)	0.6628(7)	0.6459(15)	0.0335(23)
C5	0.0294(6)	0.6934(9)	0.6149(19)	0.0335(23)
C6	−0.0161(7)	0.6372(12)	0.7185(19)	0.0335(23)
C7	0.2433(9)	0.7066(8)	0.7658(15)	0.0335(23)
C8	0.2508(9)	0.8059(8)	0.7654(15)	0.0335(23)
C9	0.2750(6)	0.8460(8)	0.9358(14)	0.0335(23)
C10	0.2367(6)	0.8365(9)	1.0859(18)	0.0335(23)
C11	0.2524(8)	0.8839(11)	1.2357(12)	0.0335(23)
C12	0.3025(8)	0.9471(10)	1.2324(14)	0.0335(23)
C13	0.3388(7)	0.9606(8)	1.0812(18)	0.0335(23)
C14	0.3253(7)	0.9102(10)	0.9347(13)	0.0335(23)
C15	0.5608(5)	0.5398(9)	0.8908(19)	0.0335(23)
C16	0.5621(6)	0.6197(11)	1.0143(13)	0.0335(23)
C17	0.5359(7)	0.7042(8)	0.9295(18)	0.0335(23)
C18	0.4914(5)	0.5309(6)	0.8081(14)	0.0335(23)
C19	0.4706(6)	0.4611(7)	0.6756(18)	0.0335(23)
C20	0.4740(4)	0.6152(6)	0.7136(11)	0.0335(23)
C21	0.4687(6)	0.6919(7)	0.8381(17)	0.0335(23)
C22	0.4021(4)	0.4974(6)	0.6079(12)	0.0335(23)
N23	0.4103(4)	0.5944(6)	0.6236(12)	0.0335(23)
C24	0.3738(6)	0.6527(5)	0.5277(16)	0.0335(23)
C25	0.3138(4)	0.6186(5)	0.4238(11)	0.0335(23)
C26	0.3469(10)	0.4535(5)	0.7190(25)	0.0335(23)
O27	0.3171(5)	0.5069(6)	0.8256(17)	0.0335(23)
N28	0.2561(6)	0.6795(8)	0.4361(14)	0.0335(23)
O29	0.3324(6)	0.3748(6)	0.7099(16)	0.0335(23)
O30	0.3844(5)	0.7324(5)	0.5327(14)	0.0335(23)
C31	0.3358(7)	0.6113(10)	0.2352(15)	0.0335(23)
H32	0.216 82	0.598 37	0.624 99	0.0436(30)
H33	0.016 62	0.686 28	0.475 91	0.0436(30)
H34	0.025 72	0.761 46	0.645 16	0.0436(30)
H35	−0.010 58	0.570 61	0.681 01	0.0436(30)
H36	−0.066 54	0.659 93	0.698 13	0.0436(30)
H37	−0.002 23	0.646 37	0.852 11	0.0436(30)
H38	0.291 66	0.676 76	0.795 82	0.0436(30)
H39	0.207 64	0.691 36	0.870 65	0.0436(30)
H40	0.204 18	0.834 28	0.728 92	0.0436(30)
H41	0.291 05	0.818 62	0.671 55	0.0436(30)
H42	0.198 25	0.7905	1.085 36	0.0436(30)
H43	0.224 84	0.872 42	1.346 79	0.0436(30)
H44	0.3123	0.983 85	1.342 53	0.0436(30)
H45	0.3759	1.009 11	1.078 49	0.0436(30)
H46	0.3544	0.919 93	0.823 28	0.0436(30)
H47	0.598 36	0.5495	0.797 02	0.0436(30)
H48	0.572 05	0.481 96	0.969 45	0.0436(30)
H49	0.611 12	0.631 44	1.064 86	0.0436(30)
H50	0.526 43	0.607 43	1.122 23	0.0436(30)
H51	0.532 55	0.757 07	1.021 48	0.0436(30)
H52	0.573 14	0.721 41	0.828 24	0.0436(30)
H53	0.466 53	0.510 93	0.928 62	0.0436(30)
H54	0.5082	0.458 08	0.574 33	0.0436(30)
H55	0.469 61	0.395 58	0.729 35	0.0436(30)
H56	0.511 64	0.635 19	0.624 31	0.0436(30)
H57	0.430 64	0.681 03	0.933 93	0.0436(30)
H58	0.455 75	0.751 95	0.767 13	0.0436(30)
H59	0.389 58	0.480 48	0.479 85	0.0436(30)
H60	0.300 14	0.553 77	0.470 57	0.0436(30)
H61	0.329 68	0.567 99	0.826 91	0.0436(30)
H62	0.223 95	0.664 11	0.335 51	0.0436(30)
H63	0.349 11	0.676 91	0.1869	0.0436(30)
H64	0.293 99	0.587 63	0.156 16	0.0436(30)
H65	0.377 59	0.568 44	0.219 84	0.0436(30)

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TABLE III. The DFT-optimized crystal structure of trandolapril calculated with fixed lattice parameters $a = 19.7695$, $b = 15.0705$, and $c = 7.6706$ Å.

Atom	*x/a*	*y/b*	*z/c*
C1	0.205 41	0.665 98	0.621 76
C2	0.135 94	0.705 07	0.581 08
O3	0.125 87	0.768 93	0.487 56
O4	0.085 98	0.660 89	0.663 37
C5	0.018 23	0.693 22	0.624 86
C6	−0.032 98	0.644 30	0.734 32
C7	0.232 55	0.707 00	0.793 11
C8	0.246 24	0.806 86	0.778 63
C9	0.268 61	0.852 11	0.945 07
C10	0.240 26	0.831 26	1.107 52
C11	0.257 62	0.878 72	1.257 25
C12	0.303 50	0.948 78	1.246 50
C13	0.332 32	0.970 36	1.085 86
C14	0.315 52	0.921 80	0.937 16
C15	0.528 27	0.524 60	0.918 96
C16	0.561 80	0.599 95	1.024 84
C17	0.544 59	0.692 55	0.950 62
C18	0.522 53	0.549 94	0.726 18
C19	0.488 84	0.479 57	0.610 41
C20	0.479 44	0.634 63	0.698 72
C21	0.474 76	0.692 24	0.863 48
C22	0.413 57	0.506 37	0.594 61
N23	0.412 81	0.602 05	0.633 33
C24	0.369 88	0.662 41	0.552 72
C25	0.307 74	0.625 20	0.454 72
C26	0.367 54	0.453 67	0.716 91
O27	0.341 94	0.498 59	0.853 22
N28	0.249 39	0.682 86	0.472 60
O29	0.354 30	0.376 00	0.692 74
O30	0.382 31	0.741 98	0.557 27
C31	0.327 50	0.619 15	0.260 73
H32	0.197 62	0.594 41	0.644 38
H33	0.008 94	0.683 43	0.485 90
H34	0.016 98	0.764 51	0.650 27
H35	−0.027 79	0.572 64	0.718 97
H36	−0.083 58	0.662 83	0.690 47
H37	−0.028 46	0.660 58	0.872 36
H38	0.279 41	0.672 48	0.828 86
H39	0.196 22	0.691 65	0.896 55
H40	0.200 05	0.839 79	0.732 39
H41	0.283 96	0.817 30	0.676 61
H42	0.203 74	0.777 80	1.118 51
H43	0.234 97	0.860 35	1.380 63
H44	0.316 11	0.986 42	1.362 46
H45	0.367 21	1.025 87	1.076 07
H46	0.337 30	0.939 46	0.811 83
H47	0.557 69	0.463 36	0.930 75
H48	0.477 86	0.509 49	0.971 36
H49	0.545 64	0.595 33	1.161 42
H50	0.616 77	0.591 40	1.024 32
H51	0.547 76	0.742 76	1.052 74
H52	0.582 12	0.711 88	0.852 70
H53	0.573 62	0.563 28	0.678 05
H54	0.511 00	0.481 08	0.480 43
H55	0.494 45	0.411 96	0.659 75
H56	0.502 51	0.674 52	0.596 14
H57	0.436 65	0.665 28	0.953 48
H58	0.457 53	0.758 75	0.828 32
H59	0.395 63	0.491 25	0.463 31
H60	0.296 35	0.557 82	0.502 65
H61	0.358 25	0.559 71	0.842 70
H62	0.221 21	0.679 85	0.362 11
H63	0.336 57	0.685 99	0.210 57
H64	0.286 40	0.588 90	0.186 19
H65	0.373 08	0.579 14	0.241 26

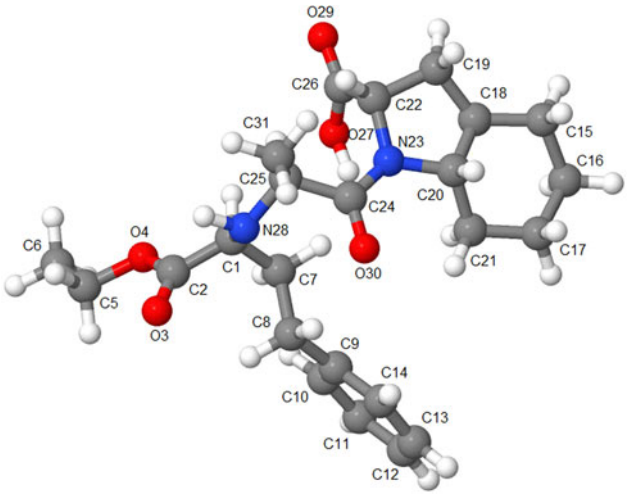

Figure 3. (Color online) The molecular structure of trandolapril, illustrating the atomic labelling used in the tables.

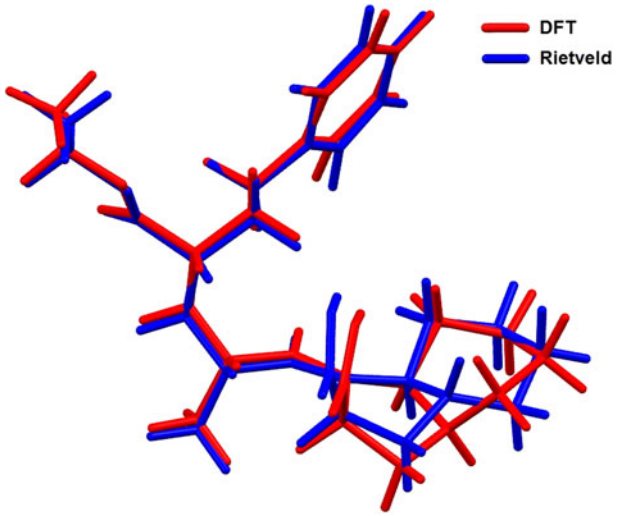

Figure 4. (Color online) Molecular overlay of the DFT (red) and Rietveld (blue) refined crystal structures of trandolapril.

highlighted in the DFT structure (C20–N23–C24, *z*-score of 3.88).

The DFT results suggest minimal hydrogen bonding, tabulated in Table IV, with one prominent intermolecular bond, N28–H62• • • O29. The hydrogen bonds through H41 and H61 are both intramolecular. It is possible that the carboxyl group (O27) is deprotonated, yielding an additional hydrogen at N28. Zwitterionic behaviour is well documented with amino acids (Sarkar and Nahar, 2007; Tilborg *et al.*, 2014) and observed in both pharmaceuticals and drug delivery moieties (Jin et al., 2014; Kostic *et al.*, 2014). Deprotonating the carboxyl group (removing H61) and adding a second H atom at N28 yields a refinement, which quickly converges with a comparable fit to the tabulated data (reduced χ^2 of 2.71).

In order to test whether more complete data would change the refined structure, a second data set was collected on the same diffractometer with an expanded 2θ range of 5°–60° using an 18° Dectris® Mythen 1 K detector (data not shown). The structure was refined using the same strategy

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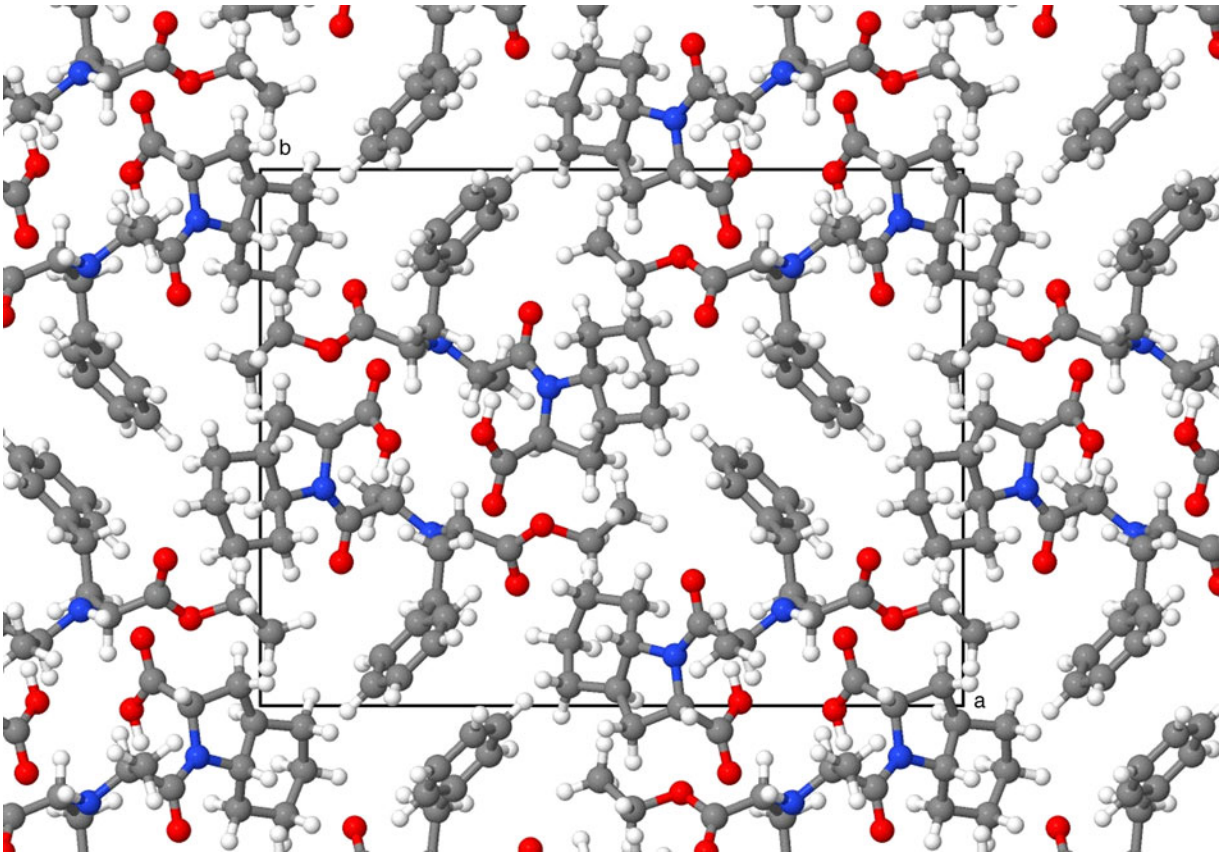

Figure 5. (Color online) The crystal structure of trandolapril, viewed along to the *c*-axis, with the C, H, N, and O atoms coloured in grey, white, blue, and red, respectively.

TABLE IV. Hydrogen bonds observed in the trandolapril structure and their parameters as determined by the DFT modelling.

D–H• • • A	D–H (Å)	H• • • A (Å)	D• • • A (Å)	D–H• • • A (°)	Overlap (*e*)
O27–H61• • • N23	0.979	2.038	2.691	122.3	0.040
N28–H62• • • O29	1.015	2.151	3.098	154.5	0.027
C8–H41• • • O30	1.092	2.430	3.328	138.5	0.015

and restraints as the initial refinement, yielding a final R_{wp} value of 0.0328. The RMS difference between the coordinates of the non-hydrogen atoms for the two experimental refinements was <0.05 Å, suggesting only marginal change in the experimental structure with more complete data. Crystallographic information files for the Rietveld refinements of both experimental data sets and the DFT-optimized structure are included in the supplementary material.

SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found at http://dx.doi.org/10.1017/S0885715616000294.

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