Tetrahedron Vol 47, No. 24, pp. 3947-3958, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00
Pergamon Press plc

SYNTHESIS, PROPERTIES AND CRYSTAL STRUCTURE OF THE TRIPEPTIDE BOC-L-PROLYL-L-PROPARGYLGLYCYL-GLYCINE METHYLESTER

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(*Received in Germany* 4 *January* 1991)

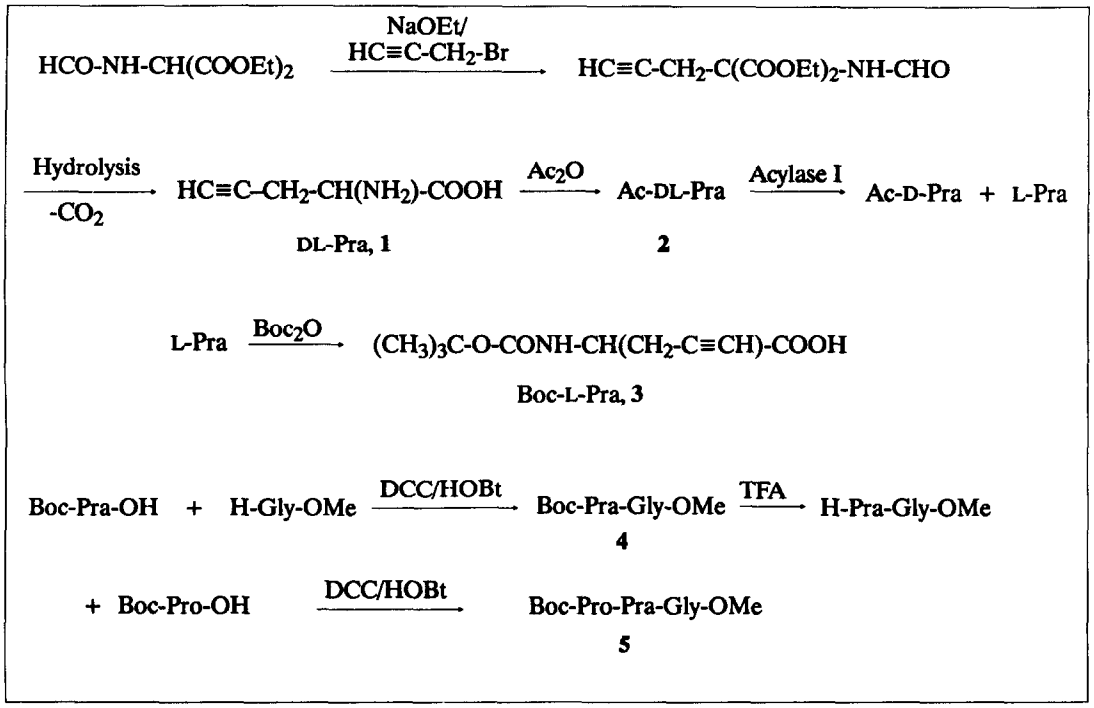
Abstract. Propargylglycine, as a powerful inhibitor of microbial growth, was built into a protected tripeptide with the sequence Pro-Pra-Gly. The peptide was employed to study its effects on the activity of prolyl 4-hydroxylase and the collagen biosynthesis. The Boc-protected tripeptide methylester was identified by mass spectrometry and NMR spectroscopy and its crystal structure was established by X-ray diffraction analysis.

Before L-propargylglycine (Pra), L-**1**, was revealed to be a natural occurring antimetabolite of methionine and leucine,[1] its racemic form was synthesized as a powerful inhibitor of bacteria and yeast.[2,3] In search of certain enzyme inactivators, L-propargylglycine was incorporated into dipeptides, resulting in strong suicidal substrates for microorganisms.[4]

To substantiate a hypothesis regarding the role of prolyl 4-hydroxylase (E.C. 1.14.11.2) in collagen biosynthesis,[5] and to design a possible suicidal substrate for this enzyme, we have synthesized the protected tripeptide Boc-L-Pro-L-Pra-Gly-OMe, **5**. The constitution was determined by field desorption mass spectrometry, proton and ^{13}C NMR spectroscopy, and the crystal structure was established by X-ray diffraction analysis.

It has been demonstrated[6] that in human skin fibroblast cultures the collagen biosynthesis is restricted by the tripeptide; as it seems, this is not due to specific inhibition of prolyl 4-hydroxylase – as it has been postulated – but on a regulatory level.

Synthesis: DL-Propargylglycine (**1**) was obtained by the reaction of propargyl bromide with diethyl formamidomalonate followed by hydrolysis and decarboxylation of the product according to Gershon et al..[2] Resolution of the N-acetyl derivative **2** with porcine kidney acylase I gave L-Pra which, after protecting with the Boc group,[7] was coupled to Gly-OMe by the DCC/HOBt method.[8] The amino group of the resulting dipeptide methyl ester **4** was deblocked by trifluoroacetic acid and then coupled to Boc-L-Pro to obtain the title tripeptide **5**. Single-crystals were produced by slow crystallization from ethyl acetate/diethyl ether. Scheme 1 shows the synthesis. Table 1 summarizes some of the properties of the peptides .



Scheme 1. Synthesis of Boc-Pro-Pra-Gly-OMe

Table 1. Determined FD MS and Physical Data of the Peptides

	TLC,† R_f in A	TLC,† R_f in B	m.p. [°C]	$[\alpha]_D^{20}$ (c = 1, MeOH)	solubility H_2O, 25°C [g/100 mL]
Boc-Pra-Gly-OMe, **4** m/z 284, $C_{13}H_{20}N_2O_5$ (M) requires m/z 284.31	0.81	0.47	94-5 (cyclo-hexane)	-11.2°	1.0
Boc-Pro-Pra-Gly-OMe, **5** m/z 382, $C_{18}H_{27}N_3O_6$ (M + H) requires m/z 382.44	0.72	0.12	123-4 (AcOEt/ Et_2O)	-80.3°	2.2

† see Experimental

Table 2. NMR Data for the Peptides: δ [ppm], Multiplicity and J_{HH} [Hz] in Parentheses

		Boc-Pra-Gly-OMe, 4		Boc-Pro-Pra-Gly-OMe, 5	
		^1H (DMSO-d_6	^{13}C ($CDCl_3$)	^1H ($CDCl_3$)	^{13}C ($CDCl_3$)
Boc	CH_3	1.38 (s)	28.2	1.40 (s)	28.1
	C–O	-	80.7	-	80.6
	C=O	-	155.3	-	155.3
Pro	α-CH	-	-	4.24 (t, 5.9)	60.7
	β-CH_2	-	-	1.89 (m, 5.9)	29.6
	γ-CH_2	-	-	2.09 (m, 5.9)	24.0
	δ-CH_2	-	-	3.41 (t, 5.9)	47.0
	C=O	-	-	-	172.3
Pra	NH	6.96 (d, 8.5)	-	7.00 (br)	-
	α-CH	4.13 (dt, 5.6/8.5)	52.4	4.61 (dt, 5.9/8.5)	50.9
	β-CH_2	3.32 (br)	22.3	2.71 (dt, 2.6/5.9)	21.6
	–C≡	-	79.2	-	79.0
	≡CH	2.81 (t, 2.5)	71.7	2.01 (t, 2.6)	71.2
	C=O	-	170.4	-	170.0
Gly	NH	8.32 (t, 5.9)	-	7.35 (br)	-
	CH_2	3.83 (d, 5.9)	41.2	3.97 (d, 5.6)	41.1
	C=O	-	169.9	-	169.5
OMe	CH_3	3.61 (s)	52.0	3.67 (s)	51.9

Structure: The cell unit consists of four pairs of two crystallographically independent molecules A and B with antiparallel orientation. Fig. 1 shows the SCHAKAL[9] drawings of the two types of peptide molecules.

Each couple of molecules A and B is hydrogen bonded by $(Gly)_AN-H\cdots O=C(Pro)_B$ (= 1.76 Å) and $(Pro)_AC=O\cdots H-N(Gly)_B$ (= 1.90 Å). This alternately stacking of A and B forms a ribbon of an antiparallel β sheet infinitely extended across the crystal which is in conformity with studies on other tripeptides of the sequence Boc-Pro-X-Gly-Y.[10, 11] The packing scheme of this antiparallel β sheet is shown in Fig. 2.

The oxygen atom of each Pra residue [O(7) and O(27), large circles in Fig. 2] is hydrogen bonded to the amide function of the appropriate Pra residue in the adjacent unit [N(22)–H(220) and N(2)–H(2) respectively, small circles in Fig. 2; bond O(7)···H(220): 2.31 Å; bond O(27)···H(2): 1.91 Å]; this bonding - combined with the hydrogen bonds between the A and B pairs - leads to the infinite β sheet.

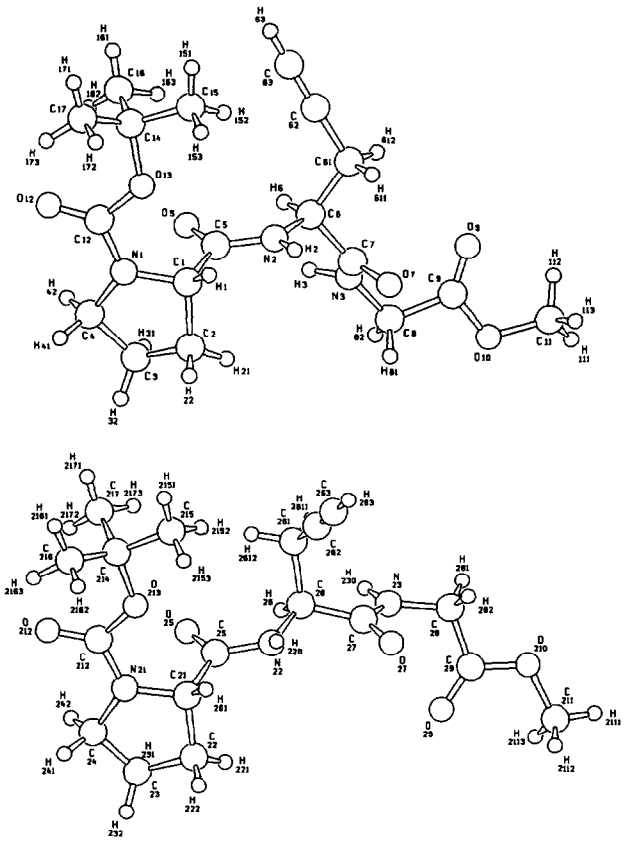


Figure 1. SCHAKAL drawings of Boc-Pro-Pra-Gly-OMe

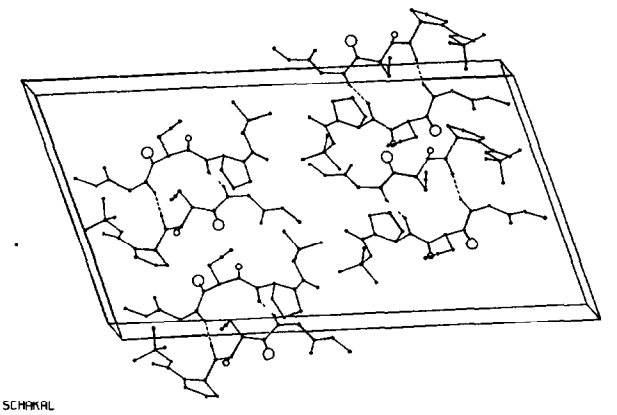


Figure 2. SCHAKAL drawing of the Boc-Pro-Pra-Gly-OMe crystal structure, viewed along the b axis (hydrogen bonds as dotted lines)

It is reported that several oligopeptides form infinitely extended antiparallel β sheets in the crystals,[10, 12-19] and this formation is obviously one of the most favorable structure patterns for linear peptide crystals.[10, 12, 13]

The conformation of A and B is essentially the same in the region of Boc-Pro-CO-NH-. There is, however, a significant difference in the orientation of the propargyl group of A and B, indicated by the torsion angles C(7)−C(6)−C(61)−C(62) = 172.98° and C(27)−C(26)−C(261)−C(262) = -63.45° respectively. The Boc-Pro amide group is not planar; the nitrogen atoms N(1) and N(21) deviate from the plane of the corresponding triangle C(1), C(4), C(12) and C(21), C(24), C(212) by 0.15 and 0.11 Å, respectively. Similar values are reported for many X-Pro peptide bonds.[11, 19]

EXPERIMENTAL

General Methods and Materials: Acylase I (16.6 U/mg) was purchased from Serva Feinbiochemica, Heidelberg, Germany. Thin layer chromatography (silica gel plates, Merck, Darmstadt, Germany) was carried out using different mobile phases, of which the following gave best results:
A: n-butanol / acetic acid / water, 4/1/1 (v/v/v)
B: diethyl ether / petroleum ether, 8/1 (v/v).

Melting points were obtained on a Büchi SMP 20 melting point apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer Modell 241 polarimeter. Amino acid analysis was achieved with a Biotronik System LC 6000 E and Integrator System 1. ^1H and ^{13}C NMR spectra were recorded with a Bruker WH 90 spectrometer. Field Desorption MS (50°C) was performed with a Varian Mat 711 A mass spectrometer.

L-Propargylglycine (L-1): The racemic amino acid was prepared according to Gershon et al.[2] and the L-enantiomer was obtained by enzymatic resolution of N-acetyl-DL-propargylglycine (2) with acylase I, as described by Scannell et al.[1]

Boc-L-Pra-OH (3): L-Propargylglycine (1) was derivatized with *tert*-butyloxycarbonyl azide by the method of Schnabel,[7] to give 3 as an oily resin: $[\alpha]_D^{25} = +15.7°$ (c = 0.6, MeOH); ^1H NMR (DMSO-d_6): δ 1.37 (s, 9H), 2.84 (t, 1H, J = 2.6), 3.33 (br, under HDO), 4.02 (m, 1H), 7.04 (d, 1H, J = 8.2).

Boc-Pra-Gly-OMe (4): To a solution of 5.33 g 3 (25 mmol) in 25 mL CH_2Cl_2 was added 3.38 g 1-hydroxybenzotriazole, HOBt, (25 mmol, in 50 mL slightly warm THF). After chilling and adding 25 mL 1 M dicyclohexylcarbodiimide, DCC, (in CH_2Cl_2), the mixture was allowed to stand for 30 min at 0°C and was then filtered into a suspension of 3.14 g glycine methylester hydrochloride (25 mmol) in 25 mL CH_2Cl_2. 5.5 mL N-methylmorpholine (50 mmol) was added, followed by stirring for 20 h at room temperature. After evaporating at 20°C, the residue was triturated with 125 mL ethyl acetate and filtered. The filtrate was washed with saturated aqueous citric acid (4 times), saturated $NaCl_{aq}$ (once), saturated aqueous $KHCO_3$ (4 times), and finally with sat. $NaCl_{aq}$ (twice). The organic layer was dried over $MgSO_4$ and evaporated to give

6.1 g crude peptide which was recrystallized from 200 mL cyclohexane; 4.87 g = 69 %: m.p., TLC, $[\alpha]_D^{20}$, FD MS and solubility see Table 1; ^1H and ^{13}C NMR see Table 2; amino acid analysis Pra/Gly = 0.85 / 1.00.

Boc-Pro-Pra-Gly-OMe (**5**): 11.4 g **4** (40 mmol) was deblocked by treating with 40 mL trifluoroacetic acid (50% solution in CH_2Cl_2) for 30 min. at room temperature, followed by thoroughly washing with ether. Peptide synthesis and work-up was performed in the way described for **4**, using 10.3 g Boc-Pro-OH (48 mmol), 6.5 g HOBt (48 mmol), 48 mL 1 M DCC, and 10 mL N-methylmorpholine (≈ 90 mmol). The crude resinoid peptide was extracted with four portions of boiling cyclohexane (100 mL each) in order to remove dicyclohexyl urea and the soluble dipeptide. The residue was dissolved in 50 mL ethyl acetate, treated with Norite A and filtered. The filtrate was evaporated to half of its volume, the tripeptide **5** precipitated by adding 50 mL of ether; 3.00 g = 20 %: m.p., TLC, $[\alpha]_D^{20}$, FD MS and solubility see Table 1; ^1H and ^{13}C NMR see Table 2; amino acid analysis Pro/Pra/Gly = 0.96 / 0.94 / 1.00.

Crystallographic data and structure determination:[20] A single crystal with the approximate dimensions 0.1 x 0.5 x 0.5 mm was chosen for the X-ray investigations. On the basis of Buerger precession photographs the monoclinic space groups *C2/m*, *Cm* or *C2* have been established, of which the latter was confirmed by further calculations. The lattice parameters were determined accurately by using an automated single-crystal diffractometer CAD4 (ENRAF-NONIUS, Delft), and 25 precisely centered high-angle reflections. Crystal data and data collection details are given in Table 3. For the structure determination 8098 intensities were measured with Cu K_α-radiation in the range θ = 3 - 65° at room temperature. After averaging over the equivalent reflections of the reciprocal lattice, there remained 6526 reflections with intensities $I > 3 \cdot \sigma(I)$. Intensity data were corrected for Lorentz and polarization effects, absorption[21] and extinction.[22]

Table 3. Crystal Data and Data Collection Summary for Boc-Pro-Pra-Gly-OMe

Molecular formula	$C_{18}H_{27}N_3O_6$	ρ (calcd), g·cm^{-3}	1.188
M_r	381.43	μ (Cu K_α), cm^{-1}	6.793
F(000)	1632	$2\theta_{max}$, deg	65
crystal class	monoclinic	scan method	ω/θ scan
space group	*C2*	scan range, $\Delta\theta$, deg	$0.95 + 0.35 \tan\theta$
lattice parameters:		scan speed	variable
a, Å	16.781 (1)	reflexions observed	6526
b, Å	8.746 (1)	weighting scheme	$1/\sigma^2$
c, Å	30.493 (1)	parameters refined	488
β, deg	107.58 (1)	value of R	0.076
cell vol, Å^3	4266.5	value of wR	0.074
formula units, Z	8		

Solution and refinement of the structure: The structure was solved by direct methods. The quantity minimized during refinement was $\sum w (|F_o| - |F_c|)^2$, where $w = \frac{1}{\sigma^2 (F_o)}$.

All calculations were performed on a DEC MicroVAX 3500 using *MOLEN*.[23, 24]

Table 4. Positional Parameters and Their Estimated Standard Deviations

Atom	x	y	z	B_{eq} [Å^2]	Atom	x	y	z	B_{eq} [Å^2]
Molecule A					Molecule B				
O(5)	0.3893(2)	0.8102(5)	0.6848(1)	5.18(8)	O(25)	0.5606(2)	0.8105(5)	0.8156(1)	5.65(9)
O(7)	0.2855(2)	0.6005(5)	0.7997(1)	6.17(9)	O(27)	0.6242(2)	1.1189(5)	0.6993(1)	6.04(9)
O(9)	0.3544(3)	0.7632(6)	0.8983(1)	8.4(1)	O(29)	0.6092(3)	0.8655(5)	0.6146(1)	7.0(1)
O(10)	0.4116(3)	0.5540(6)	0.9322(1)	7.8(1)	O(210)	0.5640(2)	1.0319(5)	0.5567(1)	5.73(9)
O(12)	0.3462(2)	0.8187(6)	0.5541(1)	6.7(1)	O(212)	0.6230(3)	0.8156(6)	0.9479(1)	9.6(1)
O(13)	0.2382(2)	0.8100(5)	0.5849(1)	4.85(8)	O(213)	0.6311(2)	1.0248(5)	0.9062(1)	5.73(9)
N(1)	0.3390(2)	0.6407(6)	0.6065(1)	4.5(1)	N(21)	0.6908(3)	0.8120(5)	0.8949(1)	4.5(1)
N(2)	0.2896(2)	0.7176(5)	0.7119(1)	4.15(9)	N(22)	0.6194(2)	0.9833(5)	0.7808(1)	3.94(9)
N(3)	0.4124(2)	0.7049(6)	0.8236(1)	5.0(1)	N(23)	0.5044(2)	1.0065(5)	0.6606(1)	4.27(9)
C(1)	0.3102(3)	0.5988(7)	0.6448(2)	4.3(1)	C(21)	0.7039(3)	0.8748(6)	0.8535(1)	4.0(1)
C(2)	0.3603(4)	0.4526(8)	0.6631(2)	6.4(2)	C(22)	0.7599(3)	0.7559(8)	0.8409(2)	5.9(2)
C(3)	0.4368(5)	0.472(1)	0.6510(3)	11.4(2)	C(23)	0.7486(5)	0.615(1)	0.8659(3)	10.8(3)
C(4)	0.4197(3)	0.5727(8)	0.6100(2)	6.2(2)	C(24)	0.7137(4)	0.6510(8)	0.9021(2)	6.6(2)
C(5)	0.3320(3)	0.7206(6)	0.6817(1)	3.8(1)	C(25)	0.6214(3)	0.8900(6)	0.8154(1)	4.0(1)
C(6)	0.3144(3)	0.8039(7)	0.7546(1)	4.4(1)	C(26)	0.5435(3)	0.9993(6)	0.7426(1)	4.0(1)
C(7)	0.3362(3)	0.6943(7)	0.7944(1)	4.5(1)	C(27)	0.5617(3)	1.0439(6)	0.6994(1)	4.2(1)
C(8)	0.4374(3)	0.6092(8)	0.8641(2)	5.4(1)	C(28)	0.5073(3)	1.0582(7)	0.6160(2)	4.7(1)
C(9)	0.3957(3)	0.6566(8)	0.8994(2)	5.5(1)	C(29)	0.5668(3)	0.9712(7)	0.5973(2)	4.5(1)
C(11)	0.3792(6)	0.586(1)	0.9695(2)	13.1(3)	C(211)	0.6171(4)	0.962(1)	0.5329(2)	7.5(2)
C(12)	0.3122(3)	0.7618(7)	0.5797(2)	4.7(1)	C(212)	0.6451(4)	0.8790(7)	0.9185(2)	6.0(1)
C(14)	0.1978(3)	0.9514(8)	0.5633(2)	5.7(1)	C(214)	0.5870(4)	1.1277(9)	0.9294(2)	6.8(2)
C(15)	0.1224(4)	0.952(1)	0.5810(2)	7.9(2)	C(215)	0.5896(6)	1.276(1)	0.9053(3)	11.2(3)
C(16)	0.2538(4)	1.0810(9)	0.5817(3)	10.2(3)	C(216)	0.6261(6)	1.134(1)	0.9781(2)	11.8(3)
C(17)	0.1730(5)	0.941(1)	0.5133(2)	9.6(2)	C(217)	0.4979(5)	1.075(2)	0.9178(4)	16.7(4)
C(61)	0.2442(4)	0.9050(7)	0.7602(2)	5.9(1)	C(261)	0.4816(3)	1.1142(8)	0.7541(2)	5.1(1)
C(62)	0.2209(4)	1.0333(9)	0.7271(2)	6.9(2)	C(262)	0.5125(3)	1.2732(8)	0.7639(2)	5.5(1)
C(63)	0.2011(5)	1.135(1)	0.7014(2)	8.9(2)	C(263)	0.5338(4)	1.3975(9)	0.7725(2)	7.4(2)

Results : Positional and atomic displacement parameters for the non-hydrogen atoms are shown i Table 4; bond angles, bond distances and torsion angles are given in Tables 5, 6, and 7 respectively. Th anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter B_e defined as:

$$B_{eq} = \frac{4}{3} \cdot \left(B_{11}\, a^2 + B_{22}\, b^2 + B_{33}\, c^2 + B_{12}\, ab \cos\gamma + B_{13}\, ac \cos\beta + B_{23}\, bc \cos\alpha \right)$$

Table 5. Bond Distances [Å]

Molecule A		Molecule B	
O(5)–C(5)	1.223(6)	O(25)–C(25)	1.236(6)
O(7)–C(7)	1.227(7)	O(27)–C(27)	1.237(6)
O(9)–C(9)	1.156(8)	O(29)–C(29)	1.189(7)
O(10)–C(9)	1.308(7)	O(210)–C(29)	1.335(7)
O(10)–C(11)	1.43(2)	O(210)–C(211)	1.445(8)
O(12)–C(12)	1.206(8)	O(212)–C(212)	1.203(9)
O(13)–C(12)	1.364(7)	O(213)–C(212)	1.330(7)
O(13)–C(14)	1.468(7)	O(213)–C(214)	1.474(8)
N(1)–C(1)	1.441(7)	N(21)–C(21)	1.453(6)
N(1)–C(4)	1.453(7)	N(21)–C(24)	1.459(8)
N(1)–C(12)	1.330(7)	N(21)–C(212)	1.336(9)
N(2)–C(5)	1.324(6)	N(22)–C(25)	1.326(6)
N(2)–C(6)	1.452(6)	N(22)–C(26)	1.450(5)
N(3)–C(7)	1.322(5)	N(23)–C(27)	1.322(5)
N(3)–C(8)	1.445(7)	N(23)–C(28)	1.448(6)
C(1)–C(2)	1.540(8)	C(21)–C(22)	1.527(8)
C(1)–C(5)	1.512(7)	C(21)–C(25)	1.521(5)
C(2)–C(3)	1.45(1)	C(22)–C(23)	1.49(1)
C(3)–C(4)	1.49(2)	C(23)–C(24)	1.43(1)
C(6)–C(7)	1.503(7)	C(26)–C(27)	1.491(7)
C(6)–C(61)	1.524(8)	C(26)–C(261)	1.561(8)
C(8)–C(9)	1.511(9)	C(28)–C(29)	1.498(8)
C(14)–C(15)	1.52(1)	C(214)–C(215)	1.50(1)
C(14)–C(16)	1.48(1)	C(214)–C(216)	1.433(8)
C(14)–C(17)	1.457(8)	C(214)–C(217)	1.50(2)
C(61)–C(62)	1.480(9)	C(261)–C(262)	1.483(9)
C(62)–C(63)	1.17(2)	C(262)–C(263)	1.15(1)

Table 6. Bond Angles [°]

Molecule A		Molecule B	
O(5)–C(5)–N(2)	122.4(4)	O(25)–C(25)–N(22)	121.9(4)
O(5)–C(5)–C(1)	121.2(5)	O(25)–C(25)–C(21)	120.5(4)
O(7)–C(7)–N(3)	121.7(5)	O(27)–C(27)–N(23)	121.2(4)
O(7)–C(7)–C(6)	121.6(4)	O(27)–C(27)–C(26)	122.7(4)
O(9)–C(9)–O(10)	124.0(6)	O(29)–C(29)–O(210)	124.6(5)
O(9)–C(9)–C(8)	127.2(6)	O(29)–C(29)–C(28)	127.4(5)
O(10)–C(9)–C(8)	109.0(5)	O(210)–C(29)–C(28)	108.0(4)
O(12)–C(12)–O(13)	125.0(5)	O(212)–C(212)–O(213)	125.9(6)
O(12)–C(12) –N(1)	126.0(5)	O(212)–C(212)–N(21)	123.8(6)
O(13)–C(12)–N(1)	109.0(5)	O(213)–C(212)–N(21)	110.4(5)
O(13)–C(14)–C(15)	99.6(6)	O(213)–C(214)–C(215)	101.5(6)
O(13)–C(14)–C(16)	108.8(4)	O(213)–C(214)–C(216)	112.6(7)
O(13)–C(14)–C(17)	111.5(7)	O(213)–C(214)–C(217)	108.0(7)
N(1)–C(1)–C(2)	102.9(5)	N(21)–C(21)–C(22)	103.2(4)
N(1)–C(1)–C(5)	111.1(4)	N(21)–C(21)–C(25)	110.8(4)
N(1)–C(4)–C(3)	104.2(5)	N(21)–C(24)–C(23)	104.1(6)
N(2)–C(5)–C(1)	116.3(4)	N(22)–C(25)–C(21)	117.4(4)
N(2)–C(6)–C(7)	109.1(5)	N(22)–C(26)–C(27)	111.7(4)
N(2)–C(6)–C(61)	112.4(3)	N(22)–C(26)–C(261)	111.4(4)
N(3)–C(7)–C(6)	116.7(5)	N(23)–C(27)–C(26)	116.0(4)
N(3)–C(8)–C(9)	111.9(5)	N(23)–C(28)–C(29)	114.4(4)
C(1)–N(1)–C(4)	111.7(4)	C(21)–N(21)–C(24)	113.2(4)
C(1)–N(1)–C(12)	124.5(5)	C(21)–N(21)–C(212)	124.5(5)
C(1)–C(2)–C(3)	104.0(6)	C(21)–C(22)–C(23)	104.4(6)
C(2)–C(3)–C(4)	108.7(6)	C(22)–C(23)–C(24)	111.2(7)
C(2)–C(1)–C(5)	109.5(4)	C(22)–C(21)–C(25)	110.7(4)
C(4)–N(1)–C(12)	120.4(5)	C(24)–N(21)–C(212)	120.6(5)
C(5)–N(2)–C(6)	122.9(5)	C(25)–N(22)–C(26)	120.3(4)
C(6)–C(61)–C(62)	114.7(5)	C(26)–C(261)–C(262)	115.7(4)
C(61)–C(62)–C(63)	178.5(9)	C(261)–C(262)–C(263)	176.8(7)
C(7)–N(3)–C(8)	120.5(5)	C(27)–N(23)–C(28)	122.8(4)
C(7)–C(6)–C(61)	106.7(4)	C(27)–C(26)–C(261)	111.0(4)
C(9)–O(10)–C(11)	115.7(7)	C(29)–O(210)–C(211)	116.5(5)
C(12)–O(13)–C(14)	121.4(4)	C(212)–O(213)–C(214)	121.3(5)
C(15)–C(14)–C(16)	111.4(6)	C(215)–C(214)–C(216)	113.8(7)
C(15)–C(14)–C(17)	111.6(5)	C(215)–C(214)–C(217)	108.9(7)
C(16)–C(14)–C(17)	113.2(7)	C(216)–C(214)–C(217)	111.5(8)

Table 7. Torsion Angles [°]

Molecule A		Molecule B	
N(1)–C(1)–C(2)–C(3)	28.7 (6)	N(21)–C(21)–C(22)–C(23)	19.2 (6)
N(1)–C(1)–C(5)–O(5)	-22.9 (7)	N(21)–C(21)–C(25)–O(25)	-23.2 (7)
N(1)–C(1)–C(5)–N(2)	161.5 (4)	N(21)–C(21)–C(25)–N(22)	161.3 (4)
N(2)–C(6)–C(7)–O(7)	-58.2 (6)	N(22)–C(26)–C(27)–O(27)	-28.6 (7)
N(2)–C(6)–C(7)–N(3)	122.3 (5)	N(22)–C(26)–C(27)–N(23)	155.3 (5)
N(2)–C(6)–C(61)–C(62)	-67.7 (7)	N(22)–C(26)–C(261)–C(262)	61.7 (5)
N(3)–C(8)–C(9)–O(9)	-6.9 (9)	N(23)–C(28)–C(29)–O(29)	1.6 (8)
N(3)–C(8)–C(9)–O(10)	171.4 (5)	N(23)–C(28)–C(29)–O(210)	-179.1 (4)
C(1)–N(1)–C(4)–C(3)	5.4 (7)	C(21)–N(21)–C(24)–C(23)	4.6 (7)
C(1)–N(1)–C(12)–O(12)	163.2 (5)	C(21)–N(21)–C(212)–O(212)	167.1 (5)
C(1)–N(1)–C(12)–O(13)	-18.3 (7)	C(21)–N(21)–C(212)–O(213)	-15.4 (7)
C(1)–C(2)–C(3)–C(4)	-26.7 (7)	C(21)–C(22)–C(23)–C(24)	-18.0 (8)
C(2)–C(1)–C(5)–O(5)	90.1 (6)	C(22)–C(21)–C(25)–O(25)	90.7 (6)
C(2)–C(1)–C(5)–N(2)	-85.5 (6)	C(22)–C(21)–C(25)–N(22)	-84.8 (6)
C(2)–C(3)–C(4)–N(1)	14.1 (8)	C(22)–C(23)–C(24)–N(21)	8.8 (8)
C(4)–N(1)–C(1)–C(2)	-21.2 (6)	C(24)–N(21)–C(21)–C(22)	-15.3 (6)
C(4)–N(1)–C(1)–C(5)	95.9 (5)	C(24)–N(21)–C(21)–C(25)	103.3 (5)
C(4)–N(1)–C(12)–O(12)	5.8 (8)	C(24)–N(21)–C(212)–O(212)	3.1 (9)
C(4)–N(1)–C(12)–O(13)	-175.7 (4)	C(24)–N(21)–C(212)–O(213)	-179.4 (5)
C(5)–N(2)–C(6)–C(7)	-116.0 (5)	C(25)–N(22)–C(26)–C(27)	-152.9 (5)
C(5)–N(2)–C(6)–C(61)	126.1 (5)	C(25)–N(22)–C(26)–C(261)	82.3 (6)
C(5)–C(1)–C(2)–C(3)	-89.5 (5)	C(25)–C(21)–C(22)–C(23)	-99.4 (5)
C(6)–N(2)–C(5)–O(5)	-9.1 (8)	C(26)–N(22)–C(25)–O(25)	2.5 (7)
C(6)–N(2)–C(5)–C(1)	166.5 (4)	C(26)–N(22)–C(25)–C(21)	178.0 (4)
C(6)–C(61)–C(62)–C(63)	172.0 (27.1)	C(26)–C(261)–C(262)–C(263)	-159.4 (10.7)
C(61)–C(6)–C(7)–O(7)	63.3 (6)	C(261)–C(26)–C(27)–O(27)	96.4 (6)
C(61)–C(6)–C(7)–N(3)	-116.2 (5)	C(261)–C(26)–C(27)–N(23)	-79.7 (6)
C(7)–N(3)–C(8)–C(9)	-71.6 (7)	C(27)–N(23)–C(28)–C(29)	79.0 (7)
C(7)–C(6)–C(61)–C(62)	173.0 (5)	C(27)–C(26)–C(261)–C(262)	-63.4 (5)
C(8)–N(3)–C(7)–O(7)	-2.5 (8)	C(28)–N(23)–C(27)–O(27)	-4.3 (8)
C(8)–N(3)–C(7)–C(6)	177.0 (5)	C(28)–N(23)–C(27)–C(26)	171.8 (5)
C(11)–O(10)–C(9)–O(9)	-4.3 (9)	C(211)–O(210)–C(29)–O(29)	-0.2 (8)
C(11)–O(10)–C(9)–C(8)	177.3 (6)	C(211)–O(210)–C(29)–C(28)	-179.5 (5)
C(12)–O(13)–C(14)–C(15)	-178.2 (4)	C(212)–O(213)–C(214)–C(215)	177.9 (5)
C(12)–O(13)–C(14)–C(16)	-61.6 (6)	C(212)–O(213)–C(214)–C(216)	55.8 (8)
C(12)–O(13)–C(14)–C(17)	64.0 (7)	C(212)–O(213)–C(214)–C(217)	-67.7 (7)
C(12)–N(1)–C(1)–C(2)	179.8 (5)	C(212)–N(21)–C(21)–C(22)	179.6 (5)
C(12)–N(1)–C(1)–C(5)	-63.2 (6)	C(212)–N(21)–C(21)–C(25)	-61.8 (6)
C(12)–N(1)–C(4)–C(3)	165.4 (5)	C(212)–N(21)–C(24)–C(23)	170.3 (6)
C(14)–O(13)–C(12)–O(12)	-7.9 (8)	C(214)–O(213)–C(212)–O(212)	1.8 (9)
C(14)–O(13)–C(12)–N(1)	173.6 (4)	C(214)–O(213)–C(212)–N(21)	-175.7 (4)

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