Crystal structure of *N*-(2,2-dimethoxyethyl)-*N'*-(trifluoroacetyl)-phenylalanyl-dehydrophenylalaninamide hydrate, $C_{24}H_{26}N_3O_5F_3 \cdot H_2O$, *a precursor of intramolecular double cyclization into imidazolopyrazinone*

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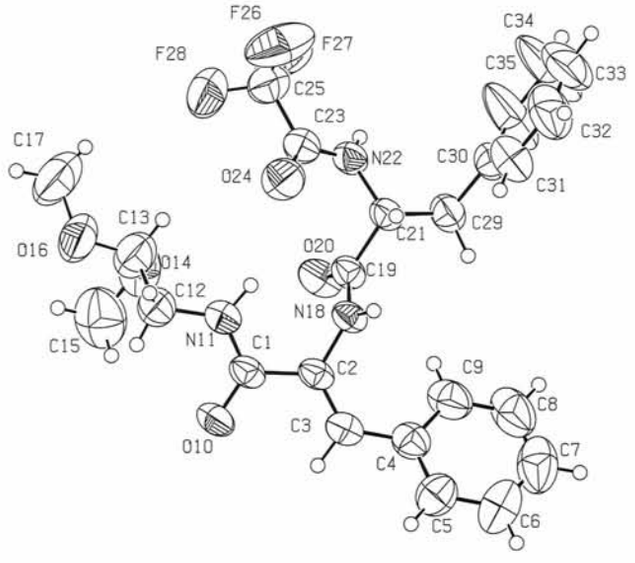

Abstract

$C_{24}H_{28}F_3N_3O_6$, monoclinic, $P12_1/c1$ (No. 14), $a = 9.677(4)$ Å, $b = 11.005(5)$ Å, $c = 24.858(7)$ Å, $\beta = 92.12°$, $V = 2645.5$ Å^3, $Z = 4$, $R_{gt}(F) = 0.064$, $wR_{ref}(F^2) = 0.199$, $T = 293$ K.

Source of material

The titled compound was obtained by coupling *N'*-(trifluoroacetyl)-phenylalanyl-dehydrophenylalanine with aminoacetaldehyde dimethylacetal in the usual conditions of peptide synthesis [1]. Chromatographic purification on silica gel (elution with CH_2Cl_2/ EtOAc 75/25; yield 59%) furnished pure compound as a white solid. Analysis: calc. for $C_{24}H_{26}F_3N_3O_5$ – C, 58.41%; H, 5.31%; N, 8.25 %; found – C, 57.99%; H, 5.29%; N, 8.40%. Recrystallization from $CHCl_3$ by slow evaporation, gave the sample presently analyzed by X-ray diffraction (white crystal; mp 334.5 K – 335.5 K) .

Experimental details

The H atoms of the CH_2, CH_3 and aromatic groups were calculated. Those of the CH, NH and water molecule were located from difference Fourier maps. The H atoms were refined with a common isotropic temperature factor ($U_{iso} = 0.127(2)$ Å^2). The CF_3 and one of the methoxy (C16–O17) groups are disordered. Two positions of these groups were localized and refined. At the end of the refinement, their site occupation factors converge to 0.66 for position A of the trifluoromethyl group and to 0.78 for the major position of the C16–O17 methoxy. Constraints were applied to the bond lengths for these two disordered groups.

Discussion

Recently, we demonstrated that imidazolopyrazinone derivatives, structurally related to coelenterazine (luciferin) [2], are endowed with excellent antioxidative properties, and protect cells [3] and animals [4] against damages induced by reactive oxygen species (ROS). For a potential development as drugs, we searched for different synthetic routes towards such molecules. One convergent approach was based on a biomimetic route [5] involving a pseudo-dehydrotripeptide as precursor [1] and its cyclization via a double intramolecular dehydration. The titled compound is a fully protected precursor of cyclization (masked aldehyde and amine functions).

The crystal structure showed the *Z* configuration of the C=C double bond, the torsion angle ∠N18–C2–C3–C4 being 4°. On the other hand, the view of the molecule showed the parallel orientation of the two chains geminally fixed on this double bond, thus favouring intramolecular interaction. Two intramolecular H-bonds involving N11, N18 and O24 help for this conformation. The intramolecular interaction is indeed favoured as after treatment of the titled compound with trimethylsilyliodide (deprotection of acetal), and then with K_2CO_3 in aqueous acetonitrile (deprotection of trifluoroacetamide), the corresponding imidazolopyrazinone was smoothly formed [1]. There are a total of six hydrogen bonds, the first two being intramolecular, the last three involving the co-crystallized water molecule.

Table 1. Data collection and handling.

Crystal:	white parallelepiped, size 0.3 × 0.3 × 0.4 mm
Wavelength:	Mo K_α radiation (0.71069 Å)
μ:	1.06 cm^{-1}
Diffractometer, scan mode:	MAR345, 100 images, $\Delta\phi = 3°$
$2\theta_{max}$:	52.74°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	30813, 5285
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 4174
$N(param)_{refined}$:	407
Programs:	SHELXS-97 [6], SHELXL-97 [7], PLATON [8]

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Table 2. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	Occ.	x	y	z	U_{iso}
H(5)	4*e*		0.3519	0.1832	0.1769	0.127(2)
H(6)	4*e*		0.5500	0.074	0.1600	0.127
H(7)	4*e*		0.6386	–0.0592	0.2233	0.127
H(8)	4*e*		0.5335	–0.0817	0.3038	0.127
H(9)	4*e*		0.3326	0.0227	0.3207	0.127
H(13)	4*e*		–0.3313	0.1457	0.3786	0.127
H(15A)	4*e*		–0.1614	0.4509	0.4239	0.127
H(15B)	4*e*		–0.3151	0.4561	0.4018	0.127
H(15C)	4*e*		–0.1951	0.4356	0.3621	0.127
H(17A)	4*e*	0.785(5)	–0.6241	0.2714	0.4162	0.127
H(17B)	4*e*	0.785	–0.4822	0.2733	0.4487	0.127
H(17C)	4*e*	0.785	–0.5353	0.1526	0.4216	0.127
H(17D)	4*e*	0.215	–0.4768	0.0927	0.4510	0.127
H(17E)	4*e*	0.215	–0.5398	0.2130	0.4268	0.127
H(17F)	4*e*	0.215	–0.4037	0.2174	0.4629	0.127

Table 2. Continued.

Atom	Site	Occ.	x	y	z	U_{iso}
H(31)	4*e*		0.1293	–0.3686	0.3231	0.127
H(32)	4*e*		0.1169	–0.5745	0.3327	0.127
H(33)	4*e*		0.1529	–0.6611	0.4147	0.127
H(34)	4*e*		0.2253	–0.5413	0.4851	0.127
H(35)	4*e*		0.2447	–0.3331	0.4754	0.127
H(3)	4*e*		0.181(3)	0.258(3)	0.241(1)	0.127
H(11)	4*e*		–0.156(3)	0.091(3)	0.315(1)	0.127
H(12A)	4*e*		–0.279(3)	0.314(4)	0.297(1)	0.127
H(12B)	4*e*		–0.368(3)	0.195(3)	0.288(2)	0.127
H(18)	4*e*		0.060(3)	–0.044(3)	0.283(1)	0.127
H(21)	4*e*		0.017(3)	–0.181(3)	0.339(1)	0.127
H(22)	4*e*		–0.009(3)	–0.159(3)	0.451(2)	0.127
H(29A)	4*e*		0.258(3)	–0.170(3)	0.361(2)	0.127
H(29B)	4*e*		0.221(3)	–0.147(3)	0.423(1)	0.127
H(101)	4*e*		0.131(3)	0.694(3)	0.042(1)	0.127

Table 3. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	Occ.	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	4*e*		–0.0501(2)	0.2186(1)	0.28409(6)	0.081(1)	0.0460(8)	0.0419(7)	0.0027(7)	0.0021(7)	0.0038(6)
C(2)	4*e*		0.0754(2)	0.1390(1)	0.28228(6)	0.076(1)	0.0416(7)	0.0402(7)	–0.0021(6)	0.0012(7)	0.0011(5)
C(3)	4*e*		0.1866(2)	0.1766(2)	0.25664(7)	0.075(1)	0.0512(9)	0.0548(9)	–0.0047(7)	–0.0003(8)	0.0045(7)
C(4)	4*e*		0.3167(2)	0.1113(2)	0.24911(8)	0.068(1)	0.058(1)	0.074(1)	–0.0087(8)	–0.0046(8)	0.0004(8)
C(5)	4*e*		0.3860(2)	0.1278(2)	0.2024(1)	0.079(1)	0.095(2)	0.075(1)	–0.001(1)	0.005(1)	–0.006(1)
C(6)	4*e*		0.5061(3)	0.0634(3)	0.1923(1)	0.077(1)	0.140(3)	0.107(2)	0.007(2)	0.009(1)	–0.032(2)
C(7)	4*e*		0.5591(3)	–0.0152(3)	0.2301(2)	0.075(2)	0.102(2)	0.177(3)	0.007(1)	–0.012(2)	–0.026(2)
C(8)	4*e*		0.4954(3)	–0.0295(3)	0.2778(2)	0.076(2)	0.091(2)	0.181(3)	–0.002(1)	–0.032(2)	0.030(2)
C(9)	4*e*		0.3748(2)	0.0329(2)	0.2880(1)	0.072(1)	0.085(2)	0.112(2)	–0.010(1)	–0.017(1)	0.028(1)
O(10)	4*e*		–0.0468(2)	0.3236(1)	0.26655(6)	0.103(1)	0.0524(7)	0.0788(9)	0.0119(6)	0.0203(7)	0.0217(6)
N(11)	4*e*		–0.1630(2)	0.1702(2)	0.30425(6)	0.0720(9)	0.0581(8)	0.0639(9)	0.0027(7)	0.0040(7)	0.0117(7)
C(12)	4*e*		–0.2911(2)	0.2372(2)	0.31083(9)	0.073(1)	0.085(1)	0.068(1)	0.011(1)	0.0001(9)	0.012(1)
C(13)	4*e*		–0.3309(3)	0.2318(3)	0.3686(1)	0.089(2)	0.142(3)	0.086(2)	0.026(2)	0.015(1)	0.022(2)
O(14)	4*e*		–0.2384(2)	0.2896(3)	0.40471(7)	0.133(2)	0.164(2)	0.066(1)	0.062(2)	–0.005(1)	0.003(1)
C(15)	4*e*		–0.2265(5)	0.4188(4)	0.3976(2)	0.156(3)	0.162(4)	0.121(3)	0.033(3)	–0.022(2)	0.001(3)
O(16A)	4*e*	0.785(5)	–0.4630(3)	0.2704(3)	0.3703(1)	0.091(2)	0.157(3)	0.120(2)	0.048(2)	0.036(1)	0.032(2)
C(17A)	4*e*	0.785	–0.5317(6)	0.2394(7)	0.4181(3)	0.134(4)	0.246(8)	0.171(5)	0.062(5)	0.084(4)	0.060(5)
O(16B)	4*e*	0.215	–0.379(1)	0.157(1)	0.3915(5)	0.18(1)	0.118(8)	0.120(8)	0.029(7)	0.073(8)	0.046(6)
C(17B)	4*e*	0.215	–0.456(2)	0.171(2)	0.4364(7)	0.10(1)	0.16(2)	0.12(1)	0.02(1)	0.026(9)	0.02(1)
N(18)	4*e*		0.0655(2)	0.0200(1)	0.30475(5)	0.0776(9)	0.0397(6)	0.0422(6)	–0.0002(6)	0.0037(6)	–0.0001(5)
C(19)	4*e*		0.0690(2)	–0.0011(1)	0.35796(6)	0.073(1)	0.0469(8)	0.0436(7)	0.0041(7)	0.0018(7)	0.0009(6)
O(20)	4*e*		0.0844(2)	0.0797(1)	0.39137(5)	0.124(1)	0.0547(7)	0.0457(6)	–0.0023(7)	0.0005(6)	–0.0059(5)
C(21)	4*e*		0.0540(2)	–0.1347(1)	0.37356(6)	0.070(1)	0.0471(8)	0.0472(8)	0.0055(7)	0.0045(7)	0.0057(6)
N(22)	4*e*		–0.0455(2)	–0.1473(1)	0.41589(6)	0.0728(9)	0.0577(8)	0.0479(7)	0.0075(6)	0.0049(6)	0.0113(6)
C(23)	4*e*		–0.1770(2)	–0.1262(2)	0.40340(8)	0.073(1)	0.069(1)	0.061(1)	0.0067(8)	0.0035(8)	0.0133(8)
O(24)	4*e*		–0.2223(2)	–0.0924(2)	0.35928(6)	0.0782(9)	0.118(1)	0.0723(9)	0.0114(8)	–0.0055(7)	0.0248(8)
C(25)	4*e*		–0.2786(3)	–0.1493(3)	0.4481(1)	0.081(2)	0.104(2)	0.090(2)	0.006(1)	0.019(1)	0.023(2)
F(26A)	4*e*	0.66(2)	–0.350(1)	–0.2460(9)	0.4378(3)	0.152(6)	0.185(8)	0.151(4)	–0.088(6)	0.053(4)	–0.015(4)
F(27A)	4*e*	0.66	–0.2227(5)	–0.1642(9)	0.4960(2)	0.113(2)	0.193(7)	0.069(2)	–0.012(3)	0.022(2)	0.037(3)
F(28A)	4*e*	0.66	–0.365(1)	–0.0564(8)	0.4525(4)	0.156(6)	0.180(6)	0.164(6)	0.082(5)	0.089(5)	0.059(5)
F(26B)	4*e*	0.34	–0.267(2)	–0.261(1)	0.465(1)	0.18(1)	0.16(1)	0.27(2)	0.04(1)	0.12(1)	0.13(2)
F(27B)	4*e*	0.34	–0.258(2)	–0.083(2)	0.4874(7)	0.20(2)	0.23(2)	0.111(9)	–0.04(1)	0.08(1)	–0.06(1)
F(28B)	4*e*	0.34	–0.4030(7)	–0.144(2)	0.4295(5)	0.072(3)	0.22(2)	0.158(7)	0.001(5)	0.025(3)	0.028(9)
C(29)	4*e*		0.1930(2)	–0.1900(2)	0.39135(9)	0.075(1)	0.061(1)	0.070(1)	0.0104(8)	0.0000(9)	0.0063(8)
C(30)	4*e*		0.1846(2)	–0.3265(2)	0.39854(8)	0.082(1)	0.063(1)	0.064(1)	0.0225(9)	0.0120(9)	0.0112(8)
C(31)	4*e*		0.1487(3)	–0.4024(2)	0.3569(1)	0.105(2)	0.066(1)	0.100(2)	0.006(1)	–0.019(1)	0.003(1)
C(32)	4*e*		0.1398(3)	–0.5265(3)	0.3625(2)	0.120(2)	0.070(2)	0.171(3)	0.006(1)	–0.011(2)	–0.015(2)
C(33)	4*e*		0.1638(6)	–0.5779(3)	0.4101(2)	0.274(6)	0.069(2)	0.171(4)	0.047(3)	0.079(4)	0.036(2)
C(34)	4*e*		0.2043(9)	–0.5061(4)	0.4517(2)	0.55(1)	0.104(3)	0.101(2)	0.130(5)	0.056(4)	0.048(2)
C(35)	4*e*		0.2155(6)	–0.3802(3)	0.4461(1)	0.383(7)	0.094(2)	0.068(2)	0.105(3)	–0.009(3)	0.005(1)
O(100)	4*e*		0.0712(2)	0.6492(2)	0.02191(6)	0.139(2)	0.144(2)	0.0515(8)	–0.055(1)	–0.0036(9)	–0.0017(9)

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