Crystal structure of *N*-(2-{[(2*E*)-3-(4-chlorophenyl)-2-propenyl]-(methyl)ammonio}methylphenyl)-*N*-(2-hydroxyethyl)-4-methoxybenzenesulfonamide dihydrogen phosphate — methanol (1:1), $[C_{26}H_{30}ClN_2SO_4][H_2PO_4]$ CH_4O

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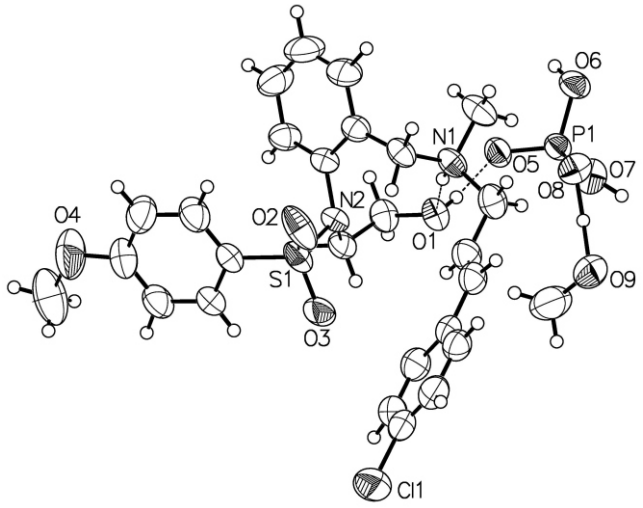

Abstract

$C_{27}H_{36}ClN_2O_9PS$, monoclinic, *C*12/*c*1 (no. 15), *a* = 36.495(3) Å, *b* = 8.5574(4) Å, *c* = 20.487(4) Å, β = 101.18(2)°, *V* = 6276.8 Å^3, *Z* = 8, $R_{gt}(F)$ = 0.052, $wR_{ref}(F^2)$ = 0.125, *T* = 295 K.

Source of material

The preparation of the title compound was previously reported in [1]. Briefly, the synthetic route starts from reductive amination of (*E*)-4-chlorocinnamaldehyde with *N*-methyl-1-(2-nitrophenyl)-methanamine. The nitro group of the resulting (*E*)-3-(4-chlorophenyl)-*N*-methyl-*N*-(2-nitrobenzylprop-2-en-1-amine) is reduced with zinc and ammonium chloride to give the corresponding aniline, which is in turn reacted with 4-methoxybenzenesulfonyl chloride to give KN-92. Finally, KN-92 is converted into KN-93 by alkylation of its sulfonamidic nitrogen with an hydroxyethyl group. Single crystals suitable for X-ray diffraction study were obtained by recrystallization from methanol at room temperature.

Experimental details

Non-hydrogen atoms were refined anisotropically. H atoms bound to C23 and C27 were constrained to the parent site and refined in the riding-model approximation with isotropic displacement parameters set at 1.5 U_{eq} of the parent atom. All remaining H atoms were located from a difference Fourier map and refined isotropically.

Discussion

Calmodulin-dependent protein kinase II (CaMKII) phosphorylates a variety of substrates. It is implicated in regulating many aspects of cellular function in response to Ca^{2+} signalling, including the regulation of carbohydrate, amino acid and lipid metabolism, ion channel/receptors, neurotransmitter synthesis and release, transcription and translation, cytoskeletal organization and calcium homeostasis [2,3]. Moreover, CaMKII can modulate opioid tolerance via its action on learning and memory. Recently, it has been reported that sufficient inhibition of CaMKII is capable of reversing chronic inflammatory pain, and that CAMKII is involved in cardiac remodelling secondary to pathological stresses such as hypertension or myocardial infarction, as well as endothelial cell pathophysiology. Generally, the studies about CaMKII activity are carried out by using a selective CaMKII inhibitor, KN-93, and its secondary amidic inactive analogue KN-92, which is used as a negative control and differs from KN-93 only for the absence of the hydroxyethyl substituent [4].

Looking for a possible explanation for the difference in activity of these two compounds, we studied the crystal structure of KN-93 dihydrogen phosphate methanol monosolvate.

In the title crystal structure, the 2-propen-1-amine N is protonated and one phosphoric OH group is deprotonated. An intramolecular N1–H O1 hydrogen bond generating an *S*(9) ring is observed. The crystal structure exhibits a strong O–H O hydrogen bond between methanol and the dihydrogen phosphate anion. This is why the O9—H8 bond is longer than the usual OH bonds. Therefore H8 hydrogen is almost equally shared between O9 and O8. The cinnamyl residue is folded over the sulfonamide group. The crystal packing is stabilized by intermolecular π–π interactions between benzenesulfonamide moieties. As anticipated on the basis of synthetic chemistry considerations, spectroscopic evidences, and quantum chemical calculations [1], the cinnamyl moiety presents *E* configuration.

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Table 1. Data collection and handling.

Crystal:	colorless block, size 0.25 0.32 0.40 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	2.8 cm ^{1}
Diffractometer, scan mode:	Bruker Nonius KappaCCD, φ/ω
$2\theta_{max}$:	55.26°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	28250, 6907
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 3760
$N(param)_{refined}$:	492
Programs:	EVAL-14 [5], SHELXS-97, SHELXL-97 [6], OLEX2 [7]

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

Atom	Site	*x*	*y*	*z*	U_{iso}
H(23A)	8*f*	0.1613	0.5895	0.0066	0.204
H(23B)	8*f*	0.1606	0.5938	0.0829	0.204
H(23C)	8*f*	0.1853	0.4701	0.0550	0.204
H(27A)	8*f*	0.4153	0.0715	0.5132	0.153
H(27B)	8*f*	0.4321	0.0038	0.4543	0.153
H(27C)	8*f*	0.4156	0.1735	0.4497	0.153
H(10A)	8*f*	0.4032(7)	0.741(2)	0.364(1)	0.042(6)
H(25A)	8*f*	0.3296(7)	0.366(3)	0.232(1)	0.054(7)
H(3)	8*f*	0.3922(7)	0.856(3)	0.601(1)	0.049(8)
H(7A)	8*f*	0.4271(8)	0.723(3)	0.533(1)	0.057(8)
H(25B)	8*f*	0.3398(8)	0.351(3)	0.311(2)	0.07(1)
H(2)	8*f*	0.3397(8)	0.908(4)	0.642(2)	0.08(1)
H(26A)	8*f*	0.3744(7)	0.174(3)	0.262(1)	0.053(7)
H(9A)	8*f*	0.4655(8)	0.647(3)	0.458(1)	0.061(8)
H(1A)	8*f*	0.4316(6)	0.510(3)	0.354(1)	0.029(7)
H(9B)	8*f*	0.4608(8)	0.470(4)	0.452(1)	0.065(8)
H(8A)	8*f*	0.3932(8)	0.515(3)	0.441(1)	0.067(9)
H(5)	8*f*	0.3393(8)	0.542(3)	0.483(2)	0.064(9)
H(1)	8*f*	0.4274(8)	0.254(3)	0.323(1)	0.06(1)
H(10B)	8*f*	0.4412(7)	0.805(3)	0.348(1)	0.056(7)
H(6A)	8*f*	0.2850(8)	0.578(3)	0.522(1)	0.070(9)
H(12)	8*f*	0.4525(8)	0.847(3)	0.239(1)	0.062(8)
H(15)	8*f*	0.3501(7)	0.539(3)	0.154(1)	0.046(7)
H(26B)	8*f*	0.3914(7)	0.310(3)	0.226(1)	0.057(8)
H(13)	8*f*	0.4315(9)	0.816(4)	0.124(2)	0.09(1)
H(14)	8*f*	0.3807(8)	0.654(3)	0.079(2)	0.08(1)
H(22)	8*f*	0.2567(8)	0.501(4)	0.260(2)	0.07(1)
H(18)	8*f*	0.3092(9)	0.836(3)	0.186(2)	0.075(9)
H(21)	8*f*	0.2099(9)	0.493(4)	0.166(1)	0.078(9)
H(19)	8*f*	0.262(1)	0.850(5)	0.093(2)	0.11(1)
H(24A)	8*f*	0.4923(7)	0.466(4)	0.366(1)	0.061(8)
H(24B)	8*f*	0.4956(9)	0.648(4)	0.360(2)	0.076(9)
H(24C)	8*f*	0.476(1)	0.545(4)	0.297(2)	0.10(1)
H(6)	8*f*	0.5342(9)	0.148(4)	0.288(2)	0.08(1)
H(7)	8*f*	0.510(1)	0.077(4)	0.420(2)	0.10(1)
H(8)	8*f*	0.483(2)	0.168(7)	0.459(3)	0.21(2)

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

Atom	Site	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
P(1)	8*f*	0.50057(2)	0.11938(8)	0.35544(3)	0.0381(4)	0.0529(4)	0.0441(4)	0.0027(3)	0.0073(3)	0.0040(3)
S(1)	8*f*	0.32415(2)	0.65546(9)	0.30142(4)	0.0343(4)	0.0776(5)	0.0583(5)	0.0067(3)	0.0083(3)	0.0165(4)
Cl(1)	8*f*	0.26660(3)	0.7942(1)	0.61378(5)	0.0765(6)	0.1154(7)	0.1033(7)	0.0216(5)	0.0409(5)	0.0204(6)
O(1)	8*f*	0.40982(6)	0.2997(2)	0.32646(9)	0.044(1)	0.052(1)	0.057(1)	0.0053(9)	0.002(1)	0.0087(9)
O(5)	8*f*	0.46707(5)	0.1389(2)	0.30065(8)	0.041(1)	0.079(1)	0.046(1)	0.0092(9)	0.0076(8)	0.0035(9)
N(2)	8*f*	0.35816(5)	0.5461(2)	0.2823(1)	0.034(1)	0.045(1)	0.051(1)	0.0027(9)	0.0128(9)	0.0037(9)
O(2)	8*f*	0.33949(5)	0.8084(2)	0.3142(1)	0.045(1)	0.075(1)	0.112(2)	0.010(1)	0.002(1)	0.047(1)
O(8)	8*f*	0.50137(5)	0.2168(2)	0.41650(9)	0.073(1)	0.051(1)	0.048(1)	0.0073(9)	0.014(1)	0.0097(8)
O(6)	8*f*	0.53677(5)	0.1585(3)	0.3287(1)	0.044(1)	0.107(2)	0.048(1)	0.019(1)	0.007(1)	0.006(1)
O(7)	8*f*	0.50295(5)	0.0565(2)	0.3750(1)	0.071(1)	0.047(1)	0.061(2)	0.0012(9)	0.003(1)	0.005(1)
C(10)	8*f*	0.42417(8)	0.7239(3)	0.3377(1)	0.037(2)	0.040(2)	0.064(2)	0.003(1)	0.007(1)	0.010(1)
N(1)	8*f*	0.44453(6)	0.5793(3)	0.3665(1)	0.036(1)	0.043(1)	0.062(2)	0.006(1)	0.007(1)	0.013(1)
C(4)	8*f*	0.37191(8)	0.6943(3)	0.5366(1)	0.053(2)	0.064(2)	0.038(2)	0.004(1)	0.005(1)	0.006(1)
C(25)	8*f*	0.34872(8)	0.3776(3)	0.2717(2)	0.040(2)	0.052(2)	0.060(2)	0.010(1)	0.004(2)	0.002(1)
C(16)	8*f*	0.37921(6)	0.6182(3)	0.2368(1)	0.040(1)	0.040(1)	0.050(2)	0.002(1)	0.015(1)	0.004(1)
C(11)	8*f*	0.41060(7)	0.7082(3)	0.2639(1)	0.043(2)	0.041(1)	0.055(2)	0.005(1)	0.012(1)	0.002(1)
C(12)	8*f*	0.42970(9)	0.7817(4)	0.2202(2)	0.062(2)	0.065(2)	0.079(3)	0.022(2)	0.017(2)	0.006(2)
C(17)	8*f*	0.28805(7)	0.6647(3)	0.2310(1)	0.036(1)	0.053(2)	0.059(2)	0.005(1)	0.009(1)	0.005(1)
C(22)	8*f*	0.25826(7)	0.5645(4)	0.2246(2)	0.039(2)	0.073(2)	0.066(2)	0.004(1)	0.008(2)	0.006(2)
C(26)	8*f*	0.38194(8)	0.2810(3)	0.2680(2)	0.050(2)	0.045(2)	0.063(2)	0.004(1)	0.000(2)	0.007(1)
C(7)	8*f*	0.40667(9)	0.6701(4)	0.5116(2)	0.055(2)	0.064(2)	0.048(2)	0.002(2)	0.001(2)	0.004(2)
C(3)	8*f*	0.3713(1)	0.8047(4)	0.5855(2)	0.061(2)	0.063(2)	0.049(2)	0.001(2)	0.005(2)	0.002(2)
C(15)	8*f*	0.36835(9)	0.5997(3)	0.1688(2)	0.056(2)	0.056(2)	0.053(2)	0.014(1)	0.015(2)	0.007(1)
O(3)	8*f*	0.31057(5)	0.5726(3)	0.3524(1)	0.049(1)	0.149(2)	0.053(1)	0.012(1)	0.021(1)	0.002(1)
C(24)	8*f*	0.48106(9)	0.5603(4)	0.3455(2)	0.042(2)	0.053(2)	0.100(3)	0.001(2)	0.023(2)	0.008(2)
C(18)	8*f*	0.28970(9)	0.7711(4)	0.1808(2)	0.053(2)	0.061(2)	0.097(3)	0.010(2)	0.003(2)	0.010(2)
C(9)	8*f*	0.44894(9)	0.5682(4)	0.4412(2)	0.053(2)	0.063(2)	0.059(2)	0.003(2)	0.000(2)	0.012(2)
C(21)	8*f*	0.23036(9)	0.5678(4)	0.1688(2)	0.047(2)	0.070(2)	0.085(3)	0.012(2)	0.001(2)	0.000(2)
C(2)	8*f*	0.3391(1)	0.8359(4)	0.6092(2)	0.076(2)	0.063(2)	0.054(2)	0.013(2)	0.014(2)	0.005(2)
C(8)	8*f*	0.41227(9)	0.5794(4)	0.4630(2)	0.054(2)	0.066(2)	0.055(2)	0.001(2)	0.005(2)	0.005(2)
C(6)	8*f*	0.30681(9)	0.6434(4)	0.5357(2)	0.054(2)	0.092(2)	0.055(2)	0.005(2)	0.003(2)	0.011(2)
C(1)	8*f*	0.30716(9)	0.7544(4)	0.5842(2)	0.063(2)	0.078(2)	0.053(2)	0.013(2)	0.011(2)	0.021(2)
C(14)	8*f*	0.3885(1)	0.6711(4)	0.1264(2)	0.089(3)	0.084(2)	0.052(2)	0.014(2)	0.019(2)	0.005(2)
C(20)	8*f*	0.23229(9)	0.6707(4)	0.1187(2)	0.060(2)	0.072(2)	0.075(2)	0.006(2)	0.013(2)	0.004(2)
O(4)	8*f*	0.20649(8)	0.6824(3)	0.0609(1)	0.098(2)	0.117(2)	0.096(2)	0.001(2)	0.038(2)	0.005(2)
C(5)	8*f*	0.33880(9)	0.6141(4)	0.5121(2)	0.065(2)	0.086(2)	0.043(2)	0.002(2)	0.003(2)	0.004(2)
C(23)	8*f*	0.1759(1)	0.5751(6)	0.0505(2)	0.091(3)	0.160(4)	0.129(4)	0.011(3)	0.049(3)	0.033(3)

Table 3. Continued.

Atom	Site	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(19)	8*f*	0.2619(1)	0.7745(4)	0.1246(2)	0.080(3)	0.078(2)	0.092(3)	0.005(2)	0.006(2)	0.032(2)
C(13)	8*f*	0.4186(1)	0.7634(4)	0.1524(2)	0.086(3)	0.088(2)	0.083(3)	0.028(2)	0.034(2)	0.017(2)
O(9)	8*f*	0.46420(7)	0.1555(3)	0.5084(1)	0.081(2)	0.094(2)	0.057(1)	0.005(1)	0.017(1)	0.007(1)
C(27)	8*f*	0.4290(1)	0.0964(5)	0.4791(2)	0.110(3)	0.123(3)	0.075(3)	0.027(3)	0.026(2)	0.012(2)

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