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Electronic Supplementary Information

Cyclic dipeptide peroxosolvates: first direct evidence for hydrogen bonding of hydrogen peroxide to peptide backbone

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Contents

1. Experimental details

1.1 Synthesis

Synthesis of cyclic disarcosine peroxosolvate, $C_6H_{10}N_2O_2•H_2O_2$ (**1**). 0.32 g of cyclic disarcosine was dissolved in 0.4 mL of 68 wt% H_2O_2. Obtained solution was kept in a closed beaker at -18 °C. Colourless crystals were formed after 1 h. Yield 43%.

Synthesis of cyclic dialanine, $C_6H_{10}N_2O_2•2(H_2O_2)$ (**2**) 0.21 g of cyclic dialanine was dissolved in 0.4 mL of 98 wt% H_2O_2. Obtained solution was kept in a closed beaker at -20 °C. Colourless crystals were formed after 1 h. Yield 40%.

Synthesis of cyclic diglycine $C_4H_6N_2O_2•2(H_2O_2)$ (**3**) 0.18 g of cyclic diglycine was dissolved in 0.4 mL of 98 wt% H_2O_2. Obtained solution was kept in a closed beaker at -20 °C. Colourless crystals were formed after 1 h. Yield 45%.

Synthesis of partially hydrated cyclic digycine peroxosolvate $C_4H_6N_2O_2•1.786(H_2O_2)•0.214(H_2O)$ (**4**) 0.14 g of cyclic diglycine was dissolved in 0.4 mL of 68 wt% H_2O_2. Obtained solution was kept in a closed beaker at -20 °C. Colourless crystals were formed after 1 h. Yield 61%.

1.2. Elemental analysis

Peroxide content was estimated by permanganometry. Carbon, hydrogen and nitrogen content was determined using the Perkin-Elmer 2400 series II Analyzer (CHN).

Anal. Calc. for $H_{12}O_4C_6N_2$ (**1**): OO (peroxide), 18.16; N, 15.90; C, 40.91; H, 6.87. Found: OO (peroxide), 18.10; N, 15.19; C, 40.64; H, 6.95.

Anal. Calc. for $H_{14}O_6C_6N_2$ (**2**): OO (peroxide), 15.22; N, 13.33; C, 34.29; H, 6.71. Found: OO (peroxide), 14.98; N, 13.41; C, 34.31; H, 6.70.

Anal. Calc. for $H_{10}O_6C_4N_2$ (**3**): OO (peroxide), 17.57; N, 15.38; C, 26.38; H, 5.53. Found: OO (peroxide), 17.43; N, 15.25; C, 26.43; H, 5.53.

Anal. Calc. for $H_{10}O_{5.786}C_4N_2$ (**4**): OO (peroxide), 17.90; N, 15.68; C, 26.88; H, 5.64. Found: OO (peroxide), 17.84; N, 15.43; C, 26.65; H, 5.42.

1.3. X-ray diffraction analysis

Crystal data and details of X-ray analysis are given in Table S1. The crystals were extracted from the mother liquor using a plastic spatula and covered immediately with inert oil to prevent contact with atmospheric moisture. After that they were rapidly mounted on the top of a fibre of hair and transferred to a cold nitrogen stream. All experimental data sets were collected on a Bruker SMART APEX II diffractometer using graphite monochromatized MoK*α* radiation (λ = 0.71073 Å) in *ω*-scan mode. Absorption corrections based on measurements of equivalent reflections were applied[1]. The structures were solved by direct methods and refined by full matrix least-squares on F^2 with anisotropic thermal parameters for all non-hydrogen atoms[2]. In **1** and **3** all hydrogen atoms were found from difference Fourier synthesis and refined with isotropic thermal parameters. In **2** all ‘‘active’’ hydrogen atoms (amino and peroxo) were found from difference Fourier synthesis and refined with isotropic thermal parameters. All other hydrogen atoms (*C*–H) were placed in calculated positions and refined using a riding model. As for **4**, all hydrogen atoms (except admixed water) were found from difference Fourier synthesis and refined with isotropic thermal parameters. Water hydrogen atoms were placed in calculated positions and refined using a riding model. In all structures (except **4**), partial substitutional disorder of hydrogen peroxide by water molecules[3–6] was not observed since no residual peaks with intensity more than 0.16 e Å^{-3} were seen in the hydrogen peroxide molecule regions.

Crystallographic data (excluding structure factors) for the structures **1**, **2**, **3** and **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC1828851, 1828852, 1828850 and 1828849, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int.code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

Table S1. X-ray structure determination summary

Compound	**1**	**2**	**3**	**4**
Empirical formula	$C_6H_{10}N_2O_2$ $\bullet H_2O_2$	$C_6H_{10}N_2O_2$ $\bullet 2(H_2O_2)$	$C_4H_6N_2O_2$ $\bullet 2(H_2O_2)$	$C_4H_6N_2O_2$ $\bullet 1.786(H_2O_2)$ $\bullet 0.214(H_2O)$
F_w	176.18	210.19	182.14	178.72
Crystal system	Monoclinic	Triclinic	Triclinic	Triclinic
Space group	$P2_1/n$	P-1	P-1	P-1
a/Å	8.2527(13)	7.439(2)	5.654(3)	5.5006(8)
b/Å	6.6341(10)	8.215(2)	5.802(3)	5.8258(8)
c/Å	15.034(2)	8.298(2)	6.648(3)	6.5611(9)
$\alpha/^o$	90	97.332(4)	76.505(8)	76.395(2)
$\beta/^o$	99.847(2)	104.578(4)	66.440(7)	67.816(2)
$\gamma/^o$	90	104.053(4)	79.984(8)	79.145(2)
V/Å^3	811.0(2)	466.4(2)	193.57(17)	188.07(5)
Z	4	2	1	1
F(000)	376	224	96	94
d_{calc}/g•cm^{-3}	1.443	1.497	1.563	1.578
μ/mm^{-1}	0.121	0.134	0.148	0.149
T/K	150	150	230	150
Data collected	7903	4702	1848	1974
Unique data (R_{int})	1955 (0.0238)	1610 (0.0377)	850 (0.0227)	909 (0.0085)
Reflections with $I>2\sigma(I)$	1740	1340	698	837
θ range/°	2.64-27.99	2.59-25.03	3.40-26.99	3.41-28.00
No of variables	157	153	94	100
R_1 [$I>2\sigma(I)$]	0.0340	0.0555	0.0417	0.0385
wR_2 (all data)	0.1046	0.1594	0.1242	0.1049
GOF	1.095	1.109	1.053	1.055
$\Delta\rho_{max,min}$/e Å^{-3}	0.347 / -0.195	0.570 / -0.259	0.170 / -0.238	0.285 / -0.222

2. Computational details

2.1. Solid-State DFT Followed by Bader Analysis of the Periodic Electronic Density.

Density functional theory computations with periodic boundary conditions (solid-state DFT) were performed in the Crystal09 software package[7,8] using B3LYP in the localized basis set 6-31G**. The B3LYP/6-31G** approximation provides reliable and consistent results in studying the intermolecular interactions in crystals.[9,10] Dispersion interactions were included using the semiempirical scheme)[11] as implemented in the Crystal17 software package.[12] Two types of optimization was employed: optimization of atomic positions with fixed cell parameters (ATOMONLY) and optimization of cell parameters and atomic positions (OPTGEOM) with preserving of system symmetry.[11] The mixing coefficient of Hartree-Fock/Kohn-Sham matrices is set to 25%. Tolerance on energy controlling the self-consistent field convergence for geometry optimizations and frequencies computations is set to 10^{-10} and 10^{-11} hartree respectively. The shrinking factor of the reciprocal space net is set to 3. All hydrogens except one corresponding to the specific hydrogen bond were treated as deuteriums (m = 2.00) in order to find the frequency of the uncoupled vibrational mode.

Frequencies of O–H stretching mode of water and hydrogen peroxide molecules were found with Gaussian 09 package[13]. For the purpose geometry HOD and HOOD molecules were calculated using B3LYP/6-31G** approximation with standard settings.

2.2. Evaluation of H-bond enthalpies/energies

The crystal with the optimized cell parameters and atomic positions were used in B3LYP/6-31G** computations of the periodic electronic wave-functions by CRYSTAL98[14]. The quantum theory of atoms in molecules and crystals (Bader) analysis of the periodic electron density[15] is performed with TOPOND[16]. The calculation methodology is presented elsewhere[17]. The energy of the considered hydrogen bond, energy E_{HB}, is evaluated according to ref. [18] as

$$E_{HB}\ [\text{kJ mol}^{-1}] = 1124\cdot G_b\ [\text{atomic units}], \qquad (1)$$

where G_b is the positively-defined local electronic kinetic energy density at the H···O bond critical point. Eq. (1) yields reasonable E_{HB} values for molecular crystals with intermolecular H-bonds[19].

The enthalpy ($-\Delta H_{HB}$) of the intermolecular H-bond in liquids, solids and solutions can be estimated via the application of empirical relationship[20]:

$$-\Delta H_{HB}\ [\text{kJ mol}^{-1}] = 0.134\cdot R(\text{H}\cdots\text{O})^{-3.05}, \qquad (2)$$

where the R(H···O) is the H···O distance (nm).

The $-\Delta H_{HB}$ value in the crystalline state can be evaluated using Equation (3):

$$-\Delta H_{HB}\ [\text{kJ mol}^{-1}] = 1.386\cdot(\Delta\nu\ [\text{cm}^{-1}] - 40)^{0.5}, \qquad (3)$$

where $\Delta\nu = \nu(\text{XH}_{\text{free}}) - \nu(\text{XH})$ represents the red-shift value of the XH stretching frequency caused by the formation of the H-bond with the OH group being the proton donor. It should be noted that $\nu(\text{XH}_{\text{free}})$ and $\nu(\text{XH})$ are the frequencies of the localized, uncoupled XH stretching vibration. Eq. (3) gives reasonable $-\Delta H_{HB}$ values for intermolecular H-bonds of moderate strength in polycrystalline amino acids and peptides[21].

The specific feature of Eqs. (1) – (3) is possibility to use the G_b, R(H···O), Δν and I values obtained from experiment (high precision X-ray diffraction, neutron diffraction, IR spectroscopy) or the solid-state DFT computations followed by the Bader analysis of the periodic electronic density.

Table S2. Theoretical parameters of the intermolecular H-bonds[a] for $C_4H_6N_2O_2\cdot 2H_2O_2$ and $C_4H_6N_2O_2\cdot 2H_2O$ obtained with different optimization procedures vs experimental data.

Fragment	X(H)···O,[b] Å	H···O, Å	X–H···O angle	Fragment	X(H)···O, Å	H···O, Å	X–H···O angle
Gly-Gly·$2H_2O_2$				Gly-Gly·$2H_2O$			
EXPERIMENTAL							
$O\cdots H\text{-}O_{p1}$	2.662	1.86	148	$O\cdots H_1\text{-}O_w$	2.857	2.06	188.9
$O\cdots H\text{-}O_{p2}$	2.779	1.85	150	$O\cdots H_2\text{-}O_w$	3.062	2.26	179
$O_{p1}\cdots H\text{-}N$	3.013	2.30	147.5	$O_w\cdots H\text{-}N$	2.886	2.02	161
$O_{p2}\cdots H\text{-}N$	3.085	2.30	162.2				
ATOMONLY[c]							
$O\cdots H\text{-}O_{p1}$	2.666	1.680	172.5	$O\cdots H_1\text{-}O_w$	2.855	1.889	169.9
$O\cdots H\text{-}O_{p2}$	2.757	1.783	168.5	$O\cdots H_2\text{-}O_w$	2.966	2.004	168.6
$O_{p1}\cdots H\text{-}N$	2.885	1.965	148.3	$O_w\cdots H\text{-}N$	2.875	1.866	165.4
$O_{p2}\cdots H\text{-}N$	3.261	2.322	152.3				
OPTGEOM[c]							
$O\cdots H\text{-}O_{p1}$	2.719	1.761	162.8	$O\cdots H_1\text{-}O_w$	2.765	1.816	162.5
$O\cdots H\text{-}O_{p2}$	2.722	1.731	175.1	$O\cdots H_2\text{-}O_w$	2.810	1.847	167
$O_{p1}\cdots H\text{-}N$	2.901	1.881	171.3	$O_w\cdots H\text{-}N$	2.828	1.828	161.8
$O_{p2}\cdots H\text{-}N$	3.365	2.447	148.3				
OPTGEOM (B3LYP-D3)[c]							
$O\cdots H\text{-}O_{p1}$	2.668	1.672	176.7	$O\cdots H_1\text{-}O_w$	2.713	1.771	166.3
$O\cdots H\text{-}O_{p2}$	2.671	1.718	160.8	$O\cdots H_2\text{-}O_w$	2.772	1.815	164.8
$O_{p1}\cdots H\text{-}N$	2.853	1.824	177.7	$O_w\cdots H\text{-}N$	2.784	1.760	170.6
$O_{p2}\cdots H\text{-}N$	3.283	2.391	144.3				

[a] O_w and O_p denote oxygen atoms of H_2O/H_2O_2 respectively; [b] X=O or N; [c] OPTGEOM, ATOMONLY, and OPTGEOM (B3LYP-D3) are defined in the text of manuscript.

Table S3. Theoretical values of the electron density at the H…O bond critical point ρ_b, the H-bond energy E_{HB} and enthalpy $-\Delta H_{HB}$ for Gly-Gly·2H_2O_2 and Gly-Gly·2H_2O computed at the OPTGEOM (B3LYP-D3) level.

Gly-Gly·2H_2O_2					Gly-Gly·2H_2O				
Fragment a)	ρ_b, a.u.	E_{HB}, kJ mol^{-1}	$-\Delta H$, kJ mol^{-1}		Fragment	ρ_b, a.u.	E_{HB}, kJ mol^{-1}	$-\Delta H$, kJ mol^{-1}	
		(1)	(2)	(3)			(1)	(2)	(3)
$O\cdots H\text{-}O_{p1}$	0.048	40.1	31.4	31.2	$O\cdots H_1\text{-}O_w$	0.036	31.9	26.3	22.6
$O\cdots H\text{-}O_{p2}$	0.042	36.3	28.9	23.8	$O\cdots H_2\text{-}O_w$	0.034	28.5	24.4	24.8
$O_{p1}\cdots H\text{-}N$	0.035	28.8	24.0	21.8	$O_w\cdots H\text{-}N$	0.038	33.1	26.8	25.6
$O_{p2}\cdots H\text{-}N$	-	-	10.5 b)						

a) O_w and O_p denote oxygen atoms of H_2O/H_2O_2 respectively; b) this value should be treated with caution, because the Bader analysis does not localize (3,-1) critical point for the $O_{p2}\cdots H\text{-}N$ bond

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