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Crystal structures and hydrogen bond analysis of five amino acid conjugates of terephthalic and benzene-1,2,3-tricarboxylic acids

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Four linear connecting amino acid derived ligands, **1**-**4**, and one potentially three connecting, **5**, were prepared by the reaction of the appropriate terephthaloyl dichloride or benzene-1,3,5-tricarbonyl trichloride with the methyl ester protected amino acid. Amino acids used here were alanine (**1**,**5**), isoleucine (**2**), leucine (**3**) and valine (**4**). Crystalline forms of four amino acid substituted terephthalamides (2,2'-(terephthaloylbis(azanediyl))dipropanoic acid dihydrate **1**; 2,2'-(terephthaloylbis(azanediyl))bis(3-methylpentanoic acid) monohydrate **2**; 2,2'-(terephthaloylbis(azanediyl))bis(4-methylpentanoic acid) dihydrate **3**; 2,2'-(terephthaloylbis(azanediyl))bis(3-methylbutanoic acid) dihydrate **4**) and one benzene-1,3,5-tricarboxamides molecules (2,2',2''-((benzene-1,3,5-tricarbonyl)tris(azanediyl))tripropionic acid hemihydrate **5**) were characterised and the single crystal structures were solved. All the compounds form hydrogen bonded 2D and 3D nets. Linear connecting amino acid derivatives can be categorised into three groups depending on the hydrogen bond patterns and final structures. Compounds **1** and **2** form 3D structures but the final structure is different due to the different hydrogen bond synthons. Compounds **3** and **4** are isostructural and form 2D hydrogen bonded structures while **5** forms a hydrogen bonded **pcu**-net. Intermolecular interactions have been analysed with Hirshfeld surfaces and graph set symbols.

Introduction

To understand the driving forces for the formation of extended assemblies is important for designing molecule based materials, be these for potential electronic,[1] magnetic[2] or porous[3, 4] applications. The idea is often to preprogram the building blocks to interact with each other in a certain way to give larger entities with the desired location and geometric relations between them. In other words, the interaction behaviour is stored in the functional groups of the molecules.

Terephthalamides and benzene-1,3,5-tricarboxamides are examples of building blocks used in preparing extended assemblies.[5-11] These molecules have a benzene ring core and usually contain flexible functional groups. In addition to stronger interactions such as coordination and hydrogen bonds, the role of non-covalent interactions is also important in the assembly of molecules. For example the benzene ring in these systems offers the possibility of aromatic interactions.

The assembly process of benzene-1,3,5-tricarboxamide derivatives have been studied widely using different techniques such as CD and UV-Vis but also with theoretical methods.[10, 12, 13] Terephthalamides and benzene-1,3,5-tricarboxamides have produced nanostructured materials, for instance nano-staircases and fibres are among reported architectures.[5, 6, 14-17] Spontaneous formation of hydrogels and their encapsulation and sorption properties of both di- and tri-substituted carboxamides have also been studied.[6, 18, 19] In addition, terephthalamides and benzene-1,3,5-tricarboxamides derivatives have been reported to form liquid columnar crystal phases (LC), preorganized surfactants and multi-component organic cages within dynamic combinatorial libraries.[20-23]

Introduction of amino acids into terephthalamide and benzene-1,3,5-tricarboxamides offers the possibility of producing enantiopure chiral building blocks and structures[5, 7, 24] with possible applications in enantioselective synthesis, separation and detection. The amino acid part can also stabilise the assemblies via hydrogen bonding and moreover provide metal coordination sites.[5, 11, 16, 17, 24-26]

The complexing abilities of amino acid substituted terephthalamide and benzene-1,3,5-tricarboxamides have been studied in preparing network structures with metals such as copper, cobalt, manganese, nickel, cadmium, zinc, lantanoids, and calcium.[7, 11, 17, 24-31] This research have focused on non-chiral glycine (-H) substituted ligands, but alanine (-CH_3) and phenylalanine (-$CH_2(C_6H_6)$) examples are also known, although reported X-ray structures of such network compounds are rare.[32, 33]

The choice of the ligand and metal is essential in producing such metal-organic frameworks (MOFs)[34] that can have application in gas sorption, catalysis and molecular recognition.[27, 35-39] These properties are incorporated into the material during preparation using different building blocks. Therefore the design of new materials with desired properties requires understanding and control of the interactions of the building blocks.

We report here the preparation and crystal structures of the amino acid derivatives **1-5** of terephthalamide and benzene-1,3,5-tricarboxamides (Figure 1). These closely related molecules give structures with differences and similarities that are investigated by traditional means, but also with graph set analysis and Hirshfeld surfaces.

Figure 1. Schematic presentation of the molecules of the studied compounds **1-5**.

Experimental

Materials

Amino acids L-phenylalanine (≥99%), L-leucine (≥99%), L-isoleucine (≥99%) and DL-valine (≥99%) were produced by Fluka. L-alanine methyl ester hydrochloride (≥99%) was purchased from Aldrich and the other amino acid methyl ester hydrochlorides were prepared according to the literature.[40] Triethyl amine (99.5%), terephthaloyl dichloride (99%), benzene-1,3,5-tricarbonyl trichloride (98%) and d-chloroform (99.8%) were manufactured by Aldrich. Anhydrous magnesium sulfate (98%) and sodium hydroxide (98%) were produced by Scharlau. Hydrochloric acid (≥37%), potassium bromide (99%) and methanol (99.7%) were manufactured by Sigma Aldrich. Dichloromethane (p.a.) was produced by Merck. Dimethylsulfoxide-d6 (99.8%) was produced by Armar Chemicals.

Experimental methods

The elemental analysis was performed by H. Kolbe Mikroanalytisches Laboratorium, Germany. The FTIR spectra measurements were performed using Bruker IFS-125 Spectrometer in KBr pellet. The ^{1}H- and ^{13}C-NMR spectra were analysed using an Agilent 400 MHz spectrometer operating at 400 and 100 MHz for proton and carbon, respectively.

X-ray Crystal Structure Determination

The crystallographic details for compounds **1-5** are summarized in Table 1. The crystals of **1-5** were immersed in cryo-oil, mounted in a Nylon loop, and measured at a temperature of 293(2) K (**1**, **5**) and 173(2) K using an Oxford Cryostream 600 (**3**) and 700 (**2**,**4**). The X-ray diffraction data were collected on Xcalibur, Sapphire3 diffractometer (**1**,**5**), a Nonius Kappa CCD diffractometer (**3**) and a Bruker DUO APEX II CCD diffractometer (**2**,**4**) using Mo Kα radiation (λ = 0.71073 Å). For (**1**,**5**) the CrysAlisPro programme package was used for cell refinements and data reductions[41], whilst for **3** DENZO was used, and for **2**, **4** and **5** data reduction and cell refinement were performed using SAINT-Plus.[42] Space groups were determined from systematic absences by XPREP[43] and confirmed using the program Layer for 2-4.[44] The structures were solved by direct methods using SHELXS-97[45] program. A semi-empirical or numerical absorption (SCALE3 ABSPACK (**1**), SADABS[46] (**2-5**)) was applied to all of the data. Structural refinements were carried out using SHELXL-97 (**1-5**).[47] Refinement procedure by full-matrix least-squares methods, based on F^2 values against all reflections was performed by SHELXL-97, including anisotropic displacement parameters for all non-H atoms. Hydrogen atoms were placed geometrically, except for O-H, N-H and water hydrogen atoms which were placed from difference Fourier maps. All other hydrogen atoms were positioned geometrically and constrained to ride on their parent atoms $U_{iso} = 1.2U_{eq}$(parent atom). The crystals of **5** have asymmetric carbon that is disordered over two sites with equal occupancies. It also contains electron density, interpreted as residual water molecules, that cannot be refined properly. This excess of electron density was cleaned using the *SQUEEZE* routine of *PLATON*.[48] CCDC 993036-993040

Table 1. Crystal data for compounds **1-5**.

	1	2	3	4	5
empirical formula	C14 H20 N2 O8	C20 H30 N2 O7	C20 H32 N2 O8	C18 H28 N2 O8	C18 H21.57 N3 O9.28
Fw	344.32	410.46	428.47	400.42	423.38
temp (K)	293(2)	173(2)	173(2)	173(2)	293(2)
l(Å)	0.71073	0.71073	0.71073	0.71073	0.71073
crystsyst	Orthorhombic	orthorhombic	monoclinic	monoclinic	Trigonal
spacegroup	P 21 21 21	P 21 21 21	P21	P21	R-3
a (Å)	7.7195(5)	6.9544(5)	12.374(3)	10.5665(10)	18.3488(5)
b (Å)	8.2128(5)	11.7552(8)	7.675(2)	7.6596(7)	18.3488(5)
c (Å)	26.453(2)	26.872(2)	12.714(3)	12.871(1)	11.1379(6)
a (deg)	90	90	90	90	90
b (deg)	90	90	107.15(3)	106.949(2)	90
g(deg)	90	90	90	90	120
V (Å^3)	1677.1(2)	2196.8(3)	1153.9(4)	996.5(2)	3247.5(2)
Z	4	4	2	2	6
r_{calc}(Mgm^{-3})	1.364	1.241	1.233	1.335	1.315
m(Mo K*a*) (mm^{-1})	0.113	0.094	0.095	0.105	0.107
No. reflns.	31431	19064	25132	9773	1468
Uniquereflns.	5974	6670	4723	6055	1468
goof	1.084	1.016	1.217	1.016	1.250
R_{int}	0.0771	0.0605	0.047 (Rmerge)	0.0286	
R1[a] (*I* ³ 2s)	0.0678	0.0615	0.0489	0.0817	0.0889
wR2[b] (*I* ³ 2s)	0.1084	0.1383	0.1206	0.2048	0.2394

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

Synthesis of dimethyl 2,2'-(terephthaloylbis(azanediyl))dipropionate

L-alanine methyl ester hydrochloride (1.39 g, 10 mmol) and triethylamine (2.52 g, 25 mmol) were placed in a round bottom flask and then dissolved in dry 20 ml of dichloromethane. Terephthaloyl dichloride (1.11 g, 5mmol) in 2 ml dry dichloromethane was added dropwise to this mixture with continuous stirring. The reaction mixture was stirred for 24 hours. Then the solvent was removed under reduced pressure and a white solid was obtained. The white solid was washed with water and then extracted with dichloromethane. The organic extracts were collected and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and product was obtained methyl ester of alanine. (2.4 g, 73%). ν_{max}(KBr)/cm^{-1} 3294 (s), 3077 (w), 3001 (w), 2954 (w), 2850 (w), 1735 (s), 1637 (s), 1546 (s), 1500 (m), 1452 (m), 1441 (m), 1372 (w), 1345 (m), 1319 (m), 1288(m), 1230 (s), 1170 (s), 1116(m), 1052 (m), 1017 (w), 980 (w), 928 (w), 874 (s), 836 (w), 747 (m), 678 (s), 574 (w), 501 (w). δ_H(400 MHz; $CDCl_3$) 7.87 (s, 4H, Bn), 6.84 (d, 2H, -NH, J=8Hz), 4.82 (m, 2H, -CH), 3.81 (s, 6H,-$COOCH_3$), 1.55 (d, 6H, -CH_3, J= 8Hz). δ_C(100 MHz; $CDCl_3$) 173.6, 165.8, 136.7, 127.3, 52.7, 48.6, 18.6.

Synthesis of 2,2'-(terephthaloylbis(azanediyl))dipropionic acid (1)

Dimethyl 2,2'-(terephthaloylbis(azanediyl))dipropionate (1.68 g,

5 mmol) and sodium hydroxide (0.6 g, 15 mmol) were dissolved in 20 mL of metanol:water mixture (4:1). The reaction mixture was stirred for eight hours at room temperature. Then the solvent was evaporated under reduced pressure. The solid product was dissolved in 10 mL of water and the solution was acidified (pH = 2) with dilute hydrochloric acid solution. The obtained white solid product was filtered and washed with water. (0.9 g, 62%). (Found: C 48.61, H 5.81, N 8.11 Calc. for $C_{14}H_{16}N_2O_6.2H_2O$ C 48.83, H 5.85, N 8.14)ν_{max}(KBr)/cm^{-1} 3394 (bs), 3060 (w), 2982 (w), 2931 (w), 2542 (mb), 2019 (mb), 1732 (s), 1705 (s), 1639 (s), 1542 (s), 1500 (m), 1456 (m), 1406 (w), 1381 (w), 1345 (m), 1323 (m), 1289 (m), 1269 (s), 1240 (s), 1181 (s), 1039 (w), 1017 (w), 945 (w), 869 (s), 829 (m), 743 (s), 646 (m), 596 (m), 555 (w). δ_H(400 MHz; DMSO) 12.54 (s, 2H,-COOH), 8.77 (d, 2H, -NH, J=8Hz), 7.95 (s, 4H, Bn), 4.42 (m, 2H, -CH), 1.39 (d, 6H,-CH_3 J= 8Hz). δ_C(100 MHz; DMSO) 174.5, 165.9, 136.7, 127.8, 48.7, 17.3.

Synthesis and analysis of dimethyl 2,2'-(terephthaloylbis(azanediyl))bis(3-methylpentanoate)

Dimethyl 2,2'-(terephthaloylbis(azanediyl))bis(3-methylpentanoate) was synthesized following the synthesis of dimethyl 2,2'-(terephthaloylbis(azanediyl))dipropionate, but using L-leucine methyl ester hydrochloride (1.8 g, 10 mmol) instead of L-alanine methyl ester hydrochloride. (2.7 mg, 64%). ν_{max}(KBr)/cm^{-1} 3325 (s), 3086 (w), 3043 (w), 2956 (s), 2871 (m), 1746 (s), 1635 (s), 1550 (s), 1503 (s), 1469 (w), 1437 (w), 1340 (s), 1278 (s), 1211 (s), 1163 (s), 1122 (w), 1088 (w), 1048 (w), 1018 (m), 991 (w), 872 (m), 847 (m), 748 (m), 730 (m), 642 (bs), 480 (w). δ_H(400 MHz; $CDCl_3$) 7.77 (s, 4H, Bn), 6.94 (d, 2H, -NH, J=8Hz), 4.87 (m, 2H, -CH), 3.78 (s, 6H, -$COOCH_3$), 1.82-1.65 (m, 6H, -CH_2 and -CH), 0.98 (d, 12H, -CH_3, J= 8Hz). δ_C(100 MHz; $CDCl_3$) 174.1, 166.1, 136.4, 127.3, 52.5, 51.1, 41.4, 25.0, 22.9, 21.8. The NMR shifts were in agreement with the literature.[16]

Synthesis of 2,2'-(terephthaloylbis(azanediyl))bis(3-methylpentanoic acid) (2)

2,2'-(terephthaloylbis(azanediyl))bis(3-methylpentanoic acid) was synthesized following the synthesis of 2,2'-(terephthaloylbis(azanediyl))dipropionic acid, but using dimethyl 2,2'-(terephthaloylbis(azanediyl))bis(3-methylpentanoate) (2.1 g, 5 mmol) instead of dimethyl 2,2'-(terephthaloylbis(azanediyl))dipropionate. (1.5 g, 77%). (Found: C 55.67, H 7.25, N 6.38 Calc. for $C_{20}H_{28}N_2O_6.2H_2O$ C 56.06, H 7.53, N 6.54)ν_{max} (KBr)/cm^{-1} 3367 (bs), 3060(w), 2962 (s), 2575 (mb), 1728 (s), 1632 (s), 1545 (s), 1499 (m), 1471 (w), 1451 (w), 1387 (w), 1338 (m), 1270 (s), 1252 (s), 1180 (m), 1169 (m), 1089 (w), 1017 (w), 967 (w), 870 (s), 854 (s), 736 (s), 600 (m). δ_H(400 MHz; DMSO) 12.61 (bs, 2H, -COOH), 8.71 (d, 2H, -NH, J=8Hz), 7.95 (s, 4H, Bn), 4.44 (m, 2H, -CH), 1.80-1.55 (m, 6H, -CH_2 and -CH), 0.91 (d, 6H, -CH_3, J= 8Hz), 0.86 (d, 6H, -CH_3, J= 8Hz).δ_C(100 MHz; DMSO) 174.5, 166.2, 136.7, 127.8, 51.4, 24.9, 23.4, 21.6.

Synthesis of dimethyl 2,2'-(terephthaloylbis(azanediyl))bis(4-methylpentanoate)

Dimethyl 2,2'-(terephthaloylbis(azanediyl))bis(4-methylpentanoate) was synthesized following the synthesis of dimethyl 2,2'-(terephthaloylbis(azanediyl))dipropionate, but using L-isoleucine methyl ester hydrochloride (1.8 g, 10 mmol) instead of L-alanine methyl ester hydrochloride. (2.7 mg, 64%). ν_{max}(KBr)/cm^{-1} 3345 (s), 3051 (w), 2966 (s), 2877 (m), 1746 (s), 1638 (s), 1547 (s), 1503 (s), 1459 (m), 1434 (m), 1372 (m), 1342 (s), 1298 (s), 1254 (m), 1201 (s), 1155 (s), 1117 (w), 1089 (w), 1008 (m), 964 (w), 878 (m), 847 (m), 769 (m), 731 (s), 679 (w), 619 (bs), 589 (m), 505 (w). δ_H(400 MHz; $CDCl_3$) 7.86 (s, 4H, Bn), 6.72 (d, 2H, -NH, J=8Hz), 4.82 (q, 2H, -CH, J= 8Hz), 3.78 (s, 6H, -$COOCH_3$), 2.03 (m, 2H, -CH), 1.53 (m, 2H, -CH_2), 1.25 (m, 2H, -CH_2), 0.97 (m, 12H, -CH_3). δ_C(100 MHz; $CDCl_3$) 172.5, 166.1, 136.9, 127.4, 56.9, 52.3, 38.2, 25.4, 15.5, 11.6. The NMR shifts were in agreement with the literature.[16]

Synthesis of 2,2'-(terephthaloylbis(azanediyl))bis(4-methylpentanoic acid) (3)

2,2'-(terephthaloylbis(azanediyl))bis(4-methylpentanoic acid) was synthesized following the synthesis of 2,2'-(terephthaloylbis(azanediyl))dipropionic acid, but using dimethyl 2,2'-(terephthaloylbis(azanediyl))bis(4-methylpentanoate) (2.1 g, 5 mmol) instead of dimethyl 2,2'-(terephthaloylbis(azanediyl))dipropionate . (1.6 mg, 83%). (Found: C 58.47, H 7.28, N 6.87 Calc. for $C_{20}H_{28}N_2O_6.H_2O$ C 58.52, H 7.37, N 6.83)ν_{max}(KBr)/cm^{-1} 3463 (bs), 3411 (s), 3315(bs), 2967 (s), 2937 (m), 2546 (w), 1725 (s), 1630 (s), 1552 (s), 1524 (s), 1495 (m), 1458 (w), 1418 (w), 1385 (w), 1348 (m), 1241 (s), 1210 (s), 1168 (m), 1083 (w), 1017 (w), 974 (w), 869 (s), 728 (s), 697 (m), 600 (w), 568 (w). δ_H(400 MHz; DMSO) 12.61 (bs, 2H, -COOH), 8.71 (d, 2H, -NH, J=8Hz), 7.95 (s, 4H, Bn), 4.44 (m, 2H, -CH), 1.80-1.55 (m, 6H, -CH_2 and -CH), 0.91 (d, 6H, -CH_3, J= 8Hz), 0.86 (d, 6H, -CH_3, J= 8Hz). 8.57 (d, 2H, -NH, J=8Hz), 7.93 (s, 4H, Bn), 4.32 (t, 2H, -CH, J= 8Hz), 1.94 (m, 2H, -CH), 1.50 (m, 2H, -CH_2), 1.26 (m, 2H, -CH_2), 0.92 (d, 6H, -CH_3, J=8Hz), 0.85 (t, 6H, -CH_3, J=8Hz). δ_C(100 MHz; DMSO) 173.5, 166.6, 136.8, 127.9, 57.8, 36.1, 25.6, 16.1, 11.5.

Synthesis of dimethyl 2,2'-(terephthaloylbis(azanediyl))bis(3-methylbutanoate)

Dimethyl 2,2'-(terephthaloylbis(azanediyl))bis(3-methylbutanoate) was synthesized following the synthesis of dimethyl 2,2'-(terephthaloylbis(azanediyl))dipropionate, but using DL-valine methyl ester hydrochloride (1.7 g, 10 mmol) instead of L-alanine methyl ester hydrochloride. (2.9 g, 75%). ν_{max}(KBr)/cm^{-1} 3298 (s), 3031 (w), 2965 (s), 2875 (m), 1744 (s), 1642 (s), 1537 (s), 1501 (s), 1468 (m), 1435 (m), 1347 (s), 1321 (s), 1295 (m), 1261 (s), 1201 (s), 1160 (s), 1121 (w), 1070 (m), 1020 (s), 1002 (m), 923 (w), 862 (s), 826 (w), 737 (m), 681 (bs), 577 (w). δ_H(400 MHz; $CDCl_3$) 7.86 (d, 4H, Bn, J=8Hz), 6.66 (2H, m, -NH), 4.77 (m, 2H, -CH), 3.77 (s, 6H, -$COOCH_3$), 2.27 (m, 2H, -CH), 0.99 (m, 12H, -CH_3). δ_C(100 MHz; $CDCl_3$) 172.5, 166.2, 136.9, 127.4, 57.5, 52.4, 31.6, 18.9, 17.9.

Synthesis of 2,2'-(terephthaloylbis(azanediyl))bis(3-methylbutanoic acid) (4)

2,2'-(terephthaloylbis(azanediyl))bis(3-methylbutanoic acid) was synthesized following the synthesis of 2,2'-(terephthaloylbis(azanediyl))dipropionic acid, but using dimethyl 2,2'-(terephthaloylbis(azanediyl))bis(3-methylbutanoate) (1.9 g, 5 mmol) instead of dimethyl 2,2'-

(terephthaloylbis(azanediyl))dipropionate. (1.5 g, 84%). (Found: C 59.15, H 6.49, N 7.55 Calc. for $C_{18}H_{24}N_2O_6$ C 59.33, H 6.64, N 7.69)ν_{max}(KBr)/cm^{-1} 3444 (bs), 3325(bs), 2967 (s), 2936 (w), 2573 (bm), 1731 (s), 1629 (s), 1537 (s), 1499 (m), 1470 (w), 1394 (w), 1375 (w), 1368 (m), 1322 (s), 1253 (w), 1236 (s), 1193 (s), 1161 (s), 1033 (w), 1017 (w), 977 (m), 915 (m), 865 (s), 815 (s), 733 (s), 636 (m), 576 (w). δ_H(400 MHz; DMSO) 8.56 (d, 2H, -NH, J=8Hz), 7.94 (s, 4H, Bn), 4.28 (tr, 2H, -CH, J= 8Hz), 2.19 (m, 2H, -CH), 0.95 (tr, 12H, -CH3, J=8Hz). δ_C(100 MHz; DMSO) 173.5, 166.7, 136.9, 127.9, 58.9, 29.9, 19.8, 19.3.

Synthesis of trimethyl 2,2',2''-((benzene-1,3,5-tricarbonyl)tris(azanediyl))tripropionate

L-alanine methyl ester hydrochloride (1.39 g, 10mmol) and triethylamine (3.53 g, 35mmol) were placed in a round bottom flask and then dissolved in dry 20 ml of dichloromethane. Benzene-1,3,5-tricarbonyl trichloride (0.8 g, 3mmol) in 2 ml dry dichloromethane was added dropwise to this mixture with continuous stirring. The reaction mixture was stirred for 24 hours. Then the solvent was removed under reduced pressure and a white solid was obtained. The white solid was washed with water and then extracted with dichloromethane. The organic extracts were collected and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and product was obtained. (3.2 mg, 69%). ν_{max}(KBr)/cm^{-1}3235 (s), 3066 (s), 2991 (s), 2952 (s), 1751 (s), 1643 (s), 1562 (s), 1457 (s), 1437 (m), 1381 (m), 1318 (s), 1282 (m), 1212 (s), 1165 (s), 1133 (w), 1054 (s), 986 (m), 933 (w), 849 (m), 828 (w), 723 (s), 692 (s).δ_H(400 MHz; $CDCl_3$) 8.13 (s, 3H, Bn), 7.72 (d, 3H, -NH, J=8Hz), 4.73 (m, 3H, -CH), 3.79 (s, 9H, -$COOCH_3$), 1.58 (d, 9H, -CH_3, J=8Hz). δ_C(100 MHz; $CDCl_3$) 173.7, 165.9, 134.8, 128.6, 52.5, 48.8, 17.4.

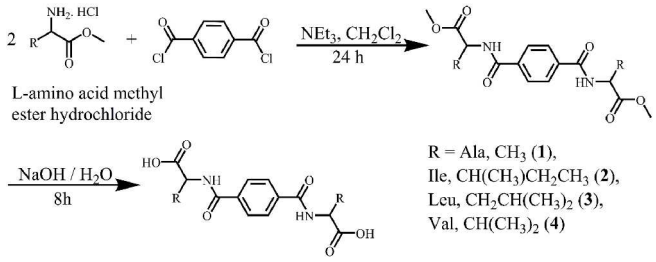
Synthesis of 2,2',2''-((benzene-1,3,5-tricarbonyl)tris (azanediyl))tripropionic acid (5)

Trimethyl 2,2',2''-((benzene-1,3,5-tricarbonyl)tris(azanediyl))tripropionate (2.3 g, 5 mmol) and sodium hydroxide (0.6 g, 15 mmol) were dissolved in 20 mL of metanol:water mixture (4:1). The reaction mixture was stirred for eight hours at room temperature. Then the solvent was evaporated under reduced pressure. The solid product was dissolved in 10 mL of water and the solution was acidified (pH = 2) with dilute hydrochloric acid solution. The obtained white solid product was filtered and washed with water. (1.9 mg, 91%). (Found: C 50.12, H 5.04, N 9.47 Calc. for $C_{18}H_{21}N_3O_9.0.5H_2O$ C 50.00, H 5.13, N 9.72)ν_{max}(KBr)/cm^{-1}3393 (bs), 3233 (m), 3066 (s), 2992 (s), 2942 (s), 1722 (s), 1644 (s), 1544 (s), 1458 (m), 1412 (w), 1382 (w), 1289 (w), 1240 (s), 1167 (s), 1053 (w), 966 (w), 922 (w), 836 (w), 741 (m), 692 (w),607 (s). δ_H(400 MHz; DMSO) 8.20 (s, 3H, Bn), 4.45 (m, 3H, -CH), 1.43 (d, 9H, -CH_3, J=8Hz). δ_C(100 MHz; DMSO) 176.5, 168.3, 134.1, 129.4, 49.4, 15.9. The NMR shifts were in agreement with the literature.[24]

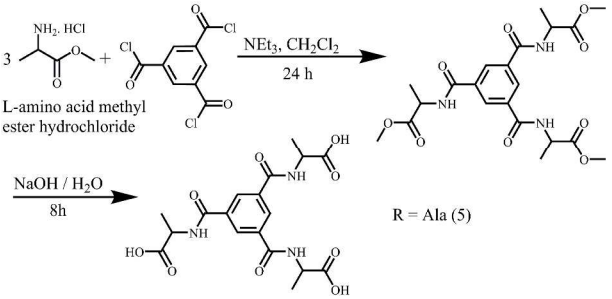
Results

Synthesis and crystallization

Compounds **1**-**5** were prepared in two steps at room temperature. In the first step protected amino acid methyl ester is introduced to terephthaloyl dichloride (**1**-**4**) or benzene-1,3,5-tricarbonyl trichloride (**5**) and in the next step the amino acid is deprotected (Schemes 1 and 2). The compounds were recrystallized from methanol (**1**, **2**), H_2O (**3**,**4**) or from D_2O (**5**) for single crystal X-ray diffraction studies. **1**-**3** were obtained enantiomerically pure while racemic valine was used to prepare **4** and **5** was obtained as a racemate.



Scheme 1. The synthesis of compounds **1**-**4**.



Scheme 2. The synthesis of racemic **5**.

Structure descriptions

A complete set of ORTEP and packing diagrams can be found in the supplementary material.

*Compound **1** dihydrate* The molecules of compound **1** are connected to each other via hydrogen bonding of N-H…O {N(1)-H(1A)…O(2)#1 3.132 Å, #1 –x+1, y-1/2, -z+1/2} and they form chains along the *b*-axis. In addition two lattice water molecules strengthens the connection of the molecules within the chain {O(7)-H(7B)…O(4)#2 2.816(3) Å, O(7)-H(7A)…O(1)#3 2.830(3) Å, #2 x-1,y,z, #3 –x,y-1/2,-z+1/2}. These chains are further connected to other chains with lattice water into a three dimensional net via hydrogen bonding {N(2)-H(2A)…O(8)#43.090 Å, O(6)-H(6A)…O(8)#5 2.611(2) Å, O(2)-H(2B)…O(7)#6 2.574(3) Å, O(8)-H(8B)…O(3)#7 2.711(2) Å, O(8)-H(8A)…O(5)#8 2.730(3) Å #4 x,y,z-1, #5 x+1,y,z-1, #6 x,y+1,z, #7 x+1/2, -y+3/2,-z+1, #8 x-1/2,-y+3/2,-z+1}.

*Compound **2** monohydrate.* Compound **2** also forms a 1D chain structure along the *b*-axis via hydrogen bonding between the carboxylic group and the ketone group {O(6)-H(6A)…O(1)#1 2.579(3) Å, #1-x+1, y-1/2, -z+3/2}. Lattice water links the chains together, forming a hydrogen bonded 3D net. Lattice water interacts with the amine groups, the ketone groups and the carboxylic groups, and act both as hydrogen bond donors and acceptors {O(3)-H(3A)…O(W1)#2 2.618(4) Å, O(W1)-H(2W1)…O(2)#3 2.748(3) Å, O(W1)-H(1W1)…O(4)#4 2.676 (3) Å, N(1)-H(1A)…O(W1) 2.948(4) Å, #2 x-1, y, z ; #3 x+1/2, -y+3/2, -z+1; #4 x-1/2, -y+3/2, -z+1}.

*Compound **3** dihydrate and compound **4** dihydrate.* Compounds **3**

and **4** are isostructural. Molecules are connected to each other via hydrogen bonding with lattice water forming a 2D hydrogen bonded network. For **3** {O(W1)-H(2W1)…O(4) 2.756(4) Å, O(W2)-H(2W2)…O(1) 2.649(4) Å, O(W1)-H(1W1)…O(2)#1 2.724(4) Å, O(3)-H(3O)…O(W1)#2 2.619(4) Å, N(1)-H(1N)…O(W1)#3 3.131(4) Å, O(W2)-H(1W2)…O(5)#4 2.705(4) Å, O(6)-H(6O)…O(W2)#5 2.609(4) Å, N(2)-H(2N)…O(W2)#6 2.909(5) Å**,** #1 x, y-1, z; #2 -x+1, y+3/2, -z+1; #3 -x+1, y+1/2, -z+1; #4 x, y+1, z; #5 -x+1, y-3/2, -z+2; #6 -x+1, y-1/2, -z+2) For **4** (O(W1)-H(2W1)…O(5)#1 2.754(5) Å, O(W1)-H(1W1)…O(1) 2.731(6) Å, N(2)-H(2N)…O(W1)#2 3.135(6) Å, O(6)-H(6O)…O(W1)#3 2.633(5) Å, O(W2)-H(1W2)…O(4) 2.711(5) Å, O(3)-H(3O)…O(W2)#4 2.599(6) Å , O(W2)-H(2W2)…O(2)#5 2.737(6)**,** #1 x, y-1, z; #2 -x+1, y+1/2, -z+2, -z+1; #3 -x+1, y+3/2, -z+2; #4 -x+1, y-3/2, -z+1; #5 x, y+1, z). There are no direct intermolecular hydrogen bonds between the amino acid derivatives.

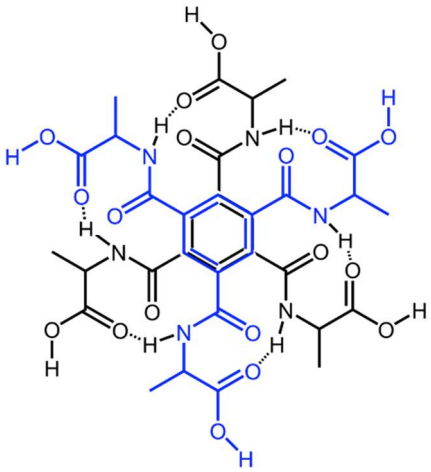


Figure 2. Schematic presentation of dimeric units (blue and black) of **5** forming via π-π stacking and hydrogen bonding (dotted line). Graph set symbol R2,2,(16).

*Compound **5***. This compound has a crystallographically imposed threefold symmetry. The methyl groups in this structure are disordered over two positions and it is therefore evident that the alanine units have racemised during preparation. This compound forms dimeric units via a completely symmetric π-π stacking (3.5 Å). In addition to aromatic interaction, the building blocks of the dimeric unit are hydrogen bonded, see Figure 2 {N(2)-H(2A)…O(2)#1 2.888(4) Å, #1 1/3+x-y,-1/3+x,2/3-z }. The hydrogen bonding also causes the substituents of the benzene rings to have the same orientation within the dimers. The substituent chains of two stacked benzene rings are anti-eclipsed/staggered. These units further connects via hydrogen bonding of O-H…O {O(3)-H(3A)…O(1)#2 2.641(4) Å, #2 1/3-x+y,2/3-x,-1/3+z} to a 3D network.

Discussion

What we want to do here is to perform a structure comparison between our compounds using first the "big picture" methods graph set analysis and Hirshfeld surfaces, and then, where needed, look into the structural details. For more general applicability we include in our discussion also the compound the earlier published structures of the glycine terephthalamide derivative **6**[32] and the glycine benzene-1,3,5-tricarboxamides derivative **7**[33].

General hydrogen bond analysis by the graph set method

Graph set analysis is a general method to investigate reoccurring hydrogen bond motifs and hydrogen bond patterns in discrete and extended assemblies.[49-51] It does not discern the different atom types such as N or O, but once criteria for hydrogen bonding are set, the analysis will generate the motifs such a chains (C) and rings (R) with the number of atoms directly involved in the bonding as well as the number of atoms linking these (in, for example, a ring). Table 2 shows graph set symbols for **1**-**7** as calculated by Mercury. We chose only to show ring-forming motifs as we believe these to be fairly distinct.

Table 2. Graph set symbols for compounds **1**-**5**

Comp.	Graph set symbol
disubst.	
1	R3,3(15); R4,4(13); R4,4(18); R3,4(17); R4,4(21)
2	R4,4(13); R4,4(18); R3,4(17); R4,4(21)
3	R4,4(13); R4,4(18); R3,4(17); R4,4(18); R4,4(21); R3,4(23)
4	R4,4(13); R4,4(18); R3,4(17); R4,4(18); R4,4(21); R3,4(23)
6	R4,4(18); R2,4(28); R3,4(17); R4,4(21); R3,4(23)
trisubst.	
5	R2,2(16); R2,2(22) R3,4(23);
7	R2,2(16); R2,2(22); R4,4(18); R4,4(20)

We note first that there a no directly hydrogen bonded dimers in the **1**-**4** compounds, because that would have implied a 2,2 designation, (i.e. two donor atoms D and two acceptor atoms H as i the acetic acid dimer with symbol R2,2(8)). Compound **1** forms hydrogen bonds directly to another building block with a loop back via a hydrogen bonded water, the R3,3 assignment. This does not happen for compound **2** that instead have chains of building block - water - building block.

Then we can also see a number of reoccurring motifs in the different structures, the shorter most likely the most significant. Thus the R4,4(13) motif is reoccurring in **1**-**4** but is absent in **6** and R2,2(16) motif is found in both **5** and **7**. An illustration to some of these motifs can be found in the supplementary material.

Comparison of compounds 1-4, and 6

Before we look into more details of structures **1**-**4** and **6** a few remarks are needed. These compounds, differing only in the amino acid chain part (R, Figure 1), all contain three distinct entities, each of them with different intermolecular "preferences". Thus we have a flat benzene ring that we often find either π - stacked or with C-H σ–π interactions. Then we have aliphatic groups (except for **6**) that will normally prefer to be in the presence of each other, and finally the polar hydrogen bond donors and acceptors that will generally "want" to have all free electron pairs and acidic hydrogens in bonding interactions.

A convenient way to get an overall picture is to use Hirshfeld surfaces. The Hirshfeld surface reveals the intermolecular interaction, and even the weaker secondary interactions such as C-H…π, C…H and H…H contacts.[52-54] This surface represents the volume where inside we have electron density dominated by the atoms in the molecule in focus, and outside electron density dominated by all other components of the crystal. Each point on the surface has one closest atom inside and one closest atom outside the surface. We can therefore determine what percentage of the surface that originates from O…H, C…C or any other close interaction. This could be a crude first way of comparing similar structures and a diagram of these percentages for compounds **1**-**4**[#] and **6**-**7** are found in Figure 3.

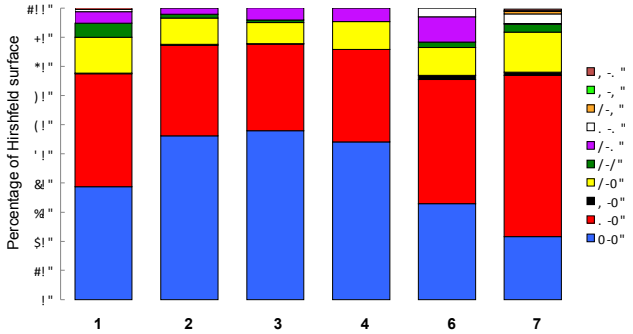


Figure 3 The major contributions to the Hirshfeld surfaces in terms of closest atom-atom interactions for compounds **1**-**4** and the glycine derivative of terephthalamide **6** and benzene-1,3,5-tricarboxamide **7**, a rough first way to compare intermolecular interactions.

We immediately see that the derivatives with longer aliphatic chains, **2**-**4** have a higher proportion of H…H interactions (blue), which is reasonable as these groups, as stated above, will tend to interaction with each other, but also, simply, because of the higher percentage of hydrogen in these molecules.[§]

Another notable feature is the higher proportion C…O (purple) in the glycine derivative **6** compared especially to **1**-**2**. This stems from the interaction of the carbonyl groups with the flat side of the benzene ring in **4**, an arrangement we suggest arises because **4** lacks the CH_3 groups that tend to come close to the aromatic ring in the alanine derivative **1**.

One thing that is not picked up so clearly in these plots is the difference between on one side compounds **3** and **4** that form the same hydrogen bonded assemblies in unit cells that are close to identical, and compound **2**.

Both of the structures **3** and **4** contain two lattice water molecules that connect the building blocks into 2D hydrogen bonded net. The interactions between the building blocks are all lattice water based. In other words there are no direct intermolecular hydrogen bonds between the actual building blocks. This is in contras to **2** that has direct hydrogen bonds between the building blocks and only one water molecule.

Worth noting here is that **3** and **4** pack with the aliphatic groups facing each other, see Figure 4, just as intuition would suggest. This leaves the aromatic ring exposed and instead of CH_3 interactions as in **1** it adopts the carbonyl interaction as in **6**.

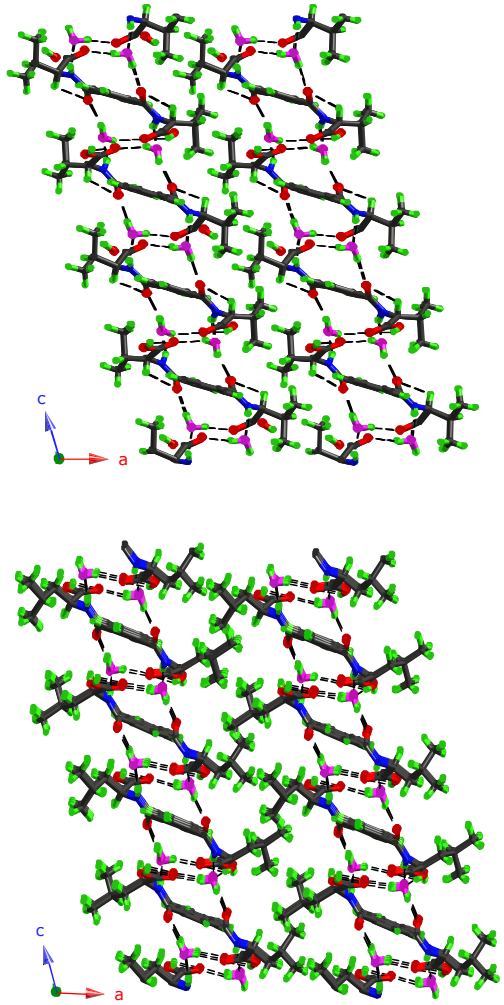


Figure 4 Packing diagrams of **3** and **4.** Note how the aliphatic groups assemble and are kept separate from the hydrogen bonding parts.

Another property of **3** and **4** that has some implications is the chirality. As racemic valine was used, **4** is a racemic compound and the crystals obtained are of the **R,S** molecule an non-chirodescriptive space group would have been expected. However, solutions in P2/1c give a significantly higher R-factor than when solved and refined in the space group $P2_1$, and the apparent centre of symmetry is only pseudo. The abnormal anisotropic displacement parameters of the C8-carbon (see figure S18) could be due to some minor R/S disorder present at the

chiral carbon, however this could not be satisfactorily modelled.

On the other hand, **3** is enantiomerically pure (some indication of very minor isomerisation can be detected and again, solutions in P2/1c give a significantly higher R-factor) and the chirodescriptive space group $P2_1$ logical. Somehow there is thus a chiral arrangement of **4**. This riddle is solved when one realizes first that the R-side is always facing another R side and vice-versa and that the aliphatic groups meet around a screw axis parallel to the b-axis, thus arranging these groups in a chiral, helical, way.

This observation then begs the question why compound **2** does not form the same kind of structure, being an isomer of **3**. It is hard to phantom why the same packing and chiral arrangement would not be possible, but we refrain from further speculation, as this may simply be a question of crystallization conditions.

Comparing compound 5 and compound 7

The local molecular structure of **5** resembles that of the earlier published glycine derivative 2,2',2''-((benzene-1,3,5-tricarbonyl)tris(azanediyl))triacetic acid trihydrate[33] **7** as they both form the R2,2(19) based dimers, see Figure 2. However, the absence of methyl groups make it possible for the protruding chains to pack closer in **7**. In addition, the glycine derivative has lattice water in the structure that participates in a hydrogen bond network.

In contrast to **7**, the dimeric units in **5** are further connected to six other dimers units via hydrogen bonding of O-H…O O(3)-H(3A)…O(1)#2 2.641(4) Å, #2 1/3-x+y,2/3-x,-1/3+z} forming a **pcu**-net, the most common of the six-connected nets[55], see Figure 5.

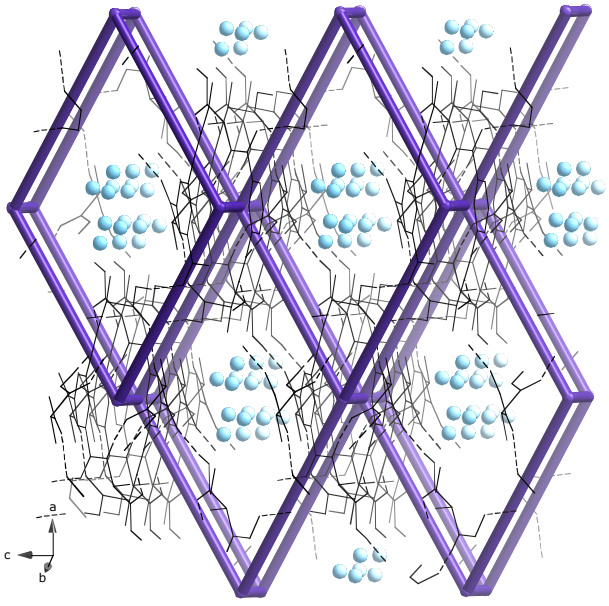


Figure 5. The hydrogen bonded **pcu**-net formed by the dimeric units of **5** with disordered water molecules (blue spheres) in the roughly 3·3 Å wide channels.

Summary and conclusions

The linear disubstituted compounds can be categorized into three groups. Compound **1** and **2** form 3D hydrogen bonded nets that have some, but not all ring graph symbols identical, thus the final structure and network is not the same. Compound **1** forms chains via direct hydrogen bond of N-H…O between the terephthalamide derivatives. In addition two water molecules assist the chain formation and further on link the chains together via hydrogen bonding. Compound **2** also contains one direct intermolecular hydrogen bond between the terephthalamide derivative molecules. However, the hydrogen bond is formed between carboxylic COH-group and ketone CO-group. Lattice water links the chains together. Compounds **3** and **4** form 2D hydrogen bonded structures where all the connections between terephthalamide derivatives are water mediated. Notably graph set symbol R4,4(18) is recurring in all these substituted compounds.

Compound **5** forms hydrogen bonded dimers and comparison with **7** suggests that this motif is strong and recurring. In contrast to the glycine derivative **7**, in compound **5** these dimers are connected to each other via hydrogen bonds and form a 3D **pcu**-net. Hirshfeld surface analyses of compounds **1**-**7** indicate some of the differences between these systems and graph set symbols are also helpful in categorising and discovering differences and similarities.

From a synthesis point of view, important for the further use of these ligands in building MOFs, it will be important to have complete control of the stereochemistry and less harsh conditions may be needed.

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Notes and references

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The disorder of **5** makes a Hirshfeld surface difficult to compare and interpret.

§ Possible ways to account for the difference in composition are to weigh the contributions by atom percentages or to calculate interactions only for the part that all molecules have in common.

† Electronic Supplementary Information (ESI) available: CIF files and additional structure and Hirshfeld plots. See DOI: 10.1039/b000000x/

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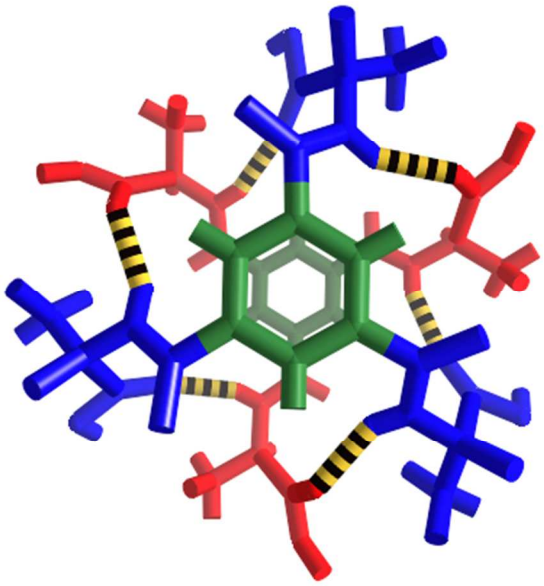
TOC Entry



This amino acid dervied (red&blue) π-stacked (green) hydrogen bonded (striped) dimer forms a **pcu**-net with water molecules in the narrow channels. Four related molecules are also presented and all were subject to graph set and Hirshfeld surface analysis.