

# An alternating chain of spider-like tris(peptides) stabilized by stacking and by N–H···N and N–H···O=C hydrogen bonding

Ramu Kannappan<sup>a</sup>, Duncan M. Tooke<sup>b</sup>, Anthony L. Spek<sup>b</sup>, Jan Reedijk<sup>a,\*</sup>

<sup>a</sup>*Gorlaeus Laboratories, Leiden Institute of Chemistry, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands*

<sup>b</sup>*Department of Crystal and Structural Chemistry, Bijvoet Center for Biomolecular Research, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands*

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## Abstract

The X-ray crystal structure of the novel spider-like trispeptide *N,N',N''*-tris(2-aminopyridine)benzene-1,3,5-tricarboxamide shows the unexpected formation of a new extended polymeric architecture. The structure is characterized by cooperative hydrogen bonding generating neighbouring pairs by self-assembly, and stacking between rings. Pairs of amide groups related by an inversion centre are connected into dimers via two N–H···O<sub>carbonyl</sub> and two N–H···N<sub>pyridyl</sub> intermolecular hydrogen bonds. The offset-stacked layers are tightly inter-linked (spacing of 3.477 Å) by hydrogen bonding and aromatic  $\pi$ – $\pi$  stacking interactions. These dimers are further linked into polymeric chains by hydrogen bonding through bridging methanol solvent molecules. The central aromatic rings of molecules in adjacent dimers are once again related by inversion symmetry, with a perpendicular separation of 3.619 Å.

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**Keywords:** Scaffold; Peptide linkage; Hydrogen bonding

## 1. Introduction

The design and synthesis of peptides and other synthetic models for complex self-assembly in the crystalline state or in solution has attracted much recent interest [1–4]. A main challenge in crystal engineering and supramolecular chemistry is to use basic concepts for design and development of structures in a desired shape, which can assemble in a predictable, pre-determined fashion to generate special structural components [5,6], such as sheets [7], ribbons [8], tubes [9] and rods [10]. Hydrogen bonds and  $\pi$ – $\pi$  aromatic contacts are commonly used as tools to link molecules into such supramolecular assemblies.

Only three reports of structures are known in which an aromatic ring has been used as the scaffold for three peptide strands [10–12]. In these and other related structures the aromatic rings typically adopt one of several known conformations, of which the most common are edge-face,

offset stacked and face–face stacked [13,14]. The offset stacked geometry is the most common geometry for aromatic interactions, but the least well studied. In the expectation of shedding new light on this subject, we report the ‘spider-like’ crystal structure of *N,N',N''*-tris(2-aminopyridine)benzene-1,3,5-tricarboxamide (1) (Fig. 1).

## 2. Experimental section

### 2.1. Physical measurements

All chemicals and solvents were used as received. C, H and N analyses were performed with a Perkin–Elmer 2400 series II analyzer. Infrared spectra (4000–300 cm<sup>–1</sup>) were recorded on a Perkin–Elmer Paragon 1000 FTIR spectrometer equipped with a Golden Gate ATR device, by using the reflectance technique. The <sup>1</sup>H NMR spectrum was recorded on a Bruker 300 DPX MHz spectrometer in CD<sub>3</sub>OD solution, using TMS as the internal standard. An Electrospray mass spectrum (ESI-MS) in methanol was recorded on Thermo finningan AQA apparatus.

\* Corresponding author. Tel.: +31 0715274450; fax: +31 0715274671.  
E-mail address: [reedijk@chem.leidenuniv.nl](mailto:reedijk@chem.leidenuniv.nl) (J. Reedijk).

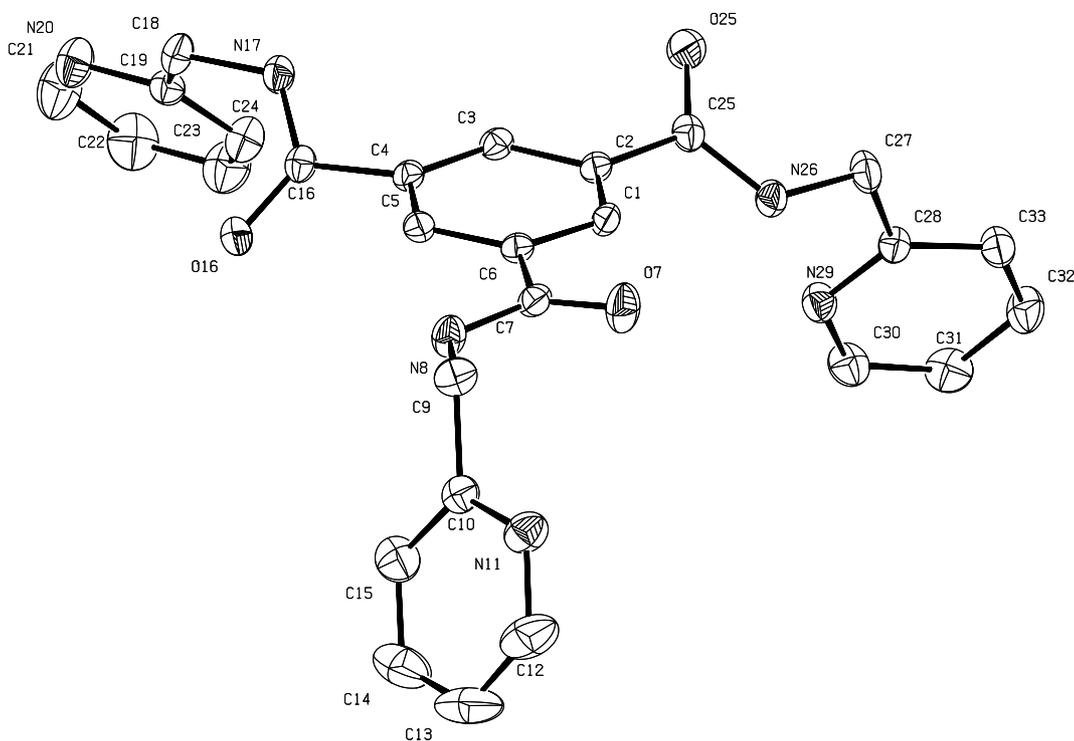


Fig. 1. An ORTEP diagram of (1) showing the atom labelling scheme. Displacement ellipsoids are shown at 50% probability. C–H hydrogen atoms and solvent molecules omitted for clarity.

## 2.2. Synthesis $N,N',N''$ -tris(2-aminopyridine)benzene-1,3,5-tricarboxamide (1)

A solution of 1,3,5-benzenetricarbonyl chloride (2.24 g, 0.0084 mol, 20 mL DMF) was added drop wise to a stirred mixture of 2-(aminomethyl)pyridine (2.7 g, 0.0252 mol) and  $\text{Et}_3\text{N}$  (3.6 mL) in 50 mL DMF at  $0^\circ\text{C}$  for 3 h. The temperature was increased to room temperature and left overnight with stirring, and the resulting solution was filtered to remove the chloride salt of  $\text{Et}_3\text{N}$ . A yellow oily residue was obtained after removing the solvent by rotaevaporation. A mixture of ethylacetate/hexane (4:1) was added to the residue and refluxed for a further 2 h. The solvent was decanted and the residue was dried by vacuum. A pale yellow solid was obtained, crude product: yield of 58.5%, mp  $29\text{--}32^\circ\text{C}$ , FT-IR (in  $\text{cm}^{-1}$ ): 3270 (s, N–H stretch), 1636 (s, C=O stretch in amide), 1654, 1539 and 1284 stretch corresponds to amide I, II, III), (1747 stretch to C(O)Cl disappeared).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , in ppm): 8.64 (s, 3H, N–H), 8.53 (s, 3H, Py), 7.88 (m, 3H, Py), 7.52(m, 3H, Py) 7.33 (m, 3H, Py).  $m/z$  (ES) Calcd for  $\text{C}_{27}\text{H}_{24}\text{N}_6\text{O}_3$  480.5. Found 480.8. Satisfactory C, H and N analyses were obtained, Calcd C, 67.48; H, 5.03; N, 17.48%. Found C, 65.56; H, 5.19; N, 17.01%.

## 2.3. X-ray crystallographic study

Transparent crystals of (1) were obtained by recrystallization from hot methanol. The X-ray data were collected

with a Nonius KappaCCD diffractometer using graphite-monochromatized  $\text{Mo K}\alpha$  radiation. An initial unit cell determination was performed using the Nonius Collect [15] software suite and the DIRAX [16] indexing program. A complete dataset was collected, and integrated by the EvalCCD [17] program. No absorption correction was applied. The structure was solved using the SHELXS-86

Table 1  
Selected crystallographic data of  $[\text{C}_{27}\text{H}_{24}\text{N}_6\text{O}_3 \cdot 2(\text{CH}_3\text{OH})]$  (1)

Empirical formula	$\text{C}_{27}\text{H}_{24}\text{N}_6\text{O}_3 \cdot 2(\text{CH}_4\text{O})$
Formula weight	544.61
Temperature (K)	293
Crystal system	Triclinic
Space group	$P\bar{1}$ (# 2)
$a$ (Å)	7.8044(7)
$b$ (Å)	11.1993(10)
$c$ (Å)	15.6103(14)
$\alpha$ ( $^\circ$ )	82.505(9)
$\beta$ ( $^\circ$ )	88.802(8)
$\gamma$ ( $^\circ$ )	88.366(7)
Volume (Å <sup>3</sup> )	1352.0(2)
$Z$	2
Calculated density ( $\text{Mg/m}^3$ )	1.338
Absorption coefficient ( $\text{mm}^{-1}$ )	0.094
Number of parameters/restraints	377, 0
Measured reflections	34950
Independent reflections	5877
$R_{\text{int}}$	0.060
Reflections with $I > 2\sigma(I)$	4033
Final $R/wR2$ [ $I > 2\sigma(I)$ ]	0.050, 0.113
Goodness-of-fit on $F^2$	1.04
Largest difference peak and hole ( $\text{e}\text{\AA}^{-3}$ )	0.36 and $-0.34$

Table 2  
Selected bond lengths (Å) and angles (°) for (1)

Bond lengths		Bond angles	
O(7)–C(7)	1.223(2)	C(7)–N(8)–C(9)	120.84(16)
O(25)–C(25)	1.223(2)	C(16)–N(17)–C(18)	122.45(16)
N(8)–C(9)	1.448(2)	C(25)–N(26)–C(27)	121.05(17)
N(11)–C(12)	1.339(3)	O(7)–C(7)–N(8)	122.75(16)
N(17)–C(18)	1.446(2)	N(17)–C(16)–C(4)	117.10(16)
N(20)–C(21)	1.339(3)	C(7)–N(8)–H(8)	120.9(14)
N(26)–C(27)	1.443(2)	C(16)–N(17)–H(17)	122.3(13)
N(29)–C(30)	1.342(2)	C(25)–N(26)–H(26)	119.8(13)
N(17)–H(17)	0.88(2)	C(10)–N(11)–C(12)	117.66(17)
O(16)–C(16)	1.237(2)	C(19)–N(20)–C(21)	117.47(17)
N(8)–C(7)	1.344(2)	C(28)–N(29)–C(30)	116.76(16)
N(11)–C(10)	1.335(2)	O(16)–C(16)–C(4)	119.76(16)
N(17)–C(16)	1.330(2)	O(25)–C(25)–N(26)	123.42(17)
N(20)–C(19)	1.339(2)	C(9)–N(8)–H(8)	118.2(14)
N(26)–C(25)	1.347(2)	C(18)–N(17)–H(17)	115.2(13)
N(29)–C(28)	1.336(2)	C(27)–N(26)–H(26)	119.1(13)
N(8)–H(8)	0.84(2)	O(7)–C(7)–N(8)–C(9)	6.1(3)
N(26)–H(26)	0.87(2)	O(16)–C(16)–N(17)–C(18)	–0.5(3)
		O(25)–C(25)–N(26)–C(27)	1.4(3)

Table 3  
Hydrogen bonding distances (Å) and angles (°) in (1)

D–H···A	D–H	H···A	D···A	D–H···A
O(34)–H(34)···N(20)	0.82	2.21	2.921(2)	146
O(35)–H(35)···N(11)	0.82	1.92	2.731(2)	173
N(17)–H(17)···O(35)	0.88(2)	1.96(2)	2.787(2)	157(2)
N(26)–H(26)···O(16)	0.87(2)	2.12(2)	2.969(2)	164(2)
N(8)–H(8)···N(29)	0.84(2)	2.23(2)	3.024(2)	159(2)

[18] program, and refined with SHELXL-97 [19]. The program PLATON [20] was used for space group determination, validation and the preparation of diagrams. C–H hydrogen atoms were placed at idealised positions and allowed to ride on the connecting atom, whereas N–H hydrogen atoms were located in a difference Fourier map and freely refined isotropically. The data have been given in Tables 1–3.

### 3. Results and discussion

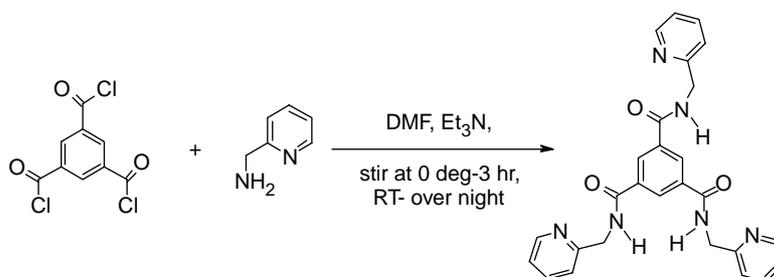
The new supramolecular tripodal ligand (1) was synthesised as indicated in Scheme 1 using the trisacid

chloride, 2-(aminomethyl)pyridine and Et<sub>3</sub>N in DMF. The structure of the ligand was elucidated using IR and UV–vis spectroscopy, elemental analysis, FAB mass spectrometry and single crystal X-ray diffraction. This tripodal ligand is reproducibly prepared with the same solvent as confirmed by spectral analytical studies. The spectral and analytical data of crude yellow solid compound are given in the experimental section. The <sup>1</sup>H NMR spectrum, δ(N–H) 8.64 ppm and the aromatic proton of centre ring and pyridine rings are in the expected range of 7.33–8.00 ppm.

The structure reported in this paper in fact represents two different modes of hydrogen bonding organisation. The molecular structure of (1) is shown in Fig. 1 and selected bond distances and angles are listed in Table 2. An aromatic ring is used as the scaffold for three peptide functions, all of which do point in the same spatial direction, roughly perpendicular to the plane of the aromatic ring. This generates an ideal self-complementary building block to be held by N–H···O and N–H···N hydrogen bonds. This supramolecular structure differs from that of Lightfoot et al. [10] and of Palmans et al. [12] by its N–H···N hydrogen bonds.

The C=O and N–H groups in each ‘arm’ are roughly planar, with bond lengths of 0.88(2) Å, 1.237(2) Å, 0.84(2) Å, 1.223(2) Å, 0.87(2) Å and 1.223(2) Å (N(17)–H(17), O(16)–C(16), N(8)–H(8), O(7)–C(7), N(26)–H(26) and O(25)–C(25), respectively), and torsion angles of 6.1(3)°, –0.5(3)°, and 1.4(3)° (O(7)–C(7)–N(8)–C(9), O(16)–C(16)–N(17)–C(18) and O(25)–C(25)–N(26)–C(27), respectively) (Table 2). The dihedral angles between ring least squares planes are 67.52(9)°, 50.84(9)°, 69.44(8)°, 65.19(10)°, 75.54(10)° and 39.65(10)° for the central ring with the N(11), N(20) and N(29) pyridyl rings, and N(11)–N(20), N(11)–N(29) and N(20)–N(29) rings, respectively.

The unit cell contains two amide and four methanol solvent molecules. Pairs of amide molecules related by an inversion centre are connected into dimers via two N–H···O<sub>carbonyl</sub> and two N–H···N<sub>pyridyl</sub> intermolecular hydrogen bonds. The central aromatic rings of the two molecules additionally feature an offset π–π interaction [21], with a ring separation of 3.477 Å and a perpendicular slippage of 0.472 Å (Fig. 2).



Scheme 1.

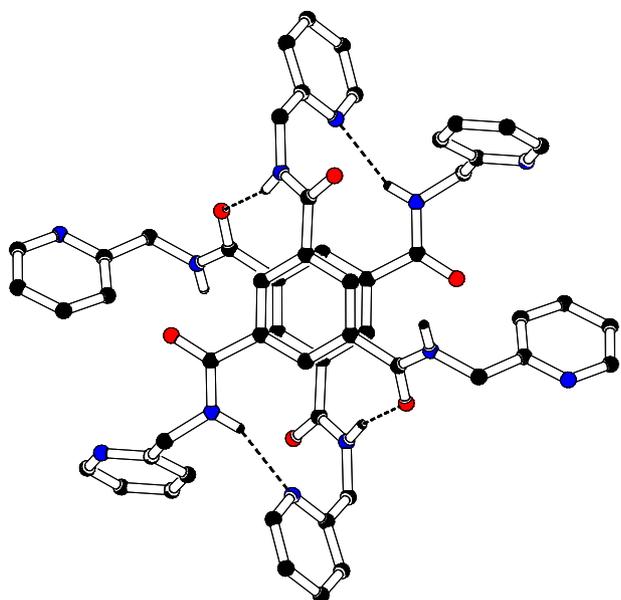


Fig. 2. Pairs of amide molecules joined over an inversion centre by intermolecular N–H $\cdots$ N hydrogen bonds. Other N–H groups are used in the formation of a chain of dimers. The view is perpendicular to the mean planes of the two rings, which are parallel by symmetry and feature an offset  $\pi$ – $\pi$  interaction with a perpendicular slippage of 0.472 Å. Solvent molecules and C–H hydrogen atoms omitted for clarity.

The co-crystallised methanol molecules contribute to an interesting hydrogen bonding pattern [22]. The dimers are connected to form a polymeric network, via hydrogen bonding with one of the two included MeOH molecules, in an N–H $\cdots$ O–H $\cdots$ N<sub>pyridyl</sub> arrangement (O(34)–H(34) $\cdots$

N(20)=2.921(2) Å and N(8)–H(8) $\cdots$ N(29)=3.024(2) Å). This arrangement leads to the formation of an infinite chain parallel to the crystallographic *a*-axis (Fig. 3). The second solvent molecule hydrogen bonds to a pyridyl nitrogen, with O(35)–H(35) $\cdots$ N(11)=2.731(2) Å, and is not involved in the formation of the polymer. The central aromatic rings of molecules in adjacent dimers are once again related by inversion symmetry, with a perpendicular separation of 3.619 Å. However, rather than the two rings being almost directly stacked they are displaced, with a perpendicular slippage of 3.604 Å.

#### 4. Conclusions

In this work, the synthesis and characterisation of the new spider-like tripeptide strands together with its crystal structure has been described. It appears that the MeOH solvent is essential to hold up the stability of the crystals, unquestionably due to its role as a guest arbitrator to connect the molecule in its specific network structure. The pair of amide molecules are related by an inversion centre and connected into dimers via two N–H $\cdots$ O<sub>carbonyl</sub> and two N–H $\cdots$ N<sub>pyridyl</sub> intermolecular hydrogen bonds. The above results indicate that hydrogen bonding provides the basis for a macrocyclic organisation. The orientation of two stacked rings may additionally have a significant effect on the magnitude of the interactions in a spider like structure, and may also have implications in the stacking of other rings such as DNA bases.

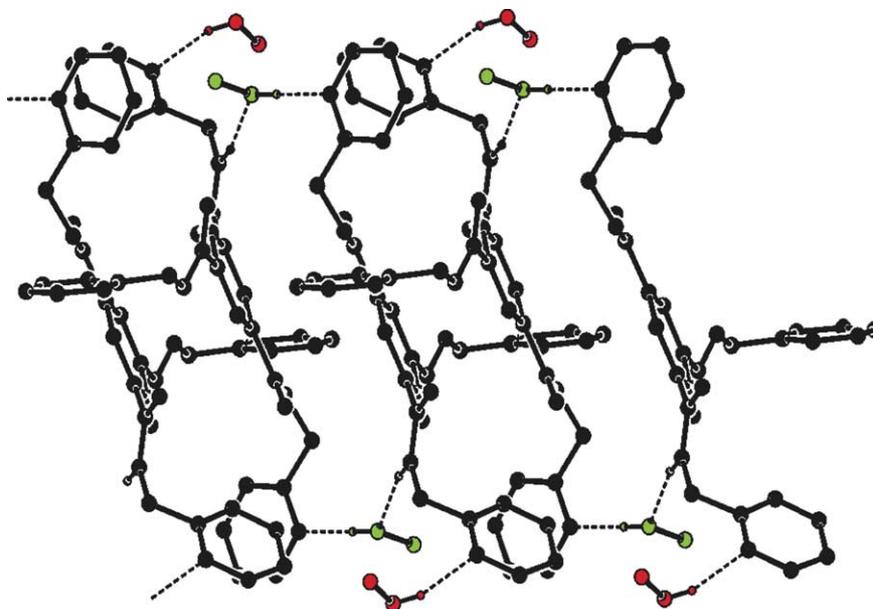


Fig. 3. Hydrogen-bonding pattern in the chain of dimers in (1). Bridging hydrogen bonded solvent molecules in green and singly hydrogen bonded solvent molecules in red. Unrelated hydrogen atoms have been omitted for clarity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

## 5. Supplementary materials

Crystallographic data for the structure reported has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number 258324, and can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [Fax: (Internet) +44 1223/336 033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)]. See <http://www.rsc.org/suppdata/nj/> for crystallographic data in cif format.

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