

Stacking of a benzenhexacarboxylic acid core in the crystal structure of benzenhexacarboxylic acid α -aminomethyl isobutyrate amide (MA-Aib₆)–sodium nitrate complex†

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Received (in Columbia, MO, USA) 20th August 2001, Accepted 4th October 2001

First published as an Advance Article on the web 22nd November 2001

MA-Aib₆ forms discrete stacks with sandwiched water, sodium and nitrate ions, presenting a novel profile, where nine out of the 12 binding sites, of the six amides present, are involved in bonding with water, sodium and nitrate ions, with no inter-amide hydrogen bonding. This is the first example of the stacking of a benzenhexacarboxylic acid core.

The design and synthesis of conformationally constrained organic scaffolds/templates that can potentiate controlled growth to protein secondary structure motifs, is of current interest.¹ Such structural mimics are important for the design of simple, low molecular weight pharmaceutical agents.² The present communication reports the synthesis of benzenhexacarboxylic acid α -aminomethyl isobutyrate amide (MA-Aib₆, C₆[CONHC(CH₃)₂COOMe]₆ (**1**) and the determination of its structure by X-ray crystallography. The choice of α -aminomethyl isobutyrate as the first spacer was logical because of the known ability of the Aib residue to control the growth of secondary structures.³

The tertiary carbon center present in Aib resisted the introduction of all the six units in a single step. The best conditions afforded only MA-Aib₅ mono imide (**2**), which, on *in situ* treatment with further Aib gave **1**. Thus, the reaction of hexamellitoyl chloride⁴ with Aib-OMe under carefully defined conditions followed by chromatography on silica gel column and elution with ethylacetate–hexane afforded nearly pure MA-Aib₆ in 41% yield.⁵ Re-chromatography under the same conditions afforded fine needles, mp 256–258 °C, that separated from the eluent (Fig. 1).

The crystal structure⁶ of MA-Aib₆ (**1**) (Fig. 2) shows its assembly to layered stacks along a two-fold screw axis where molecules of MA-Aib₆ on the one hand and water and sodium nitrate on the other, form alternate layers (Fig. 2). The ester groups, projected vertically, do not participate in the assembly. The twelve α -methyl groups from each molecule form a neat ring around the stack. The pattern of the stack is repeated every

14.3 Å. Each stack is quite independent of the others and there are no hydrogen bonds between stacks or any interdigitation.

In the stack, shown with a central MA-Aib₆ flanked by two neighbors as presented in Fig. 2, the aromatic rings are tilted slightly along the two-fold screw axis by 2.9°. The sodium ion is penta-coordinated to two proximate carbonyls of the upper layer (Na \cdots O30, 2.472 Å; Na \cdots O40, 2.488 Å) and a single carbonyl from the middle layer (Na \cdots O0, 2.255 Å), as well as to both water molecules (Na \cdots W3, 2.463 Å, Na \cdots W4, 2.415 Å). The short Na \cdots O0 distance of 2.255 Å is found in penta-coordinated Na⁺ complexes⁷ but not for tetra- or hexa-complexes. The water molecules are, in addition, bonded to carbonyls from the middle layer (W3 \cdots O10, 2.872 Å; W4 \cdots O50, 2.813 Å), the NH of the upper layer (W3 \cdots N21, 3.011 Å; W4 \cdots N51, 2.996 Å) and the nitrate ion (W3 \cdots O1S, 3.102 Å; W4 \cdots O2s, 2.824 Å). In turn, the nitrate ion is an acceptor for the NH of the middle layer (N31 \cdots O1s, 2.984 Å) and NH in the upper layer (N1 \cdots O2S, 2.805 Å). Thus, of the twelve binding sites available in the hexa-amide **1**, five carbonyl groups and four NH units are used in a unique manner; while N11 and N41 do not participate in any manner. The absence of any inter amide hydrogen bonding and the strong involvement of the nitrate counter ion in the assembly are particularly noteworthy.

A schematic profile of the stacking is presented in Fig. 3.

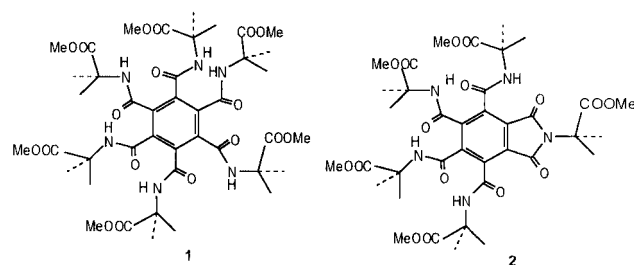


Fig. 1 Structure of **1** and **2**.

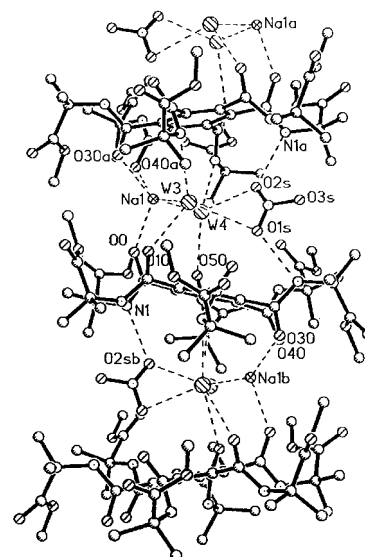


Fig. 2 The crystal structure of **1**. A Na⁺ ion, NO₃[−] ion and two water molecules (W₃ and W₄) are also indicated. The columnar stacking of molecules **1** alternating with Na⁺ and NO₃[−] ions and two water molecules. The dashed lines indicate the five ligands to Na⁺ and hydrogen bonds between water molecules, the NO₃[−] ion and **1**.

† Respectfully dedicated to Darshan Ranganathan, who passed away on June 4, 2001, her sixtieth birthday.

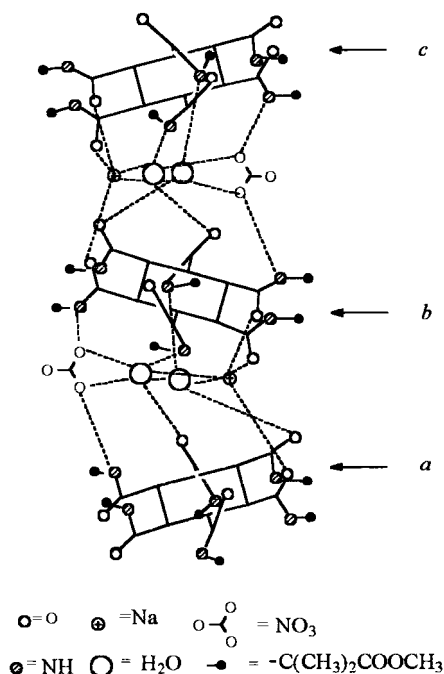


Fig. 3 Schematic drawing of the layered structure in a stack.

Using a sample of the crystal, the presence of sodium nitrate was confirmed by using positive and negative ion mass spectrometry. By negative ion mass spectrometry, the source of sodium nitrate was traced to the silica gel used for chromatography.⁸ Chromatographically pure MA-Aib₆, freed of nitrate⁹ when allowed to stand in ethyl acetate with dissolved sodium nitrate, deposited needles identical to that used for crystallographic studies.¹⁰

Further experiments have shown that in the complexation of **1**, the nature of the metal ion is important. Thus, under identical conditions lithium nitrate formed the complex whereas potassium nitrate did not.¹¹ However it is very likely that in the assembly of **1** the nitrate ion, being large and with dispersed charge, plays a controlling role to the extent that the expected hydrogen bonding involving the amide bonds is not seen.

To the best of our knowledge, this is the first report of achieving the stacking of a benzenehexacarboxylic acid core. Crystallographic data currently available relating to mellitic acid, its esters and metal salts are unexceptional.¹²

Financial support was provided by the National Institutes of Health Grant GM-30902, the Office of Naval Research and the Department of Science and Technology, New Delhi.

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- Mellitic acid [1.62 g, 4.73 mmol] was digested with PCl₅ [9.8 g, 47 mmol] at 150 °C for 24 h, excess reagent and POCl₃ distilled off, the residue triturated with dry benzene [5 × 10 ml] and dried to give 1.8 g [84%] of hexamellitoyl chloride mp 245–247 °C, whose structure was confirmed by methanolysis to mellitic acid hexamethyl ester and comparison with an authentic sample.
- A solution of hexamellitoyl chloride [0.48 g, 1.1 mmol] in dry CH₂Cl₂ (20 mL) and triethylamine (1 mL, 6.7 mmol) were simultaneously added, in drops, over a period of 0.5 h to an ice cooled and stirred solution of α-amino isobutyric acid methyl ester, generated *in situ* by addition of triethylamine (1 mL, 6.7 mmol) to an ice cooled and stirred solution of α-amino isobutyric acid methyl ester hydrochloride (1.48 g, 9.67 mmol) in dry CH₂Cl₂ (65 mL). The reaction mixture was left stirred at room temperature for two days. After this period another batch of α-amino isobutyric acid methyl ester, precisely generated as described above from the hydrochloride (1.48 g, 9.67 mmol) in dry CH₂Cl₂, was introduced, the mixture left stirred for 2 d at rt, washed successively with saturated NaHCO₃ (2 × 15 mL), 2 N H₂SO₄ (2 × 15 mL), water (2 × 15 mL), dried (MgSO₄) and the residue chromatographed on silica gel. Elution with hexane–EtOAc = 8:2 afforded 0.420 g (41%) of nearly pure MA-Aib₆ (**1**), mp 247–250 °C; δ_H (200 MHz, DMSO-d₆) 1.68 (s, 36H), 3.71 (s, 18H), 7.00 (br, 6H); FAB-MS (*m/z*) (%) 959 (M + Na⁺) (60), 820 (M + H⁺ – Aib) (44), 703 (M + H⁺ – 2Aib) (100), 586 (M + H⁺ – 3Aib) (8). Further elution gave 0.100 g (11%) of **2**, mp 203–205 °C. When the second batch was not added, work up afforded exclusively **33** of **2**, mp 203–205 °C; δ_H (200 MHz, CDCl₃) 1.66, 1.77, 1.88 (s, s, s, 30H), 3.68, 3.73, 3.78 (s, s, s, 15H), 7.13 (br, 4H); FAB-MS (*m/z*) (%) 842 (M + Na⁺) (77), 703 (M + H – Aib) (100%), 586 (M + H⁺ – 2Aib) (24).
- Crystal data for **1**: C₄₂H₆₀N₆O₁₈·2H₂O·NaNO₃, space group *Pna*2₁, *a* = 14.286(1) Å, *b* = 14.614(1) Å, *c* = 24.800(5) Å, *V* = 5177.9 Å³, *D_c* = 1.352 g cm^{–3}, Cu-Kα radiation, λ = 1.54178 Å. Least squares refinement on *F*², *R*₁ = 0.0512 for 4480 data [*|F|* > 4.0σ(*F*)] and *wR*₂ = 0.1388 for all data. Data collection at 293 °C. CCDC 173157. See <http://www.rsc.org/suppdata/cc/b1/b109465n/> for crystallographic files in .cif or other electronic format.
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- Silica gel (2.0 g), used for chromatography, was triturated with ethyl acetate (5 mL), filtered and the clear filtrate evaporated. Negative ion Ms of the residue clearly showed presence of nitrate and the positive ion Ms that of sodium ion.
- Chromatographically pure MA-Aib₆ (0.005 g, mp 247–250 °C) was triturated with distilled water (3 × 2 mL), centrifuged and dried *in vacuo* to afford sample, mp 238–239 °C which was shown to be totally free of sodium nitrate by Ms.
- Sodium nitrate (0.005 g) in water (2 mL) was shaken with ethyl acetate (2 mL), the layers separated and the organic layer filtered through cotton to give a clear solution in which salt freed MA-Aib₆ from the above experiment was dissolved and left aside. Fine needles, mp 256–258 °C, identical to that used for crystallographic studies were slowly deposited. These were demonstrated to contain sodium nitrate by positive and negative ion mass spectrometry.
- The conditions used were similar to that described above. Unlike sodium nitrate, crystals were not deposited with lithium nitrate and potassium nitrate, on standing. Solvents were evaporated, the residue washed with water to remove uncomplexed salts, centrifuged, dried and the resulting fine powders, when analyzed by both positive and negative ion mass spectra, clearly showed complexation with lithium nitrate and the absence of this with potassium nitrate. In view of the exclusive preference of the amide groups for hydrogen bonding with nitrate ions seen with **1**, the lithium nitrate complex is likely to have a structure similar to that with sodium nitrate.
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