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Structural analysis of bis-bispidine tetraazamacrocycle: Long-range weak interactions in a channeled organic crystal

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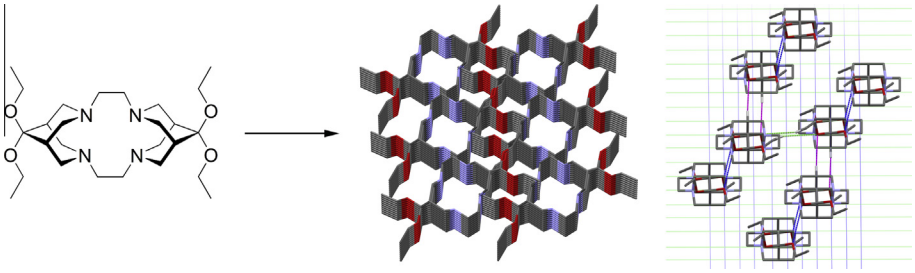
HIGHLIGHTS

- Tetraethoxy bis-bispidine macrocycles stack to form channels in the solid state.
- This is the first of bis-bispidine compounds to exhibit tubular self-assembly.
- An unusual 3D orthogonal matrix has been observed in the crystal structure.
- Long-range weak C—H···O and N—C···O—C interactions direct molecular alignment.

GRAPHICAL ABSTRACT



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ABSTRACT

A new organic crystal containing one-dimensional channels has been obtained through the synthesis and self-assembly of tetraethoxy bis-bispidine tetraazamacrocycles. The pre-fabricated macrocyclic cavities stack on each other to form ordered channels with highly basic inner cores. Based on the data of the single crystal structure, analysis of a 3D matrix indicates that weak directional interactions such as long-range C—H···O hydrogen bonds and N—C···O—C dipole–dipole interactions play an important role in the molecular alignment.

Introduction

Synthetic organic crystals which contain channeled or tubular structures are important and have attracted significant research attention in chemistry and materials science. In addition to their functions, the structures of these materials have been studied extensively in an effort to elucidate the building processes as well as to develop novel crystals [1–5]. A common approach to such materials is through self-assembly of rigid macrocycles by stacking via non-covalent interactions. However, since organic molecules tend to pack closely with minimal void space, dense structures are usually obtained without any channels [6]. A feasible strategy to align macrocycles involves the utilization of directional interactions such as hydrogen bonding, π-stacking, and dipole–dipole interactions. This has led to the assembly of tubular structures from building blocks containing aromatic [7–10], peptide [11,12], urea [13,14], and oligosaccharide units [15]. However, weak directional interactions such as C—H···O hydrogen bonds have rarely been reported as the principal driving forces in the formation of channeled organic crystals [16]. This is particularly the case at long H···O distances where the interaction becomes weaker.

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Bis-bispidine (**1**) is a new category of macrocycles whose tetramine cavity exhibits unprecedented ligand field strength (Fig. 1) [17–19]. With the cavity enclosed by a rigid molecular framework, the macrocycles have the capacity to resist buckling in the solid state, making them promising candidates in the formation of channeled organic crystals. To date, the only reported bis-bispidine crystal structures are those of the tetramethyl derivative (**1**, R = Me) and **1**·2DCl, a salt of bis-bispidine **1** (R = H) [17,18]. However, although the macrocyclic cavity has been retained in the solid state, no discernable channels are observed.

In this paper we report that bis-bispidine functionalized with ethoxy groups (**2**) can self-assemble in the solid state to form stacked columns of ordered one dimensional (1D) channels. Further detailed analysis indicates that weak directional interactions such as long-range C—H···O hydrogen bonds and N—C···O—C dipole–dipole interactions play an important role in the molecular alignment.

Experimental

General procedures and materials

All reagents and anhydrous solvents were used as received from the Aldrich company unless otherwise indicated. Dichloromethane, tetrahydrofuran, hexanes, and diethyl ether were further purified on a solvent purification system through double column filtration of the anhydrous solvents (99.8%). *N*-Boc-*N*′-allylbispidinone **3** was prepared according to literature procedure [20]. All manipulations of air-sensitive materials were performed under a nitrogen atmosphere either in a glovebox or by standard Schlenk line techniques. Column chromatography was carried out using silica gel (60 Å, 40–63 μm, 230–400 mesh), reversed-phase silica gel (C18, Carbon 17%, 60 Å, 40–63 μm), or alumina (activated, basic, Brockmann I). ^{1}H and ^{13}C NMR spectra were recorded on 300 MHz and 500 MHz spectrometers and referenced to residual protonated solvent (^{1}H) or deuterated solvent (^{13}C) unless otherwise specified. Infrared (IR) spectra were recorded on a Bruker Alpha FT-IR spectrometer with a Platinum ATR module (single reflection diamond crystal). Elemental analysis was performed on a Perkin Elmer 2400 Series II CHNS/O Analyzer operating in CHN mode.

*Synthesis of 3,7-bis(bromoacetyl)-9,9-diethoxy-3,7-diazabicyclo[3.3.1] nonane (**5**)*

To a solution of *N*-Boc-*N*′-allylbispidinone **3** (2.50 g, 8.92 mmol) in anhydrous 1,2-dichloroethane (20 mL) was added 1-chloroethyl chloroformate (1.45 mL, 13.4 mmol) at ambient temperature under N_2. The solution was stirred at 70 °C for 1 h before the solvent was removed under high vacuum (0.05 Torr). The residue was dissolved in anhydrous ethanol (20 mL), and to this solution was added HCl (22.3 mL of a 2.0 M solution in diethyl ether, 44.6 mmol). The reaction mixture was stirred at 50 °C for 1 h. Upon solvent removal, the solid residue was washed with diethyl ether (2 × 20 mL) and dried under high vacuum to give diethoxy bispidine hydrochloride **4** which was brought to the next step without further purification.

To a suspension of **4** in anhydrous dichloromethane (45 mL) was added NaOH powder (2.14 g, 53.5 mmol). The suspension was stirred at 0 °C for 15 min before bromoacetyl bromide (1.94 mL, 22.3 mmol) was added. The mixture was stirred for 15 min at 0 °C, quenched with saturated aqueous $NaHCO_3$, and separated. The aqueous layer was re-extracted with dichloromethane (3 × 10 mL) and the combined organic layers were dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes → 50% EtOAc/hexanes) to give bis(bromoacetamide) **5** as a white solid (2.02 g, 4.42 mmol, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.64 (d, *J* = 13.5 Hz, 2H), 4.03 (d, *J* = 11.4 Hz, 2H), 3.80 (d, *J* = 13.2 Hz, 2H), 3.71 (d, *J* = 11.4 Hz, 2H), 3.65 (d, *J* = 13.5 Hz, 2H), 3.50 (q, *J* = 7.2 Hz, 4H), 3.14 (d, *J* = 13.8 Hz, 2H), 2.13 (s, br, 2H), 1.24 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 96.9, 55.0, 48.6, 43.6, 34.7, 26.5, 15.0; IR (solid): 2970, 2938, 2884, 1638, 1439, 1397, 1350, 1239, 1211, 1115, 1090, 1055, 1026, 716 cm^{-1}; Anal. Calcd for $C_{15}H_{24}N_2O_4Br_2$: C, 39.50; H, 5.30; N, 6.14. Found: C, 39.64; H, 5.17; N, 6.09.

*Synthesis of 9,9,18,18-tetraethoxy-3,6,12,15-tetraazapentacyclo[13.3.1.1^{3,17}.1^{6,10}.1^{8,12}] docosane-4,14-dione (**6**)*

To a suspension of **4** (0.139 g, 0.482 mmol) in anhydrous tetrahydrofuran (3.5 mL) was added NaOH (0.210 g, 5.26 mmol). After the suspension was stirred at 60 °C for 15 min, bis(bromoacetamide) **5** (0.200 g, 0.438 mmol) in anhydrous tetrahydrofuran (1.0 mL) was added and the reaction mixture was stirred at 60 °C for 30 min. Filtration of the mixture followed by evaporation of the solvent afforded a residue which was dissolved in dichloromethane (2 mL), washed with 10% aqueous Na_2CO_3 and brine, and dried over sodium sulfate. Upon filtration, the filtrate was concentrated and purified by column chromatography (basic alumina, hexanes → 50% THF/hexanes) to give bisamide **6** as a slightly pale yellow solid (0.168 g, 0.330 mmol, 75% yield). The structure of the compound was confirmed by comparing its NMR data with that reported in the literature [21].

*Synthesis of 9,9,18,18-tetraethoxy-3,6,12,15-tetraazapentacyclo[13.3.1.1^{3,17}.1^{6,10}.1^{8,12}] docosane (**2**)*

Tetraethoxy bis-bispidine **2** was synthesized according to a modified literature procedure [21]. To a suspension of bisamide **6** (0.192 g, 0.377 mmol) in anhydrous diethyl ether (6.6 mL) at ambient temperature under N_2 was added dropwise DIBALH (1.98 mL of a 1.0 M solution in toluene, 1.98 mmol). The resulting clear solution was stirred for 2 h before it was quenched with 15% aqueous NaOH (1 mL). After 50 min of stirring, the reaction mixture was extracted with toluene (3 × 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford **2** as a slightly pale yellow solid (0.157 g, 0.327 mmol, 87% yield). X-ray quality colorless crystals (mp: 183–185 °C) were obtained by dissolving **2** in warm anhydrous hexanes followed by slow evaporation at ambient temperature. ^{1}H NMR (500 MHz, C_6D_6): δ 3.45 (q, *J* = 7.0 Hz, 8H), 2.81 (d, *J* = 9.5 Hz, 8H), 2.71 (m, 8H), 2.42 (s, 8H), 1.97 (s, 4H), 1.17 (t, *J* = 7.0 Hz, 12H); ^{13}C NMR (125 MHz, C_6D_6): δ 99.5, 54.7, 54.13, 54.08, 37.2, 15.5.

Crystallography

The X-ray crystal structure of tetraethoxy bis-bispidine **2** was obtained at −123 °C, where the crystals were covered in paratone oil and placed rapidly into the cold N_2 stream of the Kryo-Flex low-temperature device. The data was collected using the SMART soft-

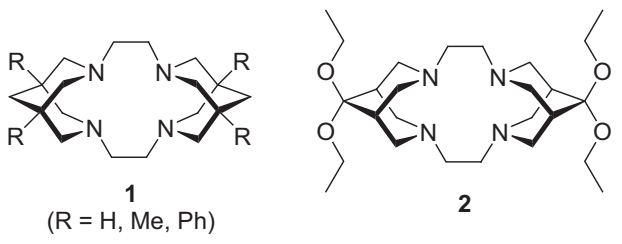

Fig. 1. Bis-bispidine tetraazamacrocycles.