Self-assembly of 3,5-bis(ethoxycarbonyl)pyrazolate anions and ammonium cations of β-phenylethylamine or homoveratrylamine into hetero-double-stranded helical structures†

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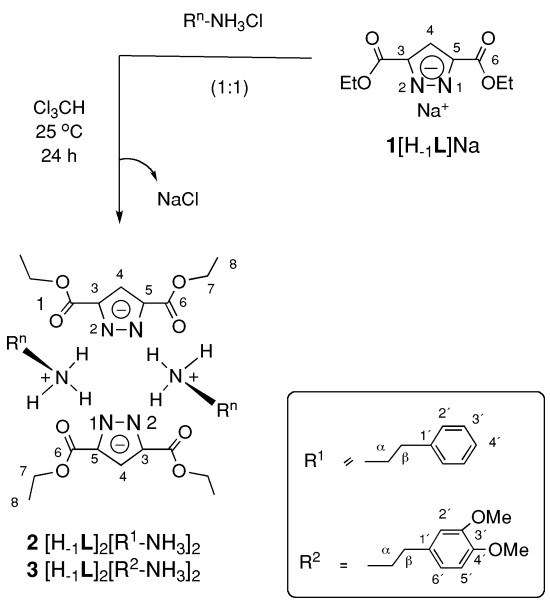
Hydrogen-bonded double-stranded hetero-helices are formed when reacting sodium 3,5-bis(ethoxycarbonyl)pyrazolate with β-phenethylammonium or homoveratrylammonium chloride, in which one of the strands is defined by the ammonium cations and the other one by the pyrazolate anions.

The self-assembly of molecular components has been used in recent years as a useful procedure for the spontaneous generation of artificial double helices.[1] A double helix is constructed by non-covalent interactions between two acyclic compounds, and homo- and hetero-double-helices can be formed depending on the relative affinity of the two compounds. A homo-double-helix is formed from two identical compounds, while the formation of a hetero-double-helix requires two distinct compounds which recognize each other. While several homo-double helices have been reported,[2] hetero-double-helices are rare because of the difficulty in designing two different acyclic compounds that recognize each other. Lehn used five coordinated Cu^{2+} ions to bind bipyridine oligomers and terpyridine oligomers to form a hetero-double-helix.[3] Huc reported the formation of a hetero-double helix between aromatic oligoamides and their *N*-oxides *via* hydrogen bonds and π–π interactions, [4] and Yashima developed a double-helical assembly composed of two crescent-shaped *m*-terphenyl derivatives[5] and their analogues[6] using amidinium–carboxylate salt bridges. However, very few reports refer to hydrogen-bonded double-stranded hetero-helices built up from simple and small molecular components.

1*H*-Pyrazole is an interesting building block since it can behave either as a donor or as an acceptor of hydrogen bonds in its neutral form, or as a double hydrogen-bond acceptor in its deprotonated pyrazolate form. In this respect, in neutral form, distinct 3,5-disubstituted 1*H*-pyrazole moieties are known to self-assemble into well-defined dimers, trimers and tetramers.[7] In a parallel way, the crystal structures of diethyl and dimethyl 1*H*-pyrazole-3,5-dicarboxylate show the formation of dimers associated through hydrogen bonding, NH···N and C=O···HN, of the two units.[8] 3,5-Dimethylpyrazole has also shown a reliable ability to form hydrogen-bonded binary systems with phenol, giving rise to mixed phenol–pyrazole chains.[9] 3,5-Pyrazole dicarboxylic acid has been shown to be a useful tool for building lamellar structures. In this regard, in 2002, Beatty *et al.* reported that the reaction of different primary or secondary amines with 3,5-pyrazole dicarboxylic acid lead to the isolation of clay-like structures in which layers of hydrogen-bonded carboxylate–carboxylic functions are cross-linked into the desired sheet through the additional hydrogen-bond donor of the pyrazole group. The primary or secondary ammonium groups are anchored to the sheets through N–H^+···O^- ammonium–carboxylate or N–H^+···N ammonium–pyrazole hydrogen bonds.[10]

Recently, we described, for the first time, the sodium pyrazolate salt of diethyl 1*H*-pyrazole-3,5-dicarboxylate (**1** in Scheme 1), which showed amphiphilic character and potential



Scheme 1

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† Electronic supplementary information (ESI) available: Experimental procedures for the preparation of **1**, **2** and **3** and NMR spectra. Crystal data for **2** and **3** (CCDC reference numbers 730786–730787). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b911053d

ability to cross the blood–brain barrier. Interaction of this salt with (+)-amphetamine hydrochloride lead to a very interesting crystal structure in which the ammonium cations and pyrazolate anions were interconnected through an extended hydrogen-bond network, forming a hetero-double-helical structure.[11]

Amphetamine (AMPH) and its many derivatives, share an α-methyl group in their β-phenethylamine skeletal structure. This methyl group has a large influence on the psychoactivity and undesirable neurotoxicity of this class of drugs.[12] β-Phenethylamine (β-PEA), an amine trace of low toxicity which differs from AMPH only in lacking the α-methyl group, has been implicated in a diverse array of human pathologies such as schizophrenia, affective disorders,[13] and recently, attention-deficit hyperactivity disorder.[14] On the other hand, it has long been known that 3,4-dimethoxyphenethylamine (homoveratrylamine, Ho), a hallucinogenic compound, the structure of which also lacks the α-methyl group, is present in urine during acute schizophrenic attacks.[15]

Taking into account the presumably steric role played by the methyl group of AMPH in its crystal structure with **1**, we have extended our studies to preparing complexes of β-PEA or Ho ammonium cations and 3,5-bis(ethoxycarbonyl)pyrazolate anions in order to check whether the double-helical structure was preserved or not, and to analyse the structural role played by the methyl groups and their influence in the 3D arrangement of the crystal.

The synthesis of the new compounds was performed in a similar way to that previously reported for the crystalline helix of (+)-AMPH with **1**.[11] The sodium pyrazolate salt **1** (mp 212–214 °C), by reaction with β-PEA or Ho hydrochloride in chloroform solution, afforded respectively, solid (2 : 2) complexes **2** (mp 108–110 °C) and **3** (mp 115–117 °C) (Scheme 1).

The compounds were characterised on the basis of their analytical and spectroscopic (IR, FAB-MS, ^{1}H and ^{13}C NMR) data. Alternatively, in agreement with previous ^{15}N cross-polarization MAS NMR studies,[16] the same complexes (**2** and **3**) were isolated by the reaction of β-PEA or Ho amines with neutral diethyl 1*H*-pyrazole-3,5-dicarboxylate ester by proton transfer between the pyrazole and the amine. Furthermore, it was verified that both complexes (**2** and **3**), obtained by the two different procedures mentioned above, after being crystallized from ethanol and analyzed by X-ray diffraction,‡ showed identical structures.

The asymmetric unit of both **2** and **3** consists of an unit of the ester in its deprotonated pyrazolate form, and either a β-PEA or a Ho unit, which are apparently not in contact with the unit. When either the ammonium or the pyrazolate ester fragments search for hydrogen-bonding contacts, the supramolecular hetero-double-helices shown in Figs. 1 and 2 appear. In the two reported structures, one of the strands is defined by the 3,5-bis(ethoxycarbonyl)pyrazolate units and other one by the ammonium cations.

As shown in Figs. 1 and 2 a helical turn involves three pyrazolate and three drug units. In both structures the helical arrangement is held together by an internal seam consisting of a T-shaped hydrogen-bond network involving the ammonium group of one drug molecule and three pyrazolate units (see stick representations at the left of Figs. 1 and 2).

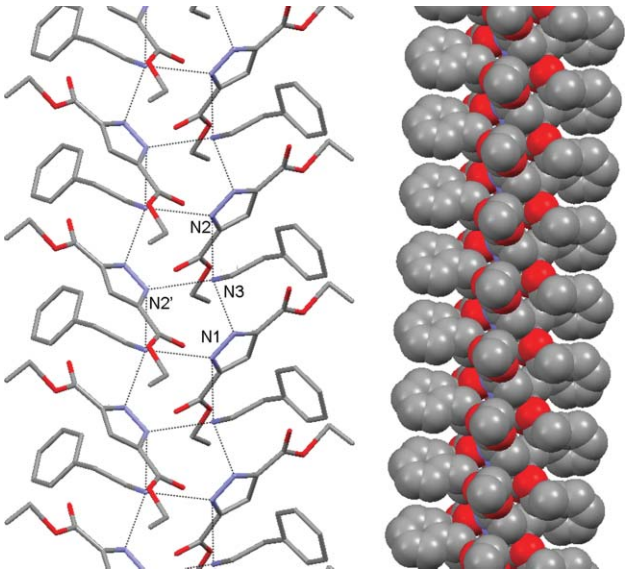

Fig. 1 Stick and space-filling representation of a portion of a hetero-double strand helix in **2**. N2 and N2′ are related by the symmetry operation $\frac{1}{2}$-x, $\frac{1}{2}$+y, $\frac{1}{2}$-z.

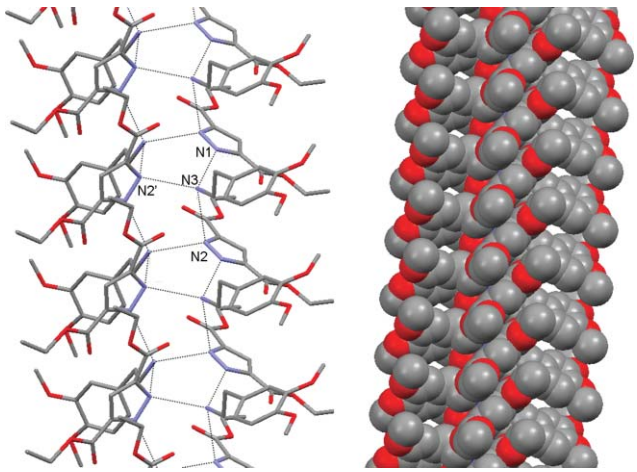

Fig. 2 Stick and space-filling representation of a portion of a hetero-double strand helix in **3**. N2 and N2′ are related by the symmetry operation $\frac{1}{2}$-x, $\frac{1}{2}$+y, $\frac{1}{2}$-z.

Two of these pyrazolate units are placed on the same side of the helical arrangement (Figs. 1 and 2) (for **2**, N3 ··· N1 = 2.867(5) Å, N3 ··· N2 = 3.093(5) Å; for **3** N3–N1 = 2.873(3) Å, N3–N2 = 2.965(3) Å and the other one is placed on the side opposite to the ammonium drug, at distances N3–N2′ = 2.839(5) Å in **2** and N3–N2′ = 2.865(3) Å in **3**. The angles of the T-shaped hydrogen-bond networks confirm their tetrahedral arrangement (**2**, N1–N3–N2 = 107.5 °, N2–N3–N2′ = 106.1 °, N2′–N3–N1 = 111.1 °; **3**, N1–N3–N2 = 102.9 °, N2–N3–N2′ = 112.6 °, N2′–N3–N1 = 108.5 °).Tables of possible hydrogen bonds for compounds **2** and **3** are provided in the ESI.† The angle between the aromatic planes of the drugs placed on opposite sides of the helix, as shown in Figs. 2 and 3, are 78.2 ° for **2** and 64.6 ° for **3**, while the angles for similarly-placed pyrazolate moieties are 79.6 and 82.5° for **2** and **3**, respectively. Also, π–π stacking interactions between the

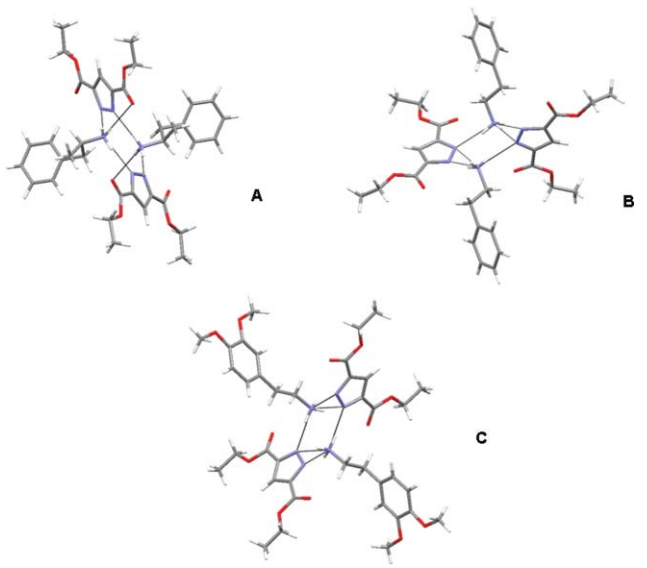

Fig. 3 View along the b-axes showing the hydrogen bond pattern (dotted lines) of crystal structures of **1**–(+)-AMPH (A), **2** (B) and **3** (C).

aromatic rings of the drugs help stabilize the double-stranded structure (see space-filing representation at the right of Figs. 1 and 2).

Although the distances between the aromatic planes of the benzene rings of the drugs are 3.04 Å in **2** and 3.43 Å in **3**, they are shifted with respect to the distances between their respective centroids, 5.44 Å and 5.70 Å for **2** and **3**, respectively. Although these two helices share common features with that previously reported for amphetamine,[11] they have very important differences induced by the lack of the hindering α-methyl group present in amphetamine.

Indeed, in the T-shaped hydrogen-bond pattern observed in the supramolecular hetero-helix **1**-amphetamine,[11] each ammonium ion of the drug was hydrogen-bonded to two pyrazolate nitrogen atoms and one carbonyl group of the ester, instead of to three pyrazolate nitrogens as found in helices **2** and **3** (Figs 1 and 2, left, and Fig. 3 in which a view along the *b*-axis is shown for **1**, **2** and **3**).

Moreover, in the hetero-helix **1**-amphetamine there was no π–π stacking of the aromatic groups of the drug. Another difference is the short contacts between the helices in the crystal packing. While in the case of hetero-helix **1**-amphetamine the distinct double-stranded helices were well separated in the crystal, in **2** and **3** the packing is much tighter. Nevertheless, these crystal structures seem to prove that the most important point for the formation of the double helix is the hydrogen-bond framework generated by the interaction of the ammonium group and the 3,5-bis(ethoxycarbonyl)pyrazolate units, which form the internal seam of the structure.

Other interactions modulate the type of hydrogen-bonding acceptor groups and the external shape of the supramolecular assembly. Therefore, this structural type might be almost general for any primary ammonium group interacting with such pyrazolate units. Currently we are exploring these points and studying the extent of preservation of these helical structures in solvents of low or medium polarity.

Acknowledgements

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Notes and references

‡ Data collection of crystals of **2** and **3** was performed at 293 K on a Nonius Kappa-CCD single crystal diffractometer using Mo Kα radiation (λ = 0.7173 Å). The crystal structures were solved with the program Sir-97 (see ref. 17). Anisotropic least-squares refinement was carried out with SHELXL-97 (see ref. 18). Crystal data for **2**: $C_{17}H_{23}N_3O_4$, M_w = 333.39 g mol^{-1}, monoclinic, space group $P2_1/n$, a = 16.2750(8), b = 5.7027(2), c = 20.1112(10), β = 100.273(3), V = 1836.63 (14) Å^3, Z = 4, 6339 measured reflections, 3771 unique reflections, R_{int} = 0.0656, 220 parameters, R_1 (all data) = 0.2209, $R_1[I > 2\sigma(I)]$ = 0.063, wR_2 (all data) = 0.3011, $wR_2[I > 2\sigma(I)]$ = 0.1837. Crystal data for **3**: $C_{19}H_{27}N_3O_6$, M_w = 393.44 g mol^{-1}, monoclinic, space group $P2_1/n$, a = 13.1760(4), b = 5.4360 (2), c = 29.7130(10), β = 99.289(2), V = 2100.28(13) Å^3, Z = 4, 6300 measured reflections, 3791 unique reflections, R_{int} = 0.0488, 258 parameters, R_1 (all data) = 0.1286, $R_1[I > 2\sigma(I)]$ = 0.0513, wR_2 (all data) = 0.1827, $wR_2[I > 2\sigma(I)]$ = 0.1399.

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