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o-Di-(pyrrole-2-carboxamides)-phenylene: pseudopolymorphs and anions recognition

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Abstract—*o*-Di-(pyrrole-2-carboxamides)-phenylene (**1**) was synthesized and its two pseudopolymorphs were identified. A helical assembly was observed when it was incorporated with methanol molecules via hydrogen bonding, whereas a channel assembly was formed when it was associated with DMSO molecules. The ^{1}H NMR study revealed that **1** can recognize certain inorganic anions.

Pseudopolymorphism, defined as crystalline forms of a compound that differ in the species or stoichiometry of the included solvent molecules, has been deemed to be of great importance in pharmaceutical industry.[1] It offers opportunities to investigate the effect of solvents on the assembly of host molecules[2] but such effect is still poorly understood.

Recently, pyrrole-2-carboxamide based compounds have shown high potential in the effective self-assembly involving hydrogen bonds. For example, Schmuck[3] demonstrated that guamidimiocarbonyl pyrrole carboxylate compounds have good self-assembling ability in highly polar solvents such as DMSO and water. Gale and co-workers[4] showed that the 2,5-diaminopyrrole-anion dimer might serve as a new motif for the construction of hydrogen-bonded molecular assemblies of dimers and polymers. Although many other pyrrole-2-carboxamide compounds were found to form discrete dimers or low-dimensional oligomers,[5] there are no reports about the helical assembly of pyrrole-2-carboxamides. *o*-Phenylenediamide may serve as a scaffold to create a helical structure when the carboxamide linking groups are constrained above and below the plane of the phenyl moiety, we thus designed and synthesized the *o*-di-(pyrrole-2-carboxamides)-phenylene (**1**) and examined its assembly nature in the present work. As shown in Figure 1, the crystal of the aimed molecule **1** does bear a twisted structure, and as further shown in Figure 2, **1** did assemble into helical chains by incorporating methanol molecules. Interestingly, when crystallized in DMSO solution, **1** assembled to form a channel structure (Fig. 4) in which the DMSO molecules were encapsulated. The latter two structures are technically referred to as pseudopolymorphs.[1] The anion recognition of **1** in DMSO was also investigated using ^{1}H NMR spectroscopy.

Compound **1** was synthesized in moderate yield (32%) by coupling pyrrole-2-carboxyl acid with *o*-phenylenediamine in the presence of dicyclohexylcarbodiimide

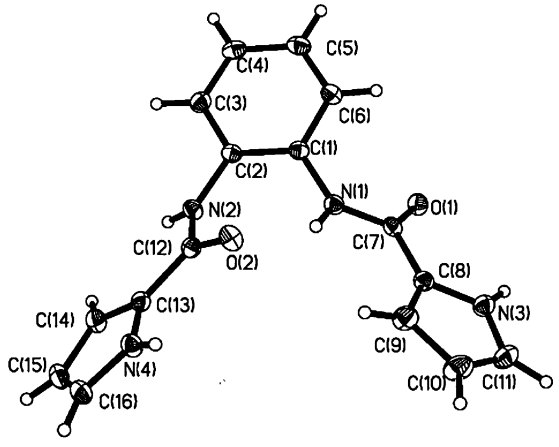

Figure 1. ORTEP diagram of **1** and atomic number.

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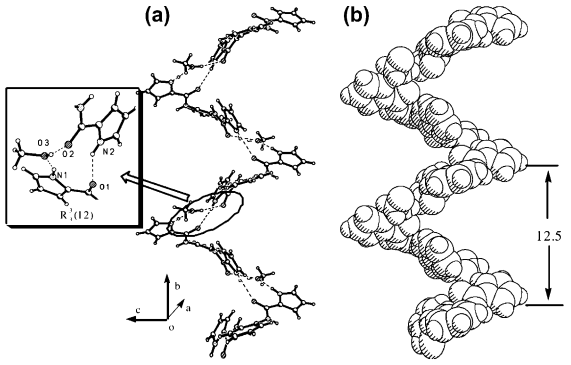
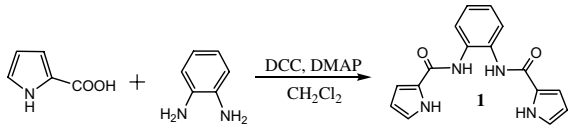


Figure 2. Helical assembly of **1** (a) ORTEP perspective, inlet: twisted R_3^3 (12) hydrogen bond motif. (N2–H···O1, 2.949 Å, 134.1°; N1–H···O3, 2.806 Å, 158.15°; O3–H···O2, 2.759 Å, 168.7) and (b) space-filling view.



Scheme 1.

(DCC) in CH_2Cl_2 and catalytic quantity of DMAP (Scheme 1).[6] The crystal of **1**·CH_3OH was obtained by slow evaporation of the methanol/ethyl acetate mixture of **1**,[7] whereas the **1**·DMSO crystal was obtained by slow diffusion of chloroform or water to the DMSO solution of **1**.[8] In both crystals, **1** has similar conformation (Fig. 1), although they belong to different space groups. As depicted in Figure 1, **1** adopts a helical conformation, even though the 2-pyrrole carboxamide moiety is planar and points up and down with respect to the phenyl plane, twisting the whole molecule. Obviously, this configuration resulted from the repulsion of the two pyrrolic amide moieties and the intramolecular hydrogen bond (O2···H–N1, the O···N distance is 2.711 Å and bond angle is 145.0°) can minimize the repulsive force between the two amide hydrogen atoms.[9] The intermolecular hydrogen bond lengths and the bond angles of the two pyrrolic amides with respect to the phenyl ring are presented in Table 1 (the numbering of atoms is the same as shown in Fig. 1).

Although the solvents only slightly affect the conformation of **1** as revealed in this table, they significantly influence the crystal packing of **1**. When viewed along the *b*-axis of the **1**·CH_3OH crystal, a helical chain was observed (Fig. 2). This was formed by repetition of a methanol molecule and **1** connected by a twisted R_3^3 (12) hydrogen bond motif (Fig. 2, a inlet).[10] The pitch of the helix is ca. 12.5 Å. These helical chains, both right-handed and left-handed, are held together by the hydrogen bonds between amide NHs and carbonyl groups on the backbone.

Table 1. Bond lengths (Å) and angles (°) of the intramolecular hydrogen bond and the torsion angles of **1** in crystals

	1·CH_3OH	**1**·DMSO	**1**·F^{-a}
O2···H	1.961	1.957	1.666
O2···N1	2.711	2.701	2.662
∠N1–H···O2	145.0	144.0	159.4
∠C2–C1–N1–C7	141.06	135.8	—
∠C1–C2–N2–C12	49.5	−51.2	—

[a] The structure of **1**·F^- complex was optimized (B3LYP/6-31G*).

In contrast, in the **1**·DMSO crystal, **1** dimerized via two intermolecular hydrogen bonds O(1A)···H–N(2B) and O(1B)···H–N(2A), with the same N···O distance of 2.969 Å and O···H–N angle of 152.5° (Fig. 3). As shown in Figure 4, the dimer appears to be as knots. When viewed down the *a*-axis of the crystal, channels can be observed with a diameter of approximately 5.5 Å. Disordered DMSOs were encapsulated in these channels and hydrogen bonded with groups on the wall of the channels. These groups are two pyrrole NHs from two neighboring **1** molecules and a carbonyl from the third **1** molecule. This kind of DMSO binding is very different from those previously observed for 2,5-diaminopyrrole compounds.[5b,11]

In **1**·CH_3OH, the methanol molecule serves to expand the hydrogen bond motif of pyrrolic amide dimers[12] by forming the NH···O–H···O hydrogen bond, resulting in more flexible hydrogen bond motif and making **1** assemble into a helical structure by the methanol molecule bridge. In comparison, without hydroxyl group, DMSO cannot act as a molecule bridge like methanol, thus a helical structure cannot be formed. In brief, the helical structure formation of **1** is most likely driven by the –OH group of methanol. The two crystals of **1** are yielded, respectively, by incorporating different solvent molecules into the crystal lattice of the host, which are considered as pseudopolymorphs of a supramolecular assembly.[1]

The intriguing solvent binding ability of **1** inspired us to investigate its anion recognition property. This was con-

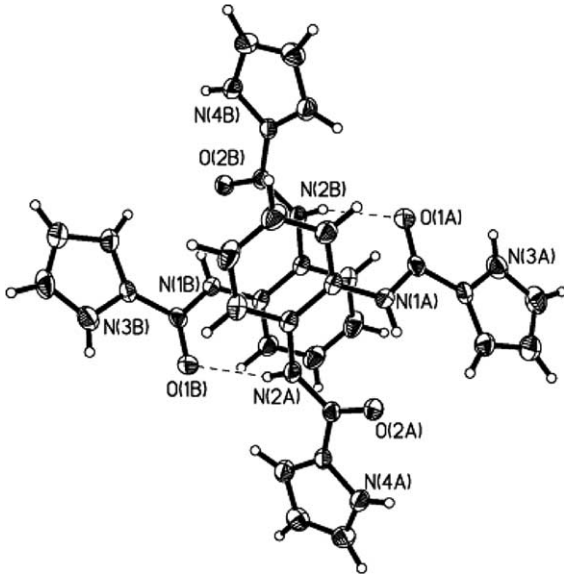


Figure 3. **1**·**1** Dimer through hydrogen bonds.

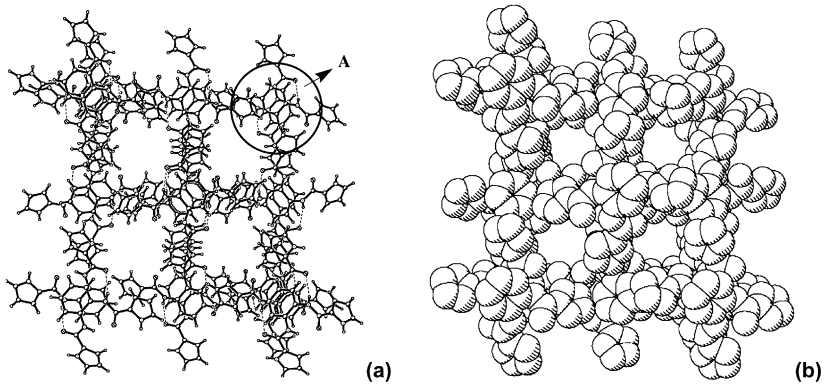


Figure 4. Channels in the crystal of **1**·DMSO when viewed down the *a*-axis. (a) ORTEP perspective. Part A is illustrated in Figure 4. (b) Space-filling view (DMSOs are omitted for clarity).

Table 2. Association constants (M^{-1}) of **1** with three kinds of anion in DMSO[a]

	F^-	$H_2PO_4^-$	Cl^-	Br^-	I^-
K_a (M^{-1})	320	100	< 10	No[b]	No[b]

[a] Anions used were in their tetrabutylammonium (TBA) salts form. Error is less than 10%.

[b] Pyrrole and amide NH signals only slightly shifted when large amount of anions added.

ducted in DMSO solution using ^1H NMR technique. The two pyrrole carboxamide arms of **1** were found to form a cleft that is suitable for binding anion through hydrogen bonds.[5b] The ^1H NMR signals of pyrrole NHs and amide NHs of **1** shifted downfield significantly (> 2 ppm) with the addition of F^- and $H_2PO_4^-$. According to the chemical shift of the amide NH, the complexes of **1** with F^-, $H_2PO_4^-$ and other anions all show the 1:1 binding model.[13] The association constants are summarized in Table 2. The results reveal that **1** has higher fluoride binding ability than 2-amidopyrrole and phenyl 2,5-diamidopyrrole derivatives,[5b] but not as good as nitrophenyl 2,5-diamidopyrrole derivatives.[11] To further understand the anion complexes of **1**, The structures of the complexes of **1**·F^- and **1**·$H_2PO_4^-$ were optimized using *density functional method b3lyp/6-31g**, and is shown in supporting information.

In conclusion, a bis-pyrrole-2-carboxamide compound, *o*-di-(pyrrole-2-carboxamides)-phenylene (**1**), was designed and synthesized in this work. A helical assembly was observed when **1** formed specific hydrogen bonds with methanol molecules, but when **1** associated with DMSO molecules, a channel assembly was observed. The preliminary anion recognition study of **1** was carried out by ^1H NMR in DMSO and revealed that **1** has good fluoride binding ability.

Acknowledgements

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Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.06.137.

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6. Spectroscopic data for **1**: ^1H NMR (300 MHz, DMSO-d_6); δ 6.14–6.17 (m, 2H, Py CH), 6.91–6.93 (m, 2H, Py CH), 6.96–6.98 (m, 2H, Py CH), 7.21–7.24 (m, 2H, ArH), 7.58–7.61 (m, 2H, ArH), 9.80 (s, 2H, CONH), 11.84 (s, 2H, Py NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 109.9, 111.8, 123.7, 125.7, 125.9, 126.2, 131.5, 160; FAB-MS: 294.2 (M^+), 224.3, 143.2; Elemental analysis: $C_{16}H_{14}N_4O_2 \cdot CH_3OH$: Calcd: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.76; H, 5.36; N, 16.96.

7. Crystal data for **1**·CH_3OH: $C_{17}H_{18}N_4O_3$, $M_r = 326.35$, $T = 293$ (2) K, Monoclinic, space group $P2(1)/n$, $a = 9.038$ (4) Å, $b = 12.555$ (5) Å, $c = 14.872$ (6) Å, $\alpha = 90$, $\beta = 93.850$ (7), $\gamma = 90$, $V = 1683.7$ (12) Å^3, $Z = 4$, $\rho_{calcd} = 1.287\,g\,cm^{-3}$, $\mu = 0.091\,mm^{-1}$, reflections collected: 9338, independent reflections: 3444 ($R_{int} = 0.0261$), Final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0413$, $wR_2 = 0.0952$, R indices (all data): $R_1 = 0.0670$, $wR_2 = 0.1088$, CCDC 205664.
8. Crystal data for **1**·DMSO: $C_{18}H_{20}N_4O_3S$, $M_r = 372.44$, $T = 293(2)$ K, orthorhombic, space group $Pbca$, $a = 11.450(3)$ Å, $b = 17.891(5)$ Å, $c = 18.562(5)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90$, $V = 3802.5$ (18) Å^3, $Z = 8$, $\rho_{calcd} = 1.301\,gcm^{-3}$, $\mu = 0.195\,mm^{-1}$, reflections collected: 20756 independent reflections: 3913 ($R_{int} = 0.0540$), Final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0475$, $wR_2 = 0.0972$, R indices (all data): $R_1 = 0.0983$, $wR_2 = 0.1170$, CCDC 220440.
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