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Molecular complexes of thionicotinamide with 18-membered crown ethers: Synthesis and crystal structures

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Abstract

The reaction of thionicotinamide (3-thioamidopyridine) with 18-membered crown ethers, 18-crown-6 (18C6), benzo-18-crown-6 (B18C6) and *cis–anti–cis*-dicyclohexyl-18-crown-6 (D18C6) results in the molecular complexes of 1:1 ratio for 18C6 (complex **1**) and B18C6 (complex **2**) and monohydrate of 2:1:1 ratio for D18C6 (complex **3**), respectively. The complexes are sustained by combination of N–H···O, O–H···N and C–H···O hydrogen bonds, and the components are associated into molecular adduct (**1**) or infinite chain (**2** and **3**).

Keywords: H-bonded adducts; Thionicotinamide; 18-Membered crown ethers; Synthesis and crystal structure

1. Introduction

In the last decade we witnessed an increased interest to the co-crystals including active pharmaceutical ingredient (API) [1–3] with the aim to produce new valuable materials. Crystalline self-assemblies are promising for improving drug solubility, dissolution rate, stability and bioavailability. Supramolecular synthesis is now being widely explored to obtain new pharmaceuticals from known APIs and a benign solid component (cyclodextrins [4–6], carboxylic [7–10] and dicarboxylic acids [11–13], etc.). The recent findings in this topic are summarized in the fresh review paper by Zaworotko and co-workers [14].

Crown ethers (CEs) exhibit themselves as very useful model compounds capable to function as do more complex chemical structures. Moreover, some simple crown ethers exhibit biological activity. These two properties make them very attractive molecules that permit a detailed analysis of interactions that are thought to be important in biology [15]. For several years we are involved in the problem of the molecular recognition of biologically important molecules (nucleic bases, drugs) by macrocyclic molecules, as the model systems mimic substrate–receptor interactions [16,17]. We have analyzed series of complexes, e.g., streptocid (4-aminobenzenesulfonamide) – 18-membered CEs (18-crown-6, dicyclohexyl-18-crown-6, benzo, cyclohexyl-18-crown-6) [18–20], PABA (4-aminobenzoic acid) – CEs (isomers of dicyclohexyl-18-crown-6, aza-12-crown-4) [21,22], hypothiazide (6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide) – CEs (18-crown-6, dicyclohexyl-18-crown-6) [23,24]. It has been shown that the interaction with the neutral macrocycle results in the genius co-crystals with the primary amino-group involved in the coordination to macrocyclic molecule, while aza-macrocycle is easily protonated and interaction results in an organic salt. The self-assembly of the drug molecules via hydrogen bonds typical for their pure forms is destroyed and is substituted by the interaction with the

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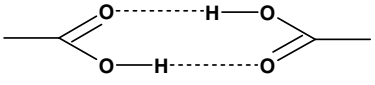
macrocyclic molecule [25]. As the rule, the complete rearrangement of the hydrogen bonds occurs, and only the strongest homosynthons typical for the pure form (as that $R_2^2(8)$ combining two carboxylic groups [26]) remain in the complex [20] (Scheme 1).

In continuation of this research, we studied the system thionicotinamide (3-thioamidopyridine) – CE [18-crown-6 (18C6), benzo-18-crown-6 (B18C6) and *cis–anti–cis*-dicyclohexyl-18-crown-6 (D18C6)] and report here on the X-ray crystal structures of three novel complexes.

The thioamide functional group is present in many drugs and agricultural chemicals, and exposure to man can result in inadvertent toxicity. Thus, a large number of potentially useful drugs containing the thioamide group are limited in their use due to the toxic side effects associated with these compounds. The diverse thioamide derivatives have been used as herbicides, antitubercular and antibacterial agents. The associated toxicity of the thioamides is explained to be linked to their oxidative metabolism, especially *S*-oxygenation [27]. Some recent studies were devoted to the synthesis of modified thionicotinamide to decrease its toxicity and maintain the useful medicinal properties [28]. Thionicotinamide is a known xenobiotic. It is a drug used for the treatment of *Chagas disease*, a common health problem in South America [29].

The crystallographic data [30] for this class of compounds are rather scanty. They are restricted by three isomeric thioamidopyridines of general formula $C_6H_6N_2S$, 2-thioamidopyridine [31], 3-thioamidopyridine [32] and 4-thioamidopyridine [33]. The structure of the 2-propyl derivative of 4-thioamidopyridine has also been reported [34]. The structural interest to these compounds has centered on the parameters of the thioamide group and the consequent electron arrangement within the group. Additional features of interest are the non-coplanarity of the pyridine ring with the thioamide group and the hydrogen-bonding schemes. The isomers have three possible coordination sites, and the packing of all of them reveals some common features. The molecules lie in the layers via $R_2^2(8)$ centrosymmetric rings built on NH···S contacts (N···S ~ 3.4 Å, a bit longer than the sum of van der Waals radii) and C(7) chains (contacts NH···N, N···N about 2.96 Å), and then these layers stack along the shortest axis (Scheme 2).



Scheme 1. Homosynthon $R_2^2(8)$ typical for carboxylic acids.

As for the multicomponent adducts involving isomers of thionicotinamide, only its S-oxide monohydrate [35] and thionicotinamidium 3,5-dinitro-4-methylbenzoate 3,5-dinitro-4-methylbenzoic acid adduct [36] are reported. From the viewpoint of crystal packing, it is interesting that only NH···N contact (N···N distance of 2.954 Å) remains in the crystal packing of the first adduct, while weaker NH···S contacts are substituted by the interaction with water molecule as a more powerful H-acceptor, while in the second compound the full rearrangement of the intermolecular interactions occurs, and two homosynthons typical for 3-thionicotinamide itself are substituted by the heterosynthons between thionicotinamidium cations and 3,5-dinitro-4-methylbenzoate anions (or 3,5-dinitro -4-methylbenzoic acid molecules).

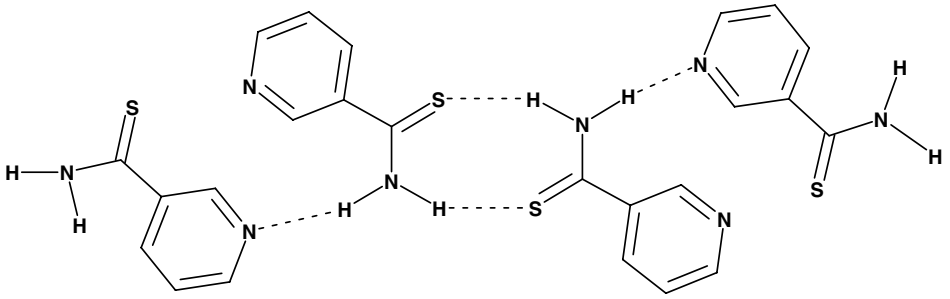
The aim of our study is to elucidate the mode of interaction of the drug molecule with the macrocycles and to compare the crystal packing motifs in the complexes.

2. Experimental

Commercially available reagents were used as received. Compounds **1**–**3** were analyzed for C, H, N and S in a Perkin-Elmer 240 C. The thin-layer chromatographic control of the substance purity was performed on Silufol UV-254 plates. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Oxford 300 NMR spectrometer.

2.1. Synthesis

*Compound **1***. A solution of 18C6 (0.264 g, 1 mmol) and thionicotinamide (0.138 mg, 1 mmol) in 2 ml of methanol and 3 ml of ethyl acetate was stored for 3–5 days at 20 °C in an open flask. The crystals, separated in a yield of 91% (0.365 g), were suitable for X-ray analysis. Yellow crystals, soluble in methanol, ethanol, acetone, m.p. 120–122 °C. Analysis: found C, 53.71; H, 7.51; N, 6.96; S, 7.97%. $C_{18}H_{30}N_2O_6S$ requires C, 53.68; H, 7.54; N, 6.93; S, 7.94%. ^{1}H NMR (CD_3OD_{d4}, 300 MHz): 3.60 s (24H, 18C6), 7.45 m, 8.26 m, 8.60 m, 9.00 m (4H, CH).



Scheme 2. The mode of association of 3-thionicotinamide molecules in the crystal.