Crystal structures of some 2-Alkoxybenzamides

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Abstract: In our search for cocrystal formation utilizing benzamides with the aim of improving solubility, stability and bioavailability during application of the molecules, we have first looked at the single crystal X-ray structures of the three *o*-alkoxybenzamides, *o*-allyloxybenzamide, *o*-propoxybenzamide, and *o*-pentoxybenzamide**.**

Introduction: The 2-alkoxybenzamide moiety can be found as a structural unit in medicinal active structures, such as dopamine (DA) receptor antagonists.[1]

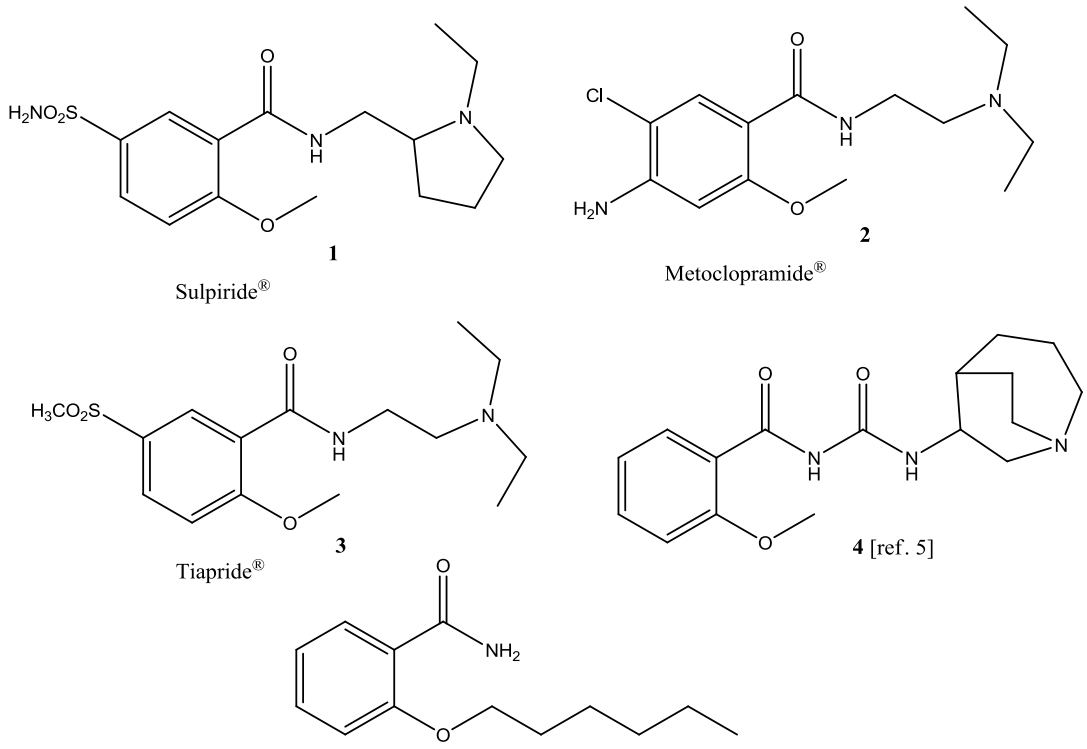


Figure 1. Biologically active 2-alkoxybenzamides

Sulpiride® (**1**) (as a neuroleptic to alleviate symptoms associated with schizophrenia), Metoclopramide® (**2**) (as an antiemetic to treat nausea and vomiting), and Tiapride® (**3**) (antipsychotic, to treat movement disorder) are typical such examples (Fig. 1). Other substituted 2-alkoxybenzamides have been forwarded as potential antagonists of chemotherapy-induced nausea,[2] as neuroleptic compounds,[3] as agonists of $\alpha 7$ nicotinic acetylcholine receptors,[4] The related 2-alkoxybenzoylureas **4** are known to have potent 5-HT3 hydroxytryptamine receptor antagonist behavior (Fig. 1).[5] Also, 2-hexyloxybenzamide (**5**) has been reported as an antifungal agent (Fig. 1).[6]

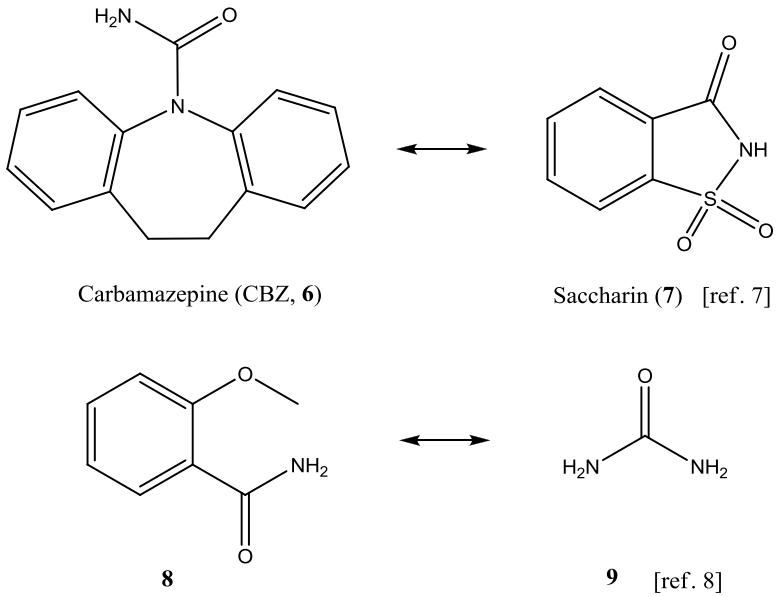


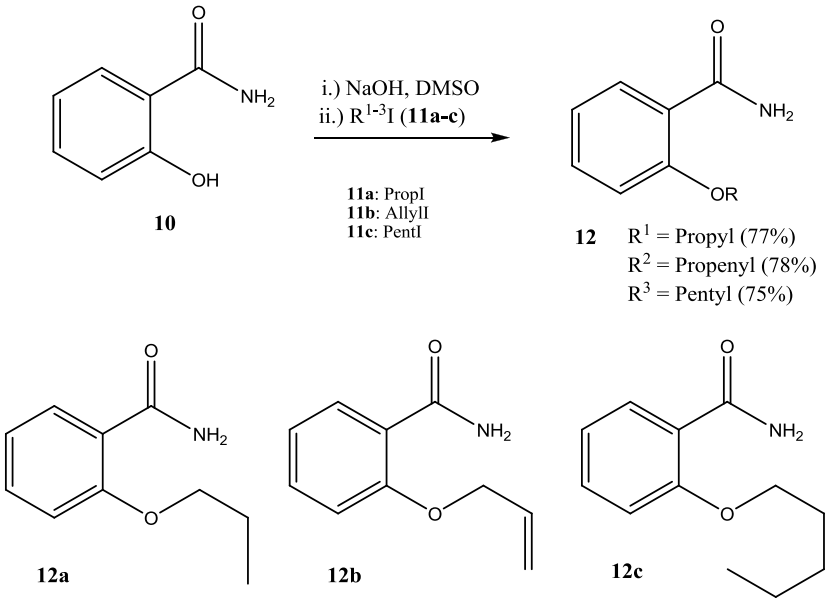
Figure 2. Typical examples of co-crystals that have been studied to-date.

Due to the possibility that multicomponent crystals which include a pharmaceutical component give new properties to that medicinally active component – these can be different solubility, enhanced stability, a changed dissolution rate and enhanced bioavailability – the study of so-called co-crystals have been eliciting much attention. A typical example has been the preparation and study of a 1:1 carbamazepine (**6**, CBZ) – saccharin (**7**) co-crystal (Fig. 2), which showed carbamazepine, which is used in the treatment of trigeminal neuralgia, exhibiting enhanced chemical and physical stability in the co-crystal.[7] R. T. Forbes et al. studied the formation of a 1:1 co-crystal of 2-methoxybenzamide and urea (Fig. 2).[8] Our interest in co-crystals of medicinal active 2-alkoxybenzamides led us to investigate the effect of the nature of the 2-alkoxy group on the co-crystal formation. Towards this goal, first the crystal formation and crystal packing of some pure 2-alkoxybenzamides were studied, which is detailed in the current account.

Results and Discussion

The 2-alkoxybenzamides were prepared from salicylamide (**10**) by *O*-alkylation using alkyl iodides and KOH as base in DMSO (Scheme 1). It is known that the amide nitrogen could also be alkylated under the conditions,[9] but in the present case very

little amide alkylation was found. This was in contrast to *ortho*-hydroxybenzenecarboxylic acids such as 2-hydroxycinnamic acid, where both the acid and phenolic hydroxyl function were alkylated equally well. The alkoxybenzamides were purified by column chromatography. Single crystals were grown by slow evaporation of the solvent from a solution of the respective compound in a mixture of M^{t}BE and chloroform.



Scheme 1. Preparation of 2-alkoxybenzamides **12**

When viewing the crystal packing of 2-propoxybenzamide (**12a**) and the unsaturated derivative 2-allyloxybenzamide (**12b**), differences in the packing are readily noticeable.[10,11] In the crystal, 2-propoxybenzamide (**12a**) is a nearly planar molecule with a small dihedral angle between the amide group and the phenylene moiety (Fig. 3). In allyloxybenzamide (**12b**), the terminal olefinic moiety is turned towards the amide function (Fig. 6). There is, however, an appreciable dihedral angle between the amide function and the phenylene group.

In 2-propoxybenzamide (**12a**), the molecules form dimers through a double hydrogen bonding motif. There is, however, no interaction between neighboring pairs within one plane. The pairs are ordered into two types of symmetry-related columns extended along the *a*-axis. The median planes of pairs in one column and pairs in the other form a dihedral angle of 84.40(1)^o. The pairs in one plane hold together the perpendicular planes of pairs of molecules belonging to the second type of symmetry related columns (view slide 15, Fig. 4 to see the interaction of a pair within one column with one molecule of a pair in the second type of column). Figure 5 and slides 16 and 17 depict the packing of **12a** in the crystal.

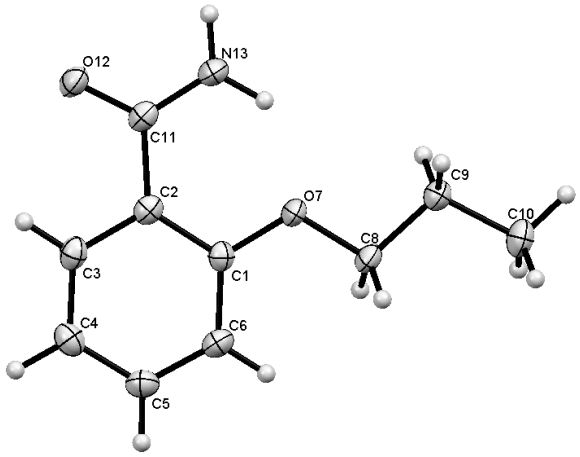


Figure 3. View of one molecule of 2-propoxybenzamide (**12a**) in the crystal.

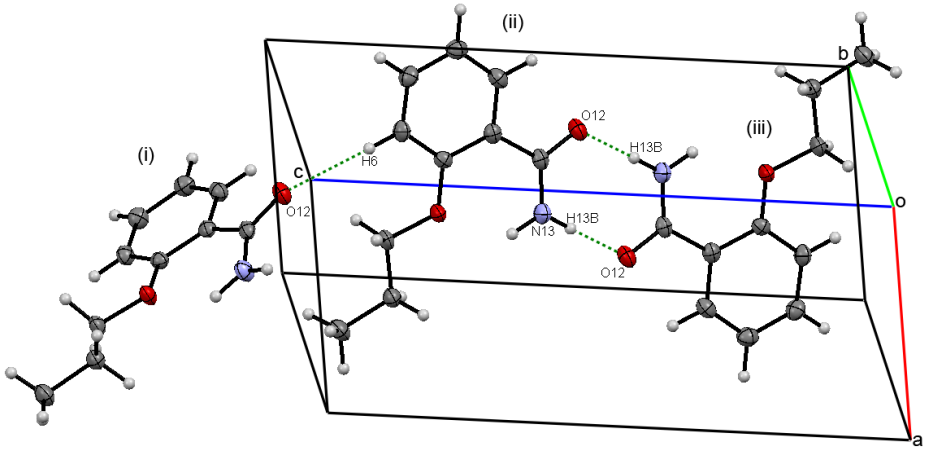


Figure 4. Interaction of a molecular pair with one molecule within the second type of molecular column.

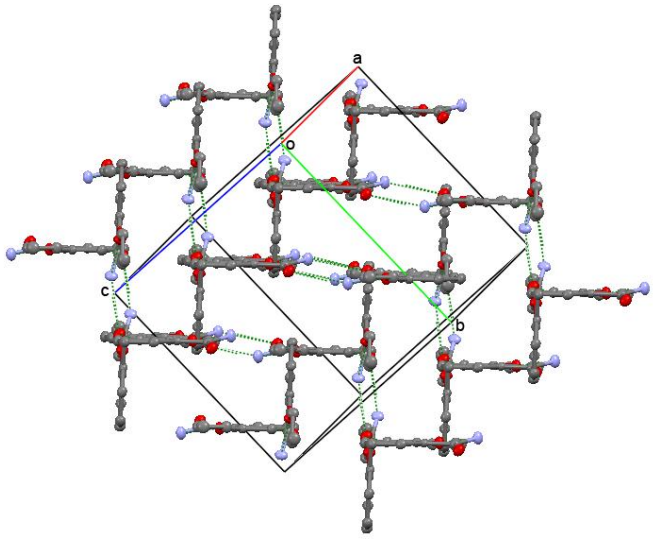


Figure 5. Overall view of the packing of **12a** in the crystal.

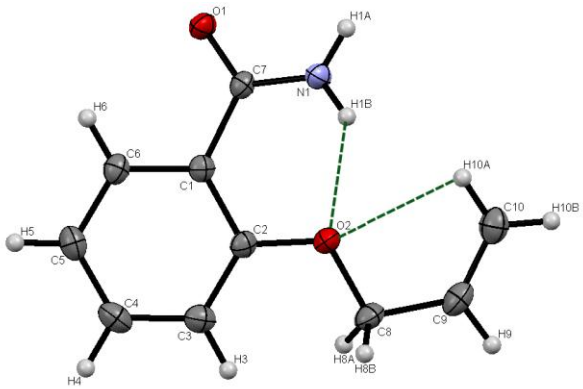


Figure 6. View of one molecule of allyloxybenzamide (**12b**) in the crystal.

In allyloxybenzamide (**12b**), each molecule interacts with more than one other molecule in the plane, namely with four, to provide molecular tapes (Fig. 7, Fig. 8). A CH-pi interaction also exists between two neighboring molecules (see slide 20).

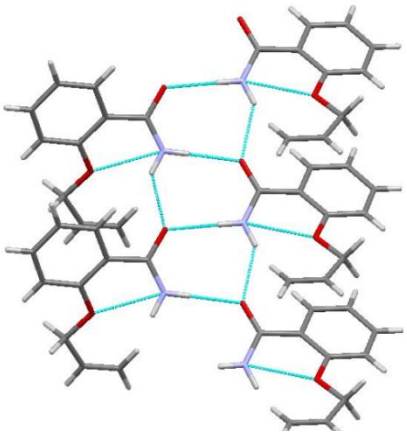


Figure 7. Interaction of **12b** to form a propagating tape of molecules.

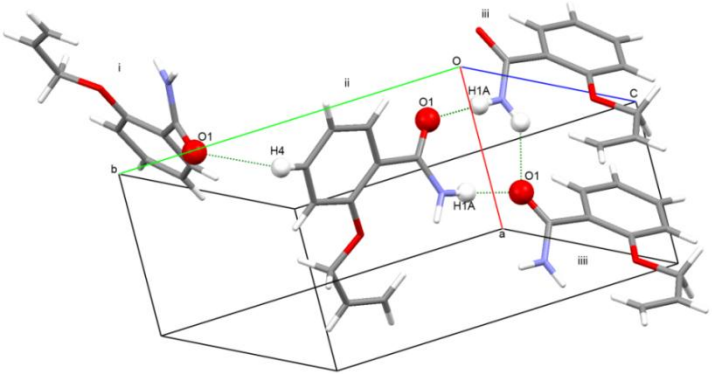


Figure 8. View of interactions of one molecule of **12b** with neighboring molecules, incl. interaction to a molecule of another molecular tape. Further information can be gained from the slide show, attached to this file. An overall view of the packing of the molecule can be gained from slides 21 and 22.

While the introduction of an unsaturation in the 2-*O*-substituent of the 2-alkoxybenzamides leads to a different conformation of the molecules and thus a different intermolecular interaction of the molecules in the crystal and to a difference in the crystal packing, a lengthening of a saturated 2-*O*-alkyl substituent does not lead to a significant change in the conformation of the molecule in the crystal, the intermolecular interactions in the crystal and the overall crystal packing. Thus, 2-propoxybenzamide (**12a**) and 2-pentoxybenzamide (**12c**) show a very similar crystal packing. The crystals do provide some intermolecular space (slide 32), which is agreeably much smaller than space typically provided in metal organic frameworks (MOFs).[12] The cross-sectional area of the cuboid space defined by the carbon frameworks of the molecules has been estimated to be 3.77 Å X 7.55 Å in **12a** (slide 32). Elongation of the alkyl chain substituent as in **12c** did not provide a larger cross-sectional area, but rather loosened the structure between pairs to overall decrease the density of the crystal from 1.246 g/cm^3 for **12a** to 1.182 g/cm^3 for **12c** (slide 32).

Experimental

General. – Melting points were measured on a Stuart SMP 10 melting point apparatus and are uncorrected. Infrared spectra were measured with a Thermo/Nicolet Nexus 470 FT-IR ESP Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 NMR spectrometer (^{1}H at 395.7 MHz, ^{13}C at 100.5 MHz). The assignments of the carbon signals were aided by DEPT 90 and DEPT 135 experiments (DEPT = Distortionless Enhancement by Polarisation Transfer). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Column chromatography, where necessary, was performed on silica gel S (0.063 mm – 0.1 mm, Riedel de Haen)**.**
Crystals were measured on an Agilent SuperNova Atlas CCD Diffractometer**.**

General procedure: To powdered KOH (1.12 g, 20.0 mmol) in DMSO (9 ml) was added salicylamide (1.37 g, 10.0 mmol), and the resulting mixture was stirred for 10 min. at rt. Thereafter, *n*-propyl iodide (4.2 g, mmol, 24.7 mmol) was added dropwise. The solution was stirred for 12 h at rt. Then, it was poured into water (200 ml) and extracted with chloroform (3 x 50 ml). The organic phase was dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and the residue was subjected to column chromatography on silica gel ($CHCl_3$/*M*^{t}BE 1:1) to give 2-propoxybenzamide (1.36 g, 77%) as colorless crystals (mp. 102 ^{o}C). The crystal was grown from chloroform/ *M*^{t}BE (*v*/*v* 1:1). IR (KBr) ν_{max} 3445, 3325, 3273, 3180, 2964, 2935, 2877, 1665, 1594, 1454, 1378, 1277, 1237, 1042, 1010, 759, 566 cm^{-1}; ^{1}H NMR (DMSO-d^6, 400 MHz) 0.97 (3*H*, t, ^3J = 7.6 Hz), 1.76 (2*H*, qt, ^3J = 7.6 Hz, ^3J = 6.4 Hz), 4.04 (2*H*, t, ^3J = 6.4 Hz), 6.99 (dd, ^3J = 8.0 Hz, ^3J = 8.0 Hz), 7.10 (1*H*, d, ^3J = 8.0 Hz), 7.43 (1*H*, ddd, 3*J* = 8.0 Hz, 3*J* = 8.0 Hz, ^4J = 2.0 Hz), 7.78 (1H, dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz); ^{1}H NMR ($CDCl_3$, 400 MHz) 1.07 (3H, t, ^3J = 7.4 Hz), 1.90 (2H, dd, ^3J = 7.4 Hz, ^3J = 6.5 Hz), 4.09 (2H, t, ^3J = 6.5 Hz), 6.07 (1H, bs, NH), 6.96 (1H, d, ^3J = 8.0 Hz), 7.05 (1H, dd, ^3J = 7.8 Hz, ^3J = 7.6 Hz), 7.44 (1H, dd, ^3J = 8.0 Hz, ^3J = 7.6 Hz, ^4J = 1.8 Hz), 7.84 (1H, bs, NH), 8.20 (1H, dd, ^3J = 7.8 Hz, ^4J = 1.8 Hz); ^{13}C NMR (DMSO-d^6, 400

MHz) 11.0, 22.3, 70.4, 113.3, 120.8, 123.1, 131.2, 132.9, 157.0, 166.8; ^{13}C NMR ($CDCl_3$, 400 MHz) 10.7, 22.6, 71.0, 112.8, 121.4, 121.7, 133.2, 134.0, 158.2, 168.1.

Crystal data for 2-propoxybenzamide:

$C_{10}H_{13}NO_2$ M_r = 179.21 Monoclinic, P2$_1$=n a = 6.0303 (4) Å
b = 11.1196 (8) Å c = 14.4140 (11) Å β = 98.647 (6)^o V = 955.54 (12) Å^3
Z = 4 Cu Kα radiation μ = 0.71 mm^{-1} T = 100 K
crystal size 0.16 X 0.10 X 0.08 mm

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