CrystEngComm

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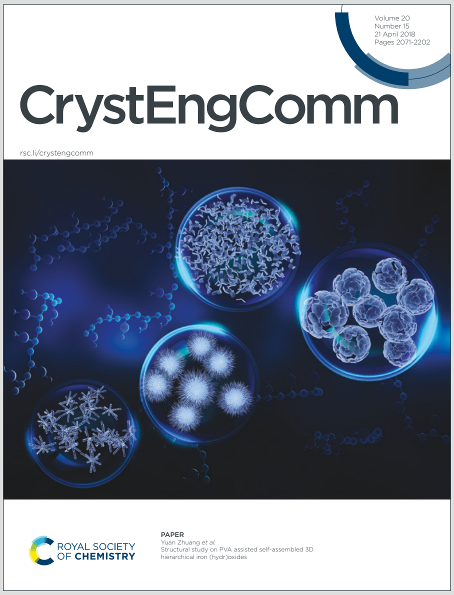

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N-H···O Hydrogen Bonding to the Alkoxy Oxygen of a Carboxylic Ester Group: Crystal Structures of Methyl 2,6-Diaminobenzoate and Its Derivatives.

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Abstract.

Methyl 2,6-diaminobenzoate and its *bis*-triphenylboron complex show hydrogen bonding from NH_2 groups to both oxygen atoms of the carboxylic ester, and there is little difference in the lengths of these types of hydrogen bond, while the crystal structure of the tetrafluoroborate salt is dominated by cation/anion hydrogen bonding. In methyl 2-amino-6-tosylaminobenzoate, the more acidic tosyl-N-H group forms a hydrogen bond to the carbonyl and the primary amino group makes a hydrogen bond to the alkoxy group. A search of the Cambridge Structural Database reveals a number of examples of N-H···O hydrogen bonding to the alkoxy oxygen of an ester group with a preference for the N-H bond lying in the ester plane. Hydrogen bonding to the ester alkoxy group should not be excluded when considering mechanistic processes in chemical or biochemical systems.

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Introduction.

The carboxylic ester functional group is ubiquitous in nature, both in biology and natural products and as a fundamental functional group in synthetic chemistry, variously as a handle for synthetic elaboration, a directing group, a protected carboxylic acid or an important molecular feature.[1] When not part of a lactone ring, the group exclusively takes the *cis* conformation (Fig. 1) even when the alkoxy group is very large, due to the overlap of the alkoxy oxygen atom's *sp²* lone pair with the carbonyl group's antibonding sigma orbital.[2] The two oxygen atoms of a carboxylic ester have quite different characteristics. Thus, protonation on the carbonyl oxygen is strongly favoured over the alkoxy oxygen[3] with *ab initio* calculations suggesting an energy difference between these two modes of protonation for methyl formate of *ca.* 20 kcal mol^{-1}. Esters alkylate on the carbonyl oxygen, as in oxonium ion **1** prepared from the corresponding carboxylic ester, by reaction at the lone pair *trans* to the C-OR bond.[4] Furthermore, they prefer to coordinate metals through the carbonyl oxygen as in *tris* complex **2**[5] though a few examples of coordination through the alkoxy oxygen are known in constrained systems such as iron complex **3**[6] and in complexes with particular crown ligands.[7] Carboxylic ester groups are often involved in hydrogen bonding to hydroxy or amino groups as observed in numerous crystal structures. Almost exclusively these bonds form to the carbonyl group and not the alkoxy oxygen atom.[8] Calculations by Lommerse *et al.* on the interaction between methyl acetate and methanol suggest that hydrogen bonding to the carbonyl group is favoured by *ca.* 9 kJ mol^{-1}, and that the preferred orientation of hydrogen bonding to the alkoxy oxygen atom occurs in the plane of the ester group.[9] More recent DFT calculations have suggested a difference in energy of 6-12 kJ mol^{-1} for hydrogen bonding of 2,2,2-trifluoroethanol to the two types of oxygens in several simple esters.[10]

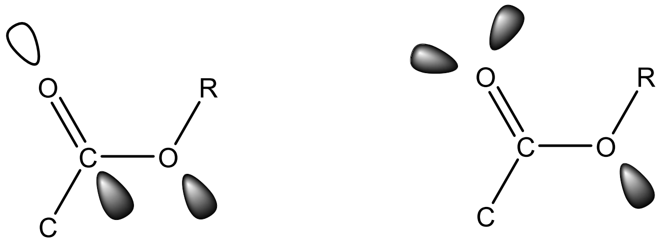

Figure 1. The preferred *cis* conformation of a carboxylic ester group, showing the alkoxy oxygen lone pair aligned with carbonyl group's σ* orbital (left), and the oxygen lone pairs available for hydrogen bonding (right).

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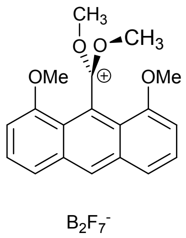
Nevertheless, hydrogen bonding to the ester's alkoxy oxygen atom can occur. Vibrational spectroscopic studies on methyl *L*-lactate in the vapour phase identified two conformations with an intramolecular hydrogen bond to the alkoxy oxygen, though they are less stable than that with a hydrogen bond to carbonyl oxygen.[11] Lectka has also demonstrated that the specifically designed model compound **4**, which contains a hydrogen bond to an ester's alkoxy oxygen atom, shows an *increase* in the stretching frequency of the carbonyl group by *ca.* 36 cm^{-1}, due to reduction of its conjugation with the alkoxy oxygen.[12] Similar results were obtained from the closely related N-protonated lactone **5**. In contrast, hydrogen bonding to the carbonyl group reduces the carbonyl stretching frequency due to promotion of conjugation with the alkoxy oxygen,[13] as demonstrated, in an intramolecular fashion, by the protonated *peri*-naphthalene **6** and its free base **7** (1686 v 1718 cm^{-1})[14] and by the naphthol derivative **8** compared with its methoxy analogue **9** (1677 v 1721 cm^{-1}).[15] However, hydrogen bonding to



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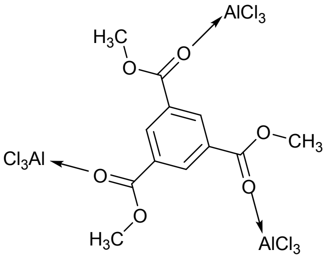

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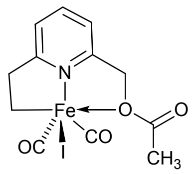

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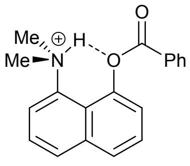

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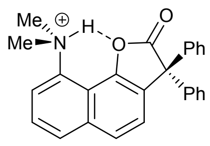

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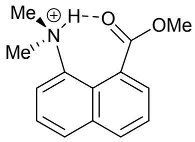

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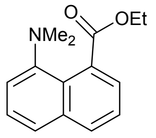

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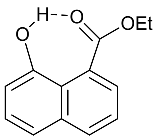

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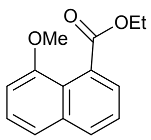

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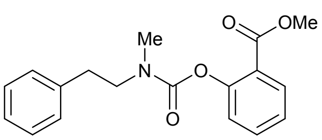

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the alkoxy oxygen may have relevance as a precursor to full protonation when it is not in direct competition with such processes at the carbonyl oxygen e.g. in a constrained environment such as an enzyme active site, or where it can lead to particular chemistry. Indeed, recently Shi has proposed that ester formation and hydrolysis proceeds via protonation of the alkoxy oxygen atom leading to a reactive acylium intermediate, based on DFT calculations,[16] and acylium ion formation has been proposed in strongly acidic conditions.[17] There is also evidence of hydrogen bonding to the alkoxy oxygen of carbamates,[18] which in the case of **10** leads to cleavage of methyl salicylate to leave a highly electrophilic isocyanate cation intermediate for subsequent cyclisation in acidic conditions at room temperature.

We were interested to investigate N-H···O hydrogen bonds to the alkoxy oxygen of carboxylic ester groups by crystallography, since this mode of bonding is still not well recognised. Indeed, a search of the Cambridge Structural Database (CSD)[19] for such intermolecular N-H···O(C=O)R cases with $H\cdots O < 2.3$ Å revealed just 17 cases, in contrast to over 2000 cases for such hydrogen bonding to the carbonyl oxygen atom (*vide infra*). We decided to study the structures of a group of compounds which have the possibility of forming two N-H···O hydrogen bonds, one to each oxygen of the ester group, and thus provide a comparison between them. Here we report the crystal structures of methyl 2,6-diaminobenzoate **11** and three of its derivatives. The hydrogen bonding between amino groups and the ester in **11** may be resonance stabilised due to donation of the nitrogen lone pair electron density through the benzene ring into the ester group. The three derivatives comprise two symmetrical ones in which the amino groups carry positive charges and thus might be stronger hydrogen bond donors, and an unsymmetrical case where the character of one amino group was modified by formation of a sulfonamide. No structures of benzoate esters with two *ortho* amino based functionalities have been reported before, though there are examples of benzoate ions with *ortho* acylamido groups.[20]

Discussion.

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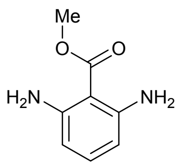
Synthesis.



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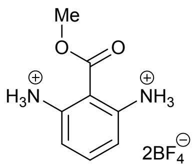

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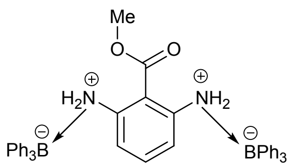

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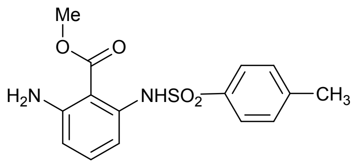

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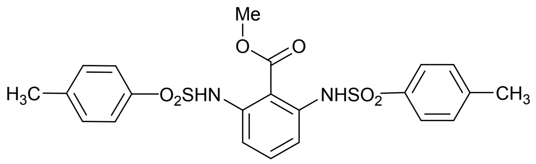

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Methyl 2,6-diaminobenzoate **11** has only been reported sparsely in the literature,[21] and it is unstable to air oxidation under ambient conditions, readily producing dark oils. It was prepared by reduction of methyl 2,6-dinitrobenzoate[22] with hydrogen at four atmospheres over palladium/charcoal. Slow evaporation of the filtered THF/methanol solution at room temperature gave a dark green oil which on standing in an inert atmosphere formed some colourless plate-like crystals. Preparation of derivatives from freshly obtained diamine **11** proved difficult, but crystals of three materials were eventually obtained. Treatment with HBF_4 in ether gave the *bis* BF_4 salt **12** in which two positively charged $-NH_3^+$ groups flank the ester group. Attempts to prepare the corresponding BPh_4 salt from the *bis* chloride salt of **11** and $NaBPh_4$ led only to the serendipitous isolation of a few crystals of the *bis* BPh_3 complex **13** in which each nitrogen atom bears a formal positive charge due to donation of its lone pair to a boron. Treatment of **11** with tosyl chloride and triethylamine gave both the mono- and di-tosylated materials **14** and **15**. The former contains two groups with different acidities and electron donating powers, - NH_2 and -NHTs, located to either side of the ester functionality The crystal structures of **11-14** were determined at low temperature. The coordinates and isotropic displacement parameters for all hydrogen atoms attached to nitrogen were refined without constraints, though the refined values may be *ca*. 0.05-0.1 Å shorter than would be determined by neutron diffraction.

Crystal Structure of methyl 2,6-diaminobenzoate 11.

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The crystal structure of **11**, determined by X-ray diffraction at 100 K, is in the monoclinic space group $P2_1/c$. The molecular structure is illustrated in Fig. 2, and the packing arrangement including inter- and intra-molecular hydrogen bonding is shown in Fig. 3. Selected molecular geometry is given in Tables 1-3. The molecule is close to planar with the best planes of the carboxylic ester group and benzene ring lying at 8.7(1)^o to each other. Each amino group makes a short (N)H···O contact to the neighbouring oxygen atom of the ester group, so that the ester group is hydrogen bonded in an intramolecular fashion at both oxygen atoms (Table 4). For the carbonyl oxygen, O1, the O(1)···H(11)-N(1) separation is 1.94(2) Å, with angles at O and H of 102.7(6) and 132(2)^o respectively. The hydrogen bond lies *ca.* 17^o from the axis of one of the oxygen's sp^2 lone pair of electrons. For the alkoxy oxygen, O2, the O(2)···H(21)-N(2) separation is similar at 2.009(18) Å with angles at O and H of 107.0(5) and 124(2)^o so that this hydrogen bond lies at *ca.* 15^o to the axis of the single sp^2 lone pair on the alkoxy oxygen. The ester group is displaced in the plane of the benzene ring from a symmetrical location by 3.0^o in the direction to make the intramolecular hydrogen bond to the carbonyl oxygen shorter. Both amino groups are displaced away from the ester group by 2.63^o (N(1)) and 3.17^o (N(2)). Compared to low temperature crystallographic data for methyl benzoate derivatives with no *ortho* substituents (Tables 1-2) (see ESI), the geometry of the ester group has been modified by the amino groups. The carbonyl group has lengthened by 0.014 Å to 1.2229(16) Å, while the C-OMe and O-Me bonds are hardly changed (C-OMe: 1.3448(16) Å *cf.* 1.340(8) Å, and O-CH_3: 1.4404(17) *cf.* 1.45(2) Å). Furthermore, the O=C-O angle has closed by 3.6^o and the other two angles have expanded, that next to the carbonyl by 1.0^o and that next to the methoxy group by 2.5^o.

Both amino groups delocalise electron density from their lone pairs into the ester group, as indicated by the low frequency of the ester carbonyl resonance at 1657 cm^{-1}. Thus, compared to crystalline aniline at 100 K,[23] the H_2N-C bonds (1.3629(19) and 1.3786(18) Å) are shortened by *ca.* 0.02 Å and the C,C bonds in the benzene ring between the substituents (1.430(2) and 1.4372(18) Å) are lengthened by 0.03-0.04 Å. The bond from the benzene ring to the ester group (1.4652(18) Å) is shortened by 0.022 Å with respect to the *ortho*-unsubstituted methyl benzoates. When compared to two crystalline esters of anthranilic acid in **16** and in the molecular complex **17**, both measured at 120 K,[24] adding a second *ortho* amino group in diamine **11**, leads to the bond between the benzene ring and ester group being a little shorter (1.4652(18) *cf.* 1.471-1.476 Å), and the ring bonds between substituents are lengthened

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Table 1. Bond lengths (Å) for **11-14** and mean bond lengths for methyl benzoates without *ortho* substituents.[a]

Bond	**11** 100 K	**12** 100 K	**13** 150 K	**14** 150 K (mean, range for six molecules.)	Average data for methyl benzoates[a]
N1-C2	1.3629(19)	1.466(2)	1.451(4)	1.421 1.415(3)-1.424(3)	-
N2-C6	1.3786(18)	1.469(2)	1.462(3)	1.357 1.354(3)-1.359(3)	-
C1-C2	1.430(2)	1.400(2)	1.406(4)	1.427 1.422(3)-1.433(3)	1.393(5)
C1-C6	1.4372(18)	1.397(2)	1.397(4)	1.421 1.416(3)-1.425(3)	1.393(6)
C2-C3	1.4044(19)	1.377(2)	1.384(4)	1.376 1.371(3)-1.381(3)	1.383(7)
C3-C4	1.373(2)	1.385(3)	1.375(4)	1.385 1.382(4)-1.389(3)	1.398(9)
C4-C5	1.381(2)	1.386(3)	1.378(4)	1.367 1.364(3)-1.370(3)	1.396(9)
C5-C6	1.3979(19)	1.382(2)	1.384(4)	1.407 1.404(3)-1.409(3)	1.386(5)
C1-C7	1.4652(18)	1.502(2)	1.495(4)	1.476 1.472(3)-1.478(3)	1.487(8)
O1-C7	1.2229(16)	1.205(2)	1.207(3)	1.221 1.219(3)-1.226(3)	1.209(6)
O2-C7	1.3448(16)	1.328(2)	1.340(3)	1.333 1.329(3)-1.335(3)	1.340(8)
O2-C8	1.4404(17)	1.455(2)	1.456(3)	1.446 1.442(3)-1.448(3)	1.449(24)
N1-B1	-	-	1.679(4)	-	-
N2-B2	-	-	1.681(4)	-	-

[a] *Ortho*-unsubstituted methyl benzoates, $R < 0.07$, T 90 -120 K, no errors or disorder, only single crystal data from neutral organic molecules.

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Table 2. Bond angles (°) for **11-14** and mean geometry for methyl benzoates.[a]

Angle	**11** 100 K	**12** 100 K	**13** 150 K	**14** 150 K (mean and range for 6 molecules.)	Average data for methyl benzoates[a]
C7-O2-C8	115.55(11)	116.06(13)	116.4(2)	116.5 116.26(18)-116.83(18)	115(2)
O1-C7-O2	119.84(12)	125.49(16)	123.2(3)	120.3 119.95(19)-120.46(19)	123.4(6)
O1-C7-C1	125.26(13)	122.95(16)	124.5(3)	125.4 125.0(2)-125.56(19)	124.3(6)
O2-C7-C1	114.86(11)	111.54(14)	112.3(3)	114.3 114.18(19)-114.96(19)	112.3(6)
C2-C1-C7	117.68(12)	119.08(15)	118.5(3)	119.1 118.7(2)-119.4(2)	118.3(6)
C6-C1-C7	123.66(13)	124.41(16)	123.9(2)	123.0 122.82(19)-123.39(19)	122.1(6)
C2-C1-C6	118.63(12)	116.50(15)	117.6(2)	117.8 117.53(19)-118.12(19)	119.5(6)
N1-C2-C1	122.74(13) .	119.72(15)	121.0(3)	119.98 118.8(2)-120.29(19)	-
N1-C2-C3	117.50(14)	118.07(16)	118.0(3)	118.8 118.2(2)-119.8(2)	-
N2-C6-C1	123.60(12)	120.24(15)	122.1(2)	124.6 124.1(2)-124.9(2)	-
N2-C6-C5	117.26(12)	117.61(15)	116.7(2)	116.4 116.2(2)-116.7(2)	-
Benzene /CO_2Me Plane	8.7(1)	35.35(7)	31.1(1)	2.1 0.56(15)-3.16(16)	7.4(4.6)

[a] *Ortho*-unsubstituted methyl benzoates, R < 0.07, T 90 -120 K, no errors or disorder, only single crystal data from neutral organic molecules.

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Table 3: Angular geometry (°) of the covalent bonding to each nitrogen atom in **11**.

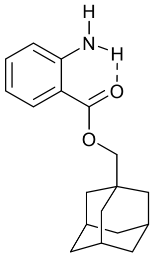
N1		N2	
Σ angles at N1	360(2)	Σ angles at N2	350(2)
H11-N1-H12	124.4(17)	H21-N2-H22	118.4(15)
H11-N1-C2	118.5(12)	H21-N2-C6	118.4(11)
H12-N1-C2	116.8(12)	H22-N2-C6	113.8(11)

Table 4: Hydrogen bonding in the crystal structure of the diamino ester **11**.

N-H···X-C(sp^2) (X=O, N)

H-bond	N-H /Å	H···X /Å	N···X /Å	Angle at H / °	Angle at X /° H···X-C(sp^2)	Torsion H···O-C-O
N1-H11···O1	0.87(2)	1.94(2)	2.6098(18)	132.3(16)	102.7(6)	176(2)
N1-H12···N2(2-x, y+1/2,1/2 -z)	0.837(19)	2.359(19)	3.1896(19)	171.6(16)	97.0(4), (N2-C6) 116.4(12), (N2-H21) 86.0(12), (N2-H22)	-
N2-H21···O2	0.901(18)	2.009(18)	2.6180(15)	123.6(15)	107.0(5), (O8-C7) 135.9(5), (O8-C8)	167(2)
N2-H22···O1(x, 3/2-y, z-1/2)	0.900(17)	2.163(17)	3.0339(15)	162.7(15)	137.6(5), (O1-C7)	31(2)

(1.430(2) - 1.4372(18) Å *cf.* 1.408-1.424 Å), consistent with increased electron donation into the ester group, though the carbonyl bond (1.2229(16) *cf.* 1.219-1.222 Å) is little changed.



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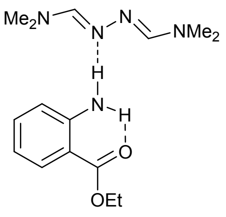

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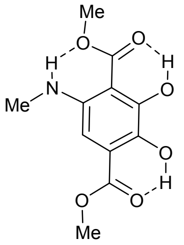

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Both amino groups are also involved in intermolecular hydrogen bonding (Table 4). The amino group adjacent to the carbonyl oxygen has almost perfect planar bonding (sum of angles

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at N(1): 360(2)^{o}) while the other amino group has a significantly pyramidalised bonding geometry (sum of angle at N(2): 350(2)^{o}). The latter amino group is an acceptor for an intermolecular hydrogen bond from N(1): N(1)-H(12)···N(2)[2-x, y+1/2, 1/2-z]: 2.359(19) Å, and this hydrogen bond aligns with the partly developed sp^3 type lone pair on N(2). The second hydrogen on amino group N(2) makes an intermolecular hydrogen bond to a carbonyl oxygen: (N(2)-H(22)···O(1) [x, 3/2-y, z-1/2]: 2.163(17) Å. Thus, the carbonyl oxygen is involved in two hydrogen bonds. This latter hydrogen bond links molecules in chains along the *c* axis, while the former links molecules in a zig-zag arrangement along the *b* axis. The hydrogen bonded networks formed, each composed of four molecules, and involving three or all four type of hydrogen bonds, are shown in Fig. 3.[25] In summary, for each amino group, one hydrogen atom makes an intramolecular hydrogen bond to the ester, and the other makes on intermolecular hydrogen bond.

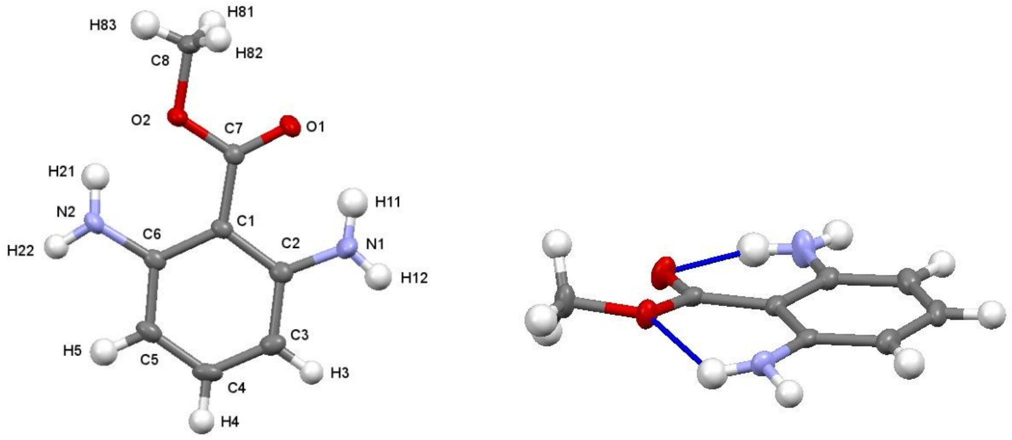

Figure 2. Molecular structure of **11** with all atomic displacement parameters drawn at the 50% level (left), and showing the hydrogen bonds between the substituents, and the small pyramidalisation at N(2) (right).

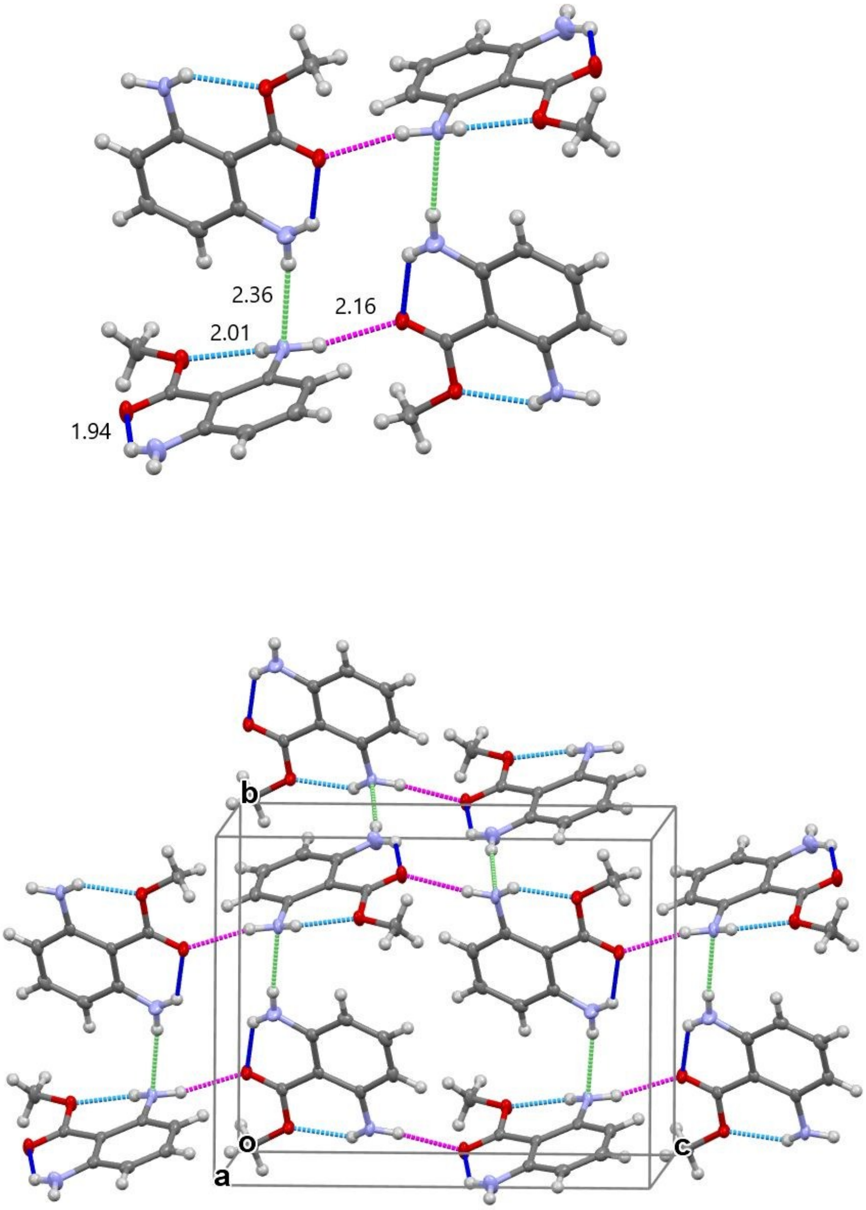

Figure 3. Hydrogen bonding arrangement in the crystal structure of **11** showing the four types of hydrogen bond in different colours: with hydrogen bond lengths in Å and showing the twelve atom network involving three hydrogen bond types (top), and showing the larger twenty-eight atom network structure involving all four types of hydrogen bond (below).

Crystal structure of the *bis* BF_4 salt 12.

A crystal of salt **12** was grown from acetonitrile and its structure determined by X-ray crystallography at 100 K in monoclinic space group $P2_1/n$. The structure is shown in Fig. 4 and molecular geometry is in Tables 1-2. Both amino groups are protonated and the $–NH_3^+$ groups are both oriented so that one N-H bond lies close to the aromatic plane directed towards the respective *ortho* hydrogen atom. The ester group is strongly twisted out of the aromatic plane by 35.35(7)°, so that the alkoxy oxygen atom makes a short contact to just one of the neighbouring (N)-H atoms (H(22)) (N-H···O: 2.23(2) Å) but with an angle of 111.5(17)° at hydrogen, while the other hydrogen (H(21)) is much more distant (2.80(2) Å). The carbonyl oxygen lies almost equidistant from two hydrogen atoms belonging to the adjacent $–NH_3^+$ group forming contacts of 2.48(2) and 2.49(2) Å but with very unfavourable angles at hydrogen (94-98°). Thus the shortest NH···O contact to the ester group is to the alkoxy oxygen atom, but it is longer than either of the two intramolecular hydrogen bonds in the diamine itself (1.94 and 2.009 Å), and has a less favourable angle at hydrogen (111° *cf.* 124 and 132°). The crystal structure is dominated by hydrogen bonding of the NH_3^+ groups to tetrafluoroborate anions (Fig. 5, Table 5). Each of the six N-H H atoms makes two or three contacts to fluorine atoms in the range 1.87-2.63 Å. Five of these N-H bonds make one H···F bond in the range 1.87(2)-2.09(2) Å, four of which are close to linear at hydrogen (160(2)-175(2)°), and longer one(s) with much less favourable angle (2.38(2)-2.63(2) Å, 117(2)-137(2)°. In contrast the hydrogen which makes a short contact to the ester alkoxy oxygen makes two intermediate length contacts to fluorine (2.21 and 2.36 Å) (see ESI).

Compared to the free base **11**, the two H_3N-C bonds are *ca.* 0.1 Å longer and the ring bonds between the groups are 0.3-0.4 Å shorter as a consequence of the loss of conjugation between the amino groups and the ester group, indicated also by the higher carbonyl stretching frequency of 1739 cm^{-1}. The bond from the ring to the ester group (1.502(2) Å) is notably lengthened by 0.038 Å and even longer than in other *ortho*-unsubstituted methyl benzoates (1.487(7) Å). Furthermore, in the ester group, both the carbonyl and C-OCH_3 bonds are reduced in length by 0.018 and 0.017 Å respectively compared to the diamine **11**, and the O-CH_3 bond is slightly lengthened by 0.015 Å. The angle between the two C,O bonds is 125.49(16)°, so has widened by *ca.* 5.7° compared to the diamine, and is wider than in typical methyl benzoates (123.4(6)°). The in-plane displacements of the functional groups follow the same pattern as for the free base **11**, but to a lesser degree. Thus the ester group is displaced by 2.7° from a symmetrical position in a direction which increases the O···H(N) contact to the alkoxy oxygen, and the NH_3^+ groups are displaced away from the ester group by 0.8 (N(1)) and 1.3° (N(2)).

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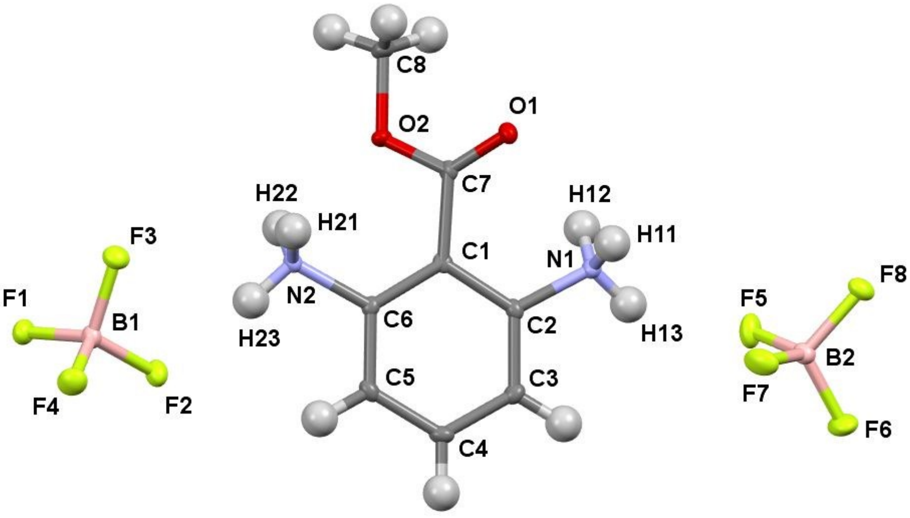

Figure 4. Structures of the dication and two tetrafluoroborate anions from the crystal structure of **12**, with anisotropic displacement parameters drawn at the 50% level.

Table 5. N-H···O Hydrogen Bonding in **12.**

N-H···O-C(*sp*^{2})

H-bond	**N-H /Å**	**H···O /Å**	**N···O /Å**	**Angle at H / º**	**Angle at O /º: H···O-C(*sp*^{2})**	**Torsion H···O-C-O**
N1-H11-O1	0.85(2)	2.48(2)	2.729(2)	98(2)	98.9(5)	155(2)
N1-H12-O1	0.95(2)	2.49(2)	2.729(2)	94(2)	83.1(5)	125(2)
N2-H22-O2	0.92(2)	2.23(2)	2.7056(19)	111.5(17)	105.9(6)	156(2)

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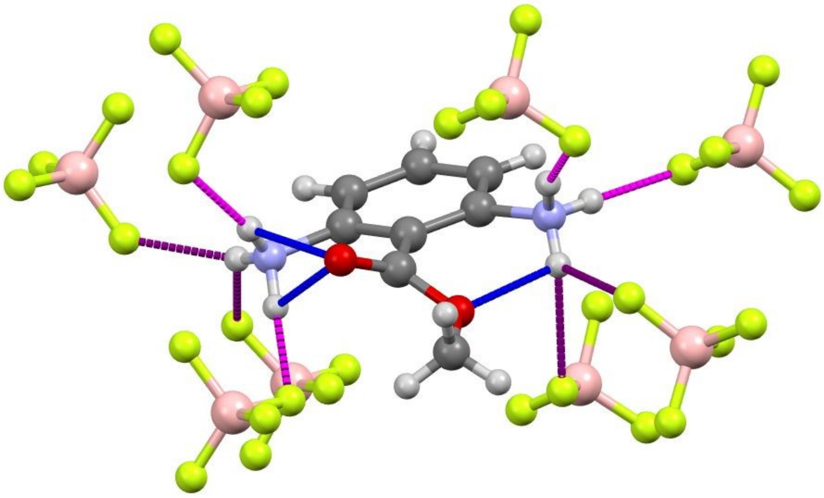

Figure 5. Hydrogen bonding in the salt **12**: O···H-N bonds in blue, short linear N -H···F bonds (1.8 -2.1 Å) in magenta, medium length N-H···F bonds in purple (2.1-2.5 Å).

Crystal Structure of the *bis* BPh_3 complex 13.

The crystal structure of **13**, the complex of free base **11** with triphenylboron, determined at 150 K, is triclinic in space group P-1. The structure shows that both amino groups are bonded to a BPh_3 unit and two acetonitriles are included in the asymmetric unit (Fig. 6, Tables 1-2). The N-B bonds of lengths 1.679(4) and 1.681(4) Å, are directed nearly perpendicular to the benzene ring of the diaminobenzoate group, *anti* to each other, which leaves one N-H group directed towards the ester group in each case. Thus, there are two N-H···O hydrogen bonds, one to the carbonyl oxygen and one to the alkoxy oxygen of similar lengths: 1.96(3) and 1.90(3) Å with angles at the hydrogen atom of 135(3)° and 144(2)° respectively (Table 6). Both hydrogens lie *ca*. 1 Å out of the plane of the ester group, so the H···O-C-O torsion angles are 150(3) and 148(3)° respectively. The ester group lies at 31.1(1)° to the benzene ring, and is displaced in the plane of the benzene ring by 2.7° from a symmetrical position, as observed in **11** and **12**, to increase the separation between the neighbouring alkoxy functionality and amino group. The two remaining N-H bonds make hydrogen bonds to the acetonitrile molecules (N-H···N: 2.09(3) and 2.10(4) Å). The bonds from the amino and ester groups to the benzene ring, and the bonds within the ring, are all similar to those observed in the *bis* BF_4 salt. However, the difference is that the anionic groups are not available as hydrogen bond acceptors to dominate the crystal packing, so the results from this structure provide a much better example of two positively charged amino groups forming hydrogen bonds to both

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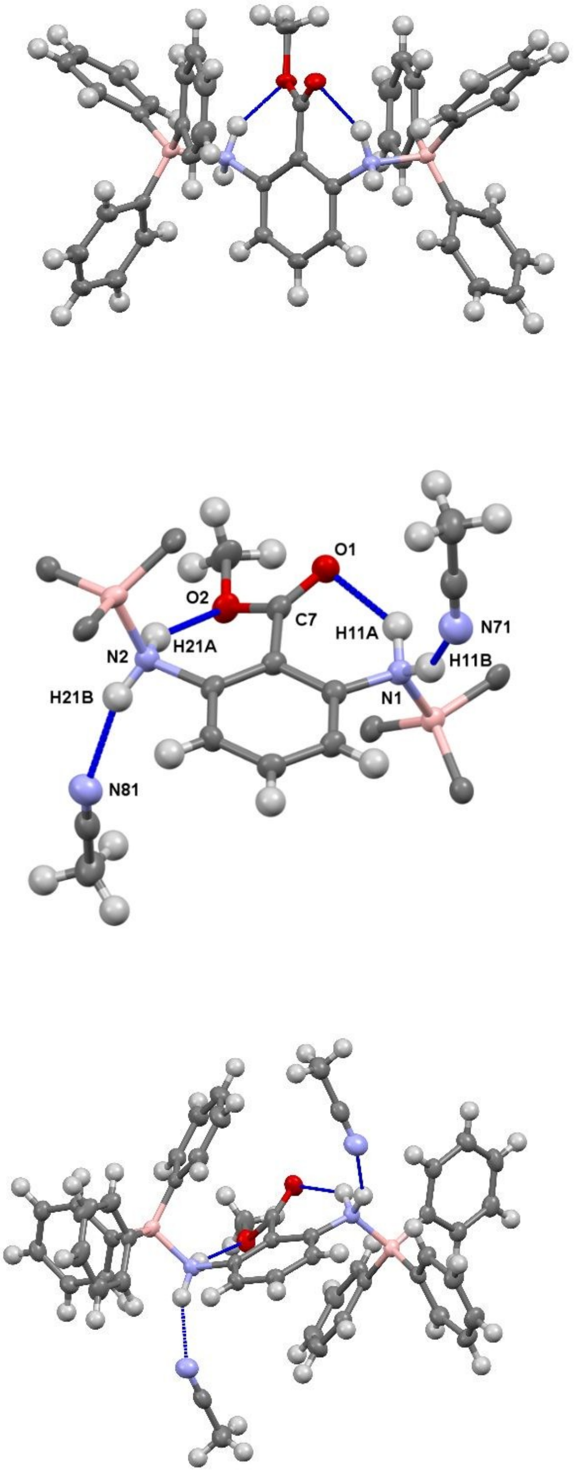

Figure 6. Views of the *bis* BPh_3 complex **13**: showing the hydrogen bonding to the ester group, acetonitriles excluded (top), a picture with most of each benzene ring omitted showing the hydrogen bonding to ester and acetonitrile and labelling of selected atoms (middle), and view of the whole hydrogen bonded complex (below).

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ester oxygen atoms. The hydrogen bond lengths, though, are not strikingly different from those in the neutral free base **11**. There are no other structures reported containing an aniline/BPh_3 complex, the nearest is that of 4-t-butylaniline with *per*-fluorinated triphenylborane $B(C_6F_5)_3$ which shows a shorter B-N bond of 1.645(3) Å.[26] Structures of three complexes of BPh_3 with secondary aliphatic amines are known (B-N: 1.651-1.691 Å).[27]

Table 6: Hydrogen bonding in the crystal structure of the triphenylboron complex **13.**

N-H···O-C(*sp*^{2}) (top) and N-H···N≡CCH_3 (below)

N-H···O	**N-H /Å**	**H···O /Å**	**N···O /Å**	**Angle at H / °**	**Angle: H···O-C(*sp*^{2})**	**Torsion H···O-C-O**
N1-H11A···O1	0.96(3)	1.96(3)	2.722(3)	135(3)	98.8(11)	150(2)
N2-H21A···O2	0.93(3)	1.90(3)	2.708(3)	144(2)	100.4(8)	148(2)

N-H···N≡CCH_3	**N-H /Å**	**H···N /Å**	**N···N /Å**	**Angle at H / °**	**Angle: H···N-C(*sp*)**
N1-H11B···N71	0.97(4)	2.10(4)	2.995(4)	152(3)	148.5(10)
N2-H21B···N81	0.95(3)	2.09(3)	2.976(4)	154(2)	145.9(9)

Crystal Structure of the tosyl derivative 14.

Remarkably the mono-tosyl derivative crystallises in the monoclinic space group $P2_1$/c with six independent molecules in the asymmetric unit which all have similar conformations, as shown for one molecule in Fig. 7. Averaged molecular geometry data for the six molecules with corresponding ranges are provided in Tables 1-2. Each of the six molecules of **14** is folded into a U-shape and with a torsion about the N-$S(O_2)$ bond between the C-N and $S(O_2)$-C bonds in the range 48.5(2)-56.0(2)°. The ester group lies almost coplanar with the benzene ring and both ester oxygen atoms make intramolecular hydrogen bonds with amino hydrogens: the carbonyl oxygen with the more acidic tosylamino N-H group, and the alkoxy oxygen with the primary amino group. There is more electron donation into the benzene ring and ester group from the primary amino group than from the tosylamino group judging from their two

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N-C(benzene) bond lengths: 1.354(3)-1.359(3) v 1.415(3)-1.424(3) Å respectively. The former is even shorter than those in diamine **11** where two amino groups can contribute electron density. Nevertheless both ring C,C bonds between the two functional groups are of similar length (averaged values: 1.421 and 1.427 Å). The short C,C bond between the benzene and ester groups (1.472(3)-1.478(3) Å), the long carbonyl bond (1.219(3)-1.226(3) Å) and the compression of the OCO angle to 119.95(19)-120.46(19)^o are also supportive of significant electron donation in the ester group as in **11**, as is the similar carbonyl stretching frequency (1661 v 1657 cm^{-1}). In contrast to the well-known resonance-assisted hydrogen bonds,[28] the carbonyl oxygen is not hydrogen bonded to the group which donates most electron density into the pi system, but favours making a hydrogen bond to the more polar tosylamino N-H group. For comparison is the terephthalic ester **18** in which one ester group has both *ortho* amino and hydroxy groups. In this case the more acidic OH group forms a hydrogen bond to the carbonyl group and the amino group forms one to the alkoxy (N-H···O: 2.03 Å).[29]

The tosylamino nitrogen atoms have strongly pyramidalised nitrogen geometries (sum of angles: 337(3)-347(3)^o) while the primary amino groups have only slightly pyramidalised nitrogen geometries (sum of angles: 353(3)-358(4)^o) but neither act as acceptors of hydrogen bonding since there are better acceptors available. Such tosylamino nitrogen atoms generally have pyramidal geometry (see ESI). The two types of hydrogen bonding to the ester group, tosylamino to carbonyl oxgen and primary amino to alkoxy oxygen, show similar lengths of 1.87(3)-1.94(3) and 1.94(3)-1.99(2) Å respectively, but the angles at hydrogen are *ca.* 18^o larger for the bond to the carbonyl than to the alkoxy oxygen: 140(3)-148(3)^o v 125(2)-131(2)^o (Table 7). In the plane of the benzene ring the ester group is displaced *ca.* 2^o from the symmetrical position towards the tosylamino group which varies only slightly (in both directions over the six molecules) from its symmetrical position. In contrast, the amino group is displaced by *ca.* 4^o away from the ester, which together with its slightly longer hydrogen bonds to the ester, is consistent with the hydrogen bonding to carbonyl being the more dominant interaction.

The six independent molecules are organised in three columns along the *a* axis, with two such molecules per column. Like molecules are linked into chains by hydrogen bonding between the primary amino group's free hydrogen atom and a sulfonyl oxygen atom (S=O···H-N: 2.09(3)-2.18(3) Å, Table 8). The two independent chains lie side by side, connected by two distinct hydrogen bonds between the primary amino group's intramolecularly-bonded hydrogen atom and the carbonyl oxygen of the opposite chain (C=O···H-N: 2.26(3)-2.44(3) Å,

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Table 8), such that both chains direct their tolyl groups to the same side of the column (Fig. 8). The combination of the chains and cross-links between them form a network composed of twelve atoms, which involve all five different types of hydrogen bonding. Two of the three independent columns along the *a* axis lie adjacent to a centrosymmetrically related column, while the third set of columns do not, and are related by screw axes or glide planes (Fig. 9).

Table 7: Intramolecular N-H···O hydrogen bonding geometry in **14**, distances in Å, angles in °.

N1 (NH-tosyl)		**N2** ($-NH_2$)	
Σ angles at N1	337(3)-347(3)	Σ angles at N2	353(3)-358(4)
N1-H1	0.79(3)-0.84(2)	N2-H21	0.84(3)-0.88(3)
O1···H1	1.87(3)-1.94(3)	O2···H21	1.94(3)-1.99(2)
N1···O1	2.580(3)-2.613(2)	N2···O2	2.593(3)-2.602(3)
Angle at H1	140(3)-148(3)	Angle at H21	125(2)-131(2)
Angle at O1	98.7(8)-100.4(8)	Angle at O2	107.8(8)-109.6(8)
Torsion H···O=C-O	177(2)-180(2)	Torsion H···O-C=O	175(2)-179(2)

Table 8: Intermolecular N-H···O hydrogen bonding geometry in **14**, distances in Å, angles in °.

N2-H21···O=C		**N2-H22--O(SO)**	
N2-H21	0.84(3)-0.88(2)	N2-H22	0.84(3)-0.88(3)
O1···H21	2.26(2)-2.44(3)	O3···H22	2.09(3)-2.20(2)
N2···O1	3.004(3)-3.162(2)	N2···O3	2.955(3)-3.016(3)
Angle at H	139(2)-144(2)	Angle at H	155(2)-172(2)

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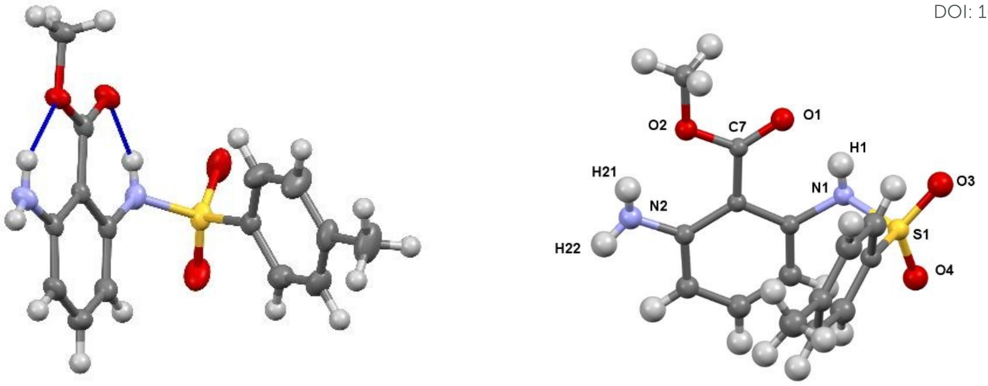

Figure 7. Molecular structure of one of six independent molecules of the mono-tosyl derivative **14** showing the two intramolecular N-H···O hydrogen bonds (left), and selected atomic labels (right).

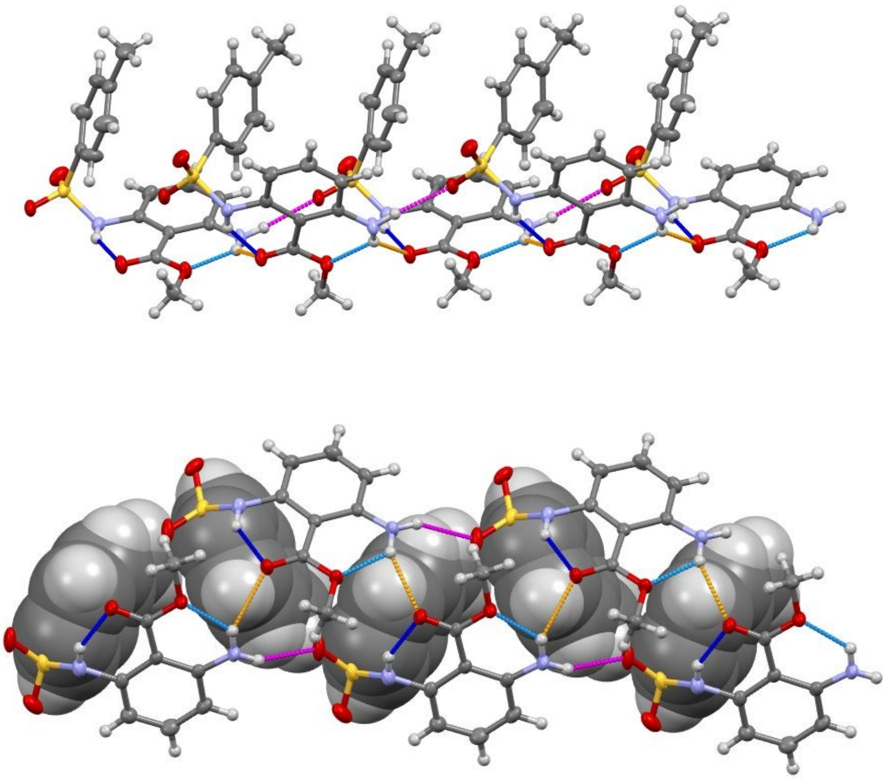

Figure 8. Intra- and intermolecular hydrogen bonding in two independent molecules of **14** forming a chain along the *a* axis: (a) showing the disposition of the tolyl groups to one side of the chain (above) and (b) showing the hydrogen bond network composed of rings of twelve atoms involving all four types of hydrogen bond which are given in different colours: blue and light blue for the intramolecular N-H···O, magenta for N-H···OSO_2 linking identical molecules in chains, and orange for N-H···O between the two independent chains (below).

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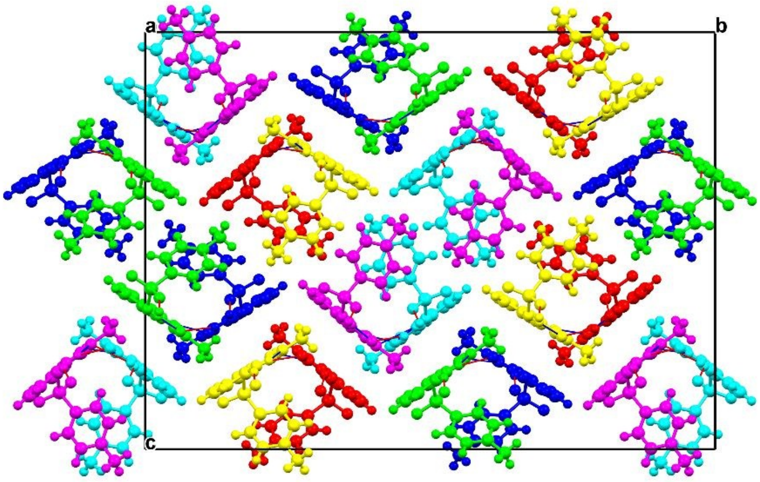

Figure 9. Crystal packing arrangement of the three independent chains in **14** running parallel along the *a* axis, each composed of two independent molecules illustrated in turquoise/purple, dark blue/green and red/yellow, and viewed down the *a* axis.

Other cases of hydrogen bonding to the ester alkoxy group.

A search of the Cambridge Structural Database[19] for intermolecular N-H···O hydrogen bonding to the alkoxy oxygen of an ester group, with the constraints of H···O less than 2.3 Å yielded 17 hits, all from the last 20 years, in contrast to 2042 hits for the corresponding type of contact to the carbonyl oxygen atom. This is consistent with the greater charge density on the carbonyl oxygen.[30] Typically the N-H···O geometry is close to linear at hydrogen, and the hydrogen atom lies close to the ester plane, so that the H···O link lies *trans* to the carbonyl group (Fig. 10). For the low temperature structures in this group, the NH···O contacts lie in range 2.13-2.29 Å (see ESI). Six of the seventeen structures show a hydrogen of a -NH_3^+ group of a dipeptide forming two hydrogen bonds to the alkoxy and hydroxy oxygens of an α-hydroxyester (Fig. 11).[31] In one particular case of anthracene-based fluorophores such as **19**, in which dimers are connected by amide/ester hydrogen bonding (Fig. 12), just a small structural change can lead to a change from hydrogen bonding to carbonyl from alkoxy oxygen.[32]

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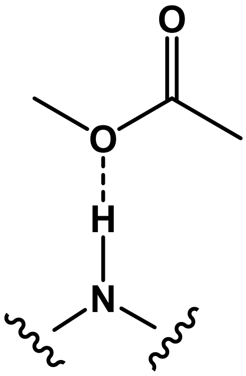

*Figure 10***.** Preferred orientation for hydrogen bonding of an amino hydrogen atom to the alkoxy oxygen of a carboxylic ester group.

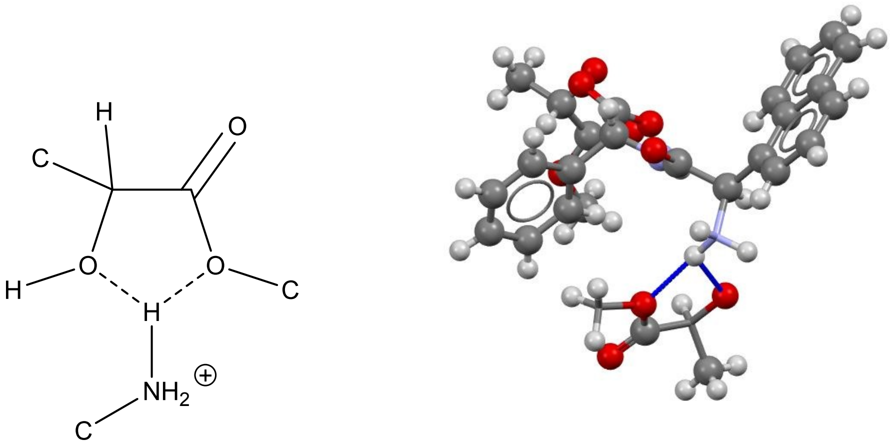

Figure 11. Diagram of the binding a peptide-ammonium to two oxygens of an α-hydroxy ester (left); particular example of this mode of binding of a dipeptide to methyl *S*-2-hydroxypropanoate (right).

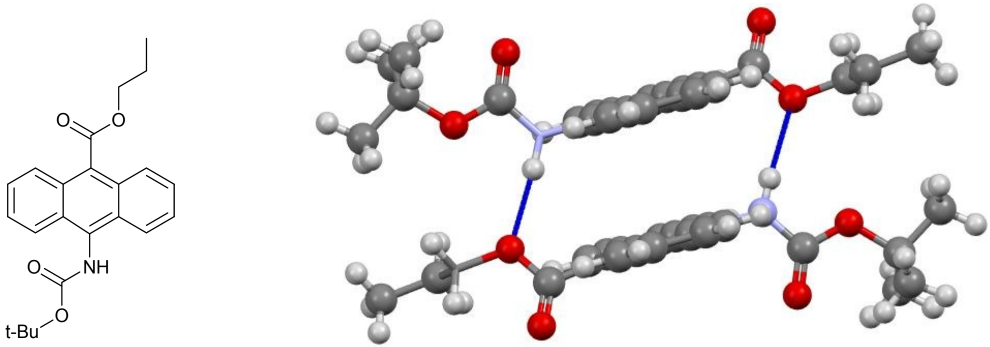

Figure 12. Hydrogen bonding between pairs of the anthracene derivative **19**.

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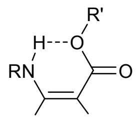
Cases of intramolecular N-H···O hydrogen bonding to the alkoxy oxygen are likely to be more frequent, and a search of the CSD found 57 cases if the N-H···O angle at hydrogen was restricted to 120-180°, while without this restriction 168 hits were found. In contrast, the same searches for intramolecular hydrogen bonding to the ester carbonyl group found 1108 and 1385 hits respectively, again showing the strong preference for hydrogen bonding to the carbonyl over alkoxy oxygen atoms. One particular common type of such intramolecular hydrogen bonding occurs in fragments of type **20** or **21**, in which there is a 1,6 resonance assisted hydrogen bond to either of the oxygens of an ester group due to electron delocalisation from the nitrogen to the ester through an intervening double bond. For hydrogen bonds up to 2.3 Å long, and with no restriction on the angle at hydrogen, there are 31 hits in the CSD when the contact is to the alkoxy oxygen as in fragment **20**, as in molecule **22**[33] or **23**[34] and 663 hits when the contact is to carbonyl oxygen as in fragment **21**. In one particular case, two crystallographically independent molecules adopt the two different modes,[35] but there are also cases such as **24** and **25** where two independent molecules both adopt the hydrogen bonding mode to the alkoxy group.[36] Presumably, the adoption of the less favoured mode, is taken when there are advantages to the overall crystal packing. Another set of interesting molecules are a series of cyclic hydrazones of type **26** with variable ring sizes.[37] In **27**, the smallest ring in the series contains two hydrogen bonds to alkoxy ester oxygens (N-H···O: 1.89 and 1.95 Å) and this general arrangement is maintained if one more methylene is included in the ring. However, addition of a further methylene to the ring as in **28**, allows one of these hydrogen bonds now to form to a carbonyl group. One hydrogen bond to an alkoxy oxygen is maintained on addition of up to two more methylene groups. Across the series these particular hydrogen bonds lie in the narrow range 1.94-2.17 Å.



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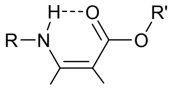

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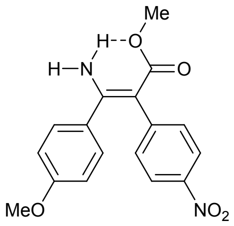

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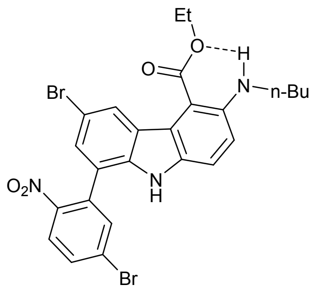

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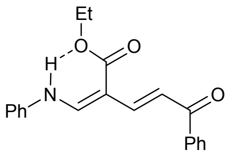

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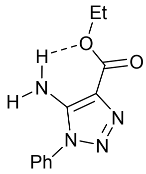

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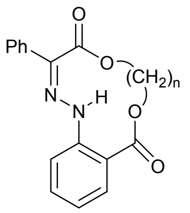

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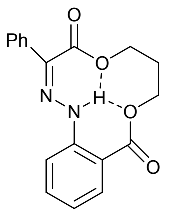

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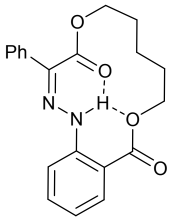
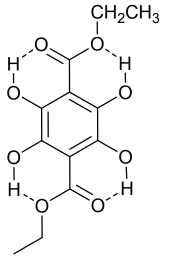


28

Intermolecular hydrogen bonding from an O-H to the ester alkoxy oxygen is also much less common than to the carbonyl oxygen in the CSD. Thus, a similar search as carried out as above yielded 105 examples for hydrogen bonding to the alkoxy oxygen but 1346 examples to the carbonyl oxygen. The shortest hydrogen bonding to the alkoxy group lie in the range 2.02-2.05 Å. There are three examples of benzoate esters with two *ortho* hydroxyl groups which have refined hydrogen positions **29-31**[38] for comparison with the 2,6- diaminobenzoate ester **11**. The hydrogen bonds to the carbonyl group (1.69-1.77 Å) are shorter than those to the alkoxy group (1.76-1.90 Å), and shorter than the corresponding bonds in diamine **11**. There is less delocalisation from the hydroxyl groups into the ester group than from the amino groups judging by the shorter intervening aromatic bonds (1.411-1.416 Å *cf.* 1.430-1.437 Å). It is notable that in compounds **32-33**,[39] which have the potential to form the same pattern of hydrogen bonds to their ester groups, the OH group adjacent to the alkoxy group prefers to make a hydrogen bond to the adjacent nitro group, indicating that of the three hydrogen bond acceptors present, the alkoxy oxygen atom is the weakest.



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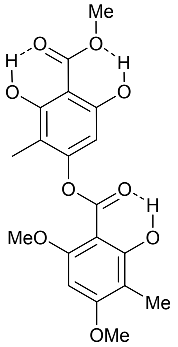

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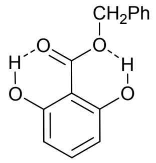

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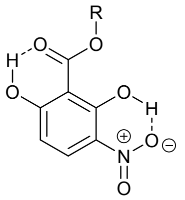

32 R = Me

33 R = CH_2Ph

Conclusions.

The structure determinations of the diaminobenzoate ester **11** and its triphenyl boron complex **13** and tosyl derivative **14** provide well determined examples of hydrogen bonding to the alkoxy oxygen of the carboxylic ester group. The lengths of the hydrogen bonds to the two types of ester oxygen are similar, lying the range 1.90-2.01 Å, and no significant difference whether the nitrogen atom is charged or not, and similar N···O separations in each case. The interactions in **11** and **14** correspond to resonance assisted hydrogen bonds, with increases in the carbonyl bond length and but little change to bonds to the alkoxy oxygen atom. The rather rigid nature of the diaminobenzoate framework does restrict the freedom of the groups in **11** and **14** to optimise the interactions between them, though both amino groups are not compelled to form intramolecular hydrogen bonds. The structures of **11**, **13** and **14** provide examples of both ester oxygens being involved in hydrogen bonding with N-H functionality. The structure of the *bis* tetrafluoroborate salt **12** is not so informative due the domination of cation/anion interactions. The great increase in the number of compounds in the CSD now reveals that, although hydrogen bonding to the carbonyl oxygen is favoured due to the larger charge density on this oxygen atom, hydrogen bonding to the alkoxy oxygen is accessible and preferentially lies in the plane of the ester group. Thus, this mode of hydrogen bonding should not be excluded from considerations of reaction mechanisms, whether in enzymes or in synthetic chemistry, or binding of substrates to larger species such as protein-based receptors.

Acknowledgements.

We thank Nottingham Trent University for financial support.

Conflicts of Interest.

None to report.

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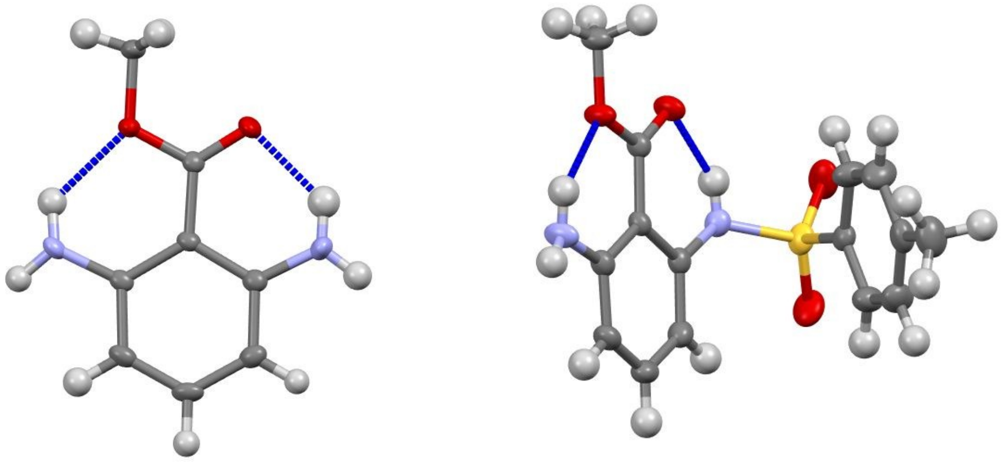
DOI: 10.1039/D0CE00495B



Molecules with hydrogen bonds from amino groups to both oxygens of a carboxylic ester are described, and other examples of hydrogen bonding to an ester's alkoxy oxygen atom are highlighted.