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Synthon trends according to acid strength and geometry in salts of N-heterocyclic bases†

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The hierarchy and robustness of homosynthons and heterosynthons formed by N-heterocyclic bases were assessed experimentally in salts of aminopyrazine (ampyz) and *trans*-1,2-bis(4-pyridyl)ethane (BPE) with common strong, moderate and weak acids, and theoretically at the M06-2X/6-31+G** level of theory. A trend for a base-pairing primary homosynthon to assemble in ampyz salts as the acid strength increases can be drawn. This homosynthon is present in chloride and bromide salts of ampyz, which is compatible with protonation at N4 and the formation of an accessory four-point heterosynthon engaging two $(ampyz)^+$ cations and two halides. This robust synthon is also present in chloride, bromide and dihydrogen phosphate salts of BPE. Among all our BPE multicomponent crystal forms, it is not found only in the uncommon phosphoric acid cocrystal of the dihydrogen phosphate salt. When ampyz was crystallized with weaker acids such as trifluoroacetic, trichloroacetic and phosphoric acids, the primary homosynthon disappears gradually as the strength acid decreases. In the last two cases, this homosynthon is not found, but the trifluoroacetate salt of ampyz is found to have both the base-pairing primary homosynthon and the two-point heterosynthon with carboxylate. Both monoprotonated forms at N1 and N4 are found together in this structure. Another trend of N1 protonation in the presence of counterions from inorganic tetrahedral oxoacids such as isopropyl sulfuric and phosphoric acids is also outlined, regardless of their acid strength.

It is known that the prediction of crystal structures and their minimal assembly frameworks, namely, the synthons,[1] is a hard task due to the delicate balance between intramolecular and intermolecular driving forces.[2] Even though some synthons are known to be robust and are even applied successfully in the design of supramolecular architectures, small molecular changes can hinder the formation of certain expected patterns of intermolecular interactions.[3] In turn, unexpected conformations and protonation states can be easily adopted in crystals as a consequence of most energetically favorable synthons.[4] Indeed, the prevalence of intramolecular effects over intermolecular ones, and *vice versa*, should not be assured *a priori* in most molecular classes, and it is always more prudent to analyze each case individually.[5]

Aminopyrazine (ampyz) is the 2-NH_2 substituted 1,4-diazine, which has been already utilized in crystal engineering studies in an attempt to find out the responses to the intra and intermolecular balance.[6] Due to its molecular simplicity and the presence of classical supramolecular functionalities, conclusions drawn from its crystal structure landscape can provide insights into the interaction pattern of more complex systems such as nucleic acids.[7] The formation of a homosynthon[8] typical of nitrogenous base pairing is observed in its free base crystal structure[9] and in a cocrystal with 1,2,4,5-tetrafluoro-3,6-di-iodobenzene,[10] succinic acid[6] and 4-(biphenyl-4-yl)-4-oxobutanoic acid,[11] while heterosynthons between either neutral or protonated ampyz and either carboxylic acid or carboxylate counterparts are found when they are crystallized together with some weak carboxylic acids.[6,12,13] Another N-heterocyclic compound bearing two pyridyl nitrogen atoms spaced by a π-electron delocalization pathway is *trans*-1,2-bis(4-pyridyl)ethane (BPE), which has been well investigated as a ligand in coordination chemistry and as a cocrystal of NLO-intended materials.[14] Its protonated form commonly assembles the charge-assisted two-point heterosynthon, where NH^+ and one of its vicinal CH moieties are hydrogen bonding donors.[15] Neutral homosynthons engaging one pyridyl nitrogen and its neighboring donor group are rarely found in BPE crystal structures.[16]

Here we were interested in probing the synthons in salts of the N-heterocyclic bases ampyz and BPE with strong,

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† Electronic supplementary information (ESI) available: PDF file describing crystal preparation, structure elucidation and DFT calculations, and Tables S1 to S3. CCDC 1566060–1566068. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ce01490b

moderate and weak acids, such as hydrobromic (pK_a = −8.72), hydrochloric (pK_a = −6.20), isopropyl sulfuric (pK_a = −2.84), trifluoroacetic (pK_a = 0.50), trichloroacetic (pK_a = 0.52) and phosphoric acids (pK_{a1} = 2.15).[17] This synthon inspection increased our knowledge about the assembly driving forces, which are the counterion geometry and the acid strength. The weaker the acid, the higher the tendency of formation of the heterosynthon between $(ampyz)^+$, with its nitrogen at position 1 (N1) protonated, and the carboxylate counterion. The protonation of the nitrogen at position 4 (N4) is observed with stronger acids, where the base-pairing primary homosynthon occurs. Concomitant to this homosynthon, there is also a four-point heterosynthon formed with two $(ampyz)^+$ cations and two halides, which also occur in two of the three new BPE multicomponent crystal forms reported here. Confirming the synthon trend as a function of acid strength, trifluoroacetic acid, which is in the middle of the acidity scale used in this study, forms a salt with both homosynthon I and $ampyz^+$–$carboxylate^-$ heterosynthon II. However, the isopropyl sulfate salt did not follow this trend since N1 protonation occurred in this structure, as well as in the dihydrogen phosphate salt. In fact, these last two salts structurally resemble each other and indicate the role of counterion geometry in the synthon and protonation patterns of the $(ampyz)^+$ salts, even though there is a great difference between the acid strengths of their acid sources.

Here, we have numbered the primary homosynthon I and primary heterosynthons with halide and carboxylate anions II and III, respectively (Fig. 1). Secondary synthons, which do not occur together with primary ones in a structure have an apostrophe after the Roman numeral in their label, while accessory synthons present with either primary or secondary ones end with a lowercase letter a. The hierarchy of synthons was established on the basis of the energy differences calculated after full geometry optimization of aggregates extracted from our crystal structures at the M06-2X/6-31+G** level of theory[18] (Table 1), except for $\Delta E_{I\rightarrow I'}$ calculated from their energy without optimization (geometry optimization of I′ has not converged). Calculations on single $(ampyz)^+$ cations were carried out at the same level. More details about the theoretical calculations can be found in the ESI,† together with methods of crystal preparation and structure elucidation. The crystal data (Table S1†) and geometric parameters of all the synthons discussed throughout the text (Tables S2 and S3†) can also be found there.

Table 1 Energy differences between primary, secondary and accessory synthons found in ampyz salts are reported here. All values were calculated at the M06-2X/6-31+G** level of theory after full geometry optimization of aggregates extracted from crystal structures, except for $\Delta E_{I\rightarrow I'}$ calculated from their energy without optimization (geometry optimization of I′ has not converged)

Synthons	ΔE/kcal mol^{-1}
I → I′	12.81
II → II′ (TCA)	2.07
II → II′ (TFA)	2.15
III → III′[a] (Cl)	3.23
III → III′[a] (Br)	4.74
II′a[b]-2-N–Hb···O (TFA)	−5.69
II′a[b]-2-N–Hb···O (TCA)	−6.08
III → IIIa (Cl)	21.07
III → IIIa (Br)	21.83
III′ → IIIa (Cl)	17.84
III′ → IIIa (Br)	17.09

[a] Since these secondary synthons are not available in crystal structures of ampyz, their inputs were generated using CHIMERA.[19] [b] The energy shown corresponds to the formation of one labeled hydrogen bond responsible for assembling the accessory synthon.

Chloride (**A1**) and bromide (**A2**) salts of ampyz are isostructural and feature the base pairi homosynthon I found also in the ampyz crystal structure (Fig. 2). Homosynthon I occurs also in cocrystals with 1,2,4,5-tetrafluoro-3,6-di-iodobenzene,[10] succinic acid[6] and 4-(biphenyl-4-yl)-4-oxobutanoic acid,[11] while

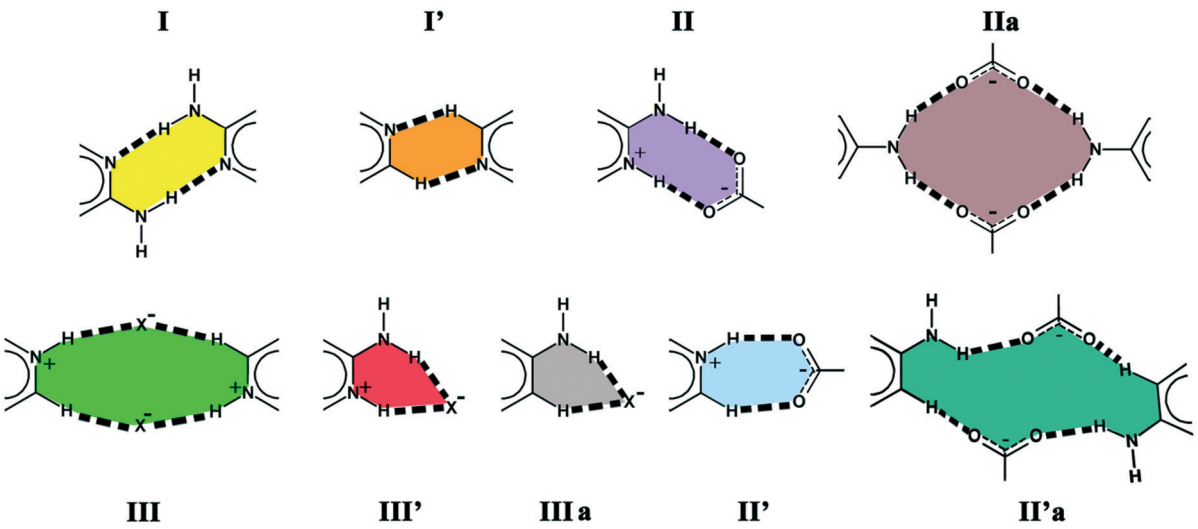

Fig. 1 Labeling and coloring scheme of synthons found in ampyz and BPE salts.

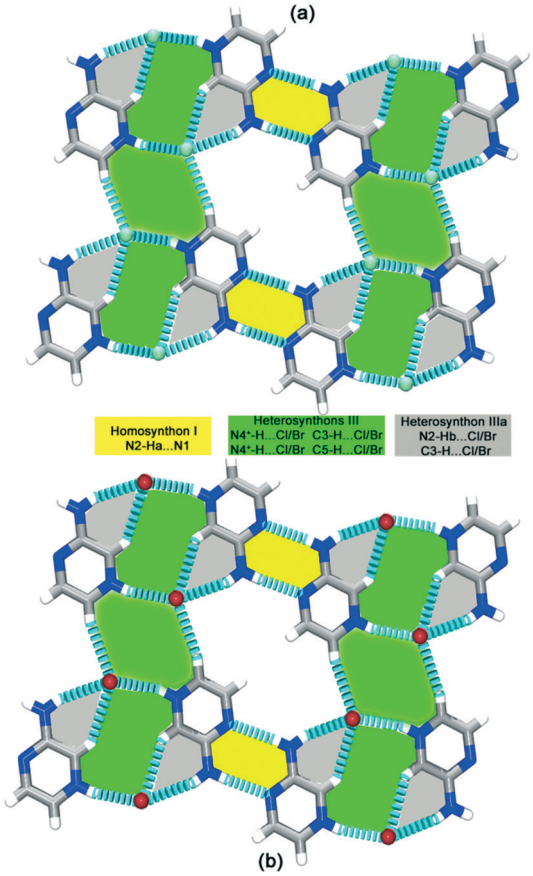

Fig. 2 Isostructurality in (a) **A1** and (b) **A2**.

in the other ten structures available up to now heterosynthons between carboxylic acid (or a carboxylate anion) and ampyz prevail.

If protonation had occurred at N1, the secondary heterosynthon III′ with halides would be expected. It is valid to comment that synthon III′, constructed from two classical hydrogen bonds, has an energy higher than synthon III having only one classical hydrogen bond and another non-classical one between the protonated N4 and the halide counterion. This is understood on the basis of the high directionality of the last two ones, which lowers the energy of synthon III. However, with N1 protonation, N4 would not be engaged in classical hydrogen bonds, even though non-classical C–H···N4 and N4···Cl/Br halogen bonds could be assembled. Such a pattern with protonated N1 and a halogen bond at N4 is even found in the ampyz salts with 2,3,5,6-tetrafluoro-4-iodobenzoate and 2,3,5,6-tetrafluoro-4-bromobenzoate[12] and also in one of our structures (see below). On the other hand, the N4 protonation is compatible with both primary homosynthon I and heterosynthon III. Furthermore, the accessory heterosynthon IIIa is formed through classical and non-classical hydrogen bond donation from 2-NH_2 and 3-CH moieties to either chloride or bromide (Fig. 2).

For the formation of homosynthon I, the protonation has occurred on N4 nitrogen rather than on N1. The latter was expected to stabilize the positive charge better due to electron conjugation from its neighboring 2-NH_2 group (Fig. 1). Indeed, this conjugation phenomenon has occurred in N1 protonated $(ampyz)^+$, but its energy is higher than that of the N4 protonated counterpart by 1.93 kcal mol^{-1}. This energy gain in N1 protonated $(ampyz)^+$ can be understood as a consequence of resonance decreasing through the whole cation, as can be structurally viewed in its different optimized N4–C bond lengths (1.358 Å and 1.301 Å). On the other hand, protonation at N4 keeps the resonance through the whole cation rather than directing it towards N1 and its neighbors, as has occurred in the N1 protonated $(ampyz)^+$. The same N4–C bond lengths are now similar in N4 protonated $(ampyz)^+$ (1.334 Å and 1.343 Å). The HOMO–LUMO gap (7.1 eV for N1 protonated $(ampyz)^+$ and 6.4 eV for the N4 one) also shows that conjugation decreases over the whole cation if N1 is protonated rather than N4. To strengthen this observation, the nucleus-independent chemical shift measured at the gravity center of the ring ($NICS_g$) was also calculated for N1 protonated $ampyz^+$ (−3.88 ppm) and the N4 one (−4.23 ppm). Given that negative NICS values indicate the presence of induced diatropic ring currents or aromaticity, whereas positive NICS values indicate paratropic ring currents or anti-aromaticity, the fact that the N4 protonated cation has a lower NICS value indicates its slightly higher aromatic character than that of the N1 one.

The robustness of the primary heterosynthon III can be found in the dihydrochloride salt dihydrate of BPE, as reported previously by us,[20] and also in hexakis(hydrogen sulfate) bis(sulfate) tetrahydrate.[21] Therefore, we assessed if it could also be formed in other BPE salts with the same acid sources attempted for ampyz. Among the three new BPE salts obtained here, this synthon was likewise observed in two of them. In both anhydrous bromide (**B1**) and bis(dihydrogen phosphate) (**B2**) salts of BPE (Fig. 3), this synthon is found, even if the halide is replaced by oxygen in the latter, similarly to the heterosynthon III found in hexakis(hydrogen sulfate) bis(sulfate) tetrahydrate.[21] However, in nitrate, trifluoroacetate and three other sulfate salt forms of BPE, heterosynthon II′ is present,[22]

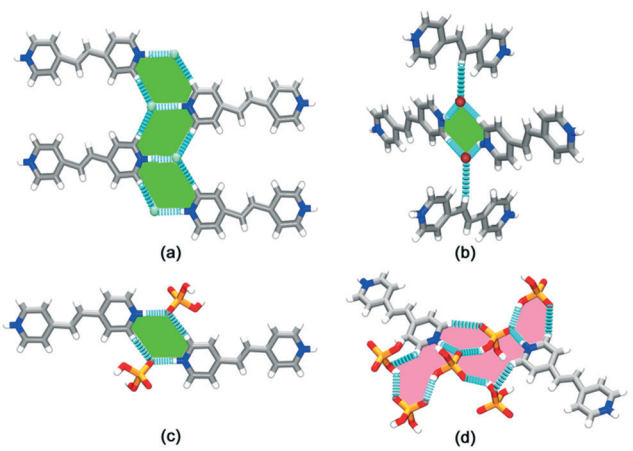

Fig. 3 The main synthons found in BPE multicomponent crystal forms. (a) Hydrochloride salt,[20] (b) **B1**, (c) **B2**, and (d) **B3**.

revealing a competition between III and II′ in BPE salts. The third new multicomponent crystal form of BPE is a phosphoric acid cocrystal of a dihydrogen phosphate salt (**B3**). It is formed by the engagement of NH^+ and both of its neighboring CH moieties as hydrogen bonding donors to dihydrogen phosphate counterions. However, heterosynthon III is not formed since each oxygen is hydrogen bonded to only one BPE^{2+}.

Nevertheless, the N4 protonation is not a direct consequence of the acid strength and seems to be also related to synthon possibilities. In the isopropyl sulfate salt (**A3**),[23] $(ampyz)^+$ and $(CH_3)_2CHOSO_3^-$ species are arranged into zigzag fashioned chains. These chains are almost planar, having three oxygen atoms from isopropyl sulfate in its plane. These three oxygen atoms are sharing the negative charge from the counterion and are involved in classical hydrogen bonds with protonated N1 and the amine group and in non-classical ones with their neighboring 3-CH and 6-CH moieties. In turn, N4 and 6-CH are responsible for connecting the $(ampyz)^+$ cations into the chains (Fig. 4a).

Upon decreasing the acid strength, homosynthon I is found again, now in the trifluoroacetate salt (**A4**) (Fig. 5). In this structure, the competition between primary synthons I and II is revealed, since both of them occur there. Two $(ampyz)^+$ cations and two $CF_3CO_2^-$ anions are present in the asymmetric unit of this salt. However, the 2-NH_2 group of each $(ampyz)^+$ is disordered over two site sets of equal occupancy. One of these site sets corresponds to the formation of primary homosynthon I and then N4 protonation and assembly of secondary synthons II′ and II′a involving the protonated N4, the 2-NH_2 and 3-CH motifs from $(ampyz)^+$ and the carboxylate one from $CF_3CO_2^-$. Another site set is devoted to the assembly of primary heterosynthon II with N1 protonation, aided by its accessory heterosynthon IIa involving another amine hydrogen, which is not paired into synthon II, and the carboxylate oxygen already hydrogen bonded to an amine group into synthon II. Secondary homosynthon I′ between N4 and 3-CH is also formed together with II and IIa (Fig. 5). One interesting observation in this structure is the bending of $(ampyz)^+$ molecules in the formation of homosynthon I, which does not occur in the halide salts reported here, in the cocrystals reported in the literature and in its single component crystal form. The least-square planes fitted through all non-hydrogen atoms of hydrogen bonded ampyz molecules are bent by 15.65(18)° in **A4**, while this value is 0.0° in its free base solid form, in **A1**, **A2**, and in the cocrystals with 1,2,4,5-tetrafluoro-3,6-di-iodobenzene and succinic acid, and is 1.2° in the cocrystal with 4-(biphenyl-4-yl)-4-oxobutanoic acid. This demonstrates the occurrence of homosynthon I even if the hydrogen bonding geometry is not as favorable as it would be in planar ampyz pairing. Without geometry optimization, this bent $(ampyz)^+$ pair held together by homosynthon I has an energy higher than that of the planar one by 10.17 kcal mol^{-1}, while after optimization both bent and planar $(ampyz)^+$ pairs converge to a planar one of the same energy.

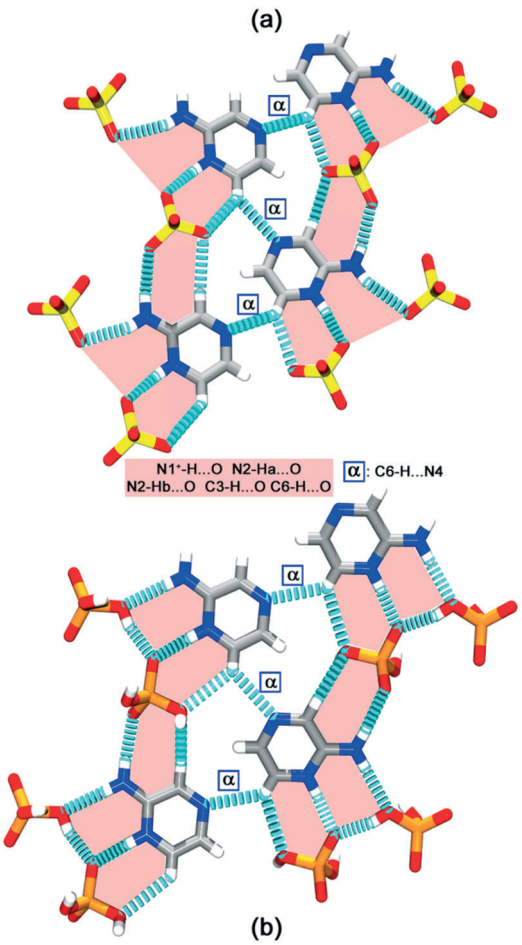

Fig. 4 Synthon conservation in (a) **A3** and (b) **A6**. Isopropyl groups, bonded to the out-of-plane oxygen atoms, were omitted in (a) for drawing clarity.

While the protonation of certain azo nitrogen depends on which synthons can be formed and the acid strength, these are not the only factors determining the final intermolecular and intramolecular features of ampyz multicomponent crystal forms. If **A4** is taken as a reference, only substituting fluorine for chlorine changes profoundly the protonation and synthon patterns in ampyz trichloroacetate (**A5**). Even though $CF_3CO_2^-$ and $CCl_3CO_2^-$ have similar acid strengths and stereochemistry of their equivalent supramolecular functionalities, only the N1 protonation and heterosynthons II and IIa occur in **A5**, while N4 participates in the halogen bonding with a chlorine atom from the counterion (Fig. 6). Homosynthon I is lost upon halogen substitution, revealing the fine balance of forces driving the protonation pattern and the crystal packing features of a simple organic molecule such as ampyz.

The crystallization screening between ampyz and phosphoric acid has resulted in a dihydrogen phosphate salt (**A6**) with the N1 protonation and synthon pattern resembling those in **A3** (Fig. 4b). This resemblance is due to the formation of classical hydrogen bonds between oxygen atoms from different $H_2PO_4^-$ units onto a planar chain and the

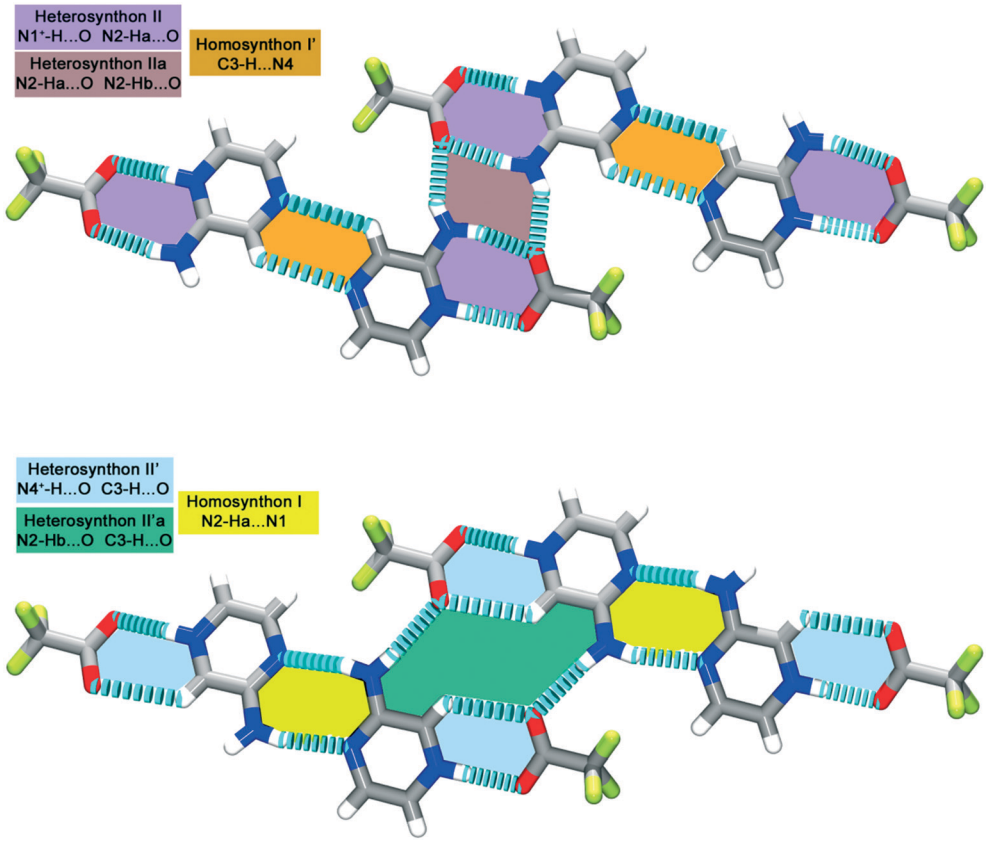

Fig. 5 The two synthon sets occurring in **A4**.

engagement of N4 as a non-classical hydrogen bonding acceptor. However, neighboring chains are packed perpendicularly in the former, while they are arranged in plane in **A3**.

Here we expanded our knowledge of the forces driving the protonation pattern and synthon assembly in multicomponent crystal forms of the important N-heterocyclic bases ampyz and BPE. A trend to form the base-pairing homosynthon as the acid strength was observed. Indeed, there is a stiff competition between the primary homo and heterosynthons, which dictate the protonation site even overcoming the basicity of the two azo nitrogen atoms. The ultimate of such a competition was observed in the TFA salt **A4**, where both the primary homo and heterosynthons were found together. However, if the competition is tended minimally towards one of these two primary synthons, the other synthon is not found in the crystal structure, as has occurred in the TCA salt **A5**. The four-point heterosynthon with two N-heterocyclic compounds and two hydrogen bonding acceptors (halide or oxygen) also seems to be robust. The other trend of N1 protonation occurs in the presence of counterions from inorganic tetrahedral oxoacids, regardless of their acid strength.

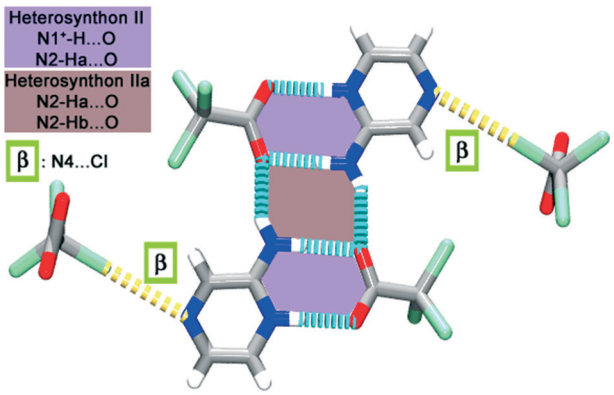

Fig. 6 The synthons found in **A5**.

Conflicts of interest

There are no conflicts to declare.

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23 We were interested to obtain a sulfate salt of ampyz, which was unsuccessful after many crystallization screenings between sulfuric acid and ampyz. Isopropyl sulfate salt was successfully obtained when there are crystallized in an isopropyl alcohol solution. The formation of isopropyl sulfuric acid from isopropyl alcohol and sulfuric acid is well known,[24] and this alkyl sulfate keeps the same acid and geometrical properties of HSO_4^-.

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