Synthon robustness in saccharinate salts of some substituted pyridines

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Synthon robustness or lack of structural interference is a sought after goal in crystal engineering. The crystal structures of saccharinate salts **1–6** show the robustness of the newly identified hydrogen bonded synthons **I** and **III**.

Introduction

Crystal engineering seeks to understand the role of various non-covalent interactions in the design of solid-state materials with desired physical and chemical properties.[1] Efforts toward this goal have concentrated on organic molecular solids.[2] However, crystal engineering of organic salts[3] is also becoming popular because they contain more easily predicted, ionic, hydrogen-bonded supramolecular synthons[4] and because these synthons are generally more robust than those in neutral organics. Salt formation is pertinent to the study of active pharmaceutical ingredients (API)[5] in the context of modulation of properties like solubility, stability, crystal morphology and bioavailability.[6] However, the structural changes that may take place upon salt formation of an API can be drastic; accordingly, the changes in the various properties above are quite unpredictable. Saccharin (pK_a 2.2) has been used as an acid (salt former) in the pharmaceutical industry[7] and the crystal structures, solubility and solution pH characteristics of several API saccharinates have been discussed by us recently.[8] Observed crystal structures result from a balance of several factors and finding a robust supramolecular synthon in a family of structures can be a difficult task.[9] This paper is a structural study of a group of pyridyl saccharinates, and identifies a new and robust supramolecular synthon,[10] which is constructed with N^+–H···O and C–H···N^- interactions.

Experimental

Sample preparation and crystallization

Crystallizations of pyridine saccharinates were performed by slow evaporation. For the preparation of salts **1** and **3**, saccharin was mixed directly with the respective liquid amines. The mixture was allowed to evaporate at ambient conditions to give single crystals. For salts **2**, **4**, **5**, **6** and **7** saccharin and the respective solid amines were dissolved in hot MeOH/benzene (3 : 1) and left at room temperature to facilitate the growth of crystals suitable for X-ray diffraction. Salts were characterized by IR spectra, and with single crystal X-ray diffraction. Melting points were recorded on a Fisher–Johns apparatus. Crystallographic data and hydrogen bond metrics are summarized in Tables 1 and 2 and ORTEP diagrams are given in Fig. 1.

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X-Ray crystallography

X-Ray diffraction intensities for all salts reported in this paper were collected on a Bruker SMART CCD APEX diffractometer (Bruker Systems Inc., 1999a)[11] using Mo Kα X-radiation. Data were processed using the Bruker *SAINT* package (Bruker Systems Inc., 1999b)[12] with structure solution and refinement using *SHELX97* (Sheldrick, 1997).[13] The structures of all the compounds were solved by direct methods and refined by full-matrix least-squares on F^2. H-atoms were located in all the structures and refined freely with isotropic displacement parameters. Crystal data and details of data collection, structure solution and refinement are summarized in Table 1. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the CCDC as deposition No. CCDC 611646–611652 (see also Table 1). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 lEZ UK (fax: + 44 (1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b608926g

Calculations

All calculations were carried out on Indigo Solid Impact and Indy workstations from Silicon Graphics. All interatomic distances, packing coefficients and related calculations were carried out with the PLATON program.[14]

Results and discussion

Scheme 1 shows the seven saccharinate salts in this study. In salts **1–3** the protonated heterocyclic N-atom is the only hydrogen bond functionality in the cation. In saccharinates **4–7** the presence of additional functionality like amine or amide perturbs the packing to differing degrees.

Fig. 2 illustrates the crystal structure of pyridyl saccharinate, **1** (space group $P\bar{1}$). The unsubstituted pyridinium cation forms both N^+–H···O and weak C–H···N^- hydrogen bonds with the saccharinate anion to give a planar two-point hetero-synthon **I** (Scheme 2). This is the prototype synthon in this family, and it has not been reported previously. Numerous C–H···O=S interactions provide further stabilisation.

In the 1 : 2 salt, **2**, of 4,4′-bipyridine and saccharin ($P2_1/c$) the heterocycle lies on an inversion centre and the crystal structure extends into a linear tape along the *a* axis *via* the saccharin–pyridine hetero-synthon **I** (Fig. 3). Numerous other

Table 1 Crystallographic parameters for compounds **1**–**7**

Salts	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Structural formula	$C_7H_4NO_3S$, C_5H_6N	$C_{10}H_{10}N_2$, $2(C_7H_4NO_3S)$	$C_7H_4NO_3S$, C_6H_8N	$C_7H_4NO_3S$, $C_6H_7N_2O$	$C_7H_4NO_3S$, $C_5H_7N_2$	$C_7H_4NO_3S$, $C_5H_7N_2$	$C_6H_{10}N_3$, $C_7H_4NO_3S$
Formula weight	262.28	522.54	276.31	305.31	277.30	277.30	306.34
Crystal system	Triclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic	Orthorhombic	Triclinic
Space group	$P\bar{1}$	$P2_1/n$	$P\bar{1}$	$P2_1/c$	$P2_1/n$	*Pbca*	$P\bar{1}$
T/K	298(2)	298(2)	100(2)	100(2)	100(2)	100(2)	100(2)
a/Å	7.4613(15)	9.705(11)	7.4299(5)	6.9157(12)	12.1321(9)	13.7712(12)	7.2644(15)
b/Å	12.954(3)	11.706(13)	11.1506(7)	17.351(3)	8.3859(6)	12.4593(11)	7.3820(15)
c/Å	14.179(3)	10.411(11)	15.3450(9)	10.6553(18)	13.1779(10)	14.3461(13)	13.752(3)
α/°	65.251(2)	90	88.0950(10)	90	90	90	98.667(3)
β/°	74.747(3)	105.089(19)	76.7170(10)	102.421(2)	112.6100(10)	90	95.025(3)
γ/°	78.160(3)	90	81.4900(10)	90	90	90	100.566(3)
V/Å^3	1193.6(4)	1142(2)	1223.67(13)	1248.6(4)	1237.66(16)	2461.5(4)	711.6(3)
Z	4	2	4	4	4	8	2
ρ_{calc}/g cm^{-3}	1.460	1.520	1.500	1.624	1.488	1.497	1.430
μ/mm^{-1}	0.272	0.285	0.270	0.281	0.269	0.271	0.243
R_1 [$I > 2\sigma(I)$]	0.0505	0.0438	0.0388	0.0417	0.0323	0.0394	0.0459
wR_2	0.1413	0.1070	0.0995	0.1010	0.0889	0.0990	0.1288
Goodness-of-fit	1.039	0.899	1.138	1.018	1.060	1.113	1.034
Reflns. collected	14741	7265	10008	7458	6231	7903	4992
Unique reflns.	4725	2744	4770	2447	2290	2293	2894
Observed reflns.	3042	1460	4486	2041	2172	2065	2430
Crystal size/mm	0.38 × 0.19 × 0.10	0.27 × 0.17 × 0.10	0.25 × 0.30 × 0.32	0.45 × 0.16 × 0.06	0.49 × 0.45 × 0.34	0.31 × 0.25 × 0.23	0.30 × 0.26 × 0.20
CCDC No.	611646	611647	611648	611649	611650	611651	611652

Table 2 Hydrogen bonds in crystal structures of the salts in this study

Compound	Hydrogen bond	d/Å (H···A)	D/Å (X···A)	θ/° ∠X–H···A
1	N–H···O	1.64	2.653(3)	176.8
	N–H···O	1.63	2.634(3)	174.1
	C–H···N	2.68	3.377(3)	121.8
	C–H···N	2.63	3.363(4)	124.1
	C–H···O	2.25	3.309(4)	164.4
	C–H···O	2.28	3.352(4)	170.9
2	N–H···O	1.70	2.707(4)	173.4
	C–H···N	2.33	3.131(5)	129.6
	C–H···O	2.44	3.154(4)	122.0
3	N–H···O	1.62	2.630(2)	179.0
	N–H···O	1.70	2.699(2)	170.9
	C–H···N	2.39	3.187(3)	129.2
	C–H···N	2.61	3.344(3)	124.2
	C–H···O	2.35	3.328(3)	149.3
	C–H···O	2.49	3.281(3)	129.0
4	N–H···O	1.68	2.690(3)	174.6
	N–H···O	1.98	2.852(3)	142.9
	C–H···N	2.45	3.133(3)	120.0
	C–H···O	2.36	3.295(3)	144.0
	C–H···O	2.39	3.183(3)	128.9
5	N–H···O	2.14	3.116(2)	161.4
	N–H···O	2.46	2.919(2)	106.7
	N–H···O	1.64	2.644(2)	173.3
	C–H···O	2.29	3.040(2)	124.3
6	N–H···O	1.71	2.716(2)	174.4
	N–H···O	1.97	2.933(2)	159.3
	N–H···N	1.96	2.965(2)	171.8
	C–H···O	2.39	3.280(3)	138.2
	C–H···O	2.43	3.304(3)	136.3
7	N–H···O	2.94	3.315(3)	103.1
	N–H···O	1.80	2.802(3)	172.2
	N–H···N	1.83	2.839(2)	176.8
	N–H···N	2.09	3.068(3)	162.9
	C–H···O	2.46	3.446(3)	151.4
	C–H···O	2.46	3.452(3)	151.4

C–H···O hydrogen bonds and van der Waals interactions give auxiliary support to the 2-D layer and the interlayer regions. The crystal structure of **2** is a simple extension of that of **1**. The crystal structure of 4-methylpyridinium saccharinate, **3** ($P\bar{1}$), is similar to those of **1** and **2**. Interestingly, the asymmetric unit is composed of two molecules of each component connected with hetero-synthon **I** (Fig. 4). Clearly Me-substitution in the 4-position does not alter the hydrogen bonding dramatically.

In the crystal structures of **4**–**6** there other hydrogen-bonding functionalities are present but the overall crystal structures are still easily understood. In the 1 : 1 salt of isonicotinamide and saccharin, **4**, ($P2_1/c$) hetero-synthon **I** occurs again but the resulting saccharin–heterocycle units are connected *via* amide homo-synthons (**II**) to form discrete tapes (Fig. 5). The principles of crystal construction are clear enough. Synthons **I** and **II** are both robust. They occur together in the crystal structure of **4** without any mutual interference and the structure is easily understood as a linear combination of these synthons.

The asymmetric unit of 3-aminopyridinium saccharinate, **5** ($P2_1/n$) consists of one molecule of each component connected by the saccharin–pyridine hetero-synthon **I**. The $-NH_2$ functionality acts as a bridge between saccharin–heterocycle dimers by forming an N–H···O hydrogen bond. The result is shown in Fig. 6.

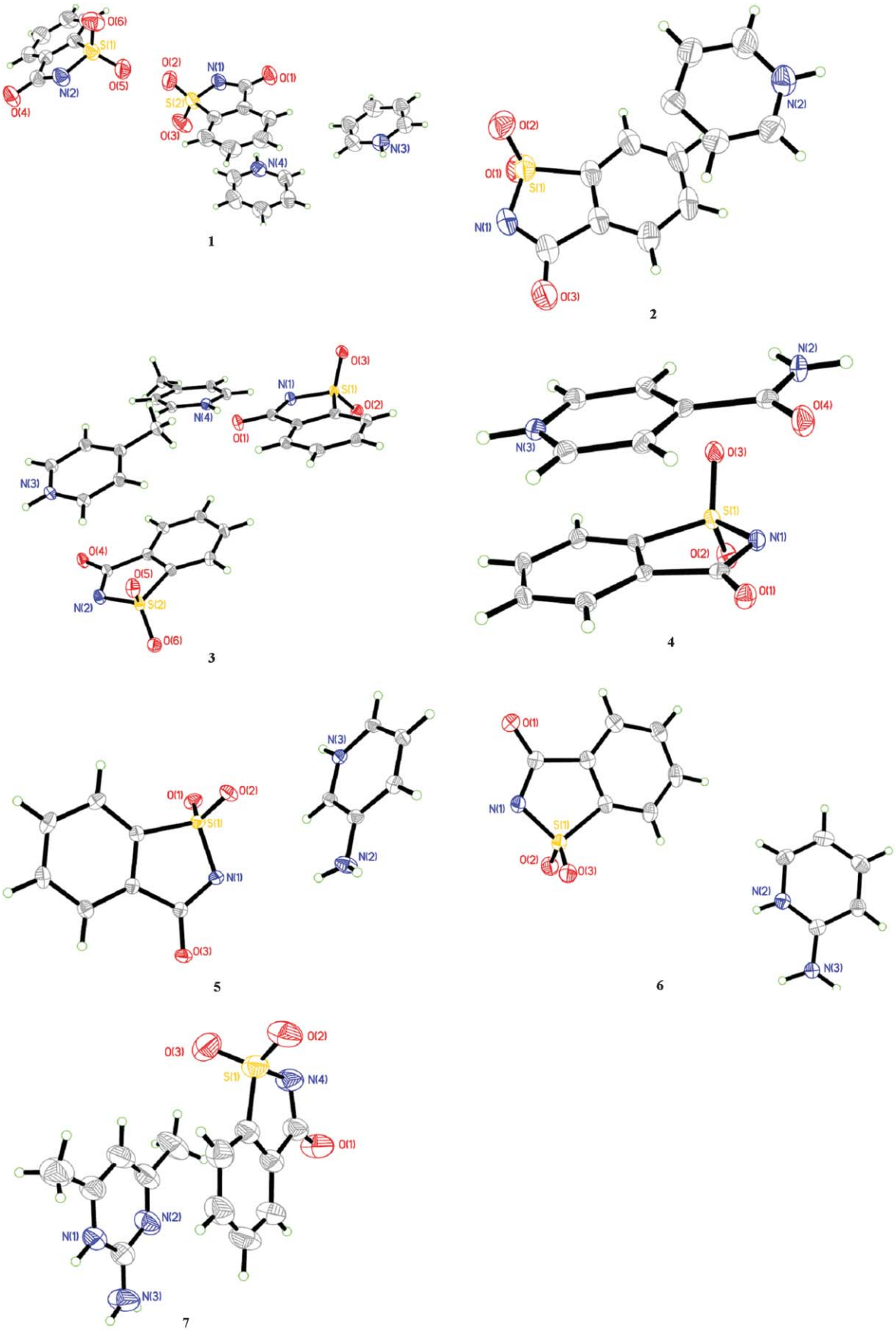
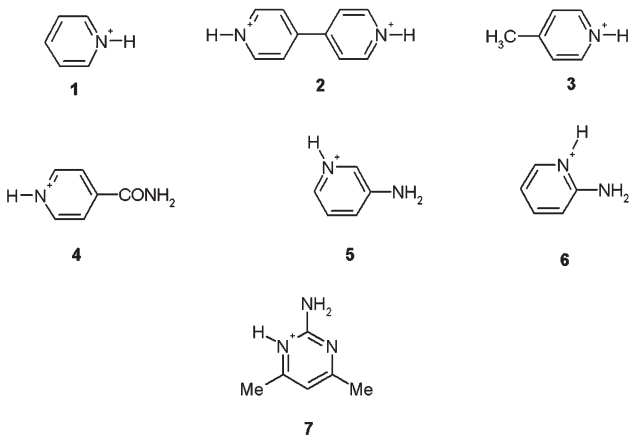


Fig. 1 Single molecule ORTEP drawings of the saccharinate salts in this paper.



Scheme 1 Heterocyclic bases in this study as found in their saccharinate salts. The numbers refer to the salts in the text.

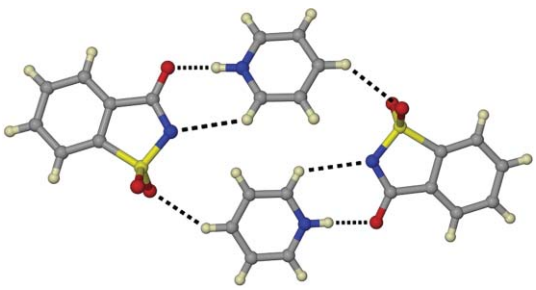
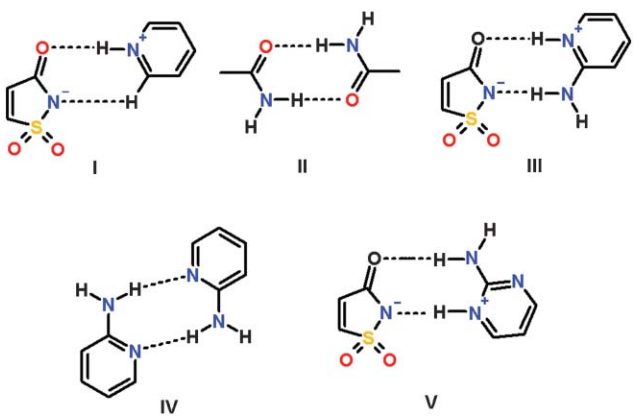


Fig. 2 Crystal structure of pyridinium saccharinate, **1**. Note supramolecular synthon **I** which is built with N^+–H···O and C–H···N^- hydrogen bonds.

The crystal structures of **1–5** show that the "strong–weak" N^+–H···O and C–H···N^- hydrogen bonded synthon **I** is a robust recognition motif that is largely insensitive to the substitution and placement of other functional groups in the pyridine fragment. In the crystal structure of 2-aminopyridinium saccharinate, **6**, however another supramolecular synthon **III** appears (Fig. 7). The formation of **III** is interesting. The pyridinium N^+–H group interacts with the C=O group to give an N^+–H···O hydrogen bond. The amino N–H competes



Scheme 2 Some homo-synthons and hetero-synthons in this study.

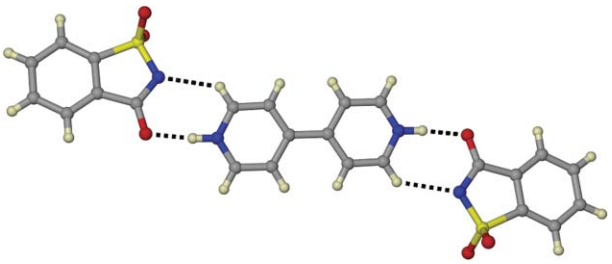


Fig. 3 Crystal structure of the 4,4′-bipyridine saccharin salt, **2**. Compare this with the pyridine salt **1**.

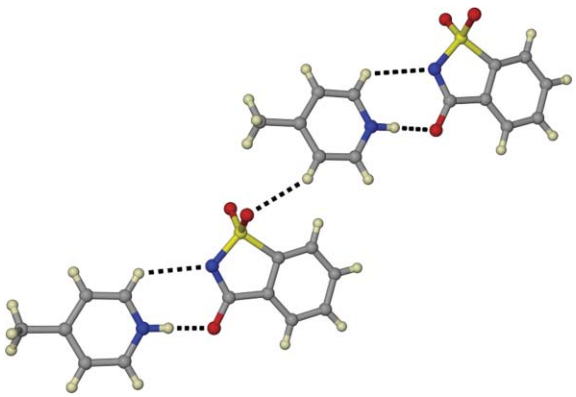


Fig. 4 Supramolecular synthon **I** in the crystal structure of **3**. Note the C–H···O=S hydrogen bonds that interlinks these synthons.

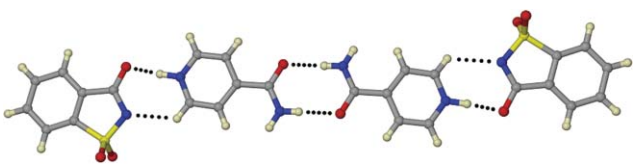


Fig. 5 Perspective views of **4** displaying the saccharin–pyridine hetero-synthon **I** and amide–amide homo-synthon **II**.

favourably with the weaker C(sp^2)–H donor and an N–H···N^- interaction is formed instead of the C–H···N^- interaction seen previously in salts **1–5**. Incidentally, synthon **III** was previously observed by us in the crystal structure of lamivudine saccharinate.[8b]

The saccharinate salt, **7**, of 2-amino-4,6-dimethylpyrimidine crystallizes in the space group $P\bar{1}$ and consists of one molecule of each component connected with a different type saccharin–aminopyridine hetero-synthon (Fig. 8). Instead of N^+–H···O and N–H···N^- interactions (as in **6**) the system forms N^+–H···N^- and N–H···O interactions (synthon **V**). Two saccharin–aminopyrimidine dimers are connected to each other *via* an N–H···N homo-synthon **IV** to form a discrete unit. These units are connected to each other *via* bifurcated C–H···O=S interactions to form a 1-D tape.

In saccharinates **1–5** a pyridinium cation and a saccharinate anion are linked with N^+–H···O and C–H···N^- hydrogen bonds to form hetero-synthon **I** (Scheme 2). This is the first reported occurrence of this synthon, and it is formed with a variety of heterocyclic bases related to pyridine. A necessary

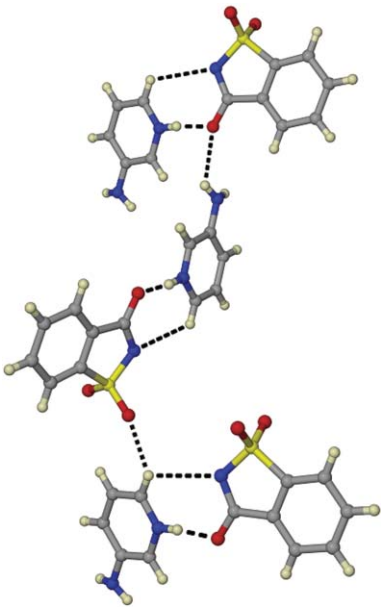


Fig. 6 Crystal structure of **5** to show hetero-synthon **I**. Note the additional N–H···O interaction.

condition for hetero-synthon[15] formation is that the hydrogen bonding between the dissimilar functional groups should be stronger than homo-aggregation. The formation of this saccharin–pyridine hetero-synthon appears to be very satisfactory because of the strong hydrogen bond donor and acceptor capability of both the pyridinium cation and the saccharinate anion. We suggest that formation of the saccharin–pyridine hetero-synthon is kinetically preferred because the strongest H bond donor (N^+–H of pyridine cation) will readily approach the C=O group of saccharinate anion. Due to delocalisation,

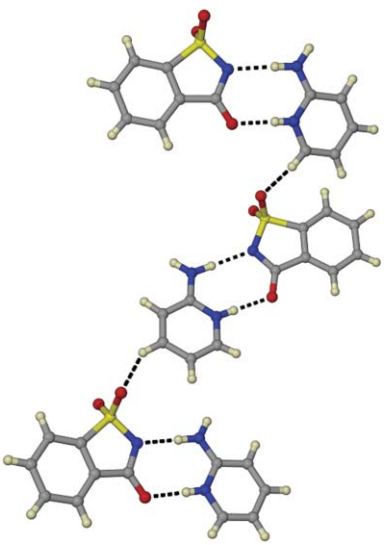


Fig. 7 Supramolecular synthon **III** in the crystal structure of **6** (*Pbca*). Note how the N–H···N^- interaction replaces the C–H···N^- interaction in **1–5**. As in **3** and **4** the saccharin–aminopyridine hetero-synthons are connected with C–H···O=S interactions to form a helical arrangement.

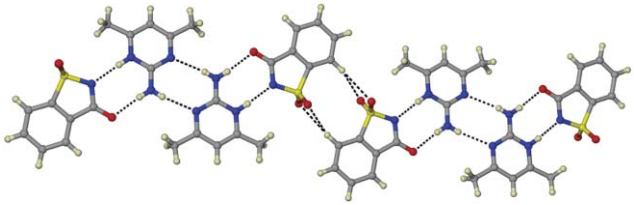


Fig. 8 Crystal structure of **7**. Note the 1-D tape which consists of synthons **IV** and **V**.

the charge on the anion is expected to reside on both N- and O-atoms and arguably, the more electronegative O-atom is the best acceptor in the system. In general, one might associate the presence of synthons wherein the hydrogen bond donors and acceptors are arranged hierarchically (strongest donor to strongest acceptor, next strongest donor to next strongest acceptor and so on[16]) with kinetic control in crystallisation, in other words with robustness. In a robust system, synthon formation is relatively insensitive to other molecular functionality. This means that a few significant interactions (which implicitly are the ones formed fastest) dominate the outcome of crystallisation. Thermodynamic crystals may or may not follow such hydrogen bond hierarchies depending upon the nature of the system. When the barrier to the nucleation of the thermodynamic form is sufficiently high, its formation will be difficult. When the kinetic and thermodynamic outcome of crystallisation is identical, polymorphism is unlikely. However, we have not investigated these latter aspects in this study as none of the salts displayed polymorphism as far as we could determine.

Conclusions

Each intermolecular interaction will have some influence on the result of the crystallization process but it is evident that some intermolecular interactions are more significant than the others. The probability that a certain synthon will emerge in the end could be taken as a measure of the yield of a supramolecular reaction.[17] The crystal structures of seven hydrogen bonded saccharinate salts have been discussed here. The N^+–H···O interaction between the N^+–H group of the pyridinium cation and the C=O group of the saccharinate anion is the most important interaction in this family of salts. At the next level, the aromatic C–H proton interacts with the saccharin N^-. Together these interactions give rise to the two-point synthon **I** in saccharinates **1–5**. However, in saccharinates **6** and **7**, a second donor functionality namely NH_2, which is a better donor than the aromatic C–H and which is suitably located in the molecule, interacts with the saccharin N^- to form synthons **III** and **V** respectively. Consequently, synthons **I** and **III** emerge as robust structural elements in these crystal structures.

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