

COMMENTARY

Occurrence of Pharmaceutically Acceptable Anions and Cations in the Cambridge Structural Database

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ABSTRACT: The occurrence of a number of pharmaceutically acceptable counterions in the Cambridge Structural Database (CSD) has been investigated. The results have been compared to the occurrence of the same counterions in a list of known pharmaceutical salts. Chloride salts are by far the highest occurring in both groups. The occurrence of hydrates in the structures of salts of pharmaceutically acceptable counterions in the CSD has also been investigated. It was found that salts of these counterions show an increased tendency to hydrate when compared to the database average. The CSD was also searched for co-crystals of the list of pharmaceutically acceptable acids and bases corresponding to the list of counterions used for the salt investigation. © 2005 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 94:2111–2120, 2005

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INTRODUCTION

The use of salt formation as a means of varying the properties of pharmaceutical compounds is well known and well documented.^{1,2} Salt formation can be used to increase or decrease solubility, to improve stability or toxicity and to reduce hygroscopicity of a drug product. There are a wide range of chemically diverse acids and bases, with a range of pK_a values, molecular weights, solubilities and other properties, used for this purpose. Of course, any counterions used in pharmaceuticals must be considered safe, and several lists of pharmaceutically approved counterions exist, which vary depending on the source.^{1,3} For the

purposes of this study, we have used the list of approved salt formers found in *Handbook of Pharmaceutical Salts*.¹

A number of lists of counterion usage and distribution in known pharmaceuticals exist, the most recent of which is to be found in the *Encyclopaedia of Pharmaceutical Technology*.³ One of the aims of this study is to compare the usage of these pharmaceutically approved counterions in pharmaceuticals with their occurrence in the Cambridge Structural Database (CSD),⁴ a database containing over 300000 organic crystal structures. High occurrence of salts of a particular acid or base in the CSD might indicate that the counterion is a good crystal former. Of course, the variety of chemical entities in the CSD is great, and this should not be forgotten when drawing conclusions. High occurrence of salts of a particular counterion may simply be as a result of bias in the database. For example the high occurrence of chloride salts in the CSD is influenced by the fact

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that this is often the first counterion used in crystallisation experiments. However high occurrence, or extremely low occurrence, of counterions in the CSD may be linked to the ability of these counterions to form good crystals.

The occurrence of hydrates⁵ and polymorphs⁶ is of great importance to the pharmaceutical industry. For this reason, the occurrence of hydrates and polymorphism within salts of these pharmaceutically acceptable counterions has also been investigated. Unfortunately, the data on polymorph and hydrate occurrence in pharmaceutical salts, which would allow a ready comparison with the CSD, exist in the private commercial domain. It is also difficult to search the CSD specifically for what might be classed as 'pharmaceutical compounds'. It is possible to search the CSD using the text string 'bioactivity', which yields a sample of about 10000 compounds, but it is found that only a small proportion of these are salts. About 1900 of these compounds contain positively charged N, and about 120 contain an alkali metal ion. These smaller samples of compounds are deserving of study in themselves, but it must be remembered that these will not have been specifically studied with a view to hydrate and polymorph screening. Also the structural variety of compounds is quite extensive, and there are many ways to divide or classify the chemical entities. For these reasons, this study has focussed on the pharmaceutically acceptable counterions. It is interesting that despite the fact that this analysis focuses on only the counterion in a salt, without taking into account the nature of the chemical entity, trends are still seen in the data.

Recently, the use of co-crystal⁷ formation as an alternative means of varying the properties of pharmaceuticals has been proposed.⁸ The occurrence of co-crystals of some pharmaceutically approved acids and bases in the CSD has therefore been determined. High occurrence of co-crystals for a particular acid or base, which is already approved for pharmaceutical applications, might show that the molecule is a potentially useful co-crystallising agent.

MATERIALS AND METHODS

List of Pharmaceutically Acceptable Salt Formers

The list of pharmaceutically acceptable acids and bases used in this study was taken from the

Handbook of Pharmaceutical Salts.¹ Polymeric salt formers were excluded, as were metal ions such as Na⁺, etc. The remaining list, consisting of 69 acids and 21 bases, together with the raw data obtained, is provided as Supplementary Material.

The exclusion of metal counterions from this study warrants some comment, as these counterions, particularly Na⁺, are the counterions of choice for salt formation with acidic pharmaceutical entities.³ However, there are difficulties concerning consistent representation of covalent or ionic bonding to metals in the CSD, as well as with assignment of charge on metal counterions.⁹ The specific search criteria used therefore have a substantial effect on the number of hits obtained. For this reason, it was decided to exclude these counterions from this analysis.

Searches

Searches to determine the number of CSD hits for each counterion were done using ConQuest¹⁰ version 1.6 on version 5.25 of the CSD with two updates (January and April 2004). The search criteria used were drawings of the respective counterions, with two filters in place: hits must have their 3-D coordinates determined and have no transition metals present. Repeat determinations of the same structure were removed from the count manually, but polymorphs were included in the count. Several counterions can occur as mono-, di- or tri-ions, and these have been treated separately. Some counterions are only approved for pharmaceutical use in a particular stereochemistry, for example only L-arginine is acceptable. In these cases, any compound labelled in the CSD as having the correct stereochemistry was counted as a hit, as well as any compound where the stereochemistry was not specified, but the space group indicated that the compound was enantiomerically pure, that is, those space groups which have no centres of symmetry, glide or mirror planes.

Due to the generalised nature of these searches, there is a great variety of molecules represented in these structures, including group 1 and 2 metal salts, large cyclic organic structures, amino acids, etc. For example, a search for mesylate gave 63 hits. Within these 63 hits, there are a large range of differing chemical entities: there are metal salts, for example the sodium mesylate salt (CSD reference code BAKLAA), simple organic salts such as the pyridinium salt (QOQVOH), salts of cyclic peptides (HEJRAP), porphyrin salts (LOG-

MOJ) and some salts of drugs, for example the pergolide (FIDYIA) and doxazosin (ULIYET) salts. Therefore, care must be taken when drawing conclusions based on the results obtained. However, a general impression of the distribution of salts of pharmaceutically acceptable counterions in the CSD can be gained.

The percentage of polymorphism occurring in each salt was calculated by counting the number of structures that were polymorphs by manual inspection, and expressing this as a percentage of the total number of hits for that counterion. For example, mesylate has 63 hits. There are two polymorphs of the pyridinium salt, and three polymorphs of the pergolide salt. Therefore, the percentage polymorphism is $(5/63) \times 100 = 7.94\%$. Again, care must be taken when interpreting these results, as the occurrence of polymorphs of a structure is not always noted in the CSD. Percentage of hydrates was calculated in a similar manner: the number of structures containing water (H_2O or H_3O^+) was expressed as a percentage of the total number of hits for that counterion.

RESULTS AND DISCUSSION

Number of Hits

The list used in this study contains a total of 69 acids and 21 bases. The total number of hits for salts of these acids and bases, as well as for several subsets of co-crystals⁷ is summarized in Table 1. There is a large range of values: for example there are 2874 hits for chloride, 61 hits for acetate and no hits for isobutyrate. The sample also shows a large spread in the percentage of structures that are hydrates. The complete list of counterions, as well as all the data obtained, is given in the Supplementary Material.

It is interesting to notice the lower percentage of hydrates in co-crystals, even those that are ionic in nature. However, the percentage of hydrates is quite high in co-crystals of salts of the acids investigated in this study. This indicates that hydrate occurrence is unusually high in the structures of these pharmaceutically acceptable counterions (*vide infra*).

The ten counterions from this list with the highest occurrence in the CSD are:

Chloride	2874 hits
Bromide	1403 hits
Nitrate	290 hits
Ammonium	265 hits
Sulfate (SO_4^{2-})	161 hits
Tosylate	118 hits
Phosphate ($H_2PO_4^-$)	97 hits
Tartrate (+L) (mono-ion)	86 hits
Ethylenediamine (di-ion)	83 hits
Maleate (mono-ion)	78 hits

The distribution of these top ten counterions in the CSD as a percentage of the total number of hits obtained in this study ($6021 + 587 = 6608$) is shown graphically in Figure 1. It should be noted that chloride salts make up 45.49% of the entire sample studied, with bromide salts making up 21.23%. All the salts containing counterions not in the 'top ten' taken together make up 17.45% of the total sample ('other').

This 'top ten' list makes an interesting comparison to the occurrence of particular counterions in known pharmaceuticals.³ The ten most frequently occurring anionic counterions in pharmaceutical salts, in order of decreasing occurrence, are chloride, sulfate, bromide, mesylate, maleate, citrate, tartrate, phosphate and acetate. The only organic cationic counterions (i.e. excluding metal cations) with a frequency greater than 1% are

Table 1. Number of CSD Hits for Salts and Co-crystals of a Selection of Pharmaceutically Acceptable Acids and Bases

	Acids	% Hydrates	Bases	% Hydrates
Number of salts	6021		587	
Hydrates of salts	1802	29.9	168	28.6
Number of neutral co-crystals	348		33	
Hydrates of neutral co-crystals	57	16.4	2	6.1
Number of ionic co-crystals	56		38	
Hydrates of ionic co-crystals	8	14.3	2	5.3
Number of co-crystals of salts	113		14	
Hydrates of co-crystals of salts	27	23.9	1	7.1

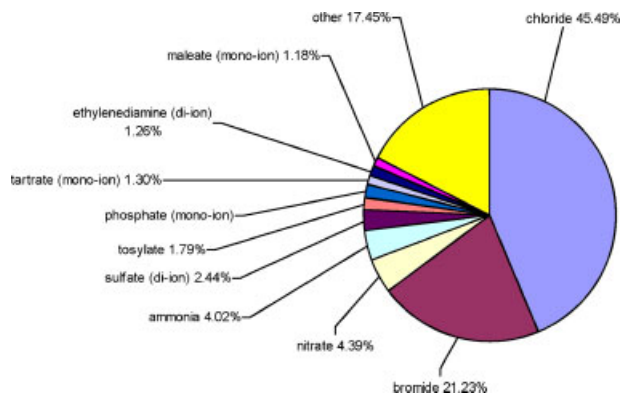


Figure 1. The occurrence of a selection of pharmaceutically acceptable counterions in the CSD as a percentage of the total number of hits obtained.

ammonium and N-methyl glucamine. The anions of the inorganic acids, as well as ammonium, are well represented in both the CSD and in pharmaceutical salts. However, the occurrence within the two groups of the organic acids and bases is quite different. In both the CSD and in pharmaceutical salts, chloride salts make up almost 50% of the samples. We suspect that if Na^+ ions could be searched for effectively in the CSD, they would also make this 'top ten' list. This would parallel the high occurrence of this counterion of over 50% in pharmaceutical salts.³

Anionic Counterions

From the list of 69 acids, only 20 anionic counterions had more than 20 hits. These are listed in Table 2 below. The hits for these 20 counterions

Table 2. Number of Unique Structures, Hydrates and Polymorphs for a Selection of Pharmaceutically Acceptable Anionic Counterions


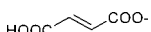
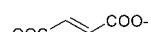
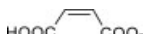
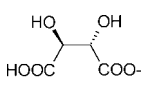
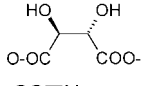
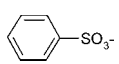
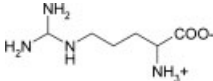



Anion		Number of Unique Structures	Number of Hydrates	% Hydrates	Number of Polymorphs	% Polymorphs
Acetate	MeCOO^-	61	27	44.3	5	8.20
Bromide	Br^-	1403	346	24.7	31	2.21
Camsylate		29	6	20.7	0	0.00
Chloride	Cl^-	2874	894	31.1	77	2.68
Formate	HCOO^-	30	11	36.7	2	6.67
Fumarate		36	5	13.9	0	0.00
		21	9	42.9	0	0.00
Maleate		78	8	10.3	2	2.56
Mesylate	MeSO_3^-	63	20	31.7	5	7.94
Nitrate	NO_3^-	290	59	20.3	14	4.83
Oxalate	$\text{HOOC}-\text{COO}^-$	61	18	29.5	4	6.56
	$-\text{OOC}-\text{COO}^-$	43	24	55.8	6	13.95
Phosphate	H_2PO_4^-	97	17	17.5	6	6.19
	HPO_4^{2-}	35	27	77.1	5	14.29
Sulfate	HSO_4^-	70	17	24.3	4	5.71
	SO_4^{2-}	161	95	59.0	5	3.11
Tartrate (+L)		86	32	37.2	4	4.65
		37	25	67.6	2	5.41
Thiocyanate	$-\text{SC}\equiv\text{N}$	73	13	17.8	0	0.00
Tosylate		118	27	22.9	9	7.63

Table 3. Number of Unique Structures, Hydrates and Polymorphs for a Selection of Pharmaceutically Acceptable Cationic Counterions

Cation		Number of Unique Structures	Number of Hydrates	% Hydrates	Number of Polymorphs	% Polymorphs
Ammonium	NH_4^+	265	85	32.1	10	3.77
Arginine (L)		28	13	46.4	0	0.00
Diethylamine		40	3	7.5	0	0.00
Ethylenediamine		83	30	36.1	5	6.02
Piperazine		56	19	33.9	0	0.00

make up 94.09% of the total number of hits for anionic counterions.

Cationic Counterions

Of the 21 bases, only five cationic counterions show more than 20 hits. These are shown in Table 3. The hits for these five counterions make up 79.90% of the total number of hits for cationic counterions.

Hydrate Formation

The percentage of structures that are hydrates for the counterions in Tables 2 and 3 is shown graphically in Figure 2. The straight line shows the percentage of hydrates in ionic organic struc-

tures in the whole CSD (23.11%). It can be seen that the salts of this selection of pharmaceutically acceptable counterions generally show a higher percentage of hydrates than is seen in the database as a whole. In fact, 18 of these 26 counterions show a greater percentage of hydration than the database average. Four counterions, oxalate (2-), phosphate (2-), sulfate (2-) and tartrate (2-), have a percentage of hydrates greater than 50%. These are all anions, and all are di-anions. The corresponding mono-anion has a considerably lower percentage of hydrates in each case. This suggests that increasing charge on a single ion leads to increasing hydrate formation. HPO_4^{2-} has the highest percentage of hydrates (77.1%), whereas H_2PO_4^- has one of the lowest percentages of hydrates (17.5%). Interestingly, PO_4^{3-} has only

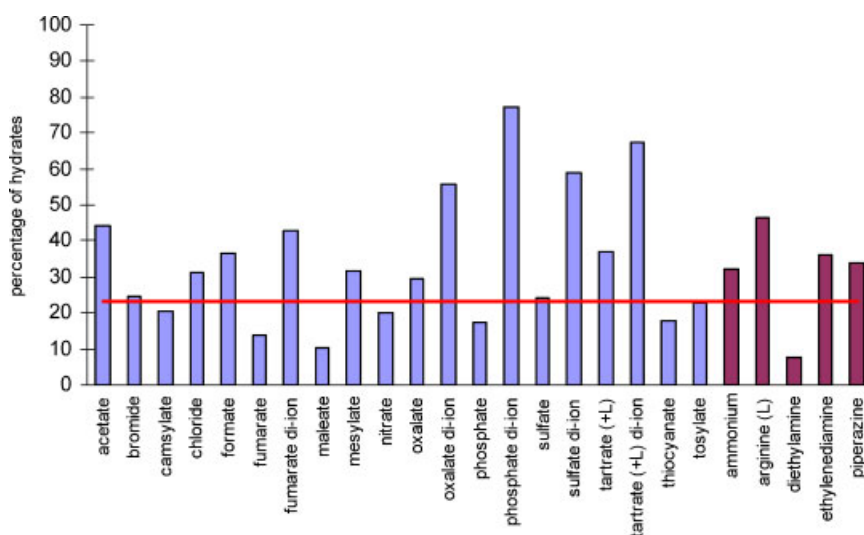


Figure 2. The percentage of structures that are hydrates for various pharmaceutically acceptable counterions (straight line represents the percentage of hydrates seen in ionic organic structures across the whole CSD, 23.1%).

Table 4. Number of CSD Hits and Hydrates for a Selection of Pharmaceutically Acceptable Long Chain Counterions (No Polymorphs Were Observed for Any of These Salts)

Counterion		Number of Hits	Hydrates	% Hydrates
Adipate		6	2	33.3
		4	0	0.0
Caprate		2	0	0.0
Caproate		2	0	0.0
Caprylate		0	—	—
Dodecylsulfate		5	4	80.0
Glutarate		2	1	50.0
		11	2	18.2
Laurate		1	0	0.0
Oleate		1	0	0.0
Palmitate		3	0	0.0
Sebacate		0	—	—
Stearate		1	0	0.0
Undecylenate		0	—	—

two hits, but both of these are hydrates. The same pattern of increasing hydrate percentage with increasing ionisation is seen for adipate, fumarate, glutarate, malate, maleate, malonate and succinate salts. The increase in hydrate formation with increasing number of carboxylate groups in a structure has been reported previously.¹¹

In contrast to the anionic counterions mentioned above, salts of the long chain acids show a very low percentage of hydrates (Tab. 4). In fact, the only counterions in this group showing any hydrates at all are the shorter chains (C₅ and C₆), and the one counterion containing a sulfonate moiety. Despite the low numbers of hits for these counterions, the observation of increasing hydrates with increasing number of carboxylates holds true for adipate and glutarate.

Observed trends, based only on the nature of the counterion, provide interesting information, but the nature of the chemical entity will also have an impact on properties such as hydrate occurrence. It has been suggested that hydrate formation is a result of an imbalance between the number of

hydrogen bond donors and acceptors in a crystal.¹² The nature of the chemical entity will also affect this ratio. An in-depth analysis of donor/acceptor ratios in each of the salts in this analysis would shed further light on this problem, but was felt to be outside the scope of this analysis.

Polymorphism

The number of structures that are polymorphs has been counted across the sample used in this study (see Tabs. 2 and 3 and Fig. 3). One general observation that can be made is that those counterions showing a higher occurrence of polymorphism are all small ions such as acetate, oxalate and phosphate. In fact, when looking at the 25 counterions that have more than 20 hits in the CSD, 90% of the polymorphs seen are of structures containing counterions with a molecular weight of less than 100. It has been noted previously¹³ that lower molecular weight compounds show a higher occurrence of polymorphism, but it is interesting that this trend should

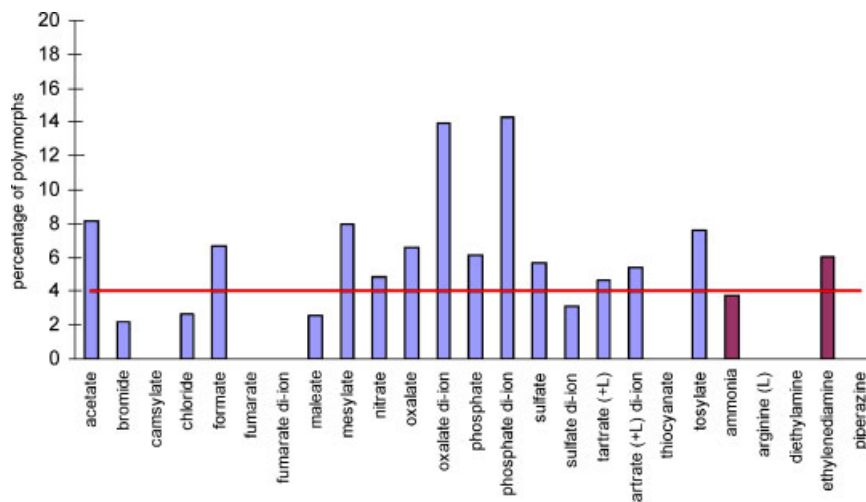


Figure 3. The percentage of structures that are polymorphs for various pharmaceutically acceptable counterions (straight line represents an approximation of the percentage of polymorphs seen in ionic structures in the whole CSD, calculated by searching for the flag 'polymorph').

still be observed when only the molecular weight of the counterion is considered. It is also interesting to note that a plot of percentage of polymorphs against the ratio [number of O atoms: total number of non-H atoms] for organic acids shows an increase in polymorphism with an increase in this ratio (Fig. 4). This could perhaps be because an increase in O atoms implies an increase in H-bond donors and acceptors, and thus an increase in possible permutations of H-bond motifs. As with hydrate formation, the nature of the chemical entity will also affect the occurrence of polymorphism (Fig. 3).

Co-Crystals

The number of various subsets of co-crystals formed with these acids and bases has been counted. The results for all acids and bases having hits for co-crystals are given in Table 5.

A closer investigation of the acid co-crystals shows a general correlation between increasing pK_a and increasing number of co-crystals (Fig. 5). This could be rationalised by observing that in order to form a salt of a weak acid (high pK_a), a strong base is needed. In other words, it is more difficult to ionise a weak acid. We would therefore

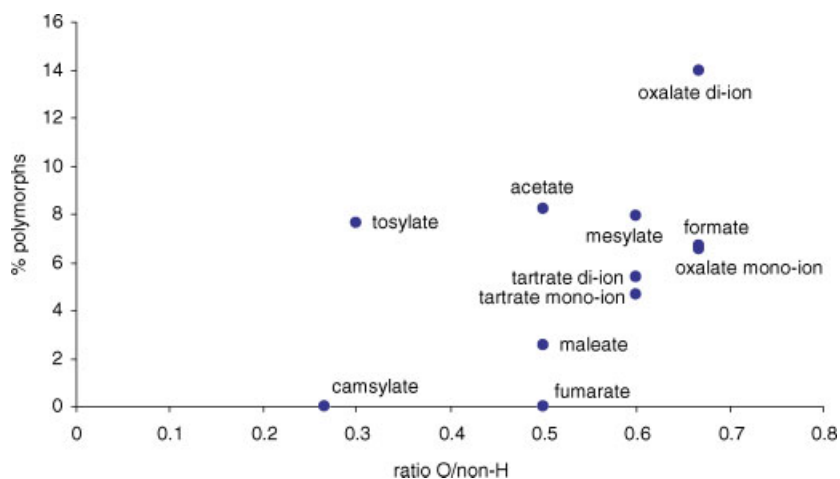


Figure 4. A plot of % polymorphic structures against the ratio [number of O atoms: total number of non-H atoms] for organic acids with more than 20 hits in the CSD.

Table 5. Numbers of Co-crystals in the CSD for a Selection of Pharmaceutically Acceptable Acids and Bases (Bold = More Co-crystals Than Salts)

Acid or Base	Number of Salts	Neutral Co-crystals	Ionic Co-crystals	Co-crystals of Salt
Acetic acid	61	96	23	17
Adipic acid (mono-ion)	4	16	0	0
4-Amino salicylic acid	1	1	0	0
Ascorbic acid (L)	4	1	0	0
Aspartic acid (L)	6	0	3	0
Benzoic acid	19	9	1	6
camphoric acid (+)	5	4	0	0
Camsylate	29	1	0	0
Capric acid	2	2	0	0
Caproic acid	2	2	0	0
Caprylic acid	0	2	0	0
Cinnamic acid (trans)	10	6	0	1
Citric acid	25	0	1	0
Formic acid	30	20	1	8
Fumaric acid (mono-ion)	36	0	0	4
Fumaric acid (di-ion)	21	23	3	5
Gentisic acid	1	2	1	0
Glutamic acid	0	1	1	0
Glutamic acid (zwitterionic form)	2	0	1	0
Glutaric acid	13	12	0	0
Hydrobromic acid	1403	10	1	0
Hydrochloric acid	2874	13	3	11
Isobutyric acid	0	1	0	0
Lauric acid	1	0	0	1
Maleic acid (mono-ion)	78	7	0	2
Malic acid (-L) (mono-ion)	16	2	2	2
Malonic acid (mono-ion)	18	6	1	4
Mandelic acid (DL)	5	1	0	0
Methane sulfonic acid	63	4	0	0
Nitric acid	290	6	1	5
Oxalic acid (di-ion)	43	24	3	8
Palmitic acid	3	2	0	0
Phosphoric acid	134	6	2	0
Propionic acid	4	14	0	0
P-toluene sulfonic acid	118	1	0	1
Pyroglutamic acid (-L)	1	1	0	0
Salicylic acid	19	7	1	3
Sebacic acid	0	9	0	0
Stearic acid	1	1	0	0
Succinic acid (di-ion)	9	18	6	6
Sulfuric acid (di-ion)	161	4	0	0
Tartaric acid (+L) (mono-ion)	86	12	1	3
Ammonium	265	4	15	3
Betaine	15	7	2	4
Choline	14	1	0	0
Diolamine	4	3	0	0
Diethylamine	40	3	0	0
Ethanolamine	14	1	0	0
Ethylenediamine (-2)	83	5	17	1
Ethylenediamine (-1)	5	0	0	2
1H-imidazole	0	2	0	0
Piperazine (-2)	56	7	0	2
Trolamine	13	1	3	0

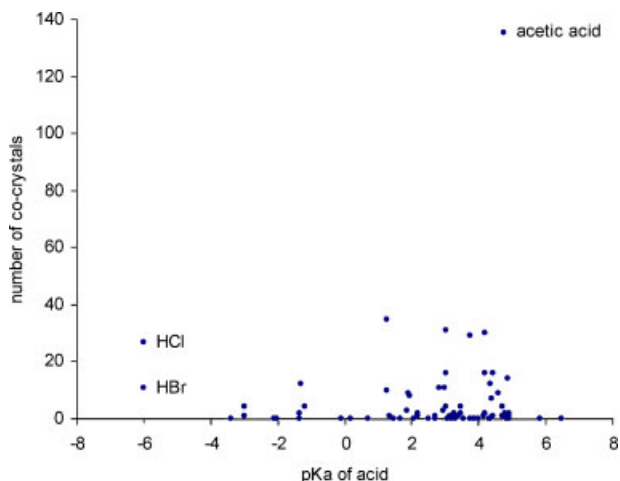


Figure 5. Plot of pK_a against number of co-crystals for pharmaceutically acceptable acids

expect to see less salt formation, and by implication higher occurrence of co-crystals, for acids with higher pK_a values. The exceptions to this are HCl and HBr, which have large numbers of co-crystals despite having the lowest pK_a values. This can possibly be explained by considering the large numbers of salts of these acids seen in the database: the larger numbers of co-crystals probably just reflect widespread usage of these acids. The four acids that have more co-crystals than salts (acetic, adipic, propionic and sebacic acids) have relatively high pK_a values. Perhaps most interesting here is the existence of 121 co-crystals of salts, in other words crystals in which the acid or base exist in both their ionised and unionised form. The acids that exhibit this phenomenon have pK_a values ranging from -6 (HBr) to 4.756 (acetic acid), but they all have a molecular weight of less than 201.

CONCLUSIONS

This analysis has shown that a number of pharmaceutically acceptable counterions are well represented in the CSD. Despite the variety in chemical entities for each counterion, some general trends have been observed based on the nature of the counterion alone. The salts of these pharmaceutically acceptable counterions show an increased tendency to hydrate when compared with organic salts in the CSD as a whole. Also, the salts of di-ionic counterions show a high tendency to be hydrated. The occurrence of polymorphism in these salts has been investigated, and a trend of

increasing occurrence of polymorphism with decreasing molecular weight of counterion has been noted.

The occurrence of co-crystals of pharmaceutically approved acids and bases has also been investigated. Small molecules with higher pK_a show an increased number of co-crystals. The existence of co-crystals of these acids and bases in the CSD confirms that co-crystal formation may be a useful alternative to salt formation in the pharmaceutical industry. A large number of co-crystals of salts (i.e. ionised and unionised species co-crystallised) were also observed in this study.

Future work in this area will involve assessing the influence on hydrate formation and polymorphism of particular counterions in combination with specific functional groups on the chemical entity. An analysis of various relationships between functional groups on the chemical entity and counterion will also be carried out, including, for example attempting to answer questions such as whether a specific functionality on a molecule makes it more amenable to salt formation with a specific counterion. We will also investigate the energies of interactions between anions and cations by modern methods.¹⁴ One example currently being explored is the occurrence of pyridinium carboxylate salts, and the tendency of these salts to form hydrates.

SUPPLEMENTARY MATERIAL

The remaining list of pharmaceutically acceptable acids and bases used in this study, together with the raw data obtained, is provided.

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