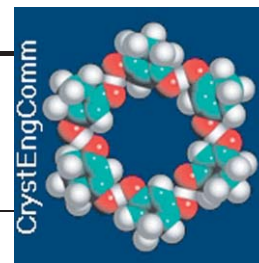


# Hydrate formation in NH<sup>+</sup>-containing salts of pharmaceutically acceptable anions: A CSD survey†



Paper

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The CSD has been systematically searched for salts of N-based cations and pharmaceutically acceptable groups of anions. The tendency of particular anions to crystallise with particular cations has been assessed, and the occurrence of hydrates within particular groups of salts has been analysed. It was found that pyridinium carboxylate salts show a reduced tendency to form hydrates when compared to other salts.

## 1. Introduction

Salts of pharmaceutical candidate molecules are often prepared in order to improve the physical properties of the molecule, such as solubility, hygroscopicity and crystallinity.<sup>1</sup> The process of salt preparation and selection of salt forms of pharmaceutical candidates can be long and expensive, and the process of choosing a counterion is not selective. We are therefore carrying out an analysis of the effect of specific counterions on crystal structure, and hence on crystal properties, with the eventual objective of enabling specific selection of a counterion to yield crystalline material with the desired properties.

Our general approach has been to begin by searching the Cambridge Structural Database (CSD)<sup>2</sup> to establish the existence of possible trends, such as the frequent occurrence of particular hydrogen bonding motifs within subsets of salts.<sup>3</sup> On the basis of these observations experiments were then designed to examine the general validity of the apparent trend.

The basic group on a drug molecule is frequently an amine, a cyclic nitrogen or an aromatic nitrogen. Stahl and Wermuth<sup>1</sup> have listed salt-forming acids that are pharmaceutically acceptable, generally taken to be acids which are biologically non-toxic and are unlikely to interfere with the action of the drug. The anions of these acids can be subdivided into carboxylates and carbonate, halides, sulfate and sulfonates, inorganic phosphate, nitrate and thiocyanate. These functional groups are all either pharmaceutically acceptable anions themselves (PO<sub>4</sub><sup>3-</sup>, Cl<sup>-</sup>, SO<sub>4</sub><sup>2-</sup>), or are the charge-carrying group on several pharmaceutically acceptable anions (MeCOO<sup>-</sup>, PhSO<sub>3</sub><sup>-</sup>).<sup>1</sup> The CSD has been systematically searched for combinations of these N-bearing cations and pharmaceutically acceptable anions, and trends in hydration across the groups have been investigated.

## 2. Methods

Searches were done on CSD version 5.25 (November 2003) using ConQuest version 1.6<sup>4</sup> (unless stated otherwise). The search criteria used were drawings of the respective ions (Fig. 1.), with two filters in place: hits must have their 3-D

coordinates determined, and have no transition metals present. Hydrate in all cases is defined as a structure containing H<sub>2</sub>O or H<sub>3</sub>O<sup>+</sup>.

The anion groups were chosen on the basis of the list of pharmaceutically acceptable acids in *Handbook of Pharmaceutical Salts* (see supplementary material†).<sup>1</sup> We have previously analysed the distribution of pharmaceutically acceptable anions in the CSD, and investigated the occurrence of hydrates of particular anions.<sup>5</sup> We have observed a slightly higher than average occurrence of hydrates in zwitterions in the CSD (22.50% hydrates in salts with zwitterions excluded, and 25.53% hydrates in zwitterions).<sup>6</sup> This effect is much more pronounced in the various anion groups under investigation in this study (Fig. 2.). We have therefore excluded zwitterions from our analysis. This gives a sample of 7439 non-zwitterionic NH<sup>+</sup>-containing salts, which is the sample used in this study.

## 3. Results and discussion

The results of CSD searches for combinations of N-based cations and pharmaceutically acceptable anions are given in Table 1. Several general observations can be made based on these data.

### 3.1 Anion profiles

Firstly we note that 2085 (28%) of the N-based organic salts in the CSD have counterions that are not in one of the pharmaceutically acceptable groups used in this study. Fig. 3 shows the anion profiles of each cation group, with the occurrence of each anion expressed as a percentage of the total number of hits for all pharmaceutically acceptable anion groups. There is a high occurrence of halide and carboxylate salts in all the cation subgroups, and a much lower occurrence of phosphates and sulfates. There is increased occurrence of halide salts in the tertiary amines and cyclic amines at the expense of the other anion groups, and a slightly higher occurrence of nitrate salts when the cation is pyridinium.

### 3.2 Hydrate formation

Analysis of the data on hydration reveals some interesting trends. Overall, there is a decrease in hydration in the halide series that correlates with the increase in ion size, *i.e.* F<sup>-</sup> shows the highest hydrate occurrence of the halides and I<sup>-</sup> shows the lowest (Table 2). There is a higher percentage of hydrate

† Electronic supplementary information (ESI) available: List of pharmaceutically acceptable acids, based on the *Handbook of Pharmaceutical Salts*, excluding polymers. See <http://www.rsc.org/suppdata/ce/b5/b503309h/>

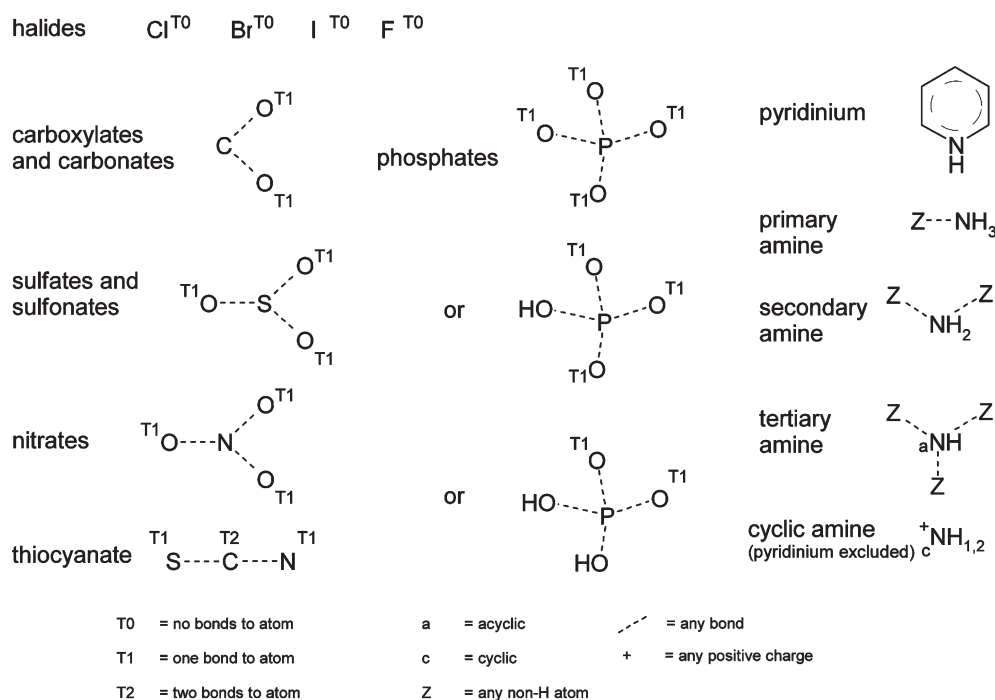


Fig. 1 Sketches used to define ion groups in ConQuest

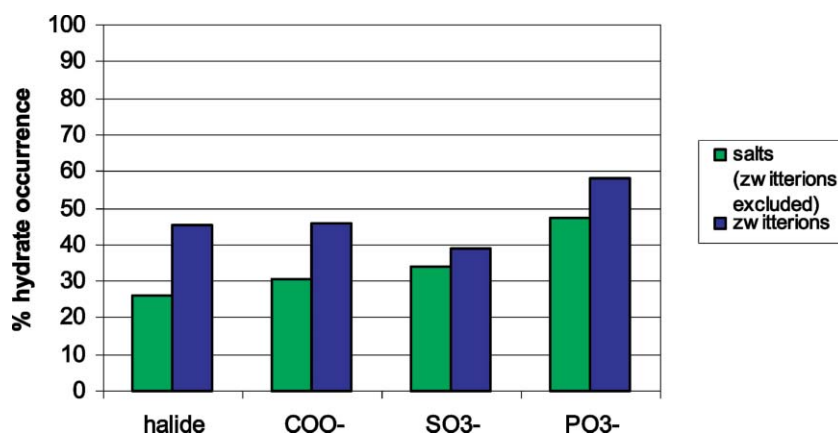


Fig. 2 Percentage occurrence of hydrates in salts with zwitterions excluded (18 003 hits) and zwitterions (4191 hits) in the CSD.

Table 1 Percentage hydrate occurrence in  $\text{NH}^+$  salts in the CSD. Ncompounds is the number of crystal structures found in each case, Nhydrates is the number of these crystals which are hydrates

Cation		Halide	Carboxylate or carbonate	Sulfate or sulfonate	Phosphate	Nitrate	$\text{SCN}^-$	Other <sup>a</sup>	Total
Pyridinium	Ncompounds	210	143	44	11	35	3	321	729
	Nhydrates	73	13	15	4	6	1	58	163
	% hydrates	34.8	9.1	34.1	36.4	17.1	33.3	18.1	22.4
1° Amine	Ncompounds	553	514	131	90	42	3	382	1710
	Nhydrates	146	114	58	32	3	0	100	453
	% hydrates	26.4	22.2	44.3	35.6	7.1	0.0	26.2	26.5
2° Amine	Ncompounds	272	172	41	25	8	2	207	725
	Nhydrates	36	30	12	17	1	0	21	117
	% hydrates	13.2	17.4	29.3	68.0	12.5	0.0	10.1	16.1
3° Amine	Ncompounds	272	72	20	6	10	1	268	649
	Nhydrates	51	12	5	6	1	0	19	94
	% hydrates	18.75	16.7	25.0	100.0	10.0	0.0	7.1	14.5
Cyclic amine (excluding pyridinium)	Ncompounds	1374	513	183	24	76	10	703	2871
	Nhydrates	412	126	80	10	15	3	133	771
	% hydrates	30	24.6	43.7	41.7	19.7	30.0	18.9	26.9
Total	Ncompounds	2809	1590	610	754	198	25	2085	7439
	Nhydrates	742	353	185	236	29	4	367	1723
	% hydrates	26.4	22.2	30.3	31.3	14.7	16.0	17.6	23.2

<sup>a</sup> These are non-pharmaceutically acceptable anions.

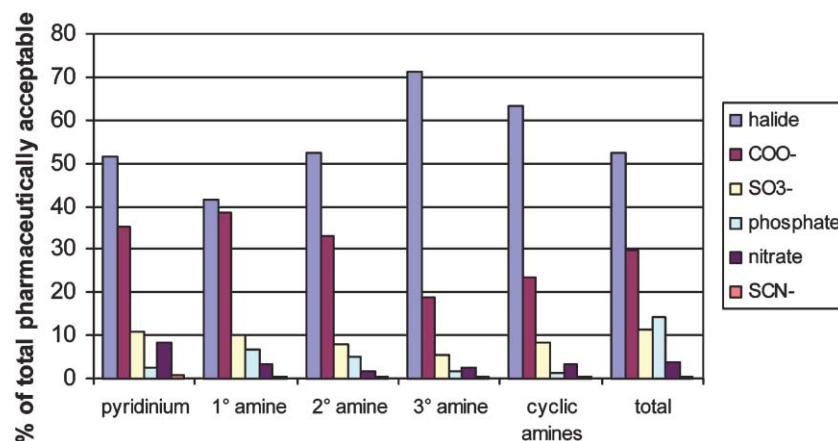


Fig. 3 Percentage occurrence of salts of N-based cations with pharmaceutically acceptable anions in the CSD

**Table 2** Hydrate occurrence in  $\text{NH}^+$ -containing halide salts in the CSD. Ncompounds is the number of crystal structures found in each case, Nhydrates is the number of these crystals which are hydrates

Cation		$\text{I}^-$	$\text{Br}^-$	$\text{Cl}^-$	$\text{F}^-$
Pyridinium	Ncompounds	8	42	156	4
	Nhydrates	1	10	62	0
	% hydrates	12.5	23.8	39.7	0.0
1° Amine	Ncompounds	28	103	420	2
	Nhydrates	4	26	115	1
	% hydrates	14.3	25.2	27.4	50.0
2° Amine	Ncompounds	8	37	225	2
	Nhydrates	2	4	29	1
	% hydrates	25.0	10.8	12.9	50.0
3° Amine	Ncompounds	9	56	202	5
	Nhydrates	1	9	41	0
	% hydrates	11.1	16.1	20.3	0.0
Cyclic amine (excluding pyridinium)	Ncompounds	56	356	958	9
	Nhydrates	12	96	300	7
	% hydrates	21.4	27.0	31.3	77.8
Total	Ncompounds	127	635	2030	22
	Nhydrates	24	151	561	9
	% hydrates	18.9	23.8	27.7	40.9

occurrence in sulfates and phosphates within all cation groups, and a lower hydrate occurrence when the anion is 'other'. The higher than average occurrence of hydrates for pharmaceutically acceptable ions has been reported by us elsewhere.<sup>5</sup> The higher occurrence of hydrates in sulfates and phosphates is not surprising, as hydrate occurrence in a total survey of the CSD increases with increasing number of polar groups on a molecule, and with increasing charge.<sup>7</sup>

Generally, within the groups of anions studied, halides tend to be more highly hydrated than carboxylates (Fig. 4). The secondary amines are an exception to this. Also, secondary and tertiary amines show generally lower levels of hydrate occurrence than the other cation groups. However, the most pronounced trend in this data is the low occurrence of hydrate formation in pyridinium carboxylate salts: only 9.1% (13 of 143 hits) of pyridinium carboxylate salts are hydrates, as compared to between 16.7 and 24.6% of carboxylate hydrates in the other cation groups. This is particularly interesting when compared to the occurrence of hydrates in pyridinium salts in general: the next lowest occurrence of hydrates is for the pyridinium nitrates at 17.1%, pyridinium halides have a hydrate occurrence of 34.8% and the overall percentage of hydrate occurrence for pyridinium salts is 22.4%.

This effect is restricted to pyridinium salts: in carboxylate salts of other aromatic  $\text{NH}^+$ -containing rings 20.6% are hydrates, 24.6% of other cyclic amine carboxylate salts are hydrates (Table 1), and in the carboxylate salts of 3-coordinate  $\text{NH}^+$  (excluding pyridinium) in general, 23.7% are hydrates. It should be noted that the sample of 143 pyridinium carboxylate salts analysed here includes a wide range of different types of molecules, from simple pyridinium trifluoroacetate (CSD reference code RUVYIQ), to complex larger molecules (e.g. RIZWIG). It is therefore surprising that there should be such a definite trend towards reduced hydration for carboxylates in the presence of the pyridinium cation. Inspection of the 13 hydrated pyridinium carboxylate salts in the CSD does not reveal any explanation as to why these salts are hydrated. In fact, at least one salt exists both as a hydrate (WADPEX) and in a non-hydrated form (DUVLUB).

Current experimental work is focussed on the synthesis and structural characterisation of a systematic series of pyridinium

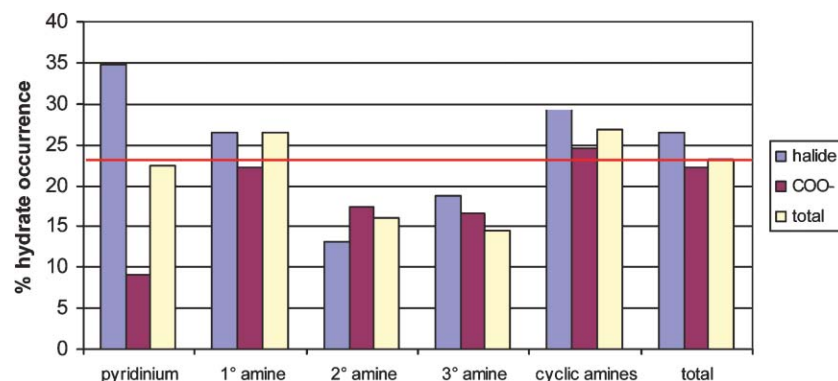


Fig. 4 Percentage of hydrates in cation groups in the CSD. The red line indicates the percentage of hydrates in non-zwitterionic salts in the CSD as a whole (22.5%).

carboxylate salts. This work aims to confirm the reduced occurrence of hydrates in pyridinium carboxylate salts, and to ensure that the results discussed here are not a result of bias in the CSD. This systematic study may also shed some light on why this trend is observed.

#### 4. Conclusions

CSD studies have revealed several potentially useful trends in  $\text{NH}^+$ -containing salts in the database. Tertiary amine and cyclic amine cations show a slight preference for crystallising with halide anions, and secondary and tertiary amine salts generally have a lower number of hydrates. However, the most pronounced trend observed was a trend towards reduced hydration in pyridinium carboxylate salts. This result implies that in choosing a counterion for a pyridinium based pharmaceutical, the choice of a carboxylate anion would give a good chance of crystal formation (approximately 35% of the pyridinium salts in the CSD are carboxylates), and a diminished chance of hydrate formation.

#### Acknowledgements

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