

A systematic study of lutidine salts formed with the pharmaceutically acceptable salt-forming agent, pamoic acid

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A series of six lutidine pamoate salts has been prepared and characterised. The crystal structures of five of these salts are reported. Four of the salts are solvates. These structures are found to have several similar features, particularly with respect to the formation of chains of pamoate ions with pendant lutidine ions.

1. Introduction

In the development of novel pharmaceuticals, salt formation is often used in order to modify the properties of compounds.^{1,2} Salt formation is usually easy to carry out, and 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, approved for this purpose. One such pharmaceutically acceptable organic acid is 4,4'-methylenebis(3-hydroxy-naphthalene-2-carboxylic acid), or pamoic acid (Scheme 1).

Pamoic acid is practically insoluble in many common solvents, including water, ethanol, ether and benzene, and the formation of a pamoate salt is used to decrease the solubility of basic drugs.¹ Pamoic acid is sparingly soluble in THF, nitrobenzene and pyridine.³ Crystals grown from a solution of pamoic acid in pyridine have been shown to be bis(pyridinium) pamoate.⁴ This structure is in fact the only pamoate salt with a determined structure in the Cambridge Structural Database⁵ (CSD, reference code TABMAK). The crystal structure of pamoic acid itself has not previously been determined, presumably due to the difficulty in growing single crystals.⁶

As part of a systematic study of the effect of counterions on the physical properties of small organic molecules,⁷ we have become interested in the formation of hydrates in pyridinium carboxylate salts. Here we focus on co-crystallising simple pyridine derivatives with a bulky anion, and have prepared a series of pamoate salts with the isomers of lutidine (Scheme 2). Crystal structures have been determined for five salts. Four of

these are THF solvates (2,3-, 2,4-, 2,6- and 3,4-lutidine pamoate). The sixth salt, 2,5-lutidine pamoate, is not a solvate, but no structure could be determined, despite several attempts.

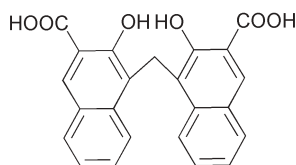
2. Results

Details of structure solution and refinement are given in the experimental section. Crystal data for the series of lutidine pamoate salts are given in Table 1. PXRD of all the materials has confirmed that the structure obtained is representative of the bulk sample.

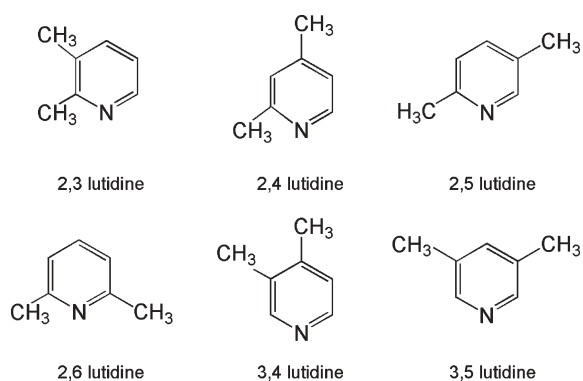
CCDC reference numbers 273067–273071. See <http://dx.doi.org/10.1039/b507408h> for crystallographic data in CIF or other electronic format.

2,3-Lutidine pamoate

This salt crystallises with a formula unit consisting of one pamoate molecule, two molecules of lutidine, and one molecule of THF. The acid is doubly deprotonated, and each carboxylate forms an internal H-bond to OH, as well as an R2,2(7) H-bonding motif with a pyridinium NH^+ .⁸ These discrete 3-molecule units can be visualised as forming a net linked by THF molecules (Fig. 1a.). A second 'net' interpenetrates with the first, forming a corrugated layer of molecules (Fig. 1b.). The layers, which are made up of columns of molecules linked at the vertices, pack alongside one another to give the 3-D structure (Fig. 1c.). Hydrogen bond parameters are given in Table 2.



Scheme 1



Scheme 2

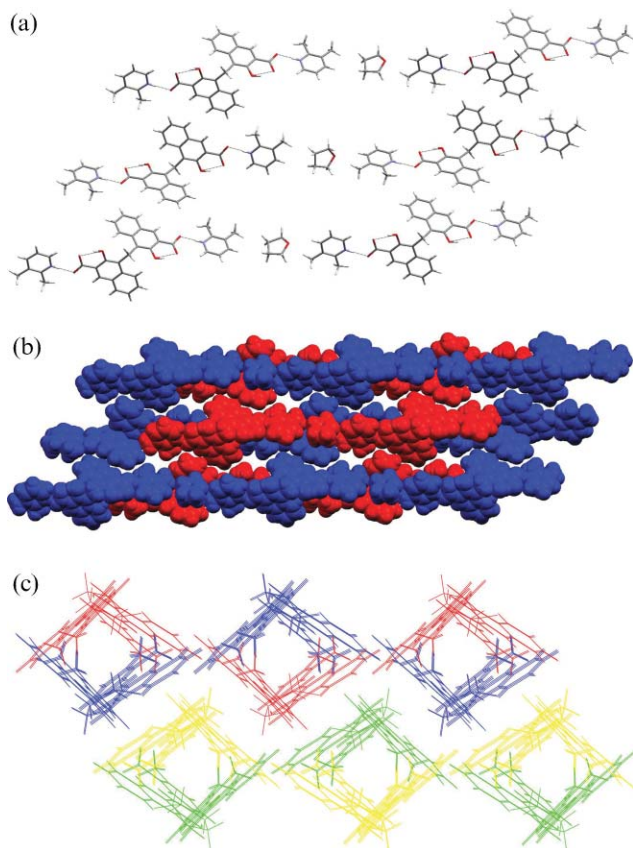
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Table 1 Selected crystal data for 7 pamoate salts. The pyridine salt of pamoic acid is included for the purposes of comparison

	Isomers of lutidine						Pyridine ⁴
	2,3-Lutidine	2,4-Lutidine	2,5-Lutidine	2,6-Lutidine	3,4-Lutidine	3,5-Lutidine	
Stoichiometry acid : base	1 : 2	1 : 1	1 : 2	1 : 1	1 : 1	1 : 1	1 : 2
Chemical formula	C ₄₁ H ₄₂ N ₂ O ₇	C ₃₄ H ₃₃ NO ₇	C ₃₇ H ₃₄ N ₂ O ₆	C ₃₄ H ₃₃ NO ₇	C ₃₄ H ₃₃ NO ₇	C ₃₀ H ₂₅ NO ₆	C ₃₃ H ₂₆ N ₂ O ₆
Formula weight	674.77	567.61		567.61	567.61	495.51	
THF solvate	✓	✓	✗	✓	✓	✗	✗
Crystal structure	✓	✓	✗	✓	✓	✓	✓
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	<i>P2₁/c</i>	<i>P2₁/n</i>		<i>P2₁/c</i>	<i>P2₁/c</i>	<i>P2₁/n</i>	<i>P</i> $\bar{1}$
<i>a</i> /Å	13.5149(3)	13.8800(2)	9.8841	13.9327(3)	13.7863(3)	14.0348(3)	11.276(2)
<i>b</i> /Å	11.8723(3)	12.5233(3)	15.8343	13.5296(3)	13.0786(3)	13.1258(3)	16.599(3)
<i>c</i> /Å	21.6996(5)	17.435(4)	19.6341	16.4802(3)	17.3905(5)	14.8509(3)	7.516(2)
α /°	90	90	90	90	90	90	99.29(2)
β /°	102.188(1)	111.189(1)	91.9883	113.424(1)	111.3485(9)	115.965(1)	101.75(2)
γ /°	90	90	90	90	90	90	98.76(1)
<i>Z</i>	4	4		4	4	4	2
Temperature/K	180(2)	240(2)		180(2)	180(2)	180(2)	
μ /mm ⁻¹	0.090	0.093		0.092	0.090	0.094	
Independent reflections	7734	6432		5196	6629	5593	
<i>R</i> _{int}	0.0455	0.0380		0.0617	0.0426	0.0267	
<i>R</i> 1 [<i>I</i> > 2σ(<i>I</i>)]	0.0600	0.0636		0.0814	0.1148	0.0436	0.045

**Fig. 1** Hydrogen bonding in 2,3-lutidine pamoate. (a) Nets of molecules; (b) nets interlace to form corrugated layers; (c) layers pack together to give a 3-D structure. Click here to access a rotatable 3-D image of Fig. 1a. Click here to access a rotatable 3-D image of Fig. 1b.

2,4-, 2,6-, 3,4- and 3,5-lutidine pamoate

Three of the salts made in this study, 2,4-, 2,6- and 3,4-lutidine pamoate, crystallise with a 1 : 1 ratio of pamoate to lutidine, with one molecule of THF per ion pair. These three salts are

isostructural (Table 1). In all three structures, there are chains of pamoate moieties linked *via* COO⁻⋯HOOC hydrogen bonds, with pendant pyridinium ions, which are shown for each of the three salts in Fig. 2a–c. Both pamoate hydroxyl groups form internal H-bonds to C=O, and the pyridinium NH⁺ forms an H-bond to the carboxylate moiety. Each carboxylate is therefore forming three hydrogen bonds: one to NH⁺, one to COOH, and an internal H-bond to OH. Hydrogen bond distances are given in Table 2.

3,5-Lutidine pamoate crystallises in 1 : 1 stoichiometry. The structure is similar to those described above, but there is no included THF. The chains of molecules formed in this salt are shown in Fig. 2d. Hydrogen bonding parameters for this salt are also given in Table 2.

The chains formed in all four salts pack together to form columns, which then stack alongside one another. In 2,4-, 2,6- and 3,4-lutidine pamoate, THF molecules fill space between the columns (Fig. 3a). However, 3,5-lutidine pamoate has no THF included in the structure. As a result, there is a less column-like arrangement (Fig. 3b).

2,5-Lutidine pamoate

Several unsuccessful attempts to determine the crystal structure of this salt have been made. Although single crystal X-ray diffraction data was collected, no solution could be obtained. The unit cell parameters have been determined, and these are given in Table 1. Microanalysis indicates that this salt crystallises in a 2 : 1 ratio (lutidine : pamoate), with no included solvent. This is confirmed by DSC and TGA.

3. Discussion

Firstly, we note that it is not surprising that all six isomers of lutidine form salts with pamoic acid, given the *pK_a* differences between the acid (2.51 and 3.10)¹ and the base (6.15–6.99).⁹ When comparing the structures of the salts of pamoic acid described above, several similarities can be noted. Firstly, the

Table 2 Selected structural parameters for a series of pamoate salts. θ is defined as the angle between pamoate and pyridinium aromatic ring planes around the $\text{NH}^+\cdots\text{OOC}$ hydrogen bond

Isomer of lutidine	$\text{O}\cdots\text{O}$ distance ($\text{COO}^-\cdots\text{HOOC}$)/Å	$\text{O}\cdots\text{O}$ distance (intramolecular)/Å	$\text{N}\cdots\text{O}$ distance ($\text{NH}^+\cdots\text{OOC}$)/Å	$\text{N}-\text{H}\cdots\text{O}$ angle ($^\circ$)	θ ($^\circ$)
2,3	—	2.528(2)	2.565(2)	179	3.3(1)
		2.525(2)	2.571(2)	177	4.5(1)
2,4	2.520(2)	2.529(2)	2.695(3)	179	76.06(5)
		2.565(2)			
2,6	2.495(3)	2.569(3)	2.759(4)	169	89.16(9)
		2.563(3)			
3,4	2.481(3)	2.530(3)	2.629(4)	156	78.6(2)
		2.552(3)			
3,5	2.49(1)	2.595(1)	2.665(2)	164	10.69(8)
		2.530(1)			
TABMAK	—	2.556	2.533	175	77.0
		2.528	2.610	160	30.5

pamoate moiety is in a very similar conformation in each of these structures (Fig. 4).

In all of the lutidine pamoate structures, as well as in the pyridinium pamoate salt (TABMAK), there is an intramolecular hydrogen bond between both OH groups and C=O on the pamoic acid moiety. There is also consistently a hydrogen bond formed between the pyridine NH^+ and the COO^- , which is to be expected.¹⁰ The $\text{N}\cdots\text{O}$ distance in these contacts ranges from 2.533–2.759 Å, which is considerably less than the sum of

the van der Waals radii¹¹ for N and O (3.07 Å), indicating a strong hydrogen bond (see Table 2). However, the known R2,2(7) motif⁸ is only seen in 2,3-lutidine pamoate.

In the two structures where the pamoate is a di-ion (2,3-lutidine pamoate and TABMAK), discrete units are formed through pyridinium moieties forming hydrogen bonds to both carboxylate groups. The θ angles are close to planar for both carboxylates in the 2,3-lutidine salt. In TABMAK, however, these angles are quite different: one is 77°, and the other 30.5°

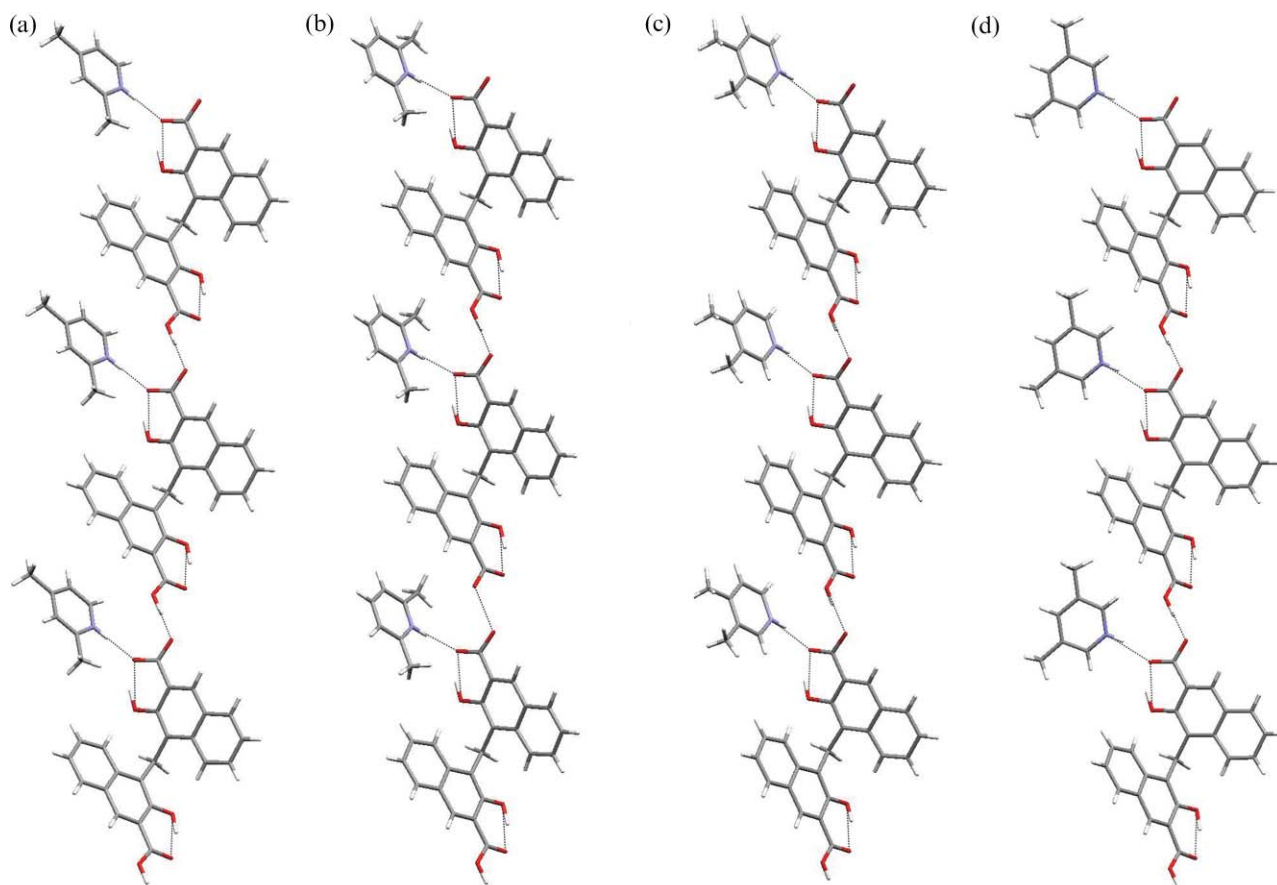


Fig. 2 Hydrogen bonded chains of molecules in some 1 : 1 lutidine pamoate salts, showing a high degree of similarity. (a) 2,4-Lutidine pamoate; (b) 2,6-lutidine pamoate; (c) 3,4-lutidine pamoate; (d) 3,5-lutidine pamoate. Click here to access a rotatable 3-D image of Fig. 2a. Click here to access a rotatable 3-D image of Fig. 2b. Click here to access a rotatable 3-D image of Fig. 2c. Click here to access a rotatable 3-D image of Fig. 2d.

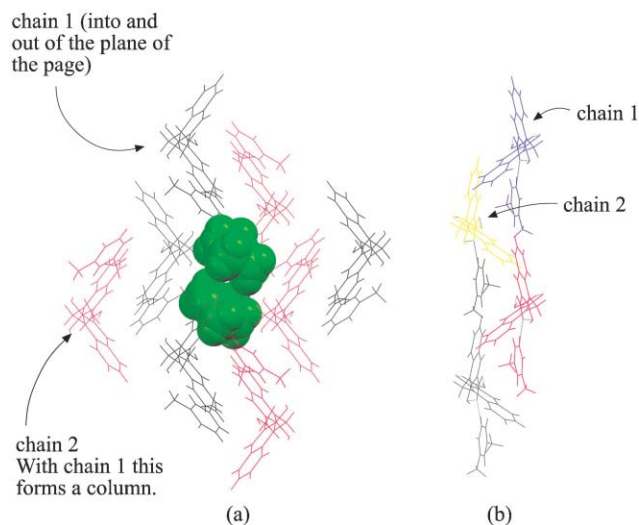


Fig. 3 Packing in 2,6- and 3,5-lutidine pamoate viewed down the direction of the hydrogen-bonded chains of molecules. (a) Packing in 2,6-lutidine pamoate:THF viewed down the *a*-axis (THF molecules are space filled). 2,4- and 3,4-lutidine pamoate are isostructural with this salt. (b) Packing in 3,5-lutidine pamoate viewed down the *a*-axis. Click here to access a rotatable 3-D image of Fig. 3a. Click here to access a rotatable 3-D image of Fig. 3b.

(Table 2). These discrete 3-molecule units pack together in a similar way in both structures, as shown in Fig. 5a. A molecule then packs into the corner formed by the pamoate moiety. This molecule, shown in green in Fig. 5b, is THF in 2,3 lutidine pamoate, and a pyridinium molecule in pyridinium pamoate. The arrays of molecules formed in this way then pack alongside one another, with the flat parts of the molecules stacking together (Fig. 5c.). The difference between the

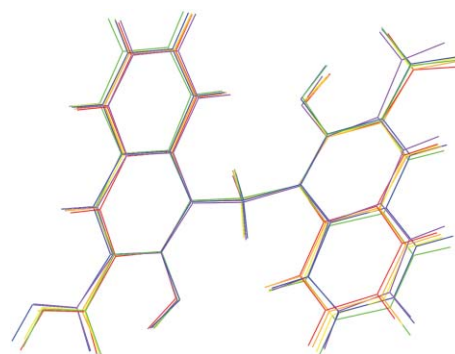


Fig. 4 Overlay of the pamoate moieties from the five salts discussed above, as well as from TABMAK.

packing in these salts becomes apparent when the structures as viewed in 5c are rotated by 90°, to give the view shown in Fig. 5d. In 2,3-lutidine pamoate, discrete columns of molecules form, which then close pack. In TABMAK, the pyridinium shown in green forms a hydrogen bond to a pamoate molecule in the next column (this molecule is in fact crystallographically equivalent to the pyridinium that forms an angle of 77° with the pamoate ring plane). The columns are therefore cross-linked, not discrete.

In the four salts where the pamoate moiety is singly deprotonated, chains of pamoates are formed, linked *via* COOH...⁻OOC hydrogen bonds. These chains have pendant lutidine ions. The chains in these four structures are in fact very similar, as shown in Fig. 6.

The difference between these structures arises in the angle of the pendant lutidine ions (θ). In 2,4-, 2,6- and 3,4-lutidine pamoate, θ is between 76 and 90°, whereas in 3,5-lutidine pamoate, this angle is approximately 11° (Table 2). This has a

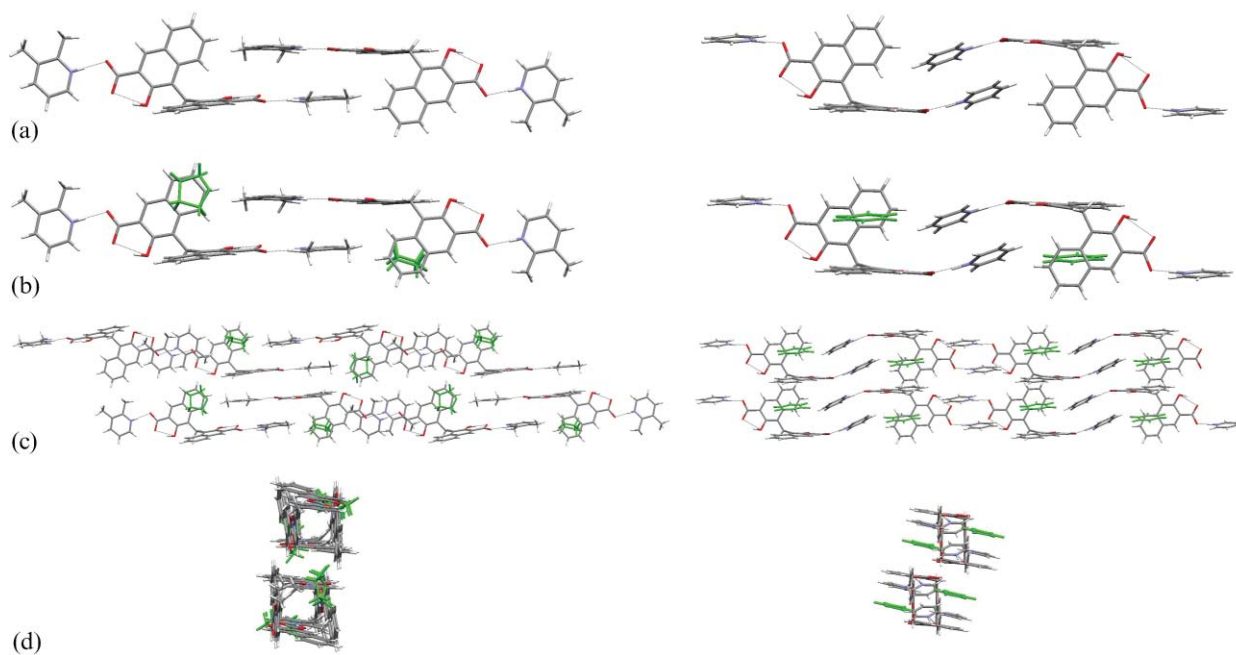


Fig. 5 Crystal packing showing the similarity between 2,3-lutidine pamoate and pyridinium pamoate (TABMAK). (a) Packing of discrete 3-molecule units; (b) molecule (shown in green) packs into pamoate; (c) arrays pack by stacking flat parts together; (d) packing shown in (c) viewed end-on.

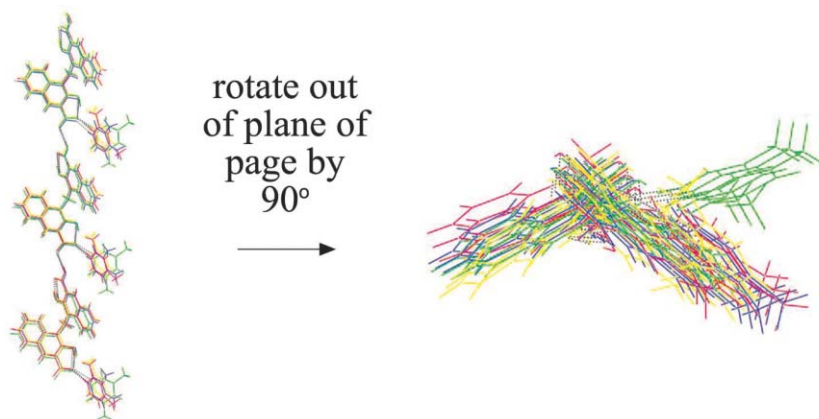


Fig. 6 Overlay of chains of molecules in 2,4-, 2,6-, 3,4- and 3,5-lutidine pamoate (3,5-lutidine pamoate is shown in green).

noticeable effect on the extended structure, as can be seen from the fact that 2,4-, 2,6- and 3,4-lutidine pamoate are THF solvates, whereas 3,5-lutidine pamoate is not. This could be rationalised as follows: in 2,4-, 2,6- and 3,4-lutidine pamoate the chains of molecules form a neat 'corner' as a result of the fact that θ is close to 90° (Fig. 6.), enabling the chains to pack into neat rectangular columns. However, there is a gap in the chain, which is then filled by THF in all 3 structures (Fig. 3.). The THF makes no strong hydrogen bonds in any of these structures, confirming the suspicion that it is fulfilling a space-filling role. In 3,5-lutidine pamoate, the angle of the lutidine ion results in a less regular 'corner' (Fig. 6.), and the columns are able to pack together in such a way as to leave no gaps (Fig. 3.). This structure is not a solvate.

The difference in θ in these structures is interesting. At first glance, this seems to be affected by the position of the methyl groups around the ring: 2,6-lutidine gives the largest angle, with a decrease in angle for other isomers. However, the most planar system is seen for 2,3-lutidine, whilst 3,4-lutidine forms an angle of 78.59° with the pamoate ion: the existence of a methyl group in the *o*-position does not imply an increase in angle. Interestingly, in the pyridinium pamoate salt, where there are no substituents to influence packing, the two independent pyridinium rings form quite different angles with the pamoate ring planes (77.0 and 30.5°).

These structures do all, however, have certain interactions in common: in all 7 salts there are interactions between the planar parts of the molecule, *i.e.* the planar parts of the molecules form stacks (Fig. 7). It seems that these interactions are more important for determining the structure. The hydrogen bonding interactions have some degree of flexibility (as evidenced by the change in θ), and this allows the accommodation of the methyl groups whilst not disrupting the stacking interactions.

Analysis (PXRD, microanalysis, thermal analysis) indicates that unsolvated 1 : 2 pamoate : lutidine forms exist for all isomers of lutidine. However, single crystals cannot be grown for any of these forms. Comparing these structures with those described above would shed further light on the precise effect of changing the positions of the methyl groups in these salts.

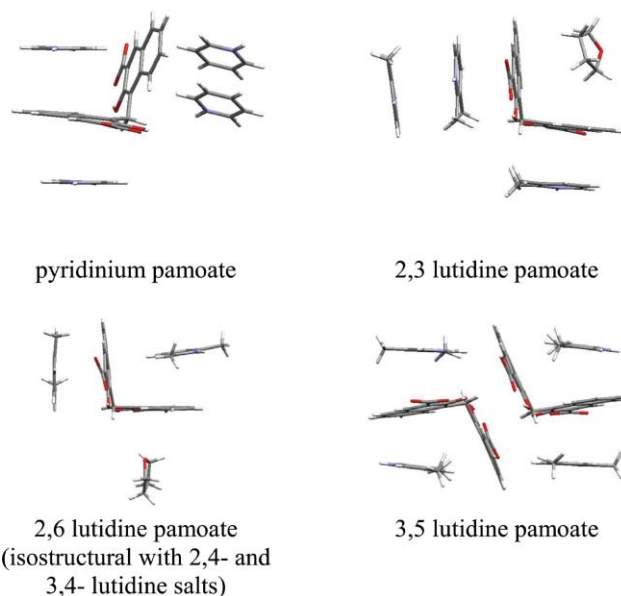


Fig. 7 Stacking interactions in pamoate salts.

Attempting to determine the structures of these unsolvated forms will be the focus of future work on this system.

4. Conclusions

This series of pamoate salts has provided an interesting insight into the various effects on crystal packing. The pamoate ion itself does not show much variation in conformation, and as a result of being a big, bulky ion, is quite structure directing: all these structures show chain/column-type arrangements of the ions in the solid state, and four of the structures are essentially the same in at least one dimension. These structures seem to be dominated by stacking interactions. In fact, three structures, with methyl groups in different positions on the aromatic ring, are isostructural (2,4-, 2,6- and 3,4-lutidine pamoate). This is in contrast to our work in progress, which shows that ions such as fumarate give much more structural variation.

Future work on this system will involve investigating the occurrence of possible polymorphs and hydrates of these salts, as well as the existence of stoichiometrically different forms.

5. Experimental

All chemicals were purchased from Aldrich and used without further purification. Salts were prepared by adding lutidine to a warm solution of pamoic acid in THF in a 1 : 1 ratio. The solution was refluxed, then cooled to room temperature, yielding suitable single crystals in all but one case.

Elemental analysis

2,3-Lutidine pamoate: Found: C 72.84, H 6.30, N 4.05; required for C₄₁H₄₂N₂O₇ C 72.98, H 6.27, N4.15

2,4-Lutidine pamoate: Found: C 71.82, H 5.86, N 2.49; required for C₃₄H₃₃NO₇ C 71.94, H 6.40, N2.70

2,5-Lutidine pamoate: Found: C 73.57, H 5.73, N 4.62; required for C₃₇H₃₄N₂O₆ C 73.74, H 5.69, N4.65

2,6-Lutidine pamoate: Found: C 71.84, H 5.87, N 2.53; required for C₃₄H₃₃NO₇ C 71.94, H 6.40, N2.70

3,4-Lutidine pamoate: Found: C 71.88, H 5.78, N 2.54; required for C₃₄H₃₃NO₇ C 71.94, H 6.40, N2.70

3,5-Lutidine pamoate: Found: C 72.66, H 5.09, N 2.87; required for C₃₀H₂₅NO₆ C 72.72, H 5.09, N2.83

X-Ray crystallography

Single crystal X-ray diffraction analyses were performed using a Nonius Kappa CCD diffractometer equipped with an Oxford Cryosystems cryostream device. Crystals were mounted on the end of glass fibres and data were collected at 180(2) K (unless otherwise stated). Data were processed using the HKL package¹² and unit cell parameters were refined

against all data. NH⁺ hydrogen atoms were located in the difference map in all cases. PXRD patterns were collected for all salts, confirming that the selected crystals were representative of the bulk material.

Acknowledgements

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References

- 1 *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, ed. P. H. Stahl and C. G. Wermuth, Wiley-VCH/VHCA, Weinheim/Zürich, 2002.
- 2 P. J. Gould, *Int. J. Pharm.*, 1986, **33**, 201–217.
- 3 *The Merck Index 13th edition*, Maryadele J. O’Neil, senior editor, Merck & Co. Inc., Whitehouse Station, NJ, 2001.
- 4 A. C. Blackburn, A. J. Dobson and R. E. Gerkin, *Acta Crystallogr., Sect. C*, 1996, **52**, 1269–1272.
- 5 F. H. Allen, *Acta Crystallogr., Sect. B*, 2002, **58**, 380–388.
- 6 The structure of pamoic acid has recently been determined in our group from powder data. This will be the subject of a future publication.
- 7 D. A. Haynes, J. A. Chisholm, W. Jones and W. D. S. Motherwell, *CrystEngComm*, 2004, **6**, 584–588; D. A. Haynes, W. Jones and W. D. S. Motherwell, *J. Pharm. Sci.*, 2005, DOI: 10.1002/jps.20441.
- 8 S. H. Dale, M. R. J. Elsegood, M. Hemmings and A. L. Wilkinson, *CrystEngComm*, 2004, **6**, 207; B. R. Bhogala and A. Nangia, *Cryst. Growth Des.*, 2003, **3**, 547–554.
- 9 D. R. Lide, editor-in-chief, *CRC Handbook of Chemistry and Physics*, CRC Press, Boca Raton, FL, 72nd edn, 1991.
- 10 M. C. Etter, *J. Phys. Chem.*, 1991, **95**, 4601–4610.
- 11 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441–452.
- 12 Z. Otwinowski and W. Minor, in *Methods in Enzymology. Vol. 276. Macromolecular Crystallography: Part A*, ed. C. W. Carter and R. M. Sweet, Academic Press, London, 1997.