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Aqueous solubility study of salts of benzylamine derivatives and *p*-substituted benzoic acid derivatives using X-ray crystallographic analysis

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Abstract

Twenty two *p*-substituted benzoic acid derivates were used to prepare salts of *N*-methylbenzylamine (**II**) and *N*,*N*-dimethylbenzylamine (**III**), respectively. Only five salts of (**II**) and two salts of (**III**) were obtained in a crystalline state. The solubility of these salts was orders of magnitude higher than those reported for the corresponding salts of benzylamine (**I**). Thermal analysis indicated that the increased solubility was caused by reduced crystal lattice energy, which was most likely due to the reduced number of strong hydrogen bonds of the salt of (**II**) and (**III**). X-ray crystallographic analysis of *p*-hydroxybenzoic acid salt of (**I**), (**II**) and (**III**) suggested that the reduced number of hydrogen bonds caused the apparent higher solubility. Further analyses of seven salts of (**I**) were performed. It was not possible to identify any relationship between the number of hydrogen bonds and the corresponding solubility of the salts.

Keywords: Benzylamine; Crystallographic analysis; Benzoic acid

1. Introduction

Salt formation is a simple means to alter the biopharmaceutical properties of drugs containing one or more ionisable groups. Several studies have been done to elucidate a relationship between salt properties and the nature of the counterion used (Chowhan, 1978; Gould, 1986; Rubino, 1989; Forbes et al., 1995; Thomas and Rubino, 1996; Fini et al., 1996; O'Connor and Corrigan, 2001; Parshad et al., 2002). However, quantitative relationships between chemical structure of counterions and physicochemical properties of drug salts are still poorly investigated (Berge et al., 1977; Gould, 1986, Bighley et al., 1996). In modern medicinal chemistry where drugs emerge having poor aqueous solubility and thus poor bioavailability (Lipinsky et al., 1997), the concept of rational design of drug salts would be of great importance. Likewise, in the interest of prolonged duration of action preparation of less soluble salts of the drugs could be important, and thus knowledge of solubility manipulation would be desirable. In a previous study (Parshad et al., 2002), salts of *p*-substituted benzoic acids and benzylamine were synthesized and

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characterized physicochemically. Multivariate data analysis was used to establish reasonable models which described the correlation between aqueous solubility of the salts and physicochemical and molecular descriptors. In the present study the effect on solubility of salts of two derivatives of benzylamine and the former 22 *p*-substituted benzoic acids is investigated. The aqueous solubility is expected to be a result of the free energy of hydration of the ions and the crystal lattice energy. In previous studies it was found that the energy of hydration only showed minor variation compared to the span in solubility, and therefore the variation must apparently be accounted for by different lattice energies. Thus, nine salts were suspected to crystallographic analysis to study the influence of the solid state structure on salt solubility.

2. Materials and methods

2.1. Materials

The compounds used for salt formation were of highest purity commercially available (list of compounds, Parshad et al., 2002). *N*-methylbenzylamine (**II**), *N*,*N*-dimethylbenzylamine (**III**) were purchased from Bie & Berntsen, Copenhagen, Denmark. Chemicals for HPLC mobile phases were of analytical grade. Deionized water was used throughout the study.

2.2. Salt preparation

The salts were prepared by mixing equivalent amounts of the benzoic acid derivative and the amine in methanol (Parshad et al., 2002). Recrystallization was done from methanol and diethyl ether. After filtration the crystals were washed with diethyl ether and stored in vacuo over phosphorous(V)-oxide. The salts were subjected to elemental analysis, and formation of 1:1 salts was confirmed by HPLC. Melting points were determined by hot-stage microscopy and from differential scanning calorimetry (DSC).

2.3. Solubility determination and intrinsic dissolution rate measurements

Solubility experiments were conducted as described previously (Parshad et al., 2002). Dissolution was performed by the rotating disk method (Prakongpan et al., 1976). In all cases the samples were withdrawn manually every 1–4 min since the dissolution rate was too high to be measured by our flow-through automated system. The dissolution experiments were stopped after max 20 min ensuring that the surface area was intact. The samples were analysed at λ_{max} for each salt on a UV-spectrophotometer (Shimadzu 160-UV).

2.4. Thermal analyses

A Perkin-Elmer DSC 6 apparatus with Pyris software was used for the determination of the molar heat of fusion and the melting point of the salts. Volatile sample pans were used, due to sublimation of the samples below melting point. Samples were scanned from 50 to 260 °C at a rate of 10 °C min^{-1} under nitrogen gas flow (20 ml min^{-1}). Measurements were done in duplo. The instrument was calibrated using indium and zinc.

2.5. Computational methods

Semi-empirical calculations of the free energy of hydration, ΔG_{hyd+}, of benzylammonium ion, *N*-methylbenzylammonium ion and *N*,*N*-dimethylbenzylammonium ion were carried out using the program Spartan 5.1.1 (Wavefunction, Inc.). Calculations for the aqueous phase were done using the AM1-SM2 method (Cramer and Truhlar, 1992).[1]

2.6. Single crystal diffraction

Single crystals were mounted and immersed in a stream of nitrogen gas (temperature = 122(1)K). Data were collected, using graphite monochromated Mo Kα radiation source (λ = 0.71073 Å) on a Nonius KappaCCD diffractometer. Data collections and cell refinements were performed using COLLECT (Nonius, 1999) and DIRAX (Duisenberg, 1992). Only for the salt, benzylamine and benzoic acid, diffraction data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Cu Kα radiation (λ = 1.54184 Å).[2]

[1] Spartan SGI version 5.1.1. Wavefunction Inc. 18401 von Karman, Suite 370 CA 92612, United States.

[2] Details of the single crystal X-ray diffraction experiments are given in Table 5. Full structural reports are provided as supplement

Table 1
Salts obtained in a crystalline state

Amines	*p*-Substituents of the benzoic acid counterions		
	Alkyl	Halogen	HB[a] donor + acceptor
I[b]	–H, $–CH_3$, $–C_2H_5$, $–C_3H_7$, i–C_3H_7, $–C_4H_9$, *–tert*-C_4H_9, $–C_6H_5$	–Cl, –Br, –I	$–OCH_3$, –OH, $–NO_2$, $–CH_2OH$, –CN, $–NH_2$, $–NHCH_3$, $–N(CH_3)_2$, $–CF_3$, $–SO_2NH_2$, $–CONH_2$
II[c]	–H, $–C_6H_5$	None	–OH, $–NH_2$, $–SO_2NH_2$
III[d]	None	None	–OH, $–SO_2NH_2$

[a] Hydrogen bond donor and/or acceptor substituents.
[b] Benzylamine (characterization, see Parshad et al., 2002).
[c] *N*-Methylbenzylamine.
[d] *N*,*N*-Dimethylbenzylamine.

Data reductions were performed using EvalCCD (Duisenberg, 1998) and DREAR (Blessing, 1987; Blessing, 1989). The structures were solved by direct methods, SHELXS97 (Sheldrick, 1997a; Sheldrick, 1990) and refinements of the structures were performed with SHELXL97 (Sheldrick, 1997b), using full matrix least squares refinement on F^2. Atomic scattering factors for neutral atoms were used as incorporated in SHELXL97 (Sheldrick, 1997b; International Tables for Crystallography, 1995). All atomic parameters for non-hydrogen atoms were independently refined with anisotropic displacement parameters, except for *N*-methylbenzylammonium *p*-hydroxybenzoate salt. Due to disorder in the salt of *N*-methylbenzylammonium the atoms of the aromatic ring of the ammonium ion were split up in three major conformations. The angles and distances within the phenyl rings were constrained to ideal values. The occupancy of the three major conformations were refined constraining the sum of those to be 1.0. Because they represent a number of intermediate conformations the displacement parameters were refined with constrained parameters (ISOR = 0.005). For all structures the positions of hydrogen atoms on the aromatic rings and the methyl groups have been calculated and refined riding on the parent atom, while the positions of the rest of the hydrogen atoms have been refined independently. Isotropic displacement parameters for all hydrogen atoms have been fixed (1.2 Ueq, but 1.5 Ueq for methyl, hydroxy, ammonium and amine). Refinement of the structures of *p*-amino and *p*-nitro in space group $P2_1/c$ leads to high *R*-values. The β-angle being close to 90 degrees suggest that the crystals are twinned by merohedry. Introducing this into the refinement gives the low *R*-values found in Table 5.

3. Results and discussion

3.1. Synthesis and characterization

All salts of benzylamine (**I**), *N*-methylbenzylamine (**II**) and *N*,*N*-dimethylbenzylamine (**III**) were prepared from mixing a methanolic solution of the amine with an equivalent amount of benzoic acid derivative.

In a previous paper 22 crystalline salts of (**I**) and *p*-substituted benzoic acids were characterized (Parshad et al., 2002). Using the same benzoic acid derivatives attempts were done to obtain the corresponding (**II**) and (**III**) salts from methanolic solutions. Only five salts of (**II**) and two salts of (**III**) were obtained in a crystalline state (Table 1). The remaining salts precipitated as oils. Several unsuccessful attempts were made to recrystallize these salts from different solvents. Counterions containing hydrogen bond donor capabilities were observed to crystallize irrespective of the amine used suggesting that hydrogen bonds are important for crystal packing (see Section 3.2.2).

Elemental analysis (CHN) and quantitative HPLC confirmed the formation of 1:1 salts. In addition, the pH of the saturated salt solution (Table 2) calculated

and atomic coordinates have been deposited with the Cambridge Crystallographic Data Centre with CCDC numbers (CCDC 217055-217063) as specified in Table 5. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 2
Characterization of the *p*-substituted benzoic acid salts of benzylamine (compounds 1–5)[a], *N*-methylbenzylamine (compounds 6–10) and *N*,*N*-dimethylbenzylamine (compounds 11 and 12)

Compound number	*p*-Substituent	*S* (mM)	pH_{calc}[b]	pH_{meas}	IDR[c]
1	H	839	6.8	7.1	>20
2	C_6H_5	12.8	6.8	6.9	1.15
3	OH	138	6.9	6.7	11.9
4	NH_2	272	7.1	7.1	>20
5	SO_2NH_2	110	6.5	6.3	6.49
6	H	3.1×10^3	6.9	7.1	>20
7	C_6H_5	26.5	6.9	8.1	1.56
8	OH	1.1×10^3	7.0	6.8	>20
9	NH_2	$>7.1\times10^3$	7.2	8.1	> 20
10	SO_2NH_2	245	6.6	6.5	17.7
11	OH	4.5×10^3	6.7	7.0	>20
12	SO_2NH_2	378	6.3	6.3	>20

Salt solubility, *S* (37 °C).
[a] Data from (Parshad et al., 2002).
[b] Calculated according to Eq. (1).
[c] IDR: intrinsic dissolution rate in $\mu M\,min^{-1}\,cm^{-2}$. RSDs were below 4% for solubility experiments and below 5% for IDR experiments.

from Eq. (1) was in most cases consistent with 1:1 salt formation.

$$pH = \tfrac{1}{2}(pK_a(acid) + pK_a(base)) \quad (1)$$

Compounds 7 and 9 (Table 2), however, gave rise to somewhat higher pH values than expected which most likely reflects the presence of some undetected basic, water-soluble impurities.

3.1.1. Solubility and intrinsic dissolution rate

The aqueous solubilities of the salts (37.0 ± 0.5 °C) (Table 2) were obtained from experiments done in triplicate (RSD below 4%) in deionized water. Equimolar concentrations of acid and base were determined by HPLC at saturation.

The intrinsic dissolution rate (IDR) could only be measured for two (compound numbers 7 and 10) of the seven investigated salts (Table 2). The other salts exhibited too fast dissolution to be measured ($>20\,\mu M\,min^{-1}\,cm^{-2}$). Previous studies have revealed linearity between IDR and the corresponding solubility of a series of related organic salts of *p*-aminobenzoic acid (Forbes et al., 1995) and, *p*-substituted benzoic acid (Parshad et al., 2002), respectively, in accordance with the Noyes–Whitney equation (Noyes and Whitney, 1897).

3.1.2. Thermal analysis

The heat of fusion, ΔH_{fus}, was measured in volatile sample pans (Table 3). The melting point of the salts were determined as the onset temperature of the endotherm peak and was found to be in accordance with the melting point determined by hot-stage microscopy (deviation below 2 °C). The heat of fusion of *p*-aminosulfonylbenzoic acid salt of (**III**) could, however, not be determined due to overlapping peaks.

Interestingly, in the present series it is observed that salt solubility increases many folds in the order: salt of (**I**) < salt of (**II**) < salt of (**III**) (Table 2). Thus, the salt solubility seems to increase as the lipophilicity, as measured by log *P*, of the benzylammonium ion increases (Table 4), which is contrary to earlier studies stating that the higher the lipophilicity of the counterion, the more likely it is to obtain a less soluble salt (Anderson, 1985). However, it is in accordance with the findings that reduced crystal lattice energy may arise from the increased ammonium ion radius and due to delocalisation of the charge leading to weaker coloumbic interactions in the solid state (Chowhan, 1978; Amis, 1983). The present study further indicates that hydrogen bonds are essential for stabilizing the crystal lattice (see Section 3.2.2). Since these are reduced for the salts of (**II**) and (**III**) this might lead to higher solubilities. According to Hess' law the

Table 3
Melting point and heat of fusion (ΔH_{fus}) of salts of (**I**)[a], (**II**)[b] and (**III**)[c]

p-Substituted benzoic acid counterions	M.p. salt (I)[d] (°C)	M.p. salt (II)[d] (°C)	M.p. salt (III)[d] (°C)	ΔH_{fus} (I) (kJ/mol)	ΔH_{fus} (II) (kJ/mol)	ΔH_{fus} (III) (kJ/mol)
–H	128	81	n.d[e]	34.5	32.3	n.d
$-C_6H_5$	176	133	n.d	35.6	56.2	n.d
–OH	218	148	123	219[f]	38.1	40.0
$-NH_2$	194	125	n.d	57.0	50.8	n.d
$-SO_2NH_2$	218	186	174	61.3	55.7	d.p[g]

[a] Benzylamine.
[b] *N*-Methylbenzylamine.
[c] *N*,*N*-Dimethylbenzylamine.
[d] The melting interval is below 5 °C at hot-stage microscopy.
[e] Salt precipitated as oil.
[f] The high value indicates that other endothermic reactions than melting occur.
[g] It could not be determined due to overlapping peaks.

observed higher aqueous solubility of the salts of (**II**) and (**III**) compared to the corresponding salts of (**I**) is either due to a lower free energy of hydration of the ammonium ion, ΔG_{hyd+}, or to a decreased crystal lattice energy. Evidently, the calculated free energy of hydration, ΔG_{hyd+}, of the ammonium ion increases from (**I**) to (**II**) and (**III**) implying that the former is most favourably solvated (Table 4). Consequently, the crystal lattice energy is expected to decrease significantly to offset the increased energy of hydration. In fact, the melting point of the salts of (**II**) and (**III**) is observed to decrease in all cases in the order (**III**) < (**II**) < (**I**) (Table 3), suggesting that the enhanced aqueous solubility is due to reduced crystal lattice energy. Likewise, in most cases the heat of fusion (ΔH_{fus}) of the salts of (**I**), (**II**) and (**III**) appear to decrease in the mentioned order.

Table 4
Aqueous solubility, free energy of hydration, distribution coefficients ($\log P_{oct./water}$) and pK_a

	Aqueous solubility[a]	ΔG_{hyd+} (kJ/mol)	$\log P$[b]	pK_a[c]
(I)[d]	9.3	−274	1.09	9.33
(II)[e]	8.3	−236	1.52	9.54
(III)[f]	0.089	−203	1.98	8.91

[a] SRC Physprop Database.
[b] Hansch et al. (1995).
[c] Determined at 25 °C (Perrin, 1965).
[d] Benzylamine.
[e] *N*-Methylbenzylamine.
[f] *N*,*N*-Dimethylbenzylamine.

3.2. X-ray crystallographic analyses

In order to obtain information on the potential relationships between solid phase characteristics and the corresponding solubility, salts were selected for X-ray crystallographic analysis. In a previous study the solubility range of 22 salts of (**I**) was 0.01–1.0 M (Parshad et al., 2002). Seven representative salts of (**I**) were selected covering this solubility range (Table 5). In addition, salts of *p*-hydroxybenzoic acid and (**II**) and (**III**) were analysed to identify a correlation between the ascending solubility and the solid state properties.[3]

Based on the crystal packings of the nine different crystal structures (Fig. 1) it is obvious that the crystal packings are not identical and a more thorough analysis of specific details has to be performed in order to describe trends. Changes in crystal packings can be a result of the ions having different molecular conformations or changes in intermolecular interactions e.g. hydrogen bonds.

3.2.1. Molecular conformation

The conformation of the benzylammonium ion is comparable in all seven crystal structures and is observed to be the expected favourable conformation with the side chain rotated 62–92° out of the plane of the benzene ring. The *p*-substituted benzoate ion is observed in a conformation with the carboxyl group nearly in the plane of the aromatic ring (deviation from

[3] Enraf-Nonius. CAD-4 Software. Version 5.0; Enraf-Nonius, Delft, The Netherlands, 1989.

Table 5
Crystal data and structure refinement for benzylamine salts with *p*-substituted benzoic acids

p-Substituent	Amino	Hydroxy	Nitro	H	Methyl	Carbamoyl	Hydroxymethyl	*N*-Methyl[a]	*N,N*-Dimethyl[b]
CCDC number[c]	217055	217056	217060	217059	217057	217061	217062	217063	217058
Empirical formula	$C_{14}H_{16}N_2O_2$	$C_{14}H_{15}NO_3$	$C_{14}H_{14}N_2O_4$	$C_{14}H_{15}NO_2$	$C_{15}H_{17}NO_2$	$C_{15}H_{16}N_2O_3$	$C_{15}H_{17}NO_3$	$C_{15}H_{17}NO_3$	$C_{16}H_{19}NO_3$
Formula weight	244.29	245.27	274.27	229.27	243.30	272.30	259.30	259.30	273.32
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Triclinic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_1/n$	$P2_1/c$	$P2_1/a$	CAD4/Cu	$P-1$	$P-1$	$P2_1/a$	$Pna2_1$
Unit cell									
a (Å)	18.2016(7)	11.9145(8)	9.9253(2)	15.667(4)	14.4988(6)	6.2372(8)	6.652(2)	10.085(3)	17.4343(5)
b (Å)	6.341(4)	17.4316(7)	9.1116(2)	6.3139(12)	6.2797(2)	10.2168(5)	9.846(3)	9.484(3)	9.6136(3)
c (Å)	22.493(3)	12.0702(4)	28.9112(4)	26.664(5)	15.2316(3)	10.4548(15)	10.310(3)	14.647(4)	8.8516(2)
α (°)	90.00	90.00	90.0	90.0	90.0	89.654(8)	82.86(2)	90.0	90.0
β (°)	90.004(10)	100.494(3)	90.044(1)	106.12(2)	105.125(2)	86.046(12)	82.53(2)	96.96(2)	90.0
γ (°)	90.00	90.00	90.0	90.0	90.0	84.783(8)	81.13(2)	90.0	90.0
Volume (Å^3)	2596.2(15)	2464.9(1)	2614.59(9)	2533.9(9)	1338.77(7)	661.88(15)	657.7(3)	1390.5(7)	1483.58(6)
Z	8	8	8	8	4	2	2	4	4
Calculated density (mg/m^3)	1.250	1.322	1.394	1.202	1.207	1.366	1.309	1.239	1.224
Absorption coefficient (mm^{-1})	0.085	0.093	0.104	0.647	0.080	0.096	0.091	0.086	0.084
F (0 0 0)	1040	1040	1152	976	520	288	276	552	584
Crystal size (mm)	0.44 × 0.28 × 0.18	0.64 × 0.39 × 0.32	0.28 × 0.21 × 0.13	0.40 × 0.14 × 0.14	0.44 × 0.16 × 0.12	0.38 × 0.20 × 0.08	0.59 × 0.18 × 0.04	0.25 × 0.10 × 0.06	0.41 × 0.36 × 0.12
θ range (°)	2.24–25.05	2.08–27.51	2.00–25.68	1.72–74.89	2.76–27.60	2.79–27.49	2.00–27.53	2.56–26.50	2.34–26.50
Limiting indices	$-21 \le h \le 21$ $-7 \le k < 7$ $-26 \le l \le 26$	$-15 \le h \le 14$ $-22 \le k < 22$ $-15 \le l \le 15$	$-11 \le h \le 12$ $-11 \le k \le 11$ $-32 \le l \le 35$	$-19 \le h \le 18$ $0 \le k < 7$ $0 \le l \le 33$	$-18 \le h \le 18$ $-8 \le k < 8$ $-19 \le l \le 19$	$-8 \le h \le 8$ $-13 \le k \le 13$ $-13 \le l \le 13$	$-8 \le h \le 8$ $-12 \le k \le 12$ $-13 \le l \le 13$	$-12 \le h \le 10$ $-11 \le k \le 11$ $-18 \le l \le 18$	$-21 \le h \le 21$ ≤ 12 $-11 \le l \le 11$
Reflections collected/unique	24169/4606	87778/5660	23338/4873	5522/5192	44360/3096	26106/3023	11540/3017	16258/2873	62269/3082
R (int)	0.0433	0.049	0.0533	0.0478	0.0372	0.0254	0.0433	0.0375	0.0284
Completeness to θ_{max}	99.8%	100.0%	98.2%		100.0%	99.9%	99.4%	99.7%	100.0%
Data/parameter	4606/356	5660/349	4873/380	5192/326	3096/173	3023/196	3017/184	2873/257	3082/189
Goodness-of-fit (on F^2)	1.096	1.097	1.097	1.073	1.076	1.086	1.140	1.073	1.023
Extinction				0.0020(3)					
Final R indices [$I > 2\sigma(I)$]									
R1	0.0349	0.0355	0.0437	0.0617	0.0379	0.0351	0.0586	0.0629	0.0289
wR2	0.0713	0.0963	0.0827	0.1566	0.0979	0.0966	0.1343	0.1359	0.0724
Reflections observed	4014	4668	3904	4257	2527	2676	2435	2087	2880
R indices (all data)									
R1	0.0470	0.0445	0.0686	0.0743	0.0474	0.0405	0.0749	0.0930	0.0324
wR2	0.0775	0.1005	0.0934	0.1700	0.1023	0.1003	0.1427	0.1466	0.0741
Largest difference									
Peak (e Å^{-3})	0.167	0.211	0.242	0.387	0.308	0.363	0.435	0.379	0.128
Hole (e Å^{-3})	−0.198	−0.338	−0.225	−0.321	−0.207	−0.225	−0.239	−0.260	−0.199
BASF (TWIN)	0.298		0.423						

[a] Salt *N*-methylbenzylammonium *p*-hydroxybenzoate.
[b] Salt *N,N*-dimethylbenzylammonium *p*-hydroxybenzoate.
[c] Cambridge Crystallographic Data Centre deposition number.

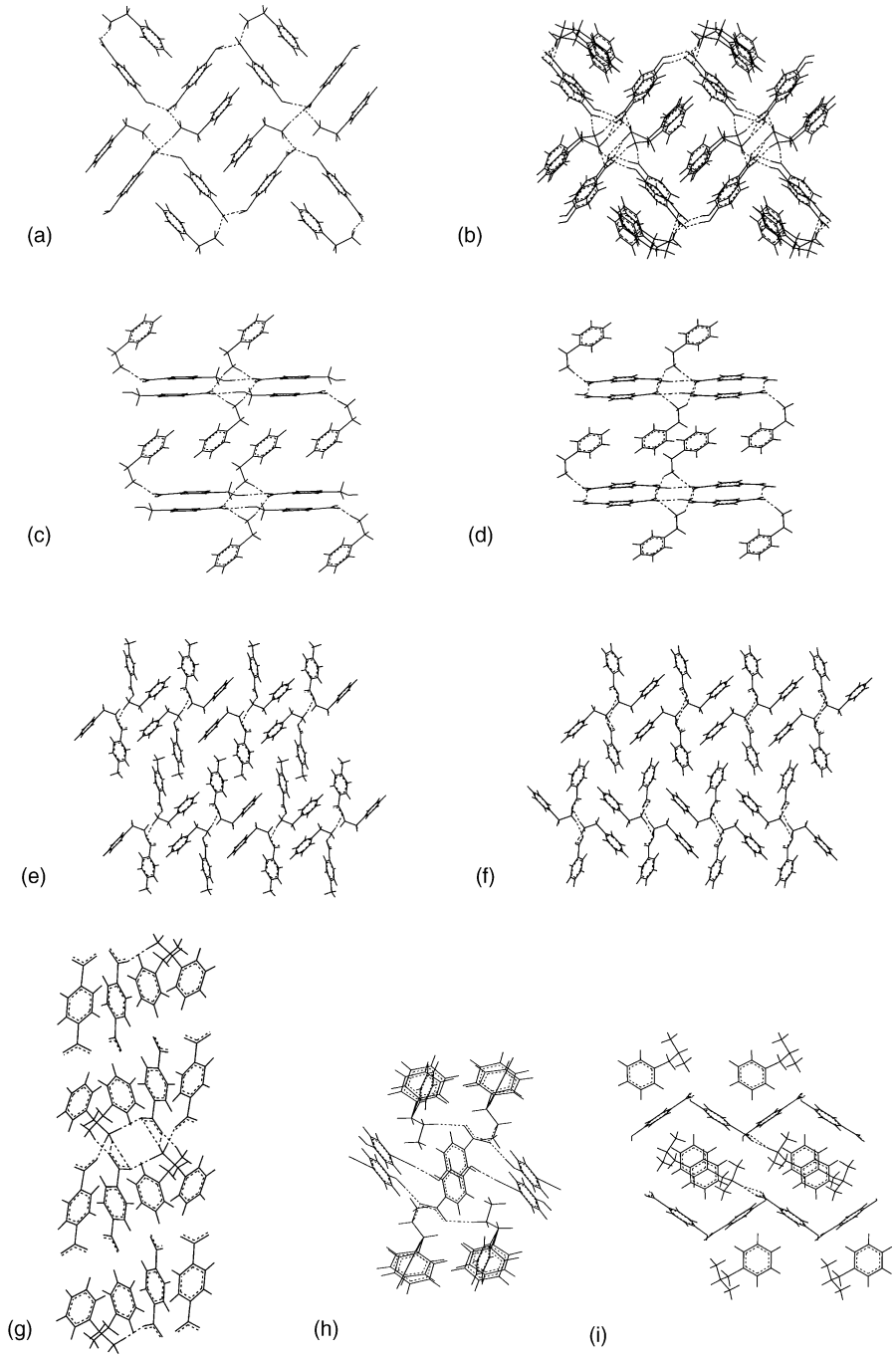

Fig. 1. Crystal packings of benzylamine salts of *p*-aminobenzoic acid (a), *p*-hydroxybenzoic acid (b), *p*-hydroxymethylbenzoic acid (c), *p*-carbamoylbenzoic acid (d), *p*-methylbenzoic acid (e), benzoic acid (f), *p*-nitrobenzoic acid (g), *N*-methylbenzylamine salt of *p*-hydroxybenzoic acid (h) and *N*,*N*-dimethylbenzylamine salt of *p*-hydroxybenzoic acid (i) (Molecular Simulations Inc., 2000).

plane up to 17°). The *p*-substituent is observed close to the plane of the aromatic ring as well. Three substituents constitute more than one heavy atom (nitro, carbamoyl and hydroxymethyl moieties) and the deviation from the plane of the aromatic ring for these moieties is in the range 14–20°. This is unexpected for the hydroxymethyl moiety, which is expected to have the same favourable conformation as benzylamine with the side chain 60–90° out of plane. Crystal packing interactions make the more planar conformation favourable.

Consequently, the conformations of the ions are not responsible for changes in the crystal packing energies.

3.2.2. Hydrogen bonds

All possible hydrogen bond donors are involved in hydrogen bonding. In the salts of benzylamine three ionic hydrogen bonds are observed between the ammonium and the carboxylate moiety, except for *p*-hydroxy- and *p*-carbamoylbenzoate, where the oxygen atom of the *p*-substituent can also be involved as an acceptor site (Table 6). In some of the salts (*p*-amino-, *p*-hydroxy-, *p*-nitro-) one of the hydrogen atoms of the ammonium group is involved in a bifurcated hydrogen bond (hydrogen atom interacts with both oxygen atoms of a carboxylate moiety), but the two interactions are not equally strong (Table 6). The benzylamine salts with *p*-amino- and *p*-carbamoylbenzoic acid both have five strong hydrogen bonds and the solubilities of the salts are 272 and 118 mM, respectively (Parshad et al., 2002). The salts of *p*-hydroxy- and *p*-hydroxymethylbenzoic acid have four strong hydrogen bonds, but for these salts a greater difference in solubility is found, 138 and 964 mM, respectively. Differences in interatomic distances might account for the observed differences in solubility, however such investigations are out of scope in present study. For some salts there is an indication that the higher the number of strong hydrogen bonds the lower the solubility of the salt. This is in particular observed for the derivatives of benzylamine, where the two salts of *p*-hydroxybenzoic acid with *N*-methylbenzylamine and *N*,*N*-dimethylbenzylamine show increasing solubility as the number of ionic hydrogen bonds decreases (benzylamine 0.138 M, *N*-methylbenzylamine 1.05 M, *N*,*N*-dimethylbenzylamine 4.5 M). However, the solubility of the salt of benzylamine and *p*-hydroxybenzoic acid is lower than expected from the number of hydrogen bonds, and for some other salts of benzylamine the solubilities are also observed to be lower than expected from the number of hydrogen bonds (*p*-nitrobenzoic (77.6 mM) and *p*-methylbenzoic acid (145 mM) with only the three ionic hydrogen bonds). Thus, the number of ionic hydrogen bonds may partly explain the observed differences in solubility but these have to be considered in conjunction with other types of hydrogen bonds, intermolecular interactions and molecular properties.

3.2.3. Crystal packing

The hydrogen bond patterns observed in the crystal packings are either found in columns (1D) or in layers (2D) (Fig. 1) (Molecular Simulations Inc.). As mentioned above the crystal packings of the salts of benzylamine are not identical but apparently pairs of salts have the same overall crystal packing, although the details are different.

The first pair of salts with nearly the same overall crystal packings is the salts with *p*-amino- and the *p*-hydroxybenzoate (Fig. 1a and b). The solubilities of these two salts differ by a factor 2.

Columns of hydrogen bonds are observed. The aromatic rings are located in between the columns. Stacks of four benzene rings are perpendicular to one another with the closest contact (C–H · · · C 2.9 Å). The second pair is the salt with *p*-hydroxymethyl- and *p*-carbamoylbenzoate (Fig. 1c and d). The solubilities of these two salts differ by a factor 8. The packing is observed as chains of benzoate ions connected by hydrogen bonds from the *p*-substituent in one ion to the carboxylate moiety in the next ion along the *b*-axis. The benzylammonium ions are located in between these chains, and the ammonium group donates hydrogen bonds to the carboxylate groups. The last pair is the salts with *p*-methylbenzoate and the unsubstituted benzoate (Fig. 1e and f). The solubilities of these two salts differ by a factor 6. The hydrogen bonds are located in columns along the *b*-axis. Surrounding these columns are benzene rings in different orientations; perpendicular interactions are observed (C–H · · · C 3.0 Å). The last benzylamine salt is with *p*-nitrobenzoic acid (Fig. 1g). The crystal packing is observed in layers (*ab*-plane). One layer include all the charged moieties and thereby all the hydrogen bonds. Between these layers a double layer

Table 6
Hydrogen bonds in X-ray structure determinations of selected salts of benzylamine

D–H···A	D–H	H···A	D···A	<DHA	Symmetry
Benzylammonium *p*-aminobenzoate					
Molecule A					
N1–HN1···O2B	0.93(2)	1.88(2)	2.764(2)	157(2)	$x, y + 1, z$
N1–HN2···O2B	0.95(2)	1.81(2)	2.744(2)	166(2)	$-x, -y + 2, -z$
N1–HN2···O1B	0.95(2)	2.57(2)	3.309(2)	135(2)	$-x, -y + 2, -z$
N1–HN3···O1B	0.96(2)	1.79(2)	2.738(2)	167(2)	
N2–H2···O1B	0.89(2)	2.08(2)	2.910(2)	154(2)	$x, y - 1, z$
N2–H1···O2B	0.96(2)	2.02(2)	2.974(2)	178(2)	
Molecule B					
N1–HN1···O2A	0.95(2)	1.79(2)	2.718(2)	165(2)	$x, y - 1, z$
N1–HN2···O1A	0.94(2)	1.85(2)	2.765(2)	163(2)	$-x + 1, y - 1/2, -z + 1/2$
N1–HN2···O2A	0.94(2)	2.53(2)	3.271(2)	136(2)	$-x + 1, y - 1/2, -z + 1/2$
N1–HN3···O1A	0.97(2)	1.87(2)	2.833(2)	172(2)	
N2–H1···O1A	0.91(2)	2.13(2)	3.007(2)	159(2)	$x, -y + 1/2, z - 1/2$
N2–H2···O2A	0.92(2)	1.98(2)	2.904(2)	179(2)	$x, -y + 3/2, z - 1/2$
Benzylammonium *p*-hydroxybenzoate					
Molecule A					
N1–H1···O4A	0.90(1)	2.03(1)	2.933(1)	173(1)	$1.5 - x, y + 0.5, -0.5 - z$
N1–H2···O2A	0.95(1)	1.84(1)	2.770(1)	166(1)	$2 - x, -y, -z$
N1–H2···O1A	0.95(1)	2.59(1)	3.180(1)	120(1)	$2 - x, -y, -z$
N1–H3···O1A	0.95(1)	1.85(1)	2.774(1)	164(1)	x, y, z
O4–H4···O1B	0.93(2)	1.65(2)	2.585(1)	174(2)	$x - 0.5, -y - 0.5, z - 0.5$
Molecule B					
N1–H1···O2B	0.95(2)	1.81(2)	2.740(1)	167(1)	$x - 1, y, z$
N1–H2···O2B	0.96(2)	1.78(2)	2.749(1)	177(1)	$2 - x, -y, -z$
N1–H2···O1B	0.96(2)	2.43(1)	3.055(1)	122(1)	$2 - x, -y, -z$
N1–H3···O2A	0.89(2)	1.99(2)	2.843(1)	161(1)	x, y, z
O4–H4···O2A	0.88(2)	1.78(2)	2.648(1)	170(2)	$x + 0.5, -y - 0.5, z - 0.5$
Benzylammonium *p*-nitrobenzoate					
Molecule A					
N1–H1···O2B	0.87(3)	1.98(3)	2.814(3)	159(3)	$-x, -y + 1, -z + 2$
N1–H1···O1B	0.87(3)	2.47(3)	3.207(3)	142(2)	$-x, -y + 1, -z + 2$
N1–H2···O2A	0.97(3)	1.87(3)	2.835(3)	169(2)	$-x + 1, -y + 1, -z + 2$
N1–H3···O2B	0.96(3)	1.91(3)	2.789(3)	152(2)	
Molecule B					
N1–H1···O1A	0.97(3)	2.40(3)	3.145(3)	133(2)	$-x + 1, -y + 1, -z + 2$
N1–H1···O2A	0.97(3)	1.93(3)	2.866(3)	160(2)	$-x + 1, -y + 1, -z + 2$
N1–H2···O1A	0.92(3)	1.87(3)	2.785(3)	171(3)	$x, y - 1, z$
N1–H3···O1B	0.90(3)	1.87(3)	2.774(3)	176(3)	$-x, -y, -z + 2$
Benzylammonium benzoate					
Molecule A					
N1–H1···O1A	0.96(3)	1.84(3)	2.780(2)	166(2)	x, y, z
N1–H2···O2A	0.87(3)	1.84(3)	2.702(2)	172(2)	$x, y + 1, z$
N1–H3···O1A	0.90(3)	1.91(3)	2.765(2)	157(2)	$0.5 - x, 0.5 + y, 1 - z$
Molecule B					
N1–H1···O1B	0.92(3)	1.95(3)	2.798(2)	154(2)	$1 - x, 1 - y, -z$
N1–H2···O2B	0.99(3)	1.69(3)	2.678(3)	177(2)	$x - 0.5, 0.5 - y, z$
N1–H3···O1B	0.90(3)	1.88(3)	2.765(2)	167(2)	$x - 0.5, 1.5 - y, z$

Table 6 (*Continued*)

D–H···A	D–H	H···A	D···A	<DHA	Symmetry
Benzylammonium *p*-methylbenzoate					
N1–H1···O1	0.93(2)	1.87(2)	2.758(1)	162(1)	$2-x, y-0.5, 1.5-z$
N1–H2···O1	0.93(2)	1.86(2)	2.767(1)	169(1)	x, y, z
N1–H3···O2	0.94(2)	1.76(2)	2.698(1)	178(2)	$x, y-1, z$
Benzylammonium *p*-carbamoylbenzoate					
N1–H1···O2	0.93(2)	1.83(2)	2.750(1)	172(1)	x, y, z
N1–H2···O1	0.93(2)	1.83(2)	2.760(1)	174(1)	$x-1, y, z$
N1–H3···O1	0.91(2)	2.24(2)	2.988(1)	138(1)	$-x, 2-y, -z$
N1–H3···O3	0.91(2)	2.34(2)	2.917(1)	122(1)	$x, y+1, z$
N2–H4···O2	0.86(2)	2.06(2)	2.920(1)	173(1)	$x, y-1, z$
N2–H5···O1	0.88(2)	2.14(2)	2.960(1)	154(1)	$1-x, 1-y, -z$
Benzylammonium *p*-hydroxymethylbenzoate					
N1–H1···O2	0.91(3)	1.91(3)	2.810(2)	173(2)	x, y, z
N1–H2···O1	0.92(3)	1.89(3)	2.764(2)	158(2)	$x-1, y, z$
N1–H3···O2	0.91(3)	1.94(3)	2.843(2)	168(2)	$1-x, -y, 1-z$
O3–HO3···O1	0.88(3)	1.83(3)	2.711(2)	176(3)	$x, y+1, z$
N-Methylbenzylammonium *p*-hydroxybenzoate					
N1–H1···O2	0.89(3)	1.85(3)	2.709(3)	162(2)	$0.5+x, -y+1.5, z$
N1–H1···O1	0.89(3)	2.63(3)	3.297(3)	133(2)	$0.5+x, -y+1.5, z$
N1–H2···O1	0.92(3)	1.83(3)	2.720(3)	164(2)	x, y, z
O3–HO3···O2	0.86(3)	1.75(3)	2.605(2)	174(3)	$x+0.5, 0.5-y, z$
N,*N*-Dimethylbenzylammonium *p*-hydroxybenzoate					
N1–H1···O1	0.96(2)	1.69(2)	2.642(1)	174(2)	$x, y-1, z$
N1–H1···O2	0.96(2)	2.49(2)	3.131(1)	124(1)	$x, y-1, z$
O3–HO3···O2	0.84(2)	1.74(2)	2.581(1)	173(2)	$1.5-x, y-0.5, z-0.5$

of aromatic rings is found. The nitro moiety is not involved in hydrogen bonds but close interactions can be found to hydrogen atoms of the aromatic rings. The last two salts have been included in the X-ray study in order to investigate the crystal packing behaviour for benzylamine (Fig. 1b), *N*-methyl (Fig. 1h) and *N*,*N*-dimethylbenzylamine (Fig. 1i) in salts formed with *p*-hydroxybenzoic acid. The solubility of the salts increases with increasing substitution of the nitrogen atom. The overall crystal packing of the salt of benzylamine (Fig. 1b) shows a zig-zag chain of benzoate ions connected by hydrogen bonds. Hydrogen bonds are located in columns with the ammonium ions interconnecting the chains. In the salt of *N*,*N*-dimethylbenzylamine (Fig 1i) the zig-zag chains of benzoate ions are observed, but due to the two methyl groups substituted on the ammonium nitrogen atom no hydrogen bond could be formed to interconnect the chains. One ionic hydrogen bond is found from the ammonium to the carboxylate moieties.

The observed crystal packing for *N*-methylbenzylamine (Fig. 1h) is rather different. The benzoate ions are connected in chains by hydrogen bonds from the *p*-hydroxy group to the carboxylate moiety and the two hydrogen atoms of the ammonium ion form hydrogen bonds to the carboxylate group. The chains of benzoate ions are packed in hydrophilic layers. Aromatic rings of the ammonium ion are observed in a hydrophobic layer. Disorder is observed for these aromatic rings and three different orientations have been observed.

In conclusion, all 22 salts prepared from (**I**) were crystalline whereas only five salts of (**II**) and two salts of (**III**) could be prepared in a crystalline state from the same 22 *p*-substituted benzoic acid counterions. Hydrogen bond donor and acceptor potentials seem to augment the precipitation of crystalline salts. The solubility of the salts of (**I**), (**II**) and (**III**) increases by orders of magnitude in mentioned order. X-ray crystallography studies indicate that lack of the ability

to create ionic hydrogen bonds in the crystal packing may be the reasons for the apparent solubility order. In the previous study (Parshad et al., 2002) it was suggested that the variation in solubility of the salts of (**I**) mainly were caused by variation in solid state properties. However, it is difficult to account for the apparent solubility of the salts of (**I**) in terms of the number of hydrogen bonds alone, possibly because the energies of these are different. Since the crystal packing of the salts differs substantially, it is difficult to relate the intermolecular contacts and molecular properties.

4. Conclusion

The aqueous solubility ranking of the prepared *p*-substituted benzoic acid salts of (**I**), (**II**) and (**III**) was found to be salt of (**III**) > salt of (**II**) > salt of (**I**). Crystallographic and thermal analysis indicates that the increased solubility is caused by a reduced number of ionic hydrogen bonds leading to decreased crystal lattice energy. The apparent solubility of salts of (**I**) is difficult to account for in terms of the crystal packing characteristics and hydrogen bond patterns since these differ substantially. Further studies involving energy considerations of hydrogen bonds and non-specific interactions are required.

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