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Hydrogen-Bonding in the Anhydrous Morpholinium Salts of the Three Isomeric Monoaminobenzoic Acids

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Abstract The structures of the anhydrous morpholinium salts of the isomeric 2-aminobenzoic acid (anthranilic acid) (1), 3-aminobenzoic acid (2) and 4-aminobenzoic acid (3), with formula $C_4H_{10}NO^+$ $C_7H_8NO_2^-$, have been determined. Crystals of 1 are monoclinic, space group $P2_1/c$, with unit cell dimensions a = 11.0696(9), b = 7.8775(6),c = 13.0180(11) Å, $\beta = 95.804(8)^{\circ}$ and Z = 4. Compound 2 is orthorhombic, space group $Pna2_1$, with unit cell dimensions a = 9.3899(4), b = 16.6789(7), c = 7.4463(3)Å and Z = 4 and compound **3** is monoclinic, space group *Cc*, with unit cell dimensions a = 5.9233(6), b = 18.048(2), c = 10.5478(10) Å, $\beta = 90.376(10)^{\circ}$ and Z = 4. In all crystals, both morpholinium N-H atoms are involved in primary inter-species hydrogen-bonding interactions with carboxyl O-atom acceptors of the anions. Secondary N-H...O hydrogen bonds between the amine groups and carboxyl (1 and 3) or both carboxyl and morpholine O-atom acceptors in 2, including in 2 a three-centre asymmetric N-H...O,O' chelate $[R_1^2(4)]$ motif, give two-dimensional layers (1 and 2) or a three-dimensional network structure (3). In 1, the interactions include a centrosymmetric cyclic $R_4^4(12)$ motif and in 2, a cyclic $R_3^2(11)$ motif but no $\pi - \pi$ aromatic ring associations are present in any of the structures.

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Graphical Abstract The structures of the anhydrous morpholinium salts of the three isomeric monoaminobenzoic acids are reported, together with their hydrogenbonding patterns.



Keywords Morpholine · Aminobenzoic acids · Hydrogenbonding

Introduction

Morpholine (tetrahydro-2*H*-1,4-oxazine) is a moderately strong base (pKa = 8.7) [1] and has value particularly as a counter cation in metal complex stabilization. The current Cambridge Structural Database (CSD) [2], contains 209 entries for the morpholinium cation, of which the majority are involved in that capacity [3]. Occasional examples exist in which the cation acts a monodentate ligand coordinating through mostly N [4] and rarely O [5] in copper(II) halide complexes.

With carboxylic acids, salts are formed but there only ca. 23 examples in the CSD, possibly because of the difficulty in producing crystalline products suitable for X-ray

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analysis. However, among those are salts which have been used as models in studies of active pharmaceutical ingredients (API's), e.g. the acetate [6], the 4-aminosalicylate [7], the monohydrogen tartrate (a monohydrate) [8], the dihydrogen citrate (also a monohydrate) [9] and the salicylate [10]. Salt-adducts are rare, an example being morpholinium 4-methoxybenzoate- 4-methoxybenzoic acid, (a 1:1:1 monohydrate) [11].

However, commonly, anhydrous organic morpholine salts are formed. Of interest to us are the packing modes of the anhydrous morpholinium salts of aromatic acids in which hydrogen bonding together with possible π – π bonding interactions may possibly produce interesting supramolecular structures. The known crystal structures of the salts of the substituted benzoic acid analogues are with 4-nitrobenzoic acid [12]; 3,5-dinitrobenzoic acid [10]; 5-nitrosalicylic acid [13]; 4-aminosalicylic acid [7], 3,5dinitrosalicylic acid [10] and 4-nitroanthranilic acid [10].

The structures of a series of isomeric chloro-nitrobenzoates (2,4-, 2,5-, 4,2-, 4,3- and 5,2-) are also known [14– 16] while the cinnamate [17] and the phenoxyacetate and three ring-substituted analogs (4-fluoro, 2,4-dichloro and 3,5-dichloro-) have also been reported [18]. In these examples in the absence of associative ring substituent groups, cation–anion N–H···O hydrogen-bonding interactions commonly generate either one-dimensional ribbons or discrete cyclic hydrogen-bonded heterotetrameric structures, featuring primarily centrosymmetric $R_4^4(12)$ ring motifs [19].

To investigate the effect of an associative ring substituent in the ring system of benzoic acid on the packing mode of morpholiniun salts, I therefore carried out the preparation of the 1:1 proton-transfer compounds with the three isomeric monoamino benzoic acids. The structures of the these anhydrous salts, with formula $C_4H_{10}NO^+$ $C_7H_8NO_2^-$, with 2-aminobenzoic acid (anthranilic acid) (1), 3-aminobenzoic acid (2) and 4-aminobenzoic acid (3) have been determined and their packing modes are reported herein (Scheme 1).

Experimental Section

Preparation

All compounds were prepared from the reaction of the appropriate acid:

2-aminobenzoic acid (anthranilic acid) (for 1), 3-aminobenzoic acid (for 2) and 4-aminobenzoic acid (for 3), by grinding together the acid with a slight excess of morpholine, added dropwise. After warming slightly for a period of several days to remove the morpholine excess,



Scheme 1 The morpholinium salts 1, 2 and 3

the solids were dissolved in 10 mL of ethanol, then allowed to undergo room temperature evaporation, giving in all cases, thin colourless crystal plates from which specimens were cleaved for the X-ray analyses.

Crystallography

X-ray diffraction data for 1-3 were acquired at 200(1) K on an Oxford Diffraction Gemini Ultra CCD-detector diffractometer employing graphite crystal monochromatized Mo K α radiation ($\lambda = 0.71073$ Å). Data collection, reduction and absorption correction (multi-scan) were completed using CrysAlis PRO [20]. The structures were solved using direct methods (SIR92 [21]) and refined with SHELXL97 [22] operating within WinGX [23]. Nitrogen bound hydrogen atoms on both cations and anions were located by difference methods but their positional parameters were restrained with d(C-H) = 0.90(2) or 0.92(2) Å, with displacement parameters riding $[U_{iso}(H) = 1.2U_{eq}]$ (N)]. Carbon-bound H atoms in all compounds were included in the refinements at calculated positions and treated as riding with C-H = 0.95–0.99 Å and U_{iso} (H) = $1.2U_{eq}(C)$. With the structure of 3, the noncentrosymmetric space group Cc rather than C2/c was confirmed with the successful structure solution and refinement in Cc, added to the improbable symmetry requirements imposed by C2/c with Z = 4. Although of no relevance with the achiral molecules in 2 and 3, the Flack structure parameters [24] being 0.4(13) for 1456 Friedel pairs (for 3) and 0.3(3) for 1511 Friedel pairs (for 3).

General crystallographic details for all compounds are provided in Table 1. The atom numbering schemes employed for all cation–anion pairs in the asymmetric units of **1–3** are shown in Figs. 1, 2, and 3 [25].

Results and Discussion

The asymmetric units in salts **1–3** comprise a morpholinium cation (B) linked to a 2-aminobenzoate anion (A) in **1** (Fig. 1), a 3-aminobenzoate anion (A) in **2** (Fig. 2) and a 4aminobenzoate anion (A) in **3** (Fig. 3), through an intermolecular morpholinium N1B–H…O11A hydrogen-bonding interaction. Hydrogen-bonding extension in **1** and **3** is through a single N1B–H…O12Aⁱ link (Tables 2, 4), whereas in **2**, the extension involves an asymmetric cyclic three-centre N–H…O,O'(carboxyl) interaction [N–H…O, 2.678(2), 3.259(3) Å (graph set $R_1^2(4)$ [19]). With 1, the N1B-H...O11Aⁱ interaction generates a centrosymmetric cyclic heterotetramer with an $R_4^4(12)$ motif, similar to those found in the morpholinium salts with 3,5-dinitrobenzoate [10], 4-aminosalicylate [7], four of the five isomeric chloronitrobenzoates [15, 16] and the unusual 4-morpholine carboxylate salt [26, 27].

In all three anions of the present salts, the carboxyl groups are rotated to a similar degree out of the benzene planes [comparative C2A–C1A–C11A–O11A torsion angles are $168.36(15)^{\circ}$ (1); $170.50(19)^{\circ}$ (2); $-167.8(3)^{\circ}$ (3)].

In 1, one H atom of the *o*-amino group of the anion is involved as expected in a short intramolecular N2A–H···O12A(carboxyl) hydrogen bond while the second

Table 1 Crystal data for compounds 1–3	Compound	1	2	3
	CCDC reference	1450196	1450197	1450198
	Molecular formula	$C_{11}H_{16}N_2O_3$	$C_{11}H_{16}N_2O_3$	$C_{11}H_{16}N_2O_3$
	$M_{ m r}$	224.26	224.26	224.26
	Temperature (K)	200	200	200
	Crystal system	Monoclinic	Orthorhombic	Monoclinic
	Space group	<i>P</i> 2 ₁ / <i>c</i>	$Pna2_1$	Cc
	a (Å)	11.0696(9)	9.3899(4)	5.9233(6)
	b (Å)	7.8775(6)	16.6789(7)	18.048(2)
	<i>c</i> (Å)	13.0180(11)	7.4463(3)	10.5478(10)
	α (°)	90	90	90
	β (°)	95.804(8)	90	90.376(10)
	λ (°)	90	90	90
	V (Å ³)	1129.36(16)	1166.19(8)	1127.6(2)
	Ζ	4	4	4
	$D_{\rm c} ~({\rm g}~{\rm cm}^{-3})$	1.319	1.277	1.321
	μ (mm ⁻¹)	0.097	0.094	0.097
	F (000)	480	480	480
	Reflections total, θ_{max} (°)	4383, 26.0	5365, 26.0	2512, 26.0
	Crystal size (mm)	$0.26 \times 0.20 \times 0.04$	$0.36 \times 0.32 \times 0.10$	$0.40 \times 0.25 \times 0.10$
	Collection range:			
	h	-13 to 11	-7 to 11	-7 to 7
	k	-9 to 9	-22 to 21	-20 to 34
	l	-15 to 16	-10 to 5	-14 to 13
	Reflections (independent)	2218	2005	1808
	Reflections $[F^2 > 2 \sigma(F^2)]$	1661	1764	1547
	R _{int}	0.0303	0.0289	0.0176
	$R1^{\rm a} \left[F^2 > 2\sigma(F^2)\right]$	0.0472	0.0379	0.0636
	wR2 ^a (all data)	0.1079	0.0802	0.1606
	S^{a}	1.06	1.06	1.04
	n_p	157	157	157
	Residuals (max/min) (eÅ ⁻³)	0.167/-0.184	0.159/-0.196	0.482/-0.331
	Transmission factors (max/min)	0.980/0.941	0.990/0.965	0.980/0.840

^a $R1 = (\Sigma |F_{o}| - |F_{c}|)/\Sigma |F_{o}|); wR2 = \{\Sigma [w(F_{o}^{2} - F_{c}^{2})^{2}]/\Sigma [w(F_{o}^{2})^{2}]\}^{\frac{1}{2}}; S = \{\Sigma [w(F_{o}^{2} - F_{c}^{2})^{2}]/(n-p)\}^{\frac{1}{2}}$

Fig. 1 The molecular conformation and atomnumbering scheme for the morpholinium-OABA cationanion pair in 1. The hydrogen bonds are indicated as *dashed lines* while non-H atoms are shown as 40 % probability displacement ellipsoids

Fig. 2 The molecular conformation and atomnumbering scheme for the morpholinium-MABA cationanion pair in 2. The hydrogen bonds are indicated as *dashed lines* while non-H atoms are shown as 40 % probability displacement ellipsoids







Fig. 3 The molecular conformation and atomnumbering scheme for the morpholinium-PABA cationanion pair in 3. The hydrogen bonds are indicated as *dashed lines* while non-H atoms are shown as 40 % probability displacement ellipsoids

Table 2 Hydrogen-bondinginteractions $(Å/^{\circ})$ for 1

D-H	Н…А	D…A	∠DH…A
0.940(15)	1.851(15)	2.7789(19)	168.8(16)
0.956(16)	1.709(16)	2.661(2)	173.5(14)
0.898(17)	1.973(17)	2.977(2)	134.2(14)
0.866(16)	2.170(16)	3.223(2)	164.0(17)
0.95	2.47	3.402(2)	168
	D-H 0.940(15) 0.956(16) 0.898(17) 0.866(16) 0.95	D-H H…A 0.940(15) 1.851(15) 0.956(16) 1.709(16) 0.898(17) 1.973(17) 0.866(16) 2.170(16) 0.95 2.47	D-H H…A D…A 0.940(15) 1.851(15) 2.7789(19) 0.956(16) 1.709(16) 2.661(2) 0.898(17) 1.973(17) 2.977(2) 0.866(16) 2.170(16) 3.223(2) 0.95 2.47 3.402(2)

Symmetry codes (i) -x + 1, -y, -z; (ii) x, $-y + \frac{1}{2}$; (iii) x - 1, $-y + \frac{1}{2}$, $z + \frac{1}{2}$

Fig. 4 A perspective view of the three-dimensional hydrogen-bonded structure in 1. Non-interactive hydrogen atoms are omitted and hydrogen bonds are shown as *dashed lines*. For symmetry codes, see Table 2





Table 3 Hydrogen-bonding interactions (Å/°) for 2

, ,	U			
D–H…A	D–H	Н…А	D…A	∠ DH…A
N1B–H11B…O11A ⁱ	0.922(19)	1.79(2)	2.678(2)	161.7(18)
N1B-H11B…O12A ⁱ	0.922(19)	2.509(18)	3.259(2)	138.8(16)
N1B-H12B…O12A	0.941(19)	1.715(19)	2.649(2)	171.2(17)
N3A–H31A…O4B ⁱⁱ	0.88(2)	2.28(2)	3.136(3)	165(2)
N3A-H32A···O12A ⁱ	0.89(2)	2.18(2)	3.050(3)	167(3)
C5B-H51B····O11A ⁱⁱⁱ	0.99	2.38	3.365(2)	175
Commentary and an (i) as	1/	1/ (::)	1/	1/ - 1.

Symmetry codes (i) $x - \frac{1}{2}, -y + \frac{1}{2}, z$; (ii) $x - \frac{1}{2}, -y + \frac{1}{2}, z - (iii) -x + \frac{1}{2}, y + \frac{1}{2}, z + \frac{1}{2}$

provides an inter-heterotetramer linkage to $O11A^{ii}$, extending the structure along the *c* axial direction. This gives a two-dimensional layered structure lying parallel to (010) (Fig. 4). A weak C4A–H…O4Bⁱⁱⁱ interaction to a morpholinium O-atom acceptor could be considered to further extend the structure into three dimensions.

For symmetry codes, see Table 2.

With **2**, one of the H atoms of the *meta*-related amino group of the anion forms an N3A–H…O12Aⁱ hydrogen bond, completing an $R_3^2(11)$ motif which involves one cation and two anions (Fig. 5). The second amino H atom extends the structure along *a* through a N3A–H…O4Bⁱⁱ hydrogen bond with the morpholinium O-atom acceptor, giving an overall two-dimensional sheet structure lying parallel to (010). For symmetry codes, see Table 3.

With **3**, only one of the H atoms of the *para*-related amino group of the anion gives an inter-anion hydrogen-

bonding association (N4A–H…O11Aⁱⁱ), generating an overall three-dimensional network structure (Fig. 6). For symmetry code, see Table 4.

The three structures reported here represent examples which demonstrate the importance of associative compared to non-associative group substituents on the supramolecular hydrogen-bonded structures generated in the morpholinium salts of the benzoic acid analogs.

Supplementary Material

CCDC entries 1450196, 1450197 and 1450198 contain the supplementary crystallographic data for compounds 1–3, respectively, from this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

Table 4 Hydrogen-bonding interactions (\AA°) for 3

D–H…A	D–H	Н…А	D…A	∠ DH…A
N1B–H11B…O12A	0.90(5)	1.88(5)	2.764(4)	167(7)
N1B-H12B…O11A ⁱ	0.88(6)	1.76(6)	2.629(4)	167(8)
N4A–H41A…O11A ⁱⁱ	0.89(5)	2.00(5)	2.882(5)	174(8)

Symmetry codes (i) x, -y, $z + \frac{1}{2}$; (ii) $x + \frac{1}{2}$, $-y + \frac{1}{2}$, $z + \frac{1}{2}$

Fig. 6 The three-dimensional hydrogen-bonded network structure of **3**, viewed along the *a* axial direction. Non-interactive hydrogen atoms are omitted. For symmetry codes, see Table 4



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