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ARTICLE TYPE

Biguanide and squaric acid as pH-dependent building blocks in crystal engineering

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In solutions containing biguanides and squaric acid, the pH value allows to control the outcome of crystallization. From *N,N*-dimethylbiguanide, *N*-phenylbiguanide and *N*-*o*-tolylbiguanide 10 different salts have been obtained as a function of proton activity. The constituents in these ionic solids reflect the species present in solution: hydrogensquarate, still a strong acid, only occurs in crystals precipitated from acidic medium, and biguanidinium monocations prevail in precipitates from basic solutions. Within these limitations, polymorphs and hydrates of different stoichiometry have been encountered. The pH of the crystallization medium also affects the nature of close contacts. The shortest hydrogen bonds in the crystalline solids do not occur between ions of opposite charge; rather, pH matching leads to close O–H···O contacts between squarate and hydrogensquarate anions which can only coexist at pH < 4.

Introduction

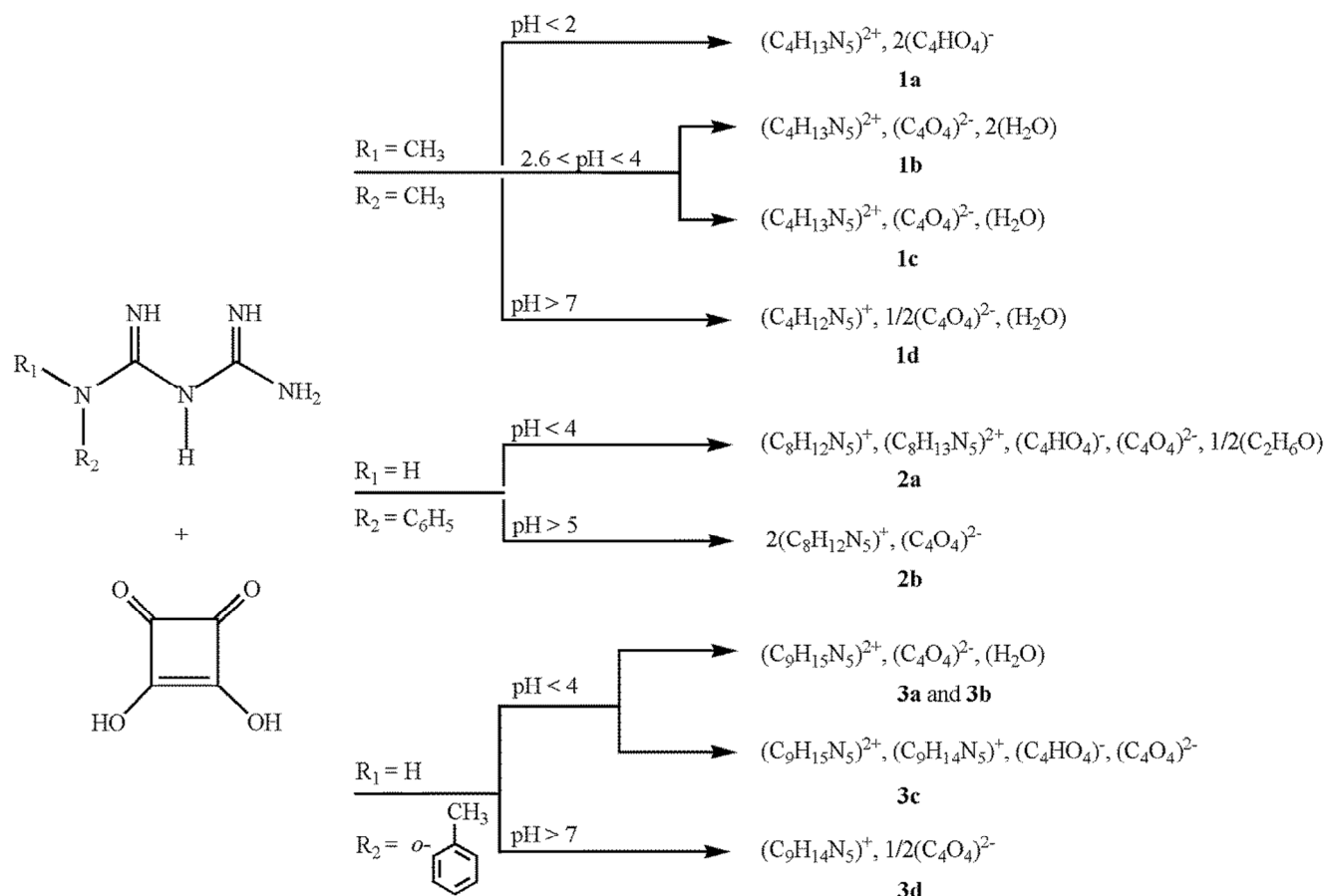
Hydrogen bonds represent a particularly popular kind of intermolecular interaction. Their relevance for structural chemistry^{1, 2} and biology³ stems from their wide occurrence among natural and synthetic compounds and from the broad range of energies they may cover.⁴ Hydrogen bonds are relevant with respect to reactivity, both in the fast developing field of organocatalysis⁵⁻⁷ and for biocatalysis by enzymes.⁸ Finally, hydrogen bonds offer an additional dimension to crystal engineering: At least those H atoms engaged in classical hydrogen bonds may be re-arranged as a function of proton activity in the surrounding medium, and intermolecular contacts may thus be tuned by adjusting the pH. In this contribution, we systematically study the effect of pH changes on salt formation from alkyl or aryl biguanide cations and (hydrogen)squarate anions. Squaric acid is a strong organic acid,⁹ and biguanides are stronger bases than ammonia.¹⁰ Quite obviously, their neutral species cannot coexist. Full deprotonation of squaric acid and double protonation of biguanide, however, are associated with

similar pK_a values; changes in the pH of the reaction mixture may therefore bring about different protonation patterns. Scheme 1 compiles the pH-dependent composition of all solids which have been structurally characterized in the context of this study. Matulkova *et al.*¹¹ have prepared biguanidinium salts of dicarboxylic acids with the intention to make novel materials for second harmonic generation available. In 2001, Gilli and co-workers¹² have reviewed the role of squaric acid and its anions as building blocks for hydrogen bonded crystals. Rao *et al.* investigated the crystalline salts formed by squaric acid and a series of amines without adjusting the proton activity of the resulting solutions.¹³ We only shortly mention alternative aspects of our reactands: Dimethylbiguanide ("Metformin") has found interest in medicinal chemistry¹⁴, and squarate C₄O₄²⁻ has been used in crystal engineering as an O donor ligand, in particular with respect to magnetic interactions.¹⁵⁻¹⁸

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Scheme 1 Composition of salts based on biguanidinium cations and (hydrogen)squarate anions as a function of pH.

Results and Discussion

The concentration of the alternative cationic species derived from biguanide and of the anions hydrogensquarate and squarate obviously depends on the proton concentration in the reaction medium. Therefore, the pH of the solution can act as a tunable parameters in crystal engineering: Fully protonated dications and hydrogensquarate as building blocks can only exist in acidic solution, whereas the corresponding monocationic species and squarate dianions prevale in basic medium. As may be anticipated from the pronounced differences in pK_a values between acid and bases,^{19,20} all solids reported here are salts and no cocrystals have been observed. We will first shortly describe the composition and hydrogen bonds in the individual structures and then proceed to a more synoptic section.

Dimethylbiguanidinium hydrochloride and squaric acid dissolve in water. The resulting strongly acidic aqueous solution (pH < 2) affords crystals of **1a**. In this solid, fully protonated dications and hydrogensquarate mono-anions interact in layers in the (1 -1 0) plane. (Fig. 1) Excellent crystals of **1a** may be obtained in

impressive sizes: consequently, this compound has been characterized by high resolution X-ray diffraction and by neutron diffraction. The complete characterization of **1a** and a detailed discussion of its *intra* and *intermolecular* bonds based on an experimental charge density study have been published.²¹ We here briefly highlight the main features for comparison: Within the layers of crystalline **1a** a large range of hydrogen bonds coexist. In addition to unexceptional classical N-H...N and N-H...O bonds and non-classical C-H...O contacts with hydrogen...acceptor distances close to the van der Waals limit, the compound features remarkably short (2.43 Å) O-H...O bonds.

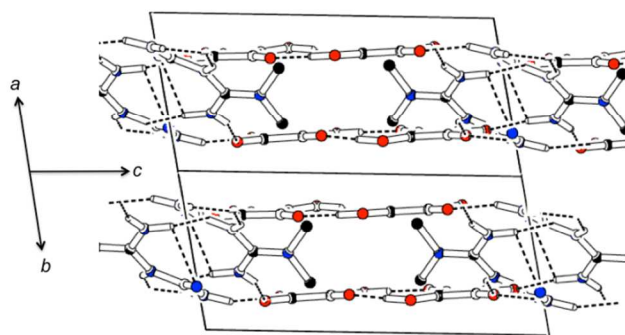


Fig. 1 Hydrogen-bonded layers in the crystal structure of **1a**; H atoms bonded to C omitted.

In contrast to the layer structure above, the remaining derivatives of dimethylbiguanide are 3D networks. In the salts obtained under less acidic conditions, i.e. in the range $2.6 < \text{pH} < 4$, biguanidinium cations are still fully protonated but squarate rather than hydrogensquarate represents the anionic species. Two reaction products **1b** and **1c** are obtained in parallel. **1b** is a dihydrate with the composition $\text{C}_4\text{H}_{13}\text{N}_5^{2+} \cdot \text{C}_4\text{O}_4^{2-} \cdot 2 \text{H}_2\text{O}$; its single crystals are sufficiently stable for diffraction experiments. In contrast to larger crystals, ground material or the microcrystalline bulk reaction product readily release one equivalent of water and convert into a monohydrate. Although this monohydrate has the same composition as **1c** (see below), its powder pattern indicates a different structure. The second reaction product **1c** is a monohydrate. **1b** and **1c** share the same building blocks, namely dimethylbiguanide dications, squarate dianions and solvent water, but the monohydrate **1c** is considerably more stable towards desolvation: its experimental powder pattern shown in Fig. 2 and its elemental analysis (cf Experimental) match the expectation. The dihydrate **1b** and the monohydrate **1c** differ significantly with respect to packing: Tab. 1 shows that O–H...O hydrogen bonds are significantly shorter than N–H...O interactions in the former solid whereas the opposite is observed in the latter. **1b** adopts the higher density and overall space filling, and it features classical N–H...N contacts shorter than 3 Å whereas in **1c** all N–H hydrogen donors are engaged in bonds to oxygen acceptors.

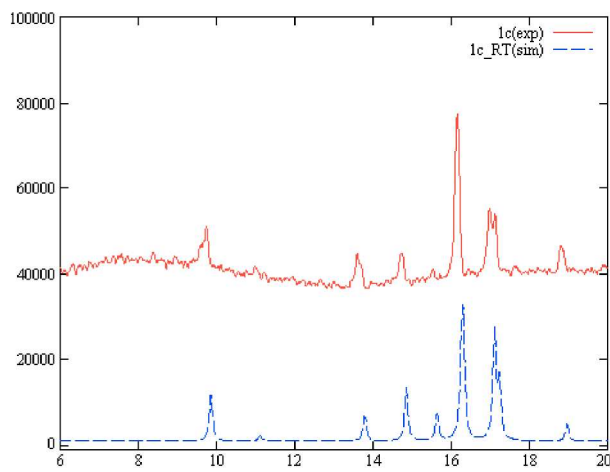


Fig. 2 Experimental and simulated powder patterns for **1c** at 293 K.

Table 1 Selected hydrogen bonds in the dimethylbiguanidinium salts **1a** - **1d**

	D—H...A	D—H [Å]	H...A [Å]	D...A [Å]	D—H...A [°]
1a	O1—H1...O6	1.048(4)	1.421(4)	2.447(3)	164.6(4)
	O5—H151...O1 ⁱ	0.86(3)	1.92(4)	2.664(3)	144(4)
1b	O5—H150...O6 ⁱⁱ	0.83(2)	1.87(2)	2.697(3)	177(4)
	N2—H20...O5	0.91(2)	1.82(2)	2.717(3)	166(2)
	N5—H50...O4	0.90(2)	1.88(3)	2.763(3)	164(2)
	N4—H40...N3	0.87(2)	2.55(3)	2.932(3)	107(2)
	N3—H31...N4	0.894(19)	2.56(3)	2.932(3)	106(2)
1c	O9—H109...O7 ⁱⁱⁱ	0.89(4)	2.05(3)	2.700(2)	129(3)
	O10—H210...O5 ^{iv}	0.901(17)	1.825(17)	2.723(2)	175.2(18)
	N7—H70...O3 ⁱ	0.908(15)	1.738(16)	2.609(2)	159.9(19)
1d	N2—H20...O1 ⁱⁱ	0.949(16)	1.692(16)	2.621(2)	165.3(19)
	O3—H3A...O1	0.857(16)	1.923(18)	2.7455(18)	161(2)
	O3—H3B...N2 ⁱⁱ	0.864(18)	1.997(18)	2.8517(18)	170(2)
	N3—H30...O3 ⁱ	0.894(17)	1.956(18)	2.809(2)	159.1(15)
	N5—H50...O1	0.877(17)	2.010(18)	2.877(2)	169.8(15)

Symmetry operators for **1b**: ⁱ=2-x,1-y,-1/2+z; ⁱⁱ=x,1+y,z;
 Symmetry operators for **1c**: ⁱ=-1+x,-1+y,z; ⁱⁱ=-x,-1/2+y,1-z; ⁱⁱⁱ=1-x,-1/2+y,1-z; ^{iv}=1-x,1/2+y,1-z;
 Symmetry operators for **1d**: ⁱ=x,1+y,z; ⁱⁱ=1-x,1-y,1-z.

A visual comparison is also straightforward: Anions and hydrate water molecules alone form layers in the (0 1 0) plane in **1b** (Fig. 3) but only chains along the crystallographic *b* axis in **1c** (Fig. 4).

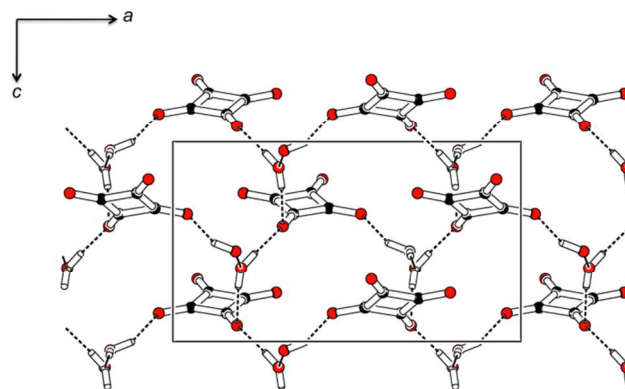


Fig. 3 Anions and hydrate water molecules form hydrogen-bonded layers in the crystal structure of **1b**.

Together with the cations, a three-dimensional hydrogen bond network is formed in both **1b** and **1c**.

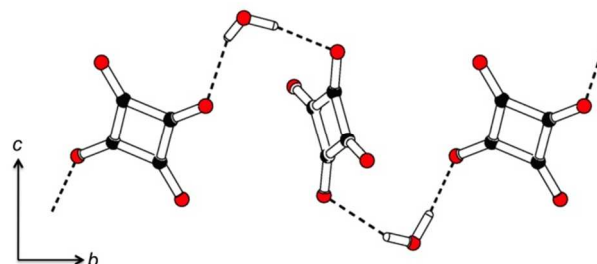


Fig. 4 Anions and hydrate water molecules form hydrogen-bonded chains in the crystal structure of **1c**.

In basic media ($\text{pH} > 7$), dimethylbiguanide exists as a monocation; as expected, the building block originating from squaric acid is fully deprotonated. The resulting compound **1d** is an unstable hydrate: In the crystal, the asymmetric unit contains a $\text{C}_4\text{H}_{12}\text{N}_5^+$ cation and a water molecule in general position and half of a squarate dianion which is located on a crystallographic inversion center. With respect to H bonds, **1d** represents the only structure described in this work which features an $\text{O}-\text{H}\cdots\text{N}$ contact. (Tab. 1) The only $\text{O}-\text{H}\cdots\text{O}$ hydrogen bond in the asymmetric unit occurs between the water molecule and the squarate dianion and is relevant for the dimensionality of the resulting overall structure: When the hydrate water molecules are omitted as in Fig. 5, the remaining H bonds in **1d** give rise to a layer structure.

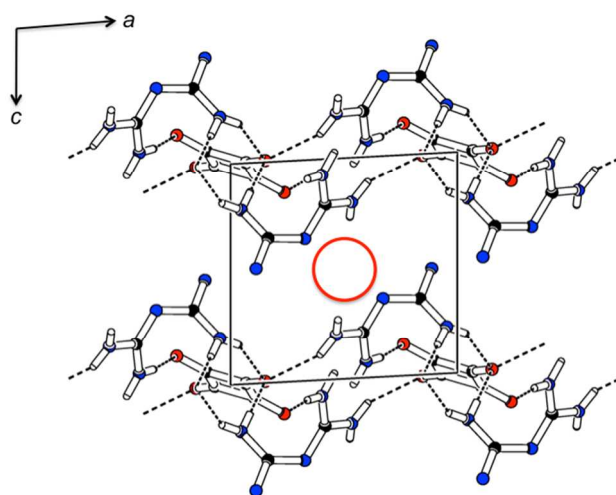


Fig. 5 Layers in the crystal of **1d**; the red circle indicates where two water molecules link consecutive layers.

Powder diffraction shows that solid **1d** readily releases its hydrate water at ambient temperature, resulting in a crystalline powder of unknown structure. In parallel, elemental analyses of bulk samples indicate a degree of hydration inferior to the one confirmed by single crystal X-ray diffraction.

In addition to dimethylbiguanide, we have included the aryl-substituted bases phenyl- and tolylbiguanide in our study. For reasons of solubility, their salts with squaric acid have been obtained in a solvent mixture water:ethanol (1:1). As a function of pH, two different compounds are accessible from phenylbiguanide and squaric acid. The rather complex solid **2a** crystallizes from acidic medium ($\text{pH} \approx 2.9$): its asymmetric unit consists of a mono- and a diprotonated biguanidinium cation, of a hydrogensquarate and a squarate anion and of half a co-crystallized ethanol molecule which is disordered about a crystallographic center of inversion. We here anticipate that **2a** is the only solid in which the cosolvent rather than water is included in the crystal structure. The immediate neighborhood of a monocation next to a dication in the same solid allows to study the structural consequences of protonation. (Fig 6)

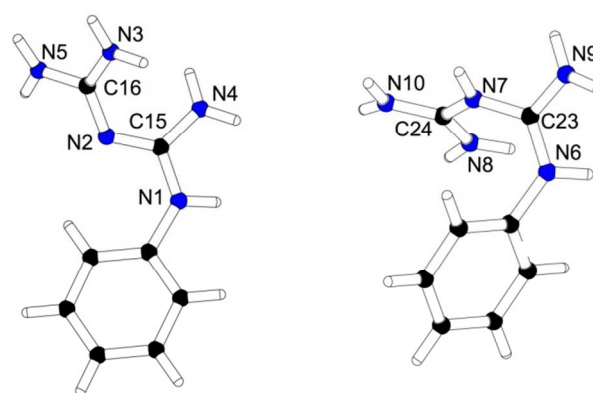


Fig. 6 Different geometries of the mono- (left) and di-cation (right) in **2a**; selected interatomic distances reflecting the protonation patterns: $\text{N2}-\text{C15} = 1.312(3)$, $\text{N2}-\text{C16} = 1.342(3)$, $\text{N7}-\text{C23} = 1.369(3)$, $\text{N7}-\text{C24} = 1.360(3)$ Å.

Due to the additional *N* protonation, *N*-*C* distances involving *N7* are significantly longer than those associated with *N2*. Similarly, the only protonated out of eight *O* atoms in the squarate and hydrogensquarate subtends the longest *O*-*C* bond. This hydroxyl group is engaged in a short classical $\text{O}-\text{H}\cdots\text{O}$ contact, with a donor \cdots acceptor distance of $2.496(3)$ Å. Table 2 summarizes the most important hydrogen bonds in **2a** and **2b**.

In basic solution, phenylbiguanide and squaric acid form salt **2b**, with two $\text{C}_8\text{H}_{12}\text{N}_5^+$ monocations and one $\text{C}_4\text{O}_4^{2-}$ dianion per asymmetric unit. The two symmetrically independent cations adopt different conformations but are very similar with respect to bond distances.

Table 2 Selected hydrogen bonds in the diphenylbiguanidium salts **2a** and **2b**.

	D—H \cdots A	D—H [Å]	H \cdots A [Å]	D \cdots A [Å]	D—H \cdots A [°]
2a	$\text{O1}-\text{H1}\cdots\text{O6}^i$	0.87(2)	1.64(2)	2.496(3)	168(4)
	$\text{N6}-\text{H60}\cdots\text{O6}^{ii}$	0.91(2)	1.80(2)	2.706(3)	172(2)
	$\text{N7}-\text{H70}\cdots\text{O8}$	0.85(3)	1.91(2)	2.706(3)	155(2)
2b	$\text{N6}-\text{H160}\cdots\text{O2}$	0.940(18)	1.854(19)	2.766(2)	163.1(18)
	$\text{N4}-\text{H141}\cdots\text{O4}^i$	0.933(18)	1.879(19)	2.790(2)	164.9(18)

Symmetry operators for **2a**: $^i = 1-x, 1/2+y, 1/2-z$; $^{ii} = x, 3/2-y, 1/2+z$;

Symmetry operator for **2b**: $^i = -x, 1-y, 1-z$.

In both phenylbiguanidinium squarates **2a** and **2b**, the heteroatoms and with them all classical hydrogen bonds arrange in layers separated by largely unpolar sections filled by aryl substituents. Fig. 7 shows this situation for **2b**.

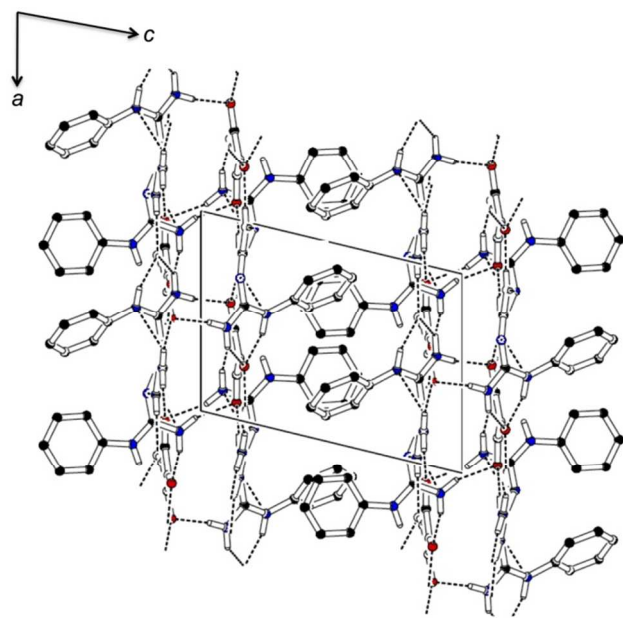


Fig. 7 In **2b**, hydrophilic and hydrophobic layers alternate in direction of the *c* axis.

As mentioned above, the structural characterization of the reaction products between phenylbiguanide and squaric acid in acidic medium was straightforward and afforded reproducibly **2a**, both for single crystals and the bulk. A more challenging situation was encountered for the related tolybiguanide: The concomitant polymorphs **3a** and **3b** were obtained in variable amount. In addition, we isolated crystals of the alternative reaction product **3c** which, however, cannot be reproduced reliably.

3a and **3b** are polymorphs in a strict sense²² with exactly the same degree of hydration and follow the composition $C_9H_{19}N_5^{2+} \cdot C_4O_4^{2-} \cdot H_2O$. **3a** crystallizes in space group $P2_1/c$, with one dication and a water molecule in general position and two dianions on crystallographic inversion centers. **3b** corresponds to a closely related but more complex and more uncommon solution of the packing problem, with three independent dications, three water molecules and two independent dianions in general position and two dianions on crystallographic inversion centers, i.e. a total of 10 independent residues in space group $P-1$. Remarkably, all three symmetrically independent cationic residues in **3b** are very similar with respect to conformation.

Fig. 8 shows that both polymorphic forms **3a** and **3b** are present in a powder pattern of the bulk.

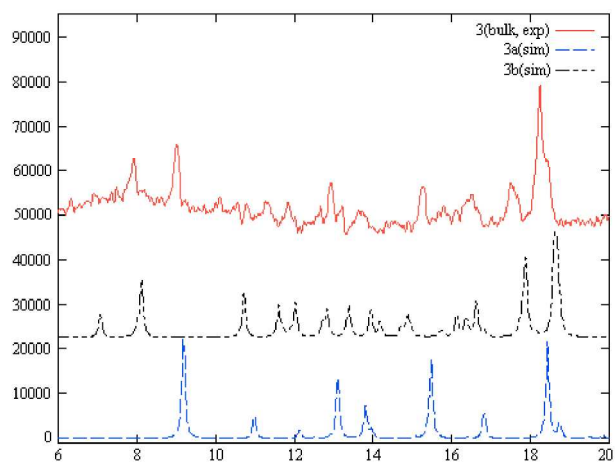


Fig. 8 Concomitant polymorphs **3a** and **3b**: Experimental powder pattern of the bulk and simulated patterns based on the single crystal data.

The polymorphs **3a** and **3b** are closely related with respect to packing. Both compounds are characterized by a similar shortest lattice parameter *a*; the *c* parameter in **3a** almost matches *b* in **3b**, and the subtended angles are also related for both compounds, with β in **3a $\approx (180^\circ - \gamma)$ in **3b**. This 2D relationship between the polymorphs might well be responsible for their concomitant formation and is visualized in the upper part of Fig. 9. The polymorphs differ with respect of the arrangement of the squarate anions (Fig. 9, bottom).**

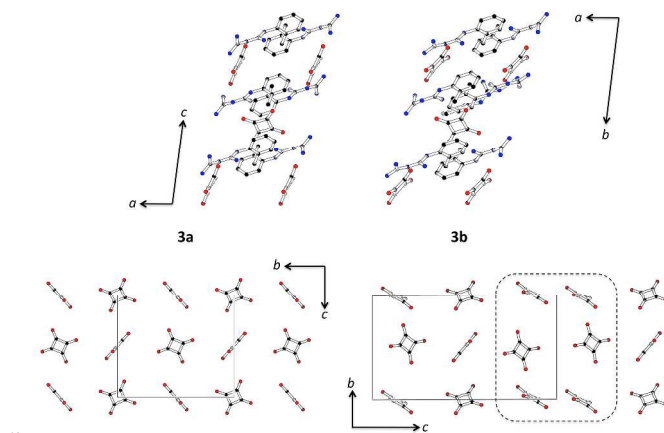


Fig. 9 Projections of the polymorphs **3a** (left) and **3b** (right); the upper part of the figures emphasizes the 2D relationship whereas the lower part highlights the different anion stacking.

The third alternative reaction product of tolybiguanide and squaric acid at $pH < 4$, compound **3c**, is an anhydrate. This compound was obtained in several batches by the same synthetic procedure as the concomitant polymorphs **3a** and **3b**, and the powder pattern showed that the bulk sample was phase pure. Despite our efforts, we have not been able to link the outcome of the crystallization to an obvious external parameter such as temperature, speed of evaporation or slight reactand excess. Single crystal X-ray diffraction revealed that **3c** contains di- and mono-cations as well as di- and mono-anions. The concomitant presence of both anionic species results in a short $O-H \cdots O$ interaction between a hydrogen squarate and a squarate, with a donor \cdots acceptor distance of 2.5120(14) Å. Selected hydrogen

bonds for all tolybiguanidinium salts **3a** - **3d** have been compiled in Table 3.

Table 3 Selected hydrogen bonds in the ditolybiguanidinium salts **3a** - **3d**.

	D—H⋯A	D—H [Å]	H⋯A [Å]	D⋯A [Å]	D—H⋯A [°]
3a	O5—H5A⋯O1	0.838(18)	1.947(18)	2.7842(18)	178(2)
	N2—H120⋯O3	0.906(15)	1.751(15)	2.6410(19)	166.5(16)
3b	O13—H23O⋯O5 ^{vii}	0.88(3)	1.96(3)	2.824(2)	168(3)
	N12—H112⋯O11 ⁱ	0.892(16)	1.780(16)	2.651(3)	165(2)
3c	O1—H1⋯O6 ⁱ	0.906(16)	1.607(16)	2.5120(14)	177(3)
	N7—H70⋯O8	0.892(16)	1.890(17)	2.7432(15)	159.6(18)
3d	N2—H20⋯O1 ⁱ	0.878(15)	1.912(15)	2.7602(15)	162.1(14)

Symmetry operators for **3b**: ⁱ = 1+x, 1+y, z; ^{vii} = 2-x, 1-y, 1-z;

Symmetry operator for **3c**: ⁱ = 1-x, 1/2+y, 1/2-z;

Symmetry operator for **3d**: ⁱ = 1/2-x, 1/2+y, 1/2-z.

In both polymorphs **3a** and **3b**, dianions and dications represent the only charged constituents. Formal re-distribution of a proton leads to the concomitant presence of all potential charged species in **3c**. We may speculate that lattice energy might favour the former and efficient hydrogen bonds the latter alternative.

In contrast to the complex outcome of the reaction between tolybiguanide and squaric acid in acid medium, a single and phase pure product is obtained from basic solutions: Compound **3d** contains one C₉H₁₄N₅⁺ cation and half of a C₄O₄²⁻ dianion in the asymmetric unit, analogous to the composition of the corresponding phenyl derivative **2b**. Fig. 10 shows that polar, hetero-atom containing and apolar layers of the tolyl residues alternate in the packing of **3d**, also similar to the situation in the corresponding phenyl derivative **2b**.

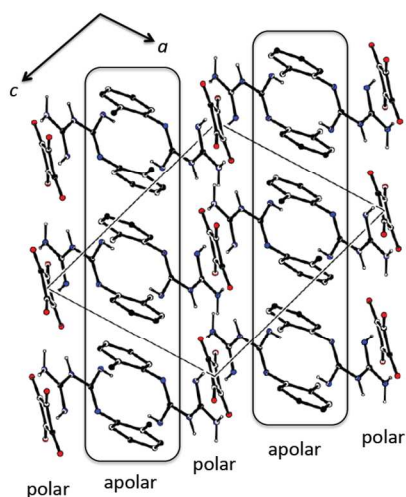


Fig. 10 Packing in **3d**; the sequence of polar and apolar layers has been emphasized.

The comparison between the individual structures **1a** - **3d** allows to identify common trends. In the first place, it is no surprise that hydrogen bonds of different type can be associated with different strength - on average, O—H⋯O bonds are shorter and presumably stronger than N—H⋯O or N—H⋯N contacts. More specifically, the three shortest hydrogen bonds in the solids **1a**, **2a** and **3c** (Tables 1 - 3) all involve hydrogensquarate as the donor; this moiety can only exist in acidic medium. In **1a**, both partaking

residues are hydrogensquarate: the OH groups of one anion interacts with an O atom of a neighbour, thus perfectly matching the pK_a equalization principle.²³ According to this concept, short O—H⋯O interactions may be expected between conjugate acid-base pairs. It is therefore not surprising that the O—H⋯O bonds in **1a** are significantly shorter than the interactions in **2a** and **3c** where the closest contacts occur between hydrogensquarate as donor and squarate dianions as acceptor species. Similar short hydrogen bonds between squarate and hydrogensquarate moieties have been described by Koleva *et al.*^{24, 25}

In agreement with the idea of charge assistance,²⁶ the closest N—H⋯O interactions are observed between biguanidinium dications and squarate dianions and can be as short as 2.609(2) Å in **1c**. A topological result refers to the dimensionality of the hydrogen-bond systems: whenever present, hydrate water molecules are included as neutral species and are engaged with three or four classical hydrogen bonds in the corresponding crystal structures. In all these hydrates, *i.e.* in structures **1b**, **1c**, **1d**, **3a** and **3b**, three-dimensional networks are encountered, whereas the anhydrates **1a**, **2b**, **3c** and **3d** and the ethanol solvate **2a** consistently form two-dimensional hydrogen-bonded layers.

Experimental

Chemical and Reagents

All reagents were purchased from Sigma Aldrich and used as received. Elemental analyses were carried out on a Heraeus CHNO-Rapid apparatus. Powder X-ray diffraction (PXRD) patterns were recorded at the Institute of Inorganic Chemistry, RWTH Aachen University, using a Stoe Imageplate-detector IP-PSD. Flat samples were measured in transmission using Cu-Kα1-radiation at ambient temperature. pH measurements were performed with a glass electrode; the pH of the solutions was adjusted using KOH or NaOH in water.

Synthesis of the *N,N*-dimethylbiguanidinium salts²⁷

N,N-dimethylbiguanidinium-bis(hydrogen squarate), **1a**
497 mg (3 mmol) dimethylbiguanide hydrochloride and 342 mg (3 mmol) squaric acid were mixed in 40 cm³ water and then heated at 60° - 70°C until the solid is dissolved and then stirred for 30 min without heating. The resulting mixture was filtered and the pH of the solution was measured (pH = 1.85). Colourless crystals were obtained from the filtrate by evaporation at room temperature.

C₁₂H₁₅N₅O₈ = (C₄H₁₃N₅)²⁺, 2(C₄HO₄)⁻; MW = 357.28 g/mol; mp 205°C. Anal. Found: H, 3.9; C, 40.8; N, 19.8; Calc. H, 4.2; C, 40.3; N, 19.6.

N,N-dimethylbiguanidinium-squarate dihydrate, **1b** and *N,N*-dimethylbiguanidinium-squarate hydrate, **1c**

The reaction mixture prepared as for **1a** was filtered and the pH of the solution was adjusted to 2.6 < pH < 4. Colourless crystals of both reaction products **1b** and **1c** were obtained. **1b**: C₈H₁₇N₅O₆ = (C₄H₁₃N₅)²⁺, (C₄O₄)²⁻, 2(H₂O); MW = 279.27 g/mol; mp 205°C.

1c: C₈H₁₅N₅O₅ = (C₄H₁₃N₅)²⁺, (C₄O₄)²⁻, (H₂O); MW = 261.25 g/mol; mp 210°C. Anal. Found H, 5.6; C, 36.4; N, 26.4; Calc. H, 5.8; C, 36.8; N, 26.8.

Alternatively, **1c** may be synthesized by reaction of

dimethylbiguanidinium hydrochloride and $\text{Ag}_2\text{C}_4\text{O}_4$.²⁸ (2:1 molar ratio) in 60 mL $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (1:1). Solid AgCl is removed by filtration, the solvent mixture is evaporated, and the product recrystallized from water.

5 Monohydrogen-(*N*, *N*-dimethylbiguanidinium)-hemisquarate hydrate, **1d**

The reaction mixture prepared as for **1a** was filtered and the pH of the solution was adjusted to $\text{pH} > 7$. Colourless crystals were obtained from the filtrate by evaporation at room temperature. $\text{C}_6\text{H}_{14}\text{N}_5\text{O}_3 = (\text{C}_4\text{H}_{12}\text{N}_5)^+, 1/2(\text{C}_4\text{O}_4)^{2-}, (\text{H}_2\text{O})$; MW = 204.22 g/mol; mp 240°C.

Synthesis of the *N*-phenylbiguanidinium salts²⁷

(Monohydrogen-*N*-phenylbiguanidinium)-(*N*-phenylbiguanidinium)-(hydrogensquarate)-squarate ethanol solvate, **2a**
600 mg (3.4 mmol) phenylbiguanide and 392 mg (3.4 mmol) squaric acid were mixed in 40 cm³ water: ethanol (1:1) and then heated at 60° - 70°C until the solid is dissolved and then stirred for 30 min without heating. The resulting mixture was filtered and the pH of the solution was measured ($\text{pH} = 2.9$). Colourless crystals were obtained from the filtrate by evaporation at room temperature.

$\text{C}_{25}\text{H}_{29}\text{N}_{10}\text{O}_{8.5} = (\text{C}_8\text{H}_{12}\text{N}_5)^+, (\text{C}_8\text{H}_{13}\text{N}_5)^{2+}, (\text{C}_4\text{HO}_4)^-, (\text{C}_4\text{O}_4)^{2-}, 1/2(\text{C}_2\text{H}_6\text{O})$; MW = 605.58 g/mol; mp 209°C. Anal. Found H, 4.7; C, 49.5; N, 23.3; Calc. H, 4.8; C, 49.6; N, 23.1.

Bis-(monohydrogen-*N*-phenylbiguanidinium)-squarate, **2b**

The reaction mixture prepared as for **2a** was filtered and the pH of the solution was adjusted to $\text{pH} > 5$. Colourless crystals were obtained from the filtrate by evaporation at room temperature.

$\text{C}_{20}\text{H}_{24}\text{N}_{10}\text{O}_4 = 2(\text{C}_8\text{H}_{12}\text{N}_5)^+, (\text{C}_4\text{O}_4)^{2-}$; MW = 468.49 g/mol; mp 220°C. Anal. Found H, 4.6; C, 50.9; N, 30.0; Calc. H, 5.2; C, 51.3; N, 29.9.

Synthesis of the *ortho*-tolylbiguanidinium salts²⁷

35 *o*-Tolylbiguanidinium-squarate hydrate, **3a** and **3b**

500 mg (2.6 mmol) tolylbiguanide and 300 mg (2.6 mmol) squaric acid were mixed in 40 cm³ water:ethanol (1:1) and then heated at 60° - 70°C until the solid is dissolved and then the heating is stopped and stirred for 30 min. The resulting mixture was filtered and the pH of the solution was measured ($\text{pH} < 4$). Colourless crystals were obtained from the filtrate by evaporation at room temperature. **3a** and **3b** are polymorphs and obtained concomitantly.

$\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_5 = (\text{C}_9\text{H}_{15}\text{N}_5)^{2+}, (\text{C}_4\text{O}_4)^{2-}, (\text{H}_2\text{O})$; MW = 323.32 g/mol; mp 211°C. Anal. Found H, 5.0; C, 48.6; N, 21.2; Calc. H, 5.3; C, 48.3; N, 21.7.

Monohydrogen-*o*-tolylbiguanidinium)-(*o*-tolylbiguanidinium)-(hydrogensquarate)-squarate, **3c**

Under the conditions above, mostly mixtures of the polymorphs **3a** and **3b** form. In a serie of consecutive syntheses, however, the anhydrous compound **3c** has been obtained instead. Despite the fact that in these occasions the product had formed in good yield and as a phase-pure solid, we have not been able to identify a clear reason for this alternative outcome of the crystallization experiments.

$\text{C}_{26}\text{H}_{36}\text{N}_{10}\text{O}_8 = (\text{C}_9\text{H}_{15}\text{N}_5)^{2+}, (\text{C}_9\text{H}_{14}\text{N}_5)^+, (\text{C}_4\text{HO}_4)^-, (\text{C}_4\text{O}_4)^{2-}$; MW

= 610.60 g/mol; mp 192°C. Anal. Found H, 5.0; C, 51.1; N, 23.1; Calc. H, 5.0; C, 51.1; N, 22.9.

60 Monohydrogen-(*o*-tolylbiguanidinium)- hemisquarate, **3d**

The reaction mixture prepared as for **3a/3b** was filtered and the pH of the solution was adjusted to $\text{pH} > 7$. Colourless crystals were obtained from the filtrate by evaporation at room temperature.

$\text{C}_{11}\text{H}_{14}\text{N}_5\text{O}_2 = (\text{C}_9\text{H}_{14}\text{N}_5)^+, 1/2(\text{C}_4\text{O}_4)^{2-}$; MW = 248.27 g/mol; mp 245°C. Anal. Found H, 5.5; C, 53.2; N, 28.1; Calc. H, 5.7; C, 53.2; N, 28.2.

Single Crystal Structure Determinations

70 All solids **1a** - **3d** are colourless; with the exception of the hydrates **1b** and **1d**, their crystals or crystalline powders are stable for at least several days at ambient conditions. Intensity data sets were collected in ω -scan mode on a Bruker D8 goniometer equipped with an APEX CCD detector using Mo *K* α radiation ($\lambda = 0.71073 \text{ \AA}$). An Oxford Cryosystems 700 controller was used to ensure temperature stability during data collection. The intensities were integrated with the help of the program SAINT²⁹ and scaled by the multi-scan technique.³⁰ Crystal data and information concerning data collection have been documented in Tables 4 and 5.

The structures were solved with direct methods³¹ and refined using full-matrix least squares on F^2 (SHELXL97).³¹ For ordered residues, anisotropic displacement parameters were assigned to non-H atoms; hydrogen atoms attached to C were constrained to idealized geometry and their isotropic displacement parameters were constrained to multiples of their parent atoms. H atoms attached to N and O were obtained as local maxima of electron density in Fourier difference syntheses and refined isotropically using distance restraints; target values of 0.84(2) Å for O-H and 0.90(2) Å for N-H bond distances were used.

In the crystal structure of **2a**, the ethanol molecule is disordered about a center of inversion; all atoms in this residue were assigned occupancy parameters of 0.5 and isotropic displacement parameters, and distance restraints were used to ensure a chemically reasonable intramolecular geometry. Most likely, this orientational disorder in the solvent contributes to a lower fraction of observed ($I < 2\sigma(I)$) intensity data.

In the crystal structure of **3c**, a tentative anisotropic refinement of the non-H atoms in the tolyl moiety C18-C24 indicated disorder. The final structure model involved a majority and a minority conformer for this residue; the sum of their occupancies was restrained to unity, and the individual occupancies refined to 0.815(3) and 0.185(3). Similarity restraints were applied to the alternative conformers, and only one overall isotropic displacement parameter was refined for all non-H atoms of the minority conformer.

In the absence of significant anomalous scattering, no absolute structures have been determined for the non-centrosymmetric crystal structures **1b** and **1c**. The former belongs to crystal class mm2, and the absolute structure parameter only determines the orientation of the sample crystal; the latter compound represents a conglomerate.

Refinement results have been compiled in Tables 4 and 5. Packing coefficients were calculated with PLATON³²; in the case

of disordered compounds, only the majority conformers were taken into account.

Table 4 Crystal data, data collection parameters and refinement results for the dimethylbiguanidinium salts **1b** - **1d** and the diphenylbiguanidinium salts **2a** and **2b**

Compound	1b	1c	1d	2a	2b
Empirical formula	C ₈ H ₁₇ N ₅ O ₆	C ₈ H ₁₅ N ₅ O ₅	C ₆ H ₁₄ N ₅ O ₃	C ₅₀ H ₅₈ N ₂₀ O ₁₇	C ₂₀ H ₂₄ N ₁₀ O ₄
Formula weight	279.27	261.25	204.22	1211.16	468.49
Crystal size (mm)	0.35-0.30-0.03	0.68-0.20-0.10	0.35-0.30-0.03	0.40-0.20-0.08	0.28-0.10-0.05
Crystal system	Orthorhombic	Monoclinic	Triclinic	Monoclinic	Triclinic
Space group	<i>Pca</i> 2 ₁	<i>P</i> 2 ₁	<i>P</i> -1	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> -1
<i>a</i> [Å]	12.809(2)	7.1418(9)	7.5760(14)	13.1608(14)	8.9093(16)
<i>b</i> [Å]	13.372(2)	10.6881(13)	8.3143(15)	12.6922(14)	10.772(2)
<i>c</i> [Å]	7.3552(11)	15.8359(19)	8.5662(16)	19.7008(18)	12.425(2)
α [°]	90.00	90.00	63.075(2)	90.00	71.502(3)
β [°]	90.00	92.827(2)	88.633(3)	120.795(2)	74.311(3)
γ [°]	90.00	90.00	81.063(3)	90.00	80.732(3)
<i>V</i>	1259.8(3)	1207.3(3)	474.58(15)	2826.8(5)	1085.0(3)
<i>Z</i>	4	4	2	2	2
ρ [g cm ⁻³]	1.472	1.437	1.429	1.423	1.434
μ (Mo <i>K</i> α) [mm ⁻¹]	0.126	0.120	0.115	0.110	0.105
<i>T</i> (K)	130(2)	130(2)	130(2)	130(2)	130(2)
<i>F</i> (000)	592	552	218	1268	492
θ range (°)	2.20-26.49	2.30-26.38	2.67-26.66	2.01-26.41	2.00-26.44
Refls. collected	14347	14473	5853	33195	13257
<i>R</i> _{int}	0.0838	0.0511	0.0313	0.0911	0.0566
Unique refls. in ref.	2607	4898	2003	5795	4464
Refls. with <i>I</i> > 2 σ (<i>I</i>)	1985	4253	1661	3000	3082
Param. refined	218	401	161	455	363
<i>R</i> ₁ (2 σ (<i>I</i>))	0.0459	0.0331	0.0376	0.0473	0.0437
<i>R</i> ₁ (all data)	0.0643	0.0378	0.0450	0.0993	0.0678
<i>wR</i> ₂	0.0856	0.0712	0.1022	0.1012	0.0860
Goodness of fit	0.909	0.967	1.093	0.929	0.924
Diff. peak/hole [e/Å ³]	-0.170/0.230	-0.204/0.257	-0.355/0.420	-0.294/0.454	-0.272/0.206
Packing coefficients	71.9%	69.9%	72.5%	72.0%	70.7%
CCDC	1018218	1018219	1018220	1018221	1018222

Table 5 Crystal data, data collection parameters and refinement results for the ditolylbiguanidinium salts **3a** - **3d**

Compound	3a	3b	3c	3d
Empirical formula	C ₁₃ H ₁₇ N ₅ O ₅	C ₁₃ H ₁₇ N ₅ O ₅	C ₂₆ H ₃₀ N ₁₀ O ₈	C ₁₁ H ₁₄ N ₅ O ₂
Formula weight	323.32	323.32	610.60	248.27
Crystal size (mm)	0.32-0.22-0.10	0.25-0.14-0.05	0.37-0.30-0.19	0.45-0.30-0.06
Crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> -1	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>
<i>a</i> [Å]	8.2558(12)	8.0245(7)	11.7133(7)	9.406(3)
<i>b</i> [Å]	14.578(2)	13.0557(11)	12.8357(7)	11.576(3)
<i>c</i> [Å]	13.1414(19)	22.2369(19)	19.3224(11)	11.779(3)
α [°]	90.00	87.683(2)	90.00	90.00
β [°]	102.833(2)	82.848(2)	90.3550(10)	107.623(4)
γ [°]	90.00	73.025(2)	90.00	90.00
<i>V</i>	1542.1(4)	2210.8(3)	2905.0(3)	1222.4(6)
<i>Z</i>	4	6	4	4
ρ [g cm ⁻³]	1.393	1.457	1.396	1.349
μ (Mo <i>K</i> α) [mm ⁻¹]	0.109	0.114	0.107	0.098
<i>T</i> (K)	130(2)	100(2)	100(2)	130(2)
<i>F</i> (000)	680	1020	1280	524
θ range (°)	2.12-27.50	2.46-26.38	1.90-28.39	2.44-26.38
Refls. collected	19615	26487	39601	14215
<i>R</i> _{int}	0.0677	0.0736	0.0506	0.0638
Unique refls. in ref.	3538	9008	7265	2498
Refls. with <i>I</i> > 2 σ (<i>I</i>)	2404	5975	6043	2075
Param. refined	249	745	488	192
<i>R</i> ₁ (2 σ (<i>I</i>))	0.0414	0.0535	0.0441	0.0353
<i>R</i> ₁ (all data)	0.0650	0.0916	0.0550	0.0413
<i>wR</i> ₂	0.0928	0.0995	0.1074	0.0985
Goodness of fit	0.893	0.953	1.051	1.062
Diff. peak/hole [e/Å ³]	-0.254/0.505	-0.304/0.280	-0.289/0.398	-0.184/0.287
Packing coefficients	68.2%	71.3%	68.1%	67.9%
CCDC	1018223	1018224	1018225	1018226

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Conclusions

The outcome of crystallization experiments in the system biguanide - squaric acid depends on the pH of the medium in more than one aspect. A very obvious relationship links the proton concentration and the pK_a of species potentially available for crystallization: substantial concentrations of hydrogensquarate anions and diprotonated biguanidinium cations are only encountered in acidic solutions. Shortest intermolecular interactions are influenced by pH, too: N–H···O contacts are ubiquitous but cover a wide range in which charge-assisted interactions turn out shortest. O–H···O hydrogen bonds only occur under conditions of partial squarate protonation, i.e. at pH < 4. These interactions are doubtlessly strong: with respect to repulsion between the anionic species squarate and hydrogensquarate. A more detailed analysis concerning the electrostatics of similar anion···anion interactions has combined database searches and computational methods.³³ The relevance of pK_a matching²³ for directing aggregation via hydrogen bonds has been emphasized by Krische and coworkers;³⁴ in this sense, the shortest hydrogen bonds between anions in our organic salts are really predictable!

In the crystal structures of the arylbiguanides **2a** and **3c**, the additional co-existence of conjugated acids and bases not only in the anionic but also in the cationic part underlines how flexible the reaction partners may adapt to the crystallization conditions.

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Notes and references

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† The structures were deposited at the Cambridge Crystallographic Data Centre and allocated the numbers: CCDC 1018218-1018226. Copies of the data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Electronic Supplementary Information (ESI) available: [Complete table of hydrogen bonds; ADP plot of the asymmetric unit in **1b-1d**, **2a-2b**, **3a-3d**; Experimental and simulated powder patterns for **2a**, **2b**, **3c**, **3d**]. See DOI: 10.1039/b000000x/

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