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The Brønsted-Lowry Reaction Revisited: Glass-Forming Properties of Salts of 1,5-Dimexylbiguanide

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ABSTRACT: Ionic molecular glasses can be conveniently prepared by reacting 1,5-dimexylbiguanide with a wide variety of carboxylic and sulfonic acids. A library of 51 salts has been prepared and studied by differential scanning calorimetry, 25 of which readily form glassy phases and do not recrystallize upon heating or standing. The crystal structures of 1,5-dimexylbiguanide and six of its salts have been solved and studied, and show extended hydrogen-bonded networks. Curiously, 1,5-dimexylbiguanide, which is extremely stable toward crystallization, crystallized in a close-packed, regular structure, unlike most related glass-forming compounds. This apparent paradox was probed with density functional theory calculations which revealed the presence of two conformers of similar energy, thus contributing to frustrate crystallization.

Introduction

Molecular glasses, or amorphous molecular materials, are organic small molecules that possess the ability to form glassy phases at ambient temperatures, in a way similar to most polymers, as opposed to more ordered phases such as crystals.¹ While working with small molecules of discrete size has several advantages including ease of purification, characterization and processing, and higher predictability of the properties of the bulk materials due to their homogeneity, challenges associated with glasses constituted from small molecules typically involve (1) the need for cooling at extremely fast rates or other special processing techniques to access the glassy state, and (2) the propensity of most glass-forming small molecules to crystallize over time, especially above their glass transition temperatures (T_g).²

In recent years, an increasing amount of compounds have been reported that show higher glass-forming ability and longevity and therefore can be made to readily form glassy phases upon slow cooling from the melt and without crystallization upon standing,³ giving rise to use in applications ranging from optoelectronics (OLEDs, photovoltaic cells)⁴ and nanolithography⁵ to amorphous drug formulations.⁶ Most of these molecular glasses are polyaromatic, nonplanar, star-shaped compounds that can adopt several conformations and typically do not interact strongly with each other.^{1a,3,4} However, we have identified a group of 4,6-bis(mexylamino)-1,3,5-triazines,⁷ along with related 1,5-dimexylbiguanide $1,^8$ which are capable of readily forming long-lived glassy phases despite the obvious presence of hydrogen-bonding groups. For these compounds, it has been shown that hydrogen bonding actually contributes to glass formation by generating supramolecular aggregates that pack poorly and interact weakly, and hydrogen bonding contributes to the stability of the glassy phase by providing a barrier toward molecular reorganization in the solid.⁹ This strategy has resulted in glasses of extreme stability, capable of withstanding extended

periods of time (over 18 months in some cases) above their $T_{\rm g}$, or shearing at rates up to 60 000 rpm, without crystallizing.^{7b,c,9b}



While there have been remarkable advances in molecular glasses in the last 20 years, few instances of molecular glasses formed of discrete ion pairs have been reported so far,¹⁰ and in these cases little effort has been deployed to understand the role of the counterion on glass formation and stability, T_{g} and other physical properties, and the organization of the glassy state at the molecular level. In contrast, ionomers are widespread and are used for several applications,¹¹ in particular thermoplastic elastomers,¹² semipermeable membranes,¹³ and dental restorative materials,¹⁴ and while most ionic liquids can form glasses upon cooling, their glass transition temperatures (T_g) are typically much lower than ambient temperature, and thus their usage for practical applications is oriented toward their liquid state.¹⁵ Ionic molecular glasses thus constitute a class of materials situated at the frontier between ionomers, ionic liquids, and "regular" molecular glasses, and show the promise of displaying unique properties unattainable with other related classes of materials.

While the bis(mexylamino)triazine molecular glass family offers a vast design space because two of the substituents on the triazine ring can be modified with retention of glass-forming ability, and ionic groups can be introduced this way; an even simpler route to ionic glasses involves using related 1,5-dimexylbiguanide 1, which is itself known to readily form glassy phases. Biguanide 1 is a moderately strong base and thus can be reacted with various acids to give a wide variety of salts where the ions are held together in the solid state by extensive networks of intermolecular interactions^{8,16} which are known to stabilize the glassy state.⁹ Since the ultimate aim of materials research is to discover new properties

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rather than new compounds, this strategy offers the promise of a wide range of accessible properties that can be easily tuned through the strategic selection of counterion. Futhermore, acid—base reactions are among the oldest reactions known, and among the highest-yielding, fastest, and most facile reactions available to the synthetic chemist, especially when there is an appreciable pK_a difference for Brønsted–Lowry cases.

Herein we describe the synthesis and screening of glass formation in various salts of 1,5-dimexylbiguanide, both organic and inorganic. The synthesized salts were studied by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) to probe the presence of glass-forming behavior and undesirable crystallization upon heating. Crystals of both 1,5-dimexylbiguanide and several of its salts were grown and their structures were determined by X-ray diffraction. While the inorganic 1,5-dimexylbiguanidinium salts reported herein typically showed no glass formation, most carboxylate and sulfonate salts have shown glass-forming behavior with no crystallization upon heating, and high stability of the glassy state.

Results and Discussion

Synthesis of 1,5-Dimexylbiguanidinium Salts. While 1,5-dimexylbiguanide itself shows excellent glass-forming properties with high resistance to crystallization, its hydrochloride salt, which is an intermediate in the synthesis of 1,5-dimexylbiguanide, does not form glasses, instead readily crystallizing. To assess the glass-forming potential of other salts of 1,5-dimexylbiguanide and the effect of the counterion on glass-forming ability, T_{g} and resistance to crystallization, a library of 1,5-dimexylbiguanidinium salts was generated in quantitative yields by dissolving stoichiometric amounts of 1,5-dimexylbiguanide with various acids in methanol followed by evaporation of the solvent and thorough drying of the sample (Scheme 1). Other short alkyl alcohols (i.e., ethanol, isopropanol) can be used, but the solubility of the resulting salts is typically lower. The acids used are listed in Table 1; to probe the scope of glass formation in 1,5-dimexylbiguanidinium salts, a wide range of acids was used, including inorganic, carboxylic, and sulfonic acids. Carboxylic acids used include mono-, di-, and tricarboxylic acids with various alkyl, haloalkyl, aryl, and hydroxyalkyl chains. For di- and triacids, initial attempts were made to generate partially deprotonated salts, but these proved unsuccessful because of disproportionation reactions leading to the free acid and stoichiometric salt, often leading to one component crystallizing out of solution. While 1,5-dimexylbiguanide can be protonated twice, doubly protonated biguanides are relatively acidic, and there is an important gap between the two pK_a values of the biguanide group (the two pK_a for phenylbiguanide are 2.2 and 10.7, respectively).¹⁷ Thus, only strong acids such as HBr, HI, nitric acid, sulfuric acid, trifluoroacetic acid, and sulfonic acids, are acidic enough to quantitatively protonate 1,5-dimexylbiguanide twice. In these cases, careful control of stoichiometry can ensure that only the monoprotonated 1,5-dimexylbiguanidinium salts will be obtained.

Thermal Behavior of 1,5-Dimexylbiguanidinium Salts. The thermal behavior of all compounds described herein has been studied by TGA and DSC. The glass transition temperatures (T_g) , crystallization temperatures (T_c) , melting points (T_m) , and decomposition temperatures (T_{dec}) are





reported in Table 1. All compounds are stable up to 150 °C, but prolonged heating at higher temperatures (or past their melting points with crystalline samples) results in extensive decomposition (representative TGA scans are shown in Figure S1, Supporting Information). NMR spectra of samples of 1,5-dimexylbiguanidinium formate (8) and adipate (23) after heating at 200 °C for 10 s are shown in Figures S2 and S3 and show several decomposition products. Because of decomposition at high temperatures, $T_{\rm g}$ and $T_{\rm m}$ were measured separately on amorphous and crystalline samples, respectively. For the formate (8), oxalate (18), succinate (19), maleate (20), fumarate (21), glutarate (22), mucate (33), phthalate (47), terephthalate (49), methanesulfonate (52), and all inorganic salts (2-7), glass formation from solution by evaporation of the solvent was not observed, and since it proved impossible to confirm the presence of a glass transition by melt cooling because of decomposition, it is assumed they do not form glasses.¹⁸ Of the aforementioned compounds, only inorganic acid salts 2-5 and 7, and the methanesulfonate (52) salt could be melted without extensive decomposition so that a $T_{\rm g}$ could be measured, and only methanesulfonate 52 showed a glass transition on cooling and subsequent heating. For the adipate (23) and malate (31) salts, evaporation from solution gave mixtures of crystalline and amorphous material, and due to decomposition fully amorphous solids could not be obtained. In contrast, all 33 other organic salts studied readily formed amorphous solids upon evaporation of the solvent and showed a glass transition on both slow heating and cooling (5 °C/min), and in most cases with no crystallization upon heating. Representative thermograms of 1,5-dimexylbiguanidinium p-toluate (37) are shown in Figure 1. Conducting the DSC on several heating/cooling cycles consistently gave similar T_{g} values both upon heating and upon cooling. For alkylcarboxylate and alkyldicarboxylate salts, glass-forming ability thus increases with increasing chain length, while for other classes of carboxylic acids it is not well understood what structural features (other than lack of solubility) prevent glass formation.

The stability toward crystallization of glass-forming compounds described herein was found to vary significantly from one compound to another. Aside from most alkylcarboxylate (9-12, 14), dichloroacetate (16), adipate (23), (-)-malate (31), and 4-aminobenzoate (41) salts, few compounds showed crystallization during DSC experiments (thermograms of acetate salt (9) are shown in Figure 2). Additionally, alkyl- and haloalkylcarboxylate salts 9-18 all started crystallizing upon prolonged standing (up to 3 months) at room temperature even when no crystallization was observed during DSC. Crystallization from the glassy state, either in ambient conditions or upon heating, seems to be correlated with structural features of the acid. While alkyl- and haloalkylcarboxylate salts tend to undergo crystallization from the glassy state relatively easily, glass-forming compounds containing aryl, amino, amide, or hydroxy groups (with the malate (31) and 4-aminobenzoate (41) salts being the sole

Table 1. Glass Transition (T_g) , Crystallization (T_c) , Melting (T_m) , and Decomposition (T_{dec}) Temperatures for Dimexylbiguanide 1 and Corresponding
Salts 2–53, Measured by DSC at 5 °C/min and by TGA at 10 °C/min ^a

compound	counterion	$T_{\rm g}$ (°C)	$T_{\rm c}$ (°C)	$T_{\rm m}$ (°C)	$T_{\rm dec}$ (°C)	crystallization solvent
1		37			166	acetonitrile
2	Cl ⁻			234	234	methanol
3	Br^{-}			216	193	isopropanol
4	I ⁻			200	207	methanol
5	NO_3^{-}			196	196	isopropanol
6	SO_4^{2-}			110 (dec.)	93/204	methanol
7	PO_4^{3-}			197	190	methanol
8	formate			194	183	isopropanol
9	acetate	55	89	199	166	methanol
10	propionate	45	119	148	153	
11	butyrate	37	86	152	156	
12	isobutyrate	51	116	142	154	
13	valerate	38		125	169	
14	isovalerate	41	128	151	169	
15	chloroacetate	41		160	159	
16	dichloroacetate	40	92	135	178	
17	trifluoroacetate	44		159	201	
18	oxalate			224	226	methanol
19	succinate			210	197	methanol
20	maleate			209	206	methanol
21	fumarate			230	225	methanol
22	glutarate			194	192	isopropanol
23	adipate (semicrystalline)	60	117	210	201	methanol
24	azelate	67			179	
25	sebacate	76			178	
26	lactate	54			192	
27	sorbate	67			167	
28	L-pyroglutamate	70			188	
29	D-gluconate	34		205	162	
30	(-)-quinate	33	1.40	205	195	isopropanol
31	(-)-malate (semicrystalline)	60	140	202	196	isopropanol
32	(+)-tartrate	93		102	191	(1 1
33	mucate	0.2		182	1/5	methanol
34 25		93			1//	
35	benzoale	49		152	180	iconnonal
30	m-toluate	55		132	100	isopropanol
3/	<i>p</i> -toluate	42		123	190	isopropanol
30	<i>o</i> -chlorobenzoate	42		105	10/	isopropation
39	<i>p</i> -chlorobelizoate	02 70			105	
40	n aminohonzoato	10	110	200	201	
41	<i>p</i> -ammobenzoate	54	119	200	201	
42	n hydroxybonzooto	54			192	
43	3.4.5 tribudroxybenzoate	83			174	
44	cinnamate	40			105	
46	hydrocinnamate	31		136	193	isopropanol
47	nhthalate	51		225	218	methanol
48	isophthalate	91		223	186	ethanol
40	terenhthalate	21		225	225	methanol
50	1.2.4-benzenetricarboxylate	114		223	187	methanoi
51	1.3.5-benzenetricarboxylate	130			196	
52	methanesulfonate	48		217	220	methanol
53	<i>p</i> -toluenesulfonate	63		211	149	methanor

^aCrystallization solvents are also included for each compound when applicable.

exceptions observed) tend to show superior glass-forming properties, higher solubility and higher resistance to crystallization, possibly through either increased bulk which disfavors efficient packing in the case of aryl groups, or further hydrogen bond formation which then renders molecular motion more difficult, as previously demonstrated with triazine-based glasses.⁹

Crystal Structures of 1,5-Dimexylbiguanide and 1,5-Dimexylbiguanidinium Salts. While crystal structures offer no direct information on the organization at the molecular level in the amorphous state, they can nonetheless provide useful insights on how certain structural features promote glass formation, as was previously shown for triazine derivatives.^{9a} While most compounds described herein readily form glasses and are thermally stable toward crystallization, crystals suitable for X-ray diffraction could still be obtained under appropriate conditions for 1,5-dimexylbiguanide itself, and some both glass-forming and nonglass-forming salts. However, attempts to crystallize some salts, in particular, 1,5-dimexylbiguanidinium tartrate (**32**), citrate (**34**), 1,2,4-benzenetricarboxylate (**50**), and 1,3,5-benzenetricarboxylate (**51**), proved futile, as the salts precipitated from solution in the amorphous state with all the solvent combinations attempted.

1,5-Dimexylbiguanide (1) precipitated out of most attempted solvent systems in the amorphous state, but crystals suitable for X-ray diffraction were successfully grown by slow evaporation from an acetonitrile solution.¹⁹ The crystals were accompanied by an appreciable amount of amorphous material. Allowing the solvent to evaporate completely



Figure 1. Representative DSC thermograms of 1,5-dimexylbiguanidinium acetate (9), measured at a heating/cooling rate of 5 °C/min (a) crystalline sample; (b) amorphous sample. T_g , T_c and T_m (in °C) are indicated on the thermograms.

yielded more amorphous compound 1, and upon standing at room temperature for three months no further crystallization of the amorphous phase was observed. Heating this semicrystalline material at rates ranging from 2 to 10 °C/min revealed, aside from a higher T_g than for the entirely amorphous material, the presence of crystallization at approximately 90-100 °C depending on the heating rate, but the crystallization signal was broad in every case with a span from 20 to 30 °C (DSC curves are shown in Figure 3, and T_{g} , $T_{\rm c}$, and $T_{\rm m}$ values are listed in Table 2). In comparison, amorphous 1,5-dimexylbiguanide does not even crystallize when heated at rates as low as 0.5 °C/min (Figure 4). Even in the presence of crystals to act as nucleating sites, the kinetics of crystallization were shown to be relatively slow, demonstrating the exceptional resistance of compound 1 to crystallization. Surprisingly, 1,5-dimexylbiguanide crystallized in the monoclinic $P2_1/c$ space group in a close-packed structure, which is unusual given the propensity of similar glassforming compounds to include large amounts of guest molecules or voids. A view of a single molecule of biguanide 1 is shown in Figure 5a. As in other biguanide crystal structures, the biguanide moiety forms a 6-membered ring held by an intramolecular hydrogen bond. The aryl rings adopt symmetrical and compact conformation I (Scheme 2), unlike previously reported structures of 1,5-diarylbiguanides.⁸ Molecules form unidimensional hydrogen-bonded ribbons where each molecule donates and accepts a single hydrogen bond with each of two neighboring molecules (Figure 6a).

Crystals of 1,5-dimexylbiguanidinium chloride (2) were grown by slow evaporation from a solution in methanol.²⁰



Figure 2. Representative DSC thermograms of 1,5-dimexylbiguanidinium *p*-toluate (**37**), measured at a heating/cooling rate of 5 °C/min (a) crystalline sample; (b) amorphous sample. T_g , T_c , and T_m (in °C) are indicated on the thermograms. The thermogram for the amorphous sample was recorded after an initial heating/ cooling cycle.



Figure 3. DSC thermograms of a semicrystalline sample of 1,5dimexylbiguanide (1), measured at 2, 5, and 10 °C/min.

Table 2. T_g , T_c , and T_m of a Semicrystalline Sample of 1,5-Dimexylbiguanide (1), Measured by DSC at Various Heating Rates

heating rate (°C/min)	$T_{\rm g}$ (°C)	$T_{\rm c}$ (°C)	$T_{\rm m}$ (°C)
2	48.86	97.41	127.24
5	52.38	103.87	128.08
10	55.48	104.55	128.61

Chloride 2 crystallized in the monoclinic $P2_1/c$ space group as an inclusion complex with a methanol molecule. Molecules of salt 2, and of all other salts reported herein, adopt a conformation similar to other diarylbiguanide salts previously reported (Figure 5b).⁸ Molecules are organized in bilayer structures with aryl groups on the outside and the



Figure 4. DSC thermograms of an amorphous sample of 1,5-dimexylbiguanide (1), measured at heating rates of 0.5, 1, and 2 °C/min. Note the absence of crystallization in each case.

hydrophilic groups on the inside. Biguanidinium moieties form interactions with bridging chloride ions to form unidimensional ribbons with a X-shaped cross-section (Figure 6b), and ribbons are joined through further interactions between dimexylbiguanidinium and chloride ions. Furthermore, each chloride ion interacts with the hydroxy group of a methanol molecule.

1,5-Dimexylbiguanidinium nitrate (5) crystallized out of the reaction mixture in isopropanol and were found to crystallize in the monoclinic $P2_1/c$ space group in a closepacked structure.²¹ The biguanidinium cations adopt a conformation similar to other salts reported herein (Figure 5c), but with smaller aryl-biguanide torsion angles and a smaller angle between both N-C(=N)-N planes of the biguanide group. Molecules associate through hydrogen bonds between alternating 1,5-biguanidinium and nitrate ions to form unidimensional ribbons with a slender 8-shaped cross-section (Figure 6c) which do not interact with each other via hydrogen bonding or electrostatically. Unlike the structures of most 1,5-dimexylbiguanidinium salts described herein which form parallel bilayer-like arrays of aggregates, in the case of nitrate salt 5, ribbons are packed in corrugated sheets.

1,5-Dimexylbiguanidinium formate (8), which does not form glasses, was crystallized directly from the reaction mixture in isopropanol.²² While no guest molecules are included in the structure with a monoclinic $P2_1/c$ space group, the CALC SOLV routine of PLATON²³ revealed that 4.5% of the volume is available to guests. A single molecule of salt 8 is shown in Figure 5d. The network formed by biguanidinium and formate ions is similar to the one found in the crystal structure of chloride salt 2, with the formation of amphiphilc bilayer structures where biguanidinium moieties form hydrogen bonds with bridging formate groups to form unidimensional ribbons with a X-shaped cross-section (Figure 6d). In turn, these ribbons interact together through lateral hydrogen bonds between dimexylbiguanidinium and formate groups to form bidimensional sheets.

Crystals of 1,5-dimexylbiguanidinium *p*-toluate (**37**) were grown from isopropanol during the reaction between biguanide **1** and *p*-toluic acid.²⁴ Unlike most previously described carboxylate salts, *p*-toluate salt **37** crystallized in the triclinic $P\overline{1}$ space group as an inclusion complex with a disordered isopropanol molecule. Besides the volume occupied by isopropanol, an additional 1.3% of the volume is accessible to guests. A single molecule is shown in Figure 5e. Unidimensional



Figure 5. Views of single molecules in the crystal structures of (a) 1,5-dimexylbiguanide (1) and related 1,5-dimexylbiguanidinium salts: (b) chloride (2), (c) nitrate (5), (d) formate (8), (e) *p*-toluate (37), (f) adipate (23), and (g) isophthalate (48). For salt 48, only one of two symmetry-independent molecules and only one of two disordered positions are shown for clarity.

ribbons are formed by hydrogen bonding between pairs of biguanidinium and *p*-toluate moieties (Figure 6e), but unlike the formate and adipate salts, because of the bulk of the *p*-tolyl groups, there are no strong interactions between ribbons, and therefore individual hydrogen-bonded ribbons do not propagate in a second dimension.

Mediocre glass former 1,5-dimexylbiguanidinium adipate (23) was crystallized from isopropanol in an attempt to generate the monobasic salt (from a 1:1 ratio of 1,5-dimexylbiguanide and adipic acid).²⁵ Rather than giving pure monobasic salt, the components disproportionated to adipic acid and dibasic salt 23 (single molecule shown in Figure 5f) which crystallized out of the reaction mixture in the triclinic $P\overline{1}$ space group. As with the formate salt, no guests are included in the structure, but 6.4% of the volume is available



Figure 6. Views of representative hydrogen-bonded aggregates of (a) 1,5-dimexylbiguanide (1) and 1,5-dimexylbiguanidinium salts: (b) chloride (2), (c) nitrate (5), (d) formate (8), (e) *p*-toluate (37), (f) adipate (23), and (g) isophthalate (48). Hydrogen bonds are represented by dotted lines. The figures on the left represent transversal views, while the figures on the right show the longitudinal views of the same aggregates. For salt 48, only one of two disordered positions is shown for clarity.

to guests. As with salts **2** and **8**, molecules are also organized in amphiphilic bidimensional layers formed of unidimensional ribbons of alternating biguanidinium and carboxylate groups held together by hydrogen bonds (Figure 6f). Adipate molecules span two different such ribbons through their aliphatic chain, resulting in ribbons being held more strongly than in salts **2**, **5**, and **8**.

1,5-Dimexylbiguanidinium isophthalate (48) was crystallized directly from the reaction mixture in ethanol,²⁶ and crystallized in the triclinic $P\overline{1}$ space group as an inclusion complex with 2.25 ethanol molecules. The crystal structure of salt 48 is the most complex of all the structures described herein, with multiple symmetry-independent moieties and extensive disorder. Each unit cell contains two pairs of symmetry-independent isophthalate ions and four pairs of symmetry-independent biguanidinium cations (one symmetryindependent salt molecule is shown in Figure 5g), two of which have disordered aryl groups. One of the ethanol molecules displays a disordered -CH₃ group, and the 0.25 ethanol molecule is positionally disordered as well, being present in only 25% of the sites. 5.2% of the crystal volume is accessible to guests, in addition to the volume occupied by ethanol molecules. Biguanidinium moieties are hydrogenbonded to isophthalate anions through one carboxylate group to generate unidimensional ribbons with roughly circular cross sections (Figure 6g), and contiguous ribbons are bridged through the isophthalate groups to generate bidimensional sheets with irregular interfaces.

Hirshfeld Surface Analysis. Hirshfeld surfaces have proved useful in providing a more quantitative tool to assess the packing efficiency of the crystal structures (or lack thereof) of triazine-based glasses. Because Hirshfeld surfaces probe all contacts between molecules as opposed to only the strongest interactions,²⁷ they can be used to quantify the inability of a given compound to crystallize in a structure with efficient packing and high numbers of short-range contacts between molecules, which is often indicative of glass-forming ability.

The Hirshfeld surfaces of 1,5-dimexylbiguanide 1 and salts 2, 5, 8, 23, 31, and 42 were generated with the Crystal-Explorer software,^{28,29} and the surfaces of both single molecules and small aggregates mapped with the d_{norm} property are illustrated in Figure 7. It can be observed that for all compounds most of the contacts between molecules where the interatomic distance is smaller than the sum of van der Waals radii (shown in red) are concentrated among the atoms participating in hydrogen bonding. On the other hand, the aromatic regions of the molecules participate in a few strong interactions, as evidenced by large regions where the intermolecular distances are equal or larger than the sum of van der Waals radii (shown in white and blue, respectively).

While it is visually difficult to differentiate between the crystal structures of 1,5-dimexylbiguanide (1) and its salts 2, 5, 8, 23, 37, and 48 with Hirshfeld surfaces alone, the various

Scheme 2





Figure 7. Hirshfeld surfaces mapped with the d_{norm} property of 1,5-dimexylbiguanide (1) and salts 2, 5, 8, 23, 37, and 48. (a) Single molecule, and (b) aggregate of biguanide 1; (c) single molecule, and (d) aggregate of chloride salt 2; (e) single molecule, and (f) aggregate of nitrate salt 5; (g) single molecule, and (h) aggregate of formate salt 8; (i) single molecule, and (j) aggregate of *p*-toluate salt 37; (k) single molecule, and (l) aggregate of isophthalate salt 48. For salt 48, only one of two symmetry-independent molecules and only one of two disordered positions are shown for clarity.

contacts in the crystal structures can be conveniently summarized with fingerprint plots which display the distances of intermolecular contacts as d_i vs d_e .^{30,31} It has been shown that for 4,6-bis(mexylamino)-1,3,5-triazines, the crystal structures of glass-forming compounds usually show a high number of long-distance contacts (both d_i and $d_e > 2.4$ Å) while related nonglass-forming compounds show few, if any, contacts in this distance range. The fingerprint plots for compounds 1, 2, 5, 8, 23, 37, and 48 are displayed in Figure 8. It can be observed that the intermolecular contacts in the crystal structure of 1,5-dimexylbiguanide (1) itself and inorganic salts 2 and 5 are mainly concentrated at short distances, while a "trail" of long-range contacts can be found in the fingerprint plots of all four carboxylate salts (8, 23, 37, and 48). Unlike for the triazine series, this "trail" does not seem to be correlated with glass-forming ability, as formate salt 8 did not show any glass-forming ability and glass formation in

adipate salt **23** is accompanied by a significant amount of crystallization. On the other hand, biguanide **1** showed a very compact fingerprint plot but displays exceptional glass-forming ability.

The Kitaigorodskii packing indices³² of the crystal structures described herein were calculated with the CALC VOID routine of PLATON^{23,29} and are listed in Table 2, along with the percentages of void space for each structure.³³ It should be noted that for all crystal structures with voids, the void spaces are isolated pockets and are not connected by continuous channels that could allow guest diffusion. The calculated packing indices, which are an indication of the packing efficiency of a given crystal structure, reflect the Hirshfeld surface fingerprint plots. While 1,5-dimexylbiguanide (1) and its chloride (2) and nitrate (5) salts show packing indices superior to the "usual" value of 65%, the values for adipate (23) and *p*-toluate (37) salts close to 65% (though



Figure 8. Fingerprint plots for the crystal structures of (a) 1,5-dimexylbiguanide (1) and 1,5-dimexylbiguanidinium salts: (b) chloride (2), (c) nitrate (5), (d) formate (8), (e) *p*-toluate (37), (f) adipate (23) and (g) isophthalate (48). For salt 48, the fingerprint plot of only one of two symmetry-independent molecules is shown.

nearly 15% of the volume in the structure of salt **37** is occupied by guest isopropanol molecules), and the formate **(8)** and isophthalate **(48)** salts show clearly inferior packing indices.

The Hirshfeld surface and packing index analysis did not allow to differentiate clearly between compounds with good glass-forming ability and those with poor or no glass-forming ability, as was the case with bis(mexylamino)triazine derivatives. While both inorganic salts crystallized in structures with efficient packing and did not display glass formation, no correlation could be established between packing efficiency and glass-forming ability for the four carboxylate salts studied. All four compounds packed suboptimally, with a large number of long-range contacts, void space, and solvent inclusion in the case of both molecular glasses **37** and **48**. These observations suggest that the formate and adipate salts could potentially show glass formation from melt cooling (if it did not result in decomposition) or by



Figure 9. Views of dimers of 1,5-dimexylbiguanide 1. (a) Crystal structure geometry. (b) Optimized geometry using DFT (B3LTP/6-31G(d)). In both cases, the hydrogen bond is indicated as a dotted line.

evaporation from solution using different solvents, but in both cases.

DFT Calculations on 1,5-Dimexylbiguanide. Even stranger, despite the fact that 1,5-dimexylbiguanide (1) readily forms glasses with high longevity and shows unusually slow crystallization kinetics, it crystallizes in a simple and compact fashion, with no features typically associated with molecular glasses such as disorder, presence of voids, solvent inclusion, or multiple symmetry-independent molecules. One possible explanation is that the limiting factor to the crystallization of biguanide 1 is related to the kinetically driven crystallization process rather than the inability of compound 1 to crystallize efficiently. In order to crystallize, the molecules need to adopt a similar conformation and orient themselves in an ordered fashion, both positionally and directionally. It has already been shown with glassforming triazine derivatives that the ability to form hydrogen-bonded aggregates in the solid state hinders crystallization by providing an additional energy barrier for the reorganization of molecules. The strength of the hydrogen bond in the crystal structure of biguanide 1 was calculated with DFT calculations (B3LYP,6-31G(d)) on both the crystal structure itself and on molecules with optimized geometries by calculating the energy difference between dimers and monomers ($\Delta E = E_{\text{dimer}} - 2E_{\text{monomer}}$). The geometries of both dimers are shown in Figure 9. The calculations gave hydrogen bonding energies of -4.3 kcal/mol for the crystalline geometry and -8.4 kcal/mol for the optimized structures. While these values are weaker than that of the hydrogen bond pairs for triazine-based glasses, the greater flexibility of the hydrogen bonding interaction (highlighted by the higher difference in both geometry and hydrogen bonding energy between the crystalline and optimized geometries) and the fact that there are redundant hydrogen

Table 3. Kitaigorodskii Packing Indices and Volume Accessible to Guests for Crystal Structures of 1,5-Dimexylbiguanide (1) and 1,5-Dimexylbiguanidinium Salts 2, 5, 8, 23, 37, and 48^a

compound	counterion	packing index (%)	volume accessible to guests (%)	solvent included	aggregates
1		68.1	0.0		1-D
2	Cl	68.2	0.0	MeOH	2-D
5	nitrate	67.6	0.0		1-D
8	formate	62.9	4.6		2-D
37	<i>p</i> -toluate	64.5	1.3	iPrOH	1-D
23	adipate	65.0	6.5		2-D
48	isophthalate	61.9	5.2	2.25 EtOH	2-D

^{*a*} Included solvent molecules and the dimensionality of hydrogenbonded aggregates for each structure are also included for reference.

 Table 4. Relative Energies of Conformers I–IV of 1,5-Dimexylbiguanide

 (1) Optimized by DFT (B3LYP, 6-31G(d))^a

conformation	relative E (kcal/mol)	relative population (298 K, %)	relative population (310 K, %)	relative population (376 K, %)
I	0.00	73	71	67
П	+0.63	25	26	28
III	+2.18	2	2	4
IV	+2.74	1	1	2

 a The estimated relative populations of all four conformers are indicated for 298 K, $T_{\rm g}$ and $T_{\rm c}$ (recorded at 5 °C/min).

bond donors provides a certain ambiguity in the intermolecular interactions which can contribute to frustrate crystallization.

The geometries of conformations II–IV were also optimized using DFT (B3LYP/6-31G(d)) and their energies were compared with that of the optimized geometry of conformation I calculated previously. The relative energies of conformations I–IV are listed in Table 4 along with the populations of each conformation at 298 K, T_g and T_c (for the semicrystalline sample). It should be noted that conformations II and III are tautomers in rapid exchange. It can be observed that most molecules adopt conformation I and tautomer pair II–III in a 7:3 ratio. The presence of two or more distinct conformations close in energy is already known to frustrate crystallization in the solid state, and is a structural feature often encountered in small glass-forming compounds.¹

The crystal structure of biguanide 1 shows none of the features observed with triazine-based glasses and some of the 1,5-dimexylbiguanidinium salts reported herein, such as suboptimal packing, the presence of guest molecules, several symmetry-independent molecules, disorder, etc., instead crystallizing in a "happy" close-packed, regular structure. However, it is at the same time one of the most stable and long-lived glassy materials synthesized in our group. This apparent paradox can be rationalized with the results of the DFT calculations, which show that there exist (1) several possible conformers of similar energy leading to important populations in a bulk sample for two distinct conformers, and (2) intermolecular interactions which pose an additional energetic barrier to molecular reorganization while still providing a flexible interaction that allows many possible geometries. These three combined factors make it difficult for all molecules in a given sample to adopt the same conformation and orient in an ordered fashion, thus hindering crystallization.

For 1,5-dimexylbiguanidinium salts, it proved more difficult to estimate bonding energies because of the

sheer number of interactions present between ions in the solid and the fact that ionic interactions are orders of magnitude stronger in the gas phase. As it would be desirable to estimate the hydrogen bonding energies in the solid state, this aspect will be further investigated in future studies.

Conclusion

We have shown that many carboxylate and sulfonate salts of 1,5-dimexylbiguanide, which can be conveniently prepared by reacting 1,5-dimexylbiguanide with the corresponding acids, readily form glassy phases in a fashion similar to the parent compound. These glasses are thus composed of discrete ion pairs and their properties have found to vary depending on the choice of counterion. While some of these salts rapidly crystallize upon heating, other salts have demonstrated a tremendous resistance to crystallization. The crystal structures of 1,5-dimexylbiguanide and some of its salts were solved and while some of the structures display poor packing, inclusion of solvent molecules and disorder, those features did not accurately reflect glass-forming behavior. In particular, 1,5-dimexylbiguanide itself crystallizes in a regular, closepacked structure but forms extremely stable glassy phases. With DFT calculations, we have rationalized this behavior as being the result of a kinetic resistance to crystallization due to significant populations of two conformers coupled with a flexible intermolecular hydrogen bond. The materials developed herein represent a class of materials at the crossroads between ionomers, ionic liquids and regular molecular glasses, and show the promise of displaying physical properties similar to each of these classes of materials when considered individually but unique as a whole.

Experimental Section

1,5-Dimexylbiguanide (1) and its hydrochloride salt (2)⁷ were prepared according to literature procedures, while all other reagents were commercial products and were used without further purification. NMR spectra were recorded on a Bruker Avance 400 MHz or on a Varian Mercury 300 MHz spectrometer at 298 K unless otherwise noted. FTIR spectra were recorded on a Perkin-Elmer Spectrum GX spectrometer as KBr pellets.

1,5-Dimexylbiguanidinium Formate (8). To a solution of 1,5dimexylbiguanide (0.309 g, 1.00 mmol) in methanol (5 mL) in a 20-mL screw-top vial was added formic acid (0.0377 mL, 0.0460 g, 1.00 mmol), then the solution was briefly shaken to ensure homogeneity. The solvent was then evaporated under reduced pressure, and the sample was further dried under vacuum to yield 0.355 g salt **8** in crystalline form (1.00 mmol, 100%); $T_{\rm m}$ 194 °C; IR (CHCl₃/ KBr) 3464, 3351, 3233, 3041, 2991, 2950, 2920, 2887, 2851, 2785, 2727, 2705, 1655, 1614, 1576, 1403, 1372, 1347, 1304, 1260, 1188, 1163, 1114, 1032, 1018, 938, 867, 836, 798, 757, 743, 713, 682 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.45 (s, 2H), 7.13 (s, 4H), 6.77 (s, 2H), 5.31 (m, ³*J* = 6.4 Hz, 1H), 2.27 (s, 12H), 1.42 (d, ³*J* = 6.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 164.7, 163.1, 138.6, 137.4, 126.1, 119.0, 70.8, 21.6, 21.3.

Other 1,5-dimexylbiguanidinium salts 3-53 were prepared in a similar fashion. For salts with solid acids, the mixture was briefly heated to solubilize the acid. In cases where the salt showed poor solubility, a larger volume of methanol was used. For salts **30** and **33**, the corresponding acid was dissolved in 1 mL H₂O prior to addition. For salts 3-7 and **29**, appropriate volumes of commercially available aqueous solutions (48% HBr, 57% HI, 70% HNO₃, 95% H₂SO₄, 85% H₃PO₄ and 50% D-gluconic acid) were used.

Thermogravimetric analysis (TGA). Measurements were made with a TA Instruments 2050 apparatus. For each experiment, 5-12 mg of sample was loaded on a platinum pan and the sample was

submitted to a temperature ramp from 30 to 300 $^{\circ}\mathrm{C}$ at a rate of 10 $^{\circ}\mathrm{C/min}.$

Measurement of T_g by Differential Scanning Calorimetry (DSC). Measurements were made with a TA Instruments Q100 calorimeter, using heating/cooling rates of 5 °C/min. Starting temperatures ranged from 0 to 20 °C, and the samples were heated up to 150 to 250 °C depending on the compound. Measurements were done separately on amorphous and crystalline samples to ensure the absence of decomposition products that could alter observed T_{g} values. For amorphous samples, the results reported were recorded after an initial cycle of heating and cooling and T_{g} was taken as the average of the values recorded for the heating and cooling cycles, except for compounds which crystallized during heating, in which case $T_{\rm g}$, $T_{\rm c}$, and $T_{\rm m}$ were recorded on the first heating run. For crystalline samples, $T_{\rm m}$ values were reported on the first heating cycle because of ensuing decomposition after melting in most cases. For experiments on semicrystalline and amorphous samples of biguanide 1, freshly prepared samples were subjected to a single heating ramp from 20 to 150 °C at heating rates ranging from 2 to 10 °C/min (for semicrystalline samples), or from 20 to 120 °C at heating rates between 0.5 and 2 °C (for amorphous samples).

Crystallization of 1,5-Dimethylbiguanidinium Formate (8). To a solution of 1,5-dimexylbiguanide (0.309 g, 1.00 mmol) in isopropanol (5 mL) in a 20-mL screw-top vial was added formic acid (0.0377 mL, 0.0460 g, 1.00 mmol), then the solution was briefly shaken to ensure homogeneity. The mixture was allowed to stand at room temperature for 18 h, giving crystals suitable for X-ray diffraction.

Crystalline samples of compounds **5**, **23**, **37**, and **48** were generated in a similar fashion, in 5 mL isopropanol for salts **5**, **23**, and **37**, and in 10 mL of ethanol for salt **48**.

Crystallization of 1,5-Dimexylbiguanide (1). Crystals of biguanide 1 suitable for X-ray diffraction were grown by slow evaporation of a saturated solution of compound 1 in acetonitrile; an appreciable quantity of amorphous material was also obtained along with the crystals.

Crystallization of 1,5-Dimexylbiguanidinium chloride (2). Crystals of chloride salt **2** were grown by slow evaporation of a saturated solution of compound **2** in methanol.

Crystal Structure Determination. Crystals of compounds 1, 2, 5, 8, 23, 37, and 48 were mounted on a glass fiber with grease and cooled to -93 °C in a stream of nitrogen gas controlled with Cryostream Controller 700. Data collection was performed on a Bruker SMART APEX II X-ray diffractometer with graphitemonochromated Mo K_{α} radiation ($\lambda = 0.71073$ Å), operating at 50 kV and 30 mA. No significant decay was observed during the data collections. Reflection data were processed on a PC using the Bruker AXS Crystal Structure Analysis Package.³⁴ Neutral atom scattering factors were taken from Cromer and Waber.³⁵ The structures were all solved by direct methods. Full-matrix leastsquares refinements minimizing the function $\sum w (F_o^2 - F_c^2)^2$ were applied to the compounds. All non-hydrogen atoms, except some disordered atoms, were refined anisotropically. Some H atoms involved in H-bonds and attached to N or O were located from difference Fourier maps and refined with Uiso(H) = 1.5 Ueq(O orN). All of the other H atoms were placed in geometrically calculated positions, with N-H = 0.88, C-H = 0.95 (aromatic), and 0.98 Å (CH_3) , and refined as riding atoms, with Uiso(H) = 1.5 UeqC-(methyl), or 1.2 Ueq(N or other C).

DFT Calculations. Theoretical calculations were performed with the Wavefunction Spartan 06 software with the restricted density functional theory (DFT) method at the B3LYP level of theory and with the 6-31G(d) basis set. The hydrogen bonding energy of the molecules in the crystalline state was estimated by calculating and comparing the energies of a monomer and a hydrogen-bonded dimer from the crystal structure. The geometries of both the monomer and dimer were then optimized and the hydrogen bonding energy was again given by comparing the energy of the dimer with that of two isolated monomers (calculated by multiplying the energy for one monomer by two). For the relative energies of conformers II–IV, were optimized and their energies were compared with that of the optimized geometry of conformer I (previously used for calculating the optimized geometry hydrogen bond energy).

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Supporting Information Available: Spectroscopic data for salts **3–53**, representative TGA thermograms of salts **23** and **37**, additional views of the crystal structures and Hirshfeld surfaces for compounds **1**, **2**, **5**, **8**, **23**, **37**, and **48**, and input and output data for DFT calculations on biguanide **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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