Pergamon

Tetrahedron 58 (2002) 683–690

TETRAHEDRON

Hydrogen bond controlled aggregation of guanidinium-carboxylate derivatives in the solid state

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Received 18 June 2001; revised 3 August 2001; accepted 4 August 2001

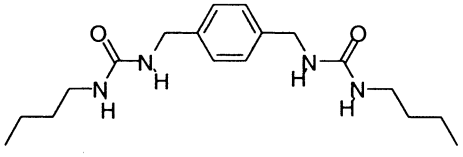
Abstract—In this paper, we report the synthesis and aggregation properties of new self-complementary organic molecules containing guanidinium and carboxylate groups. The crystal structures of the guanidinium carboxylates showed linear bidentate hydrogen bonding between the guanidinium and the carboxylate groups. In the case of phenyl derivative **7**, steric factors force a non-planar geometry for the hydrogen bonding subunit. Substitution of the phenyl by a pyridine leads to the formation of an intramolecular hydrogen bond and a planar conformation for the subunit. As a result, the simple intramolecularly hydrogen bonded molecule maintains a rigid control of binding group disposition in a manner similar to more complex multiple fused ring systems.

1. Introduction

There is an increasing need for new materials with specific optical and electronic properties due to the rapidly emerging fields of nanotechnology and molecular electronics.[1] One strategy to functional materials and molecular devices uses the controlled aggregation of small molecular subunits to form assemblies with properties unlike those of the component parts.[2] The ability to control the orientation and number of subunits within the aggregate becomes an essential element in influencing its final electronic and chemical properties. In recent years, there has been extensive focus on the use of hydrogen bonding interactions to control the packing and relative orientation of subunits both in the crystal and in aggregation in solution.[3] Several different strategies have been used to control the position and complementarity of hydrogen bonding groups within small molecule subunits that then aggregate in a well defined and controlled manner.[4] The key problem is to establish a strong binding motif that self-assembles to give specific aggregates under a range of different conditions.

We have shown that the bidentate hydrogen bonding interaction between the urea and the carboxylate functional groups can be a powerful organizing force in solution and in the solid state.[5] For example, bis ureas of type **1** form strong complexes of type **2** with bis-carboxylate salts that survive changing from a non-polar organic solvents such as $CDCl_3$ to polar hydrogen bonding solvents such as DMSO.[6] Similarly, in the solid state, molecules containing both the urea and carboxylate groups within the same molecular framework, such as **3**, can self-assemble to form infinite chains that are organized through bidentate hydrogen bonding interactions, as in **4**.[7] However, the neutral character of the hydrogen bond donors in **2** and **4** results in relatively weak interactions that are destroyed in the presence of hydroxylic solvents such as methanol or water.

There is a strong need to identify more robust intermolecular interactions that will be preserved in a range of solvent or cocystallizing conditions. One such improvement should be presented by the bidentate hydrogen bonding between guanidinium and carboxylate groups. The addition of ion pairing to the hydrogen bond energy of the interaction should greatly enhance its strength. We had earlier shown



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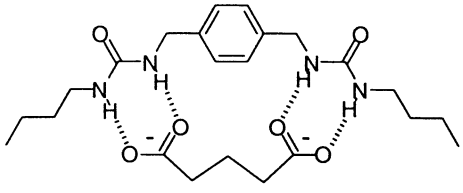

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Keywords: guanidinium; carboxylate groups; hydrogen bonding.
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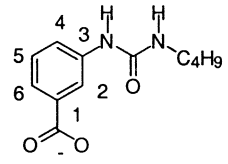

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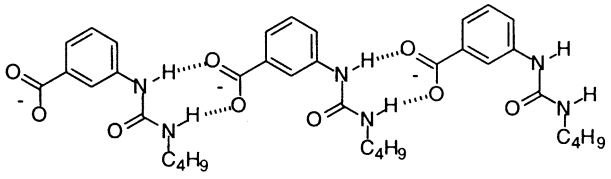

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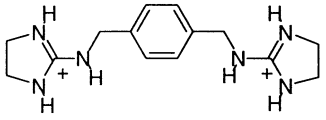
that bis-guanidinium derivatives such as **5** can bind to complementary bis-carboxylates with high affinity through a bis-bidentate ion pairing interaction, as in **6**.[6,8] Most importantly, these derivatives were sufficiently stable to withstand methanol and even aqueous methanol solutions. In the present paper, we show that this strategy can be extended into the solid state with the synthesis of some simple subunits containing both guanidinium and carboxylate groups within the same monomer. In particular, we show that these molecules can self-assemble in the solid state through head-to-tail hydrogen bonding between the electrostatically complementary functional groups to give well defined ribbon networks.



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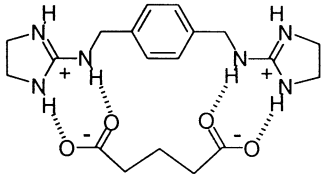

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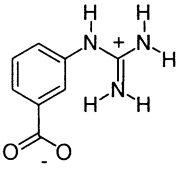
2. Molecular design

In addition to improving binding affinity, an advantage of replacing the urea group in **3** with a guanidinium is that the resulting monomer becomes potentially zwitterionic. As a result, counterions no longer are a factor in determining crystal packing, with the potential of forming more densely packed linear hydrogen bonding ribbon structures. Simple modification of **3** gives guanidinium-carboxylate **7**, in which there are only two complementary bidentate hydrogen bonding sites but two additional NH groups on the guanidinium that might influence the structure. The guanidinium group in **7** is also expected to show out-of-plane bending in order to avoid the unfavorable steric interaction between the aromatic 2-proton and the guanidinium N–H. Replacement of the phenyl C-2 carbon by a nitrogen (as in **8**) should lead to an intramolecular hydrogen bond between the pyridine and guanidinium and an essentially planar structure. The corresponding 4-substituted derivatives (**9** and **10**) should give an alternative projection of the binding groups. In the cases of **9** and **10**, 2-aminotetrahydroimidazole groups were used to investigate the effect of blocking one pair of the potentially bidentate guanidino–NH hydrogen bond donating groups.



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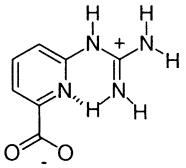

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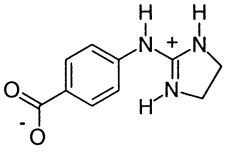

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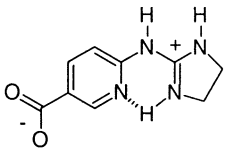

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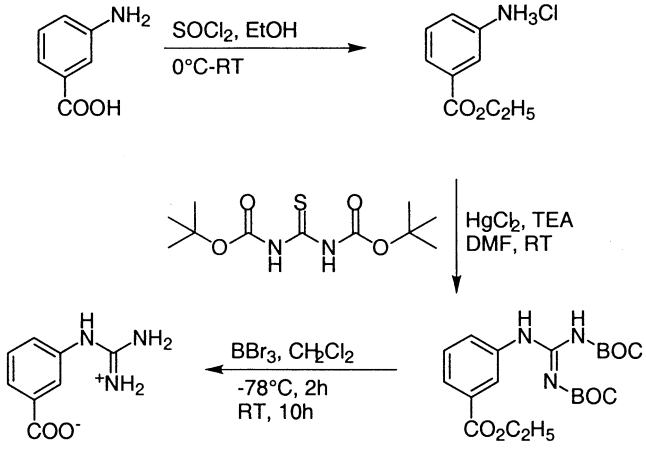
3. Synthesis

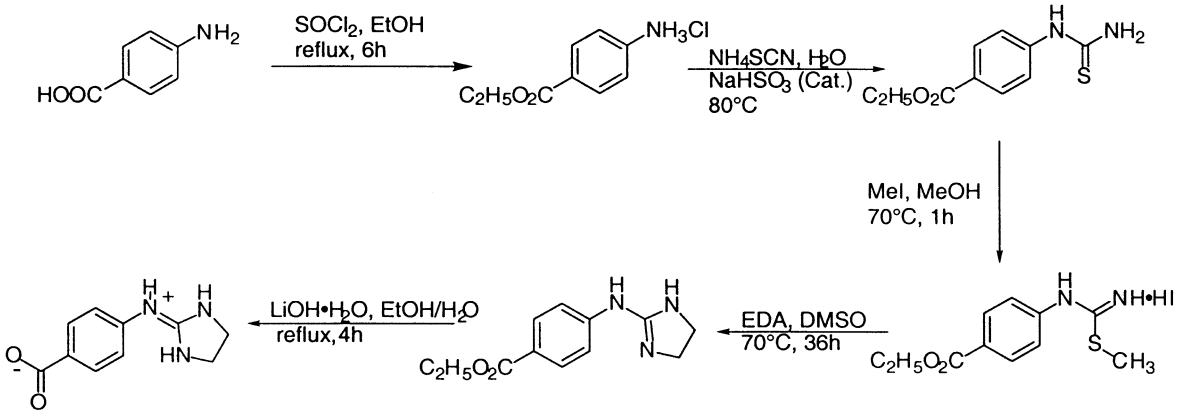
3-Guanidiniobenzoate (**7**) was synthesized in four steps as shown in Scheme 1. 3-Aminobenzoic acid was converted to its ethyl ester and reacted with the bis-(*t*-butoxycarbonyl) derivative of thiourea using $HgCl_2$ to activate the thiourea towards nucleophilic attack.[9] The resultant bis-protected guanidinium ethyl ester was reacted with BBr_3[10] to obtain the target molecule **7**.

4-Guanidinobenzoate **9** was synthesized starting from 4-aminobenzoic acid as in Scheme 2. The acid was protected as its ethyl ester followed by the reaction with ammonium thiocyanate to give the thiourea. Guanidinylation was performed by converting the thiourea to its thiouronium salt with methyl iodide[11] followed by reaction with ethylenediamine.[12] Deprotection under basic conditions gave the guanidinobenzoic acid **9**.

Application of this route to the pyridine analogue **10**



Scheme 1. Synthesis of guanidinium-benzoate **7**.



Scheme 2. Synthesis of guanidinium-carboxylate **9**.

resulted in low yields of the final product. A modified route was developed from 6-aminonicotinic acid ethyl ester using benzoylisothiocyanate[11,13] to form the benzoylthiourea derivative. Selective deprotection of the benzoyl group under mild conditions with anhydrous potassium carbonate in absolute ethanol gave the pyridinothiourea which could be converted into guanidinonicotinic acid **10** using the same sequence of MeI activation, ethylenediamine reaction and deprotection as shown in Scheme 2.

4. Results and discussion

A key issue in this study was the extent to which the strong bidentate hydrogen bonding interaction between the guanidinium and carboxylate groups in each monomer would influence the packing arrangement in the aggregate. X-Ray quality crystals of **7** were obtained by recrystallization from water at 5°C. The crystals were monoclinic and possessed a $P2_1/n$ space group. The crystal structure (Fig. 1) shows a linear ribbon arrangement of the subunits with bidentate hydrogen bonding between each neighboring guanidinium and carboxylate groups, similar to that seen with the related urea carboxylate **3**. However, unlike the urea, the guanidinium group is out of the plane of the aromatic ring by 31.5°. This out-of-plane bending clearly avoids the unfavorable steric interaction between the guanidinium hydrogen and the aromatic proton at C-2. Only one face of the guanidinium group is involved in bidentate hydrogen bonding (NH···O=1.98 Å).

The linear hydrogen bonded ribbons pack within each layer in a sheet arrangement with a distance between each ribbon of 5.3 Å (C2···C5). Stacking between layers seems to be stabilized by a number of factors. In each unit cell, there are two water molecules that form hydrogen bonds between two carboxylate groups from antiparallel ribbons in the upper and lower layers (CO···HOH=1.84–1.85 Å) (Fig. 2). The two carboxylate groups are positioned parallel and directly above each other (OC···CO=3.99 Å) with the

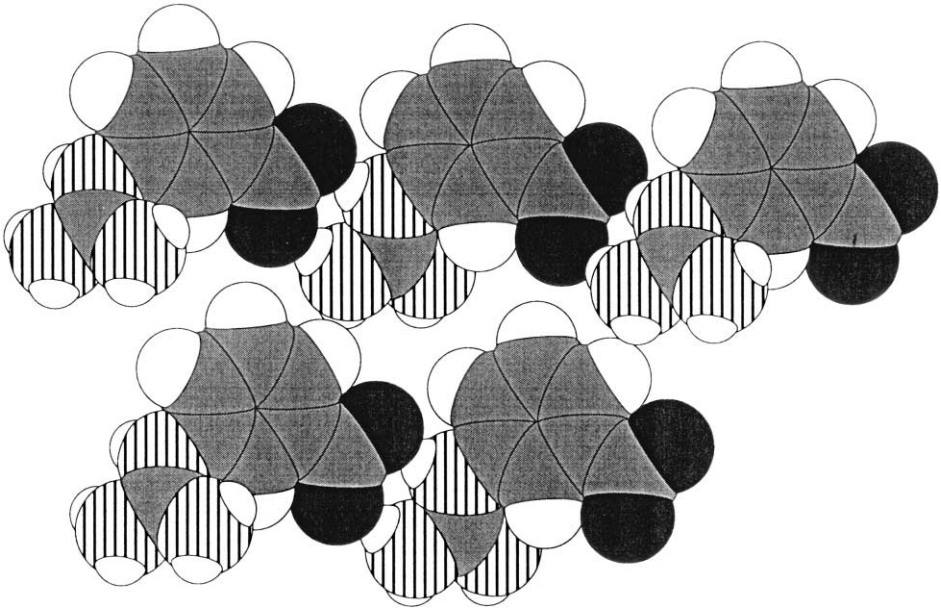


Figure 1. Top view of the two adjacent linear hydrogen bonded arrays within a layer.

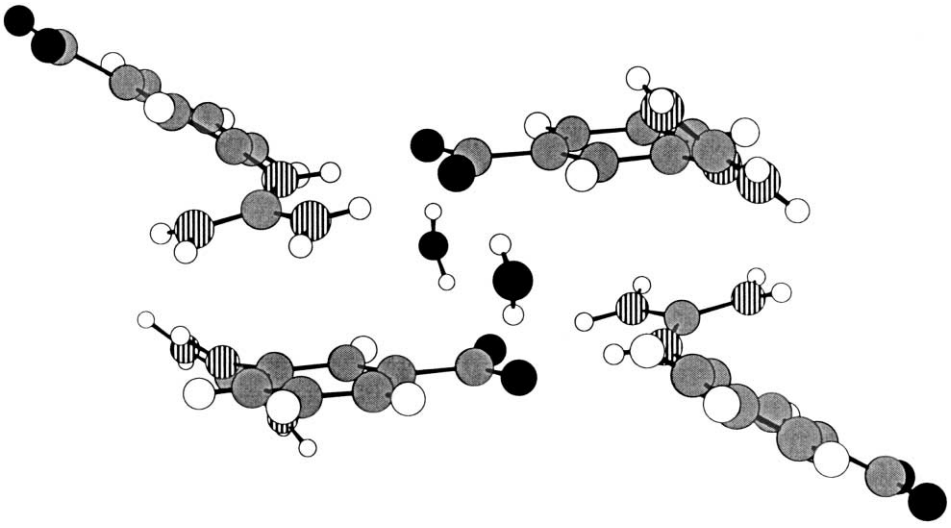


Figure 2. The packing of two layers with bridging water molecules.

bridging waters forming a four hydrogen bonded twelve membered ring. A further contribution to the layer packing comes from the guanidinium–NH_2 group opposite to the bidentate NH pair which forms two hydrogen bonds to the water bridged carboxylate group (NH···O=1.76–1.84 Å) in the layer above. This arrangement places each guanidinium group parallel to and at $\pi-\pi$ stacking distance with a phenyl group in the layer directly above (or below) leading to an interlayer distance of 3.52 Å (C1···CO).

In addition to changing the relative positions of the hydrogen bonding groups from 1,3- to 1,4-, compounds **9** and **10** also limit, through the imidazoline ring, the number of additional hydrogen bonds that can be formed to other subunits in the crystal lattice. Unfortunately, 4-guanidinobenzoate (**9**) was only sparingly soluble in both aqueous and organic solvents and no conditions were found for the growth of diffraction quality crystals. However, guanidinonicotinate **10** could be recrystallized from aqueous solution at 35°C to give X-ray quality crystals in the $P2_1/n$ space group. The crystal structure of **10** shows (Fig. 3) that the molecule adopts a planar conformation stabilized by an intramolecular hydrogen bond between the guanidinium N–H and the pyridine N (N–H···N=2.2 Å). This confirms an important feature of the present design, that a well-positioned intramolecular hydrogen bond within a simple structure can replace the complex architecture of polycyclic molecules (such as **11**) in projecting binding groups in a rigidly controlled orientation.

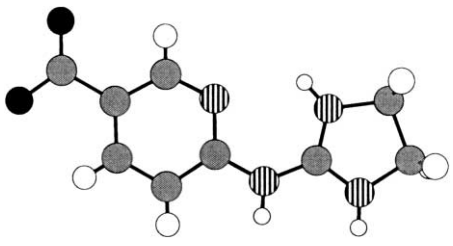
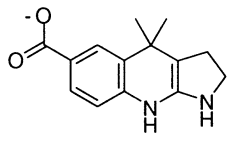


Figure 3. X-ray structure of **10**.



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In the case of **10**, the intramolecular hydrogen bond enforces a 120° angle between the projection vectors of the guanidinium and carboxylate groups. As a result, hydrogen bonding occurs between guanidinium and carboxylate groups in adjacent subunits (alkyl N–H···O=1.93 Å, aryl N–H···O=2.07 Å) to give a more extended ribbon structure compared to **7**. Solvent molecules are also found in the lattice and positioned between the different hydrogen bonded ribbons. Each water molecule is hydrogen bonded to a carboxylate oxygen and imidazolinyl N–H from adjacent ribbons (CO···OH_2=2.85–2.93 Å, N–H···OH_2= 2.24 Å) and also to the similar groups in the layer directly above or below (Fig. 4).

The enforced planarity of the intramolecularly hydrogen bonded subunit leads to an efficient packing of the layers. The hydrogen bonded ribbons stack on top of each other in such a way that the carboxylate groups in the layer right above or below are as far apart as possible. As a result, the guanidinium groups are again positioned directly above the π-system of the aromatic ring. This leads to an antiparallel layer arrangement and an interlayer distance that ranges from 3.57 to 3.32 Å.

5. Conclusions and outlook

In summary, we have introduced the synthesis and aggregation properties of two new self-complementary organic molecules containing guanidinium and carboxylate groups. The crystal structures of both flexible (**7**) and rigid (**10**) guanidinium carboxylates were solved and showed linear bidentate hydrogen bonding between the guanidinium and the carboxylate groups. This study reinforces the

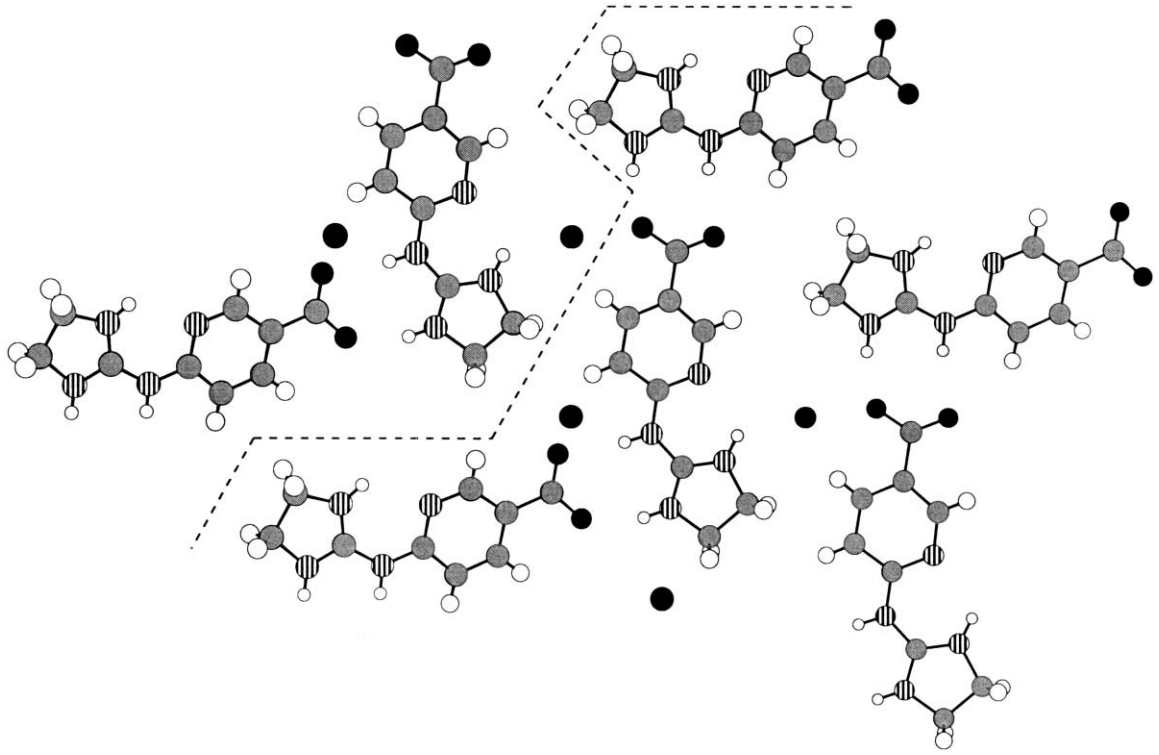

Figure 4. Packing of linear hydrogen bonded ribbons within a layer in the X-ray structure of **10**.

importance of intramolecular hydrogen bonding in controlling the conformation and orientation of the self-complementary groups. In the case of **7**, a non-planar structure leads to extensive interaction between adjacent layers. However, with **10** an intramolecular hydrogen bond enforces planarity and minimizes available hydrogen bonding groups for inter-layer interactions. The long-term goals for this strategy lie in controlling the relative position and orientation of the subunits that make up the solid. By varying the location and character of the interacting functional groups, we can potentially alter the electronic and optical properties of the material in a systematic way. We have previously demonstrated that this approach can lead to self-assembled materials with interesting non-linear optical behavior.[14] In the current work, we have particularly aimed to combine inter- and intramolecular hydrogen bonding in a predictable way as the key determining influences on solid state structure. In the future, this strategy will allow us to generate novel solids from more complex components whose conformation and self-assembly can be controlled.

6. Experimental

6.1. General methods

CH_2Cl_2 was obtained from Fisher and distilled from P_2O_5. Et_2O and THF were obtained from Fisher and distilled from sodium benzophenone ketyl. All other reagents, unless otherwise noted, were obtained from the Aldrich Chemical Company and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300 and 75 MHz, respectively). NMR chemical shifts are reported in ppm downfield from internal TMS. FT-IR spectra were obtained on a Mattson Cygnus 100 instrument. A CaF_2 IR cell having a path length of 1.0 mm was used. Mass spectra were determined at the Department of Chemistry, University of Pittsburgh. EI and FAB mass spectra (MS) were obtained using a Varian MAT CH-5 or VG 7070 mass spectrometer under the direction of Dr Kasi V. Somayajula. Melting points were determined using an Electrothermal capillary melting point apparatus and are uncorrected. Elemental analysis was carried out by Atlantic Microlab, Norcross, GA. Analytical thin layer chromatography (TLC) was conducted using PolyGram 0.25 mm silica gel precoated plates with fluorescent indicator UV_{254}. Silica gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM) (EM Science) was used for flash chromatography.

6.1.1. 3-Aminobenzoic acid ethyl ester hydrochloride. 3-Aminobenzoic acid (5.0 g, 36.5 mmol) was dissolved in ethanol (70 mL). The solution was cooled in an ice bath. Thionyl chloride (4 mL, 54.7 mmol) was added dropwise to the cold solution. The thick slurry was refluxed for 12 h and the mixture was cooled to room temperature to crystallize out the product. The crystalline product was filtered and washed with diethyl ether to afford the hydrochloride salt of the desired ester (5.9 g, 80%): mp 191–193°C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.35 (3H, br s, N–H), 7.92–7.89 (2H, m, Ph-H), 7.66–7.57 (2H, m, Ph-H), 4.3 (2H, q, J=7.2 Hz, OCH_2), 1.29 (3H, t, J=7.2 Hz, ester CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.8, 133.4, 131.1, 130.3, 128.0, 127.7, 123.4, 61.2, 14.1; HRMS *m/e* calcd for $C_9H_{11}NO_2$: 165.0789, found 165.0785.

6.1.2. 3-(3,3′-Di-*tert*-butoxycarbonylguanidino)-benzoic acid ethyl ester. The hydrochloride salt of 3-aminobenzoic acid ethyl ester (0.56 g, 2.78 mmol) was dissolved in DMF

(15 mL). To this solution were added 1,3-bis-Boc-thiourea (0.76 g, 2.78 mmol), triethylamine (1.3 mL, 9.78 mmol), and $HgCl_2$ (0.83 g, 3.04 mmol). The mixture was heated at 38–40°C for 20 h. Excess ethyl acetate was then added and the reaction mixture was filtered through celite. The solution was then extracted with a brine/water mixture (1:1) and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated on a rotary evaporator to give the crude product. The crude material was purified by silica gel chromatography using hexane/ether (5:1, v/v) as the eluent to afford a light yellow solid as the desired product (0.65 g, 58%): mp 121–122°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.63 (1H, s, C–NH-Boc), 10.44 (1H, s, Ph-NH), 8.13 (1H, d, J=1.5 Hz, Ph-H at C-2), 8.00 (1H, dd, J_a=9.0 Hz, J_b=1.2 Hz, Ph-H at C-6), 7.78 (1H, d, J=9.0 Hz, Ph-H at C-4), 7.40 (1H, t, J=8.1 Hz, Ph-H at C-5), 4.36 (2H, q, J=7.2 Hz, OCH_2), 1.54 (9H, s, *t*-butyl CH_3), 1.50 (9H, s, *t*-butyl CH_3), 1.39 (3H, t, J=7.2 Hz, ester CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 163.4, 153.5, 153.3, 131.1, 129.0, 126.5, 125.7, 122.7, 83.9, 79.7, 77.2, 61.0, 28.1, 28.0, 14.3; MS *m/e* calcd for $C_{20}H_{29}N_3O_6$: 407.2056, found 407.2044; Anal. calcd for $C_{20}H_{29}N_3O_6$: C, 58.95; H, 7.17; N, 10.31; found: C, 59.0; H, 7.22; N, 10.37.

6.1.3. 3-Guanidiniumbenzoate (7). In a 100 mL flask the bis-Boc-ethylester (0.3 g, 0.73 mmol) was dissolved in dichloromethane (30 mL). The solution was cooled to −78°C in a dry ice/acetone bath. A 1 M solution of boron tribromide in dichloromethane (8 mL, 8 mmol) was added to the reaction flask. The flask was covered using a rubber septum and stirred at −78°C for 2 h. The temperature was raised to room temperature and the contents were stirred for another 10 h. Water was then added at 0°C to precipitate out boric acid. The solution was then filtered and the filtrate was extracted twice with dichloromethane. The aqueous layer was then evaporated to dryness on a rotary evaporator. The residue was thoroughly washed with cold THF to obtain the pure hydrobromide salt of the desired product. The salt was dissolved in water and the pH was adjusted to 5.75 using saturated sodium bicarbonate solution. The crystalline product slowly precipitated out of solution on refrigeration. The product was then filtered and dried under vacuum (0.08 g, 64%): mp 303°C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.92 (1H, s, Ph-NH), 8.11 (4H, br s, guanidinium N–H), 7.71 (2H, m, Ph-H), 7.35 (2H, m, Ph-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.6, 155.5, 135.6, 132.1, 130.2, 128.8, 127.2, 125.0; MS *m/e* calcd for $C_8H_9N_3O_2$: 179.0694, found 179.0691.

6.1.4. 4-Aminobenzoic acid ethyl ester hydrochloride. 4-Aminobenzoic acid (10.0 g, 73 mmol) was dissolved in ethanol (75 mL). The solution was cooled in an ice bath. Thionyl chloride (8 mL, 109 mmol) was added dropwise (caution) to the acid solution. The reaction mixture was refluxed for about 6 h. The solvent was then evaporated on the rotary evaporator. The solid residue was recrystallized with ethanol and washed with diethyl ether to isolate the desired hydrochloride salt as the product (12.5 g, 85%): mp 195–197°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.14 (3H, s, NH_3), 7.91 (2H, d, J=8.4 Hz, Ph-H at C-2 and C-2′), 7.32 (2H, d, J=8.4 Hz, Ph-H at C-3 and C-3′), 4.24 (2H, q, J=7.2 Hz, OCH_2), 1.25 (3H, t, J=7.2 Hz, ester CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 140.2, 130.8, 126.5, 121.5, 60.8, 14.3; MS *m/e* calcd for $C_8H_{10}N_2O_2$: 166.0742, found 166.0750.

6.1.5. 4-Thioureidobenzoic acid ethyl ester. The hydrochloride salt of 4-aminobenzoic acid ethyl ester (2.0 g, 9.9 mmol) was dissolved in water (25 mL). Ammonium thiocyanate (1.6 g, 21.8 mmol) and ammonium bisulfite (0.05 g, 0.5 mmol) were added to the amine solution. The reaction mixture was heated at 80–90°C for 15 h and then refluxed for several days. The solution was cooled to room temperature and the precipitate was filtered and washed with water and 2N HCl. The product was dried under vacuum and identified as the thiourea (0.85 g, 38%): mp 147–149°C; ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 9.41 (1H, s, Aryl N–H), 7.48 (2H, d, J=8.6 Hz, Ph-H), 7.19 (2H, d, J=8.6 Hz, Ph-H), 6.78 (2H, br s, urea NH_2), 3.85 (2H, q, J=7.1 Hz, OCH_2), 0.90 (3H, t, J=7.1 Hz, ester CH_3); MS *m/e* calcd for $C_{10}H_{12}N_2O_2S$: 224.0619, found 224.0617.

6.1.6. 4-(2-Methylisothioureido)-benzoic acid ethyl ester hydroiodide. The forgoing thiourea (0.2 g, 0.92 mmol) was dissolved in methanol (30 mL). Methyl iodide (0.08 mL, 1.28 mmol) was added to the methanol solution. The reaction mixture was refluxed for 1 h. The solvent was evaporated and the crude product was dried under vacuum for 6 h. The product was characterized by ^{1}H NMR and used in the next step without any purification: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.5 (br, aryl N–H), 8.05 (2H, d, J=8.6 Hz, Ph-H), 7.47 (2H, d, J=8.6 Hz, Ph-H), 4.32 (2H, q, J=7.1 Hz, OCH_2), 3.38 (br s, urea N–H), 2.69 (3H, s, S–CH_3), 1.31 (3H, t, J=7.1 Hz, ester CH_3).

6.1.7. 4-(4,5-Dihydro-1*H*-imidazol-2-ylamino)-benzoic acid ethyl ester. The crude thiouronium salt from the previous step (~4.45 mmol) was dissolved in DMSO (25 mL). To this solution was added ethylenediamine (0.33 mL, 4.9 mmol). The reaction mixture was heated at 70°C for 12 h and then at 110°C for another 3 h. The solution was cooled to room temperature. Water (25 mL) and aqueous ammonia (50 mL, 15%) were then added to the reaction mixture to precipitate out the guanidine. The precipitate was filtered and washed several times with water. The product was dried under vacuum and characterized as the desired guanidine (0.6 g, 58%): mp 150°C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (2H, d, J=8.1 Hz, Ph-H at C-2 and C-2′), 6.98 (2H, d, J=8.1 Hz, Ph-H at C-3 and C-3′), 5.13 (2H, br, urea NH_2), 4.31 (2H, q, J=7.0 Hz, OCH_2), 3.50 (4H, s, guanidinyl CH_2), 1.35 (3H, t, J=7.0 Hz, ester CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 158.2, 154.6, 130.9, 123.3, 122.4, 60.4, 42.4, 14.3; MS *m/e* calcd for $C_{12}H_{15}N_3O_2$: 233.1164, found 233.1153.

6.1.8. 4-(4,5-Dihydro-1*H*-imidazolium-2-ylamino)-benzoate (9). The above guanidine (0.1 g, 0.43 mmol) was dissolved in a mixture of ethanol/water (50 mL, 4:1). Lithium hydroxide monohydrate (0.02 g, 0.47 mmol) was added to the solution and the reaction mixture was refluxed for 4 h. The solvent was then removed on a rotary evaporator and the residue was dissolved in water (5 mL). The solution was then filtered to remove any insoluble material and the pH was adjusted to 6.8 using 2N HCl and saturated sodium bicarbonate. The precipitated guanidinium-carboxylate

was filtered and washed with water and methanol and dried under vacuum to afford the desired product (0.06 g, 68%): mp 280°C (decomp.); ^{1}H NMR (300 MHz, TFA-d) δ 7.92 (2H, m, Ph-H at C-2 and C-2′), 7.07 (2H, m, Ph-H at C-3 and C-3′), 3.62 (4H, s, guanidinyl CH_2); MS *m/e* calcd for $C_{10}H_{11}N_3O_2$: 205.0851, found 205.0859.

6.1.9. 6-(3-Benzoylthioureido)-pyridine-3-carboxylic acid ethyl ester. To a solution of benzoyl isothiocyanate (0.27 g, 1.65 mmol) in benzene (50 mL) was added ethyl 6-aminonicotinate (0.25 g, 1.50 mmol) and the reaction mixture was refluxed for 12 h. The solvent was then removed under reduced pressure and the crude material was purified by silica gel chromatography using a mixture of hexane and diethyl ether (3:1, R_f=0.1) as the eluent followed by drying under vacuum to afford a yellow solid as the desired product (0.23 g, 47%): mp 150–152°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.25 (br, urea N–H), 9.08–8.99 (3H, m, urea N–H, Pyr. C–H at C-2 and C-4), 8.37 (1H, dd, J_a=2.2 Hz and J_b=8.7 Hz, Pyr. C–H at C-5), 7.92 (2H, d, J=7.4 Hz, Ph-H at C-2 and C-2′), 7.66 (1H, t, J=7.4 Hz, Ph-H at C-4), 7.55 (2H, t, J=7.8 Hz, Ph-H at C-3 and C-3′), 4.41 (2H, q, J=7.1 Hz, OCH_2), 1.41 (3H, t, J=7.1 Hz, ester CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 166.6, 164.9, 154.4, 150.4, 139.4, 134.1, 131.6, 129.4, 128.5, 127.8, 123.9, 114.6, 61.5, 14.5; MS *m/e* calcd for $C_{16}H_{15}N_3O_3S$: 329.0834, found 329.0825; Anal. calcd for $C_{16}H_{15}N_3O_3S$: C, 58.35; H, 4.59; N, 12.76; S, 9.73; found: C, 58.45; H, 4.62; N, 12.74; S, 9.62.

6.1.10. 6-Thioureidopyridine-3-carboxylic acid ethyl ester. To a solution of the above benzoylthiourea (0.5 g, 1.518 mmol) in absolute ethanol (50 mL) was added anhydrous potassium carbonate (0.21 g, 1.52 mmol) and the reaction mixture was refluxed for 2 h. After cooling, the reaction mixture was filtered and the residue was washed with excess ethanol and then with excess water and dried under vacuum to afford the deprotected thiourea **16** (0.23 g, 66%): mp 245°C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.88 (1H, s, N–H at pyridine), 10.5 (1H, s, hydrogen bound urea N–H), 9.15 (1H, s, urea N–H), 8.75 (1H, d, J=2.1 Hz, C–H at C-2 on pyridine), 8.18 (1H, dd, J_a=2.4 Hz and J_b=8.7 Hz, C–H at C-4 on pyridine), 7.21 (1H, d, J=8.7 Hz, C–H at C-5 on pyridine), 4.28 (2H, q, J=6.9 Hz, OCH_2), 1.28 (3H, t, J=6.9 Hz, ester CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 180.7, 164.2, 156.0, 148.2, 139.1, 119.6, 112.3, 60.8, 14.1; MS *m/e* calcd for $C_9H_{11}N_3O_2S$: 225.0571, found 225.0581; Anal. calcd for $C_9H_{11}N_3O_2S$: C, 47.99; H, 4.92; N, 18.65; S, 14.23; found: C, 48.08; H, 4.97; N, 18.61; S, 14.16.

6.1.11. 6-(2-Methylisothioureido)-pyridine-3-carboxylic acid ethyl ester. To a solution of the above thiourea (0.1 g, 0.44 mmol) in methanol (20 mL) was added methyl iodide (41.5 μL, 0.66 mmol) and the reaction mixture was heated at 70°C for 15 h. The solvent was then removed on a rotary evaporator and the crude material was dried under vacuum and used for the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (1H, s, Pyr. C–H at C-2), 8.31 (1H, br s, urea N–H), 8.18 (1H, d, J=8.6 Hz, Pyr. C–H at C-3), 6.83 (1H, d, J=8.7 Hz, Pyr. C–H at C-4), 4.38 (2H, q, J=7.1 Hz, ester CH_2), 2.17 (3H, s, S–CH_3), 1.39 (3H, t, J=7.1 Hz, ester CH_3).

6.1.12. 6-(4,5-Dihydro-1*H*-imidazol-2-ylamino)-pyridine-3-carboxylic acid ethyl ester. To a solution of the crude activated thiourea from the previous step in DMSO (10 mL), was added ethylenediamine (33 μL, 0.44 mmol) and the reaction mixture was heated at 110°C for 15 h. The mixture was then cooled to room temperature and water (20 mL) was added followed by the addition of a 15% solution of ammonium hydroxide (10 mL). The precipitated product was extracted with diethyl ether (2×25 mL). The combined ether extract was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was then dried under vacuum for 30 min to afford a brown solid as the desired product (0.07 g, 69% based on the previous step): mp 154°C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (1H, d, J=2.7 Hz, Pyr. C–H at C-2), 8.03 (1H, dd, J_a=2.4 Hz and J_b=8.7 Hz, Pyr. C–H at C-4), 6.77 (1H, d, J=8.4 Hz, Pyr. C–H at C-5), 4.34 (2H, q, J=7.2 Hz, OCH_2), 3.69 (4H, s, guanidine CH_2), 1.63 (1H, br, guanidine N–H), 1.37 (3H, t, J=7.2 Hz, ester CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 165.6, 162.9, 149.5, 137.9, 117.3, 60.7, 42.2, 14.5; MS *m/e* calcd for $C_{11}H_{14}N_4O_2$: 234.1116, found 234.1113; Anal. calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92; found: C, 56.41; H, 6.04; N, 23.82.

6.1.13. 6-(4,5-Dihydro-1*H*-imidazol-2-ylamino)-pyridine-3-carboxylate (10). To a solution of the above ethyl ester (0.50 g, 2.15 mmol) in a mixture of 4:1 ethanol and water (40 mL) was added lithium hydroxide monohydrate (0.1 g, 2.37 mmol). The reaction mixture was then refluxed for 2 h. The solvent was then evaporated under reduced pressure and the residue was dissolved in water. The aqueous solution was filtered and the pH of the filtrate was adjusted to 6.5 by using HCl (6 M) and saturated $NaHCO_3$ solution. The light yellow precipitate was filtered and washed with excess water and dried under vacuum to afford a light yellow solid (0.4 g, 90%): mp 303°C (decomp.); MS *m/e* calcd for $C_9H_{10}N_4O_2$: 206.0803, found 206.0801; Anal. calcd for $C_9H_{10}N_4O_2 \cdot H_2O$: C, 48.21; H, 5.39; N, 24.99; found: C, 47.60; H, 5.30; N, 24.76. We were not able to characterize this compound by NMR because of extremely low solubility in most solvents. However, the structure was confirmed by X-ray crystallography (see text).

Acknowledgements

We thank the National Science Foundation for their financial support of this work.

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