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Synthesis and properties of novel guanidine bases. N,N',N''-Tris(3-dimethylaminopropyl)-guanidine

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Abstract—The synthesis of novel N, N', N''-tris(3-dimethylaminopropyl)-guanidine 1 is described and X-ray structure of its hexa-fluorophosphate salt measured (1H·PF₆). The hydrogen bonding in protonated 1 and in 1H·PF₆ is also discussed. © 2005 Published by Elsevier Ltd.

1. Introduction

There has been growing interest in theoretical modelling^{1,2} and the synthesis^{1c,3,4} of strong novel organic bases in recent years primarily due to their high catalvtic potential in a number of synthetically important reactions. These studies have been mainly concerned with acyclic and cyclic guanidines, biguanides, vinami-dines and phosphazenes.^{5–8} The present study was motivated by a recent theoretical prediction that multiple dimethylaminopropyl substitutions of the parent guanidine lead to high intrinsic gas phase basicities and proton affinities (PA) culminating in PA = $275.5 \text{ kcal mol}^{-1}$ (at the MP2/6-311+G**//HF/6-31G* level of theory) in N, N', N''-tris(3-dimethylaminopropyl)-guanidine 1.9 The reason behind the high proton affinity of 1 was identified as being due to the cooperative action of strong cationic resonance in the central guanidine moiety and formation of intramolecular multiple hydrogen bonding (IMHB), which is enhanced upon protonation. The present study provides firm evidence in favour of formation of IMHB in hexafluorophosphate salt of 1 $(1H \cdot PF_6)$ in the solid state, as well as in solution.

The target guanidine derivative **1**, the synthesis of which has not been described in the literature so far, was prepared in three steps starting from 3-dimethylaminopropan-1-amine according to Scheme 1 in an overall yield of 76%.¹⁰

The structure of compound **1** was unequivocally identified by spectroscopic methods (IR, ¹H and ¹³C NMR, HRMS) and by X-ray analysis of its HPF₆ salt. The latter was prepared by reacting **1** with ammonium hexafluorophosphate in dry acetonitrile.^{11,12} X-ray structure of **1H**·PF₆ is shown in Figure 1 together with selected bond lengths and angles.

Inspection of X-ray structure revealed that the guanidinium moiety lies diagonally within the unit cell with a C_3 axis of symmetry passing exactly through the central carbon atom of the guanidine fragment. Furthermore, the mutual orientation of the dimethylaminopropyl chains and close contacts between nitrogen atoms in the protonated subunit (Fig. 1b) provided strong evidence for the formation of three N–H···N intramolecular hydrogen bridges with the distance between nitrogen atoms of 2.886(4) Å being in agreement with earlier theoretical prediction.⁹

Keywords: Organic synthesis; X-ray diffraction analysis; Hydrogen bonds; Density functional calculations; AIM calculations.

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Scheme 1. Reagents and conditions: (a) CS₂, EtOH, reflux, 22 h; (b) yellow HgO, rt, 2 h; (c) 3-dimethylaminopropan-1-amine/THF, reflux, 24 h.



Figure 1. X-ray structure of the (a) 1H·PF₆ unit cell^{13,14} and (b) guanidinium cation substructure extracted from the X-ray data as obtained using the Mercury 1.2 program.^{14a} Discontinuation lines show the hydrogen bonding. Selected geometrical parameters:¹⁵ C1–N1: 1.326(3) Å; N1–C2: 1.445(4) Å; C2–C3: 1.508(4) Å; C3–C4: 1.490(4) Å; N2–C4: 1.456(4) Å; N1'···N2: 2.885(4) Å; N1'-H: 0.85(4); C1–N1–C2: 124.7(3)°; N1–C2–C3: 115.5(3)°; C2–C3–C4: 115.3(3)°; C3–C4–N2: 114.0(3)°; N1–C1–N1'–N1'': -179.3(5)°; N1'–C1–N1–C2: -20.9(5)°; C1–N1–C2–C3: 106.4(3)°; N1–C2–C3–C4: -61.7(4)°; C2–C3–C4: -50.7(4)°. Numbering of atoms is shown in Figure 2.

Another point of interest concerns the existence of IMHB in $1H \cdot PF_6$ in solution. To this end we tackled this problem by comparing FT-IR and ¹H NMR spectra of 1H·PF₆ and N, N', N''-tri-*n*-propylguanidinium hexafluorophosphate (4H·PF₆), in which intramolecular hydrogen bonding is not possible. Measurements were carried out in acetonitrile (fully deuterated in the case of NMR analysis) as a solvent. Analysis of the IR spectra of 4H·PF₆ revealed the presence of a strong N–H stretching vibration at 3360 cm^{-1} , whereas no band in this region was observed for 1H·PF₆. Instead, a new broad vibration band (in the region of $2900-3100 \text{ cm}^{-1}$) appeared, as would be expected for systems involving intramolecular N-H \cdots N hydrogen bonding.¹⁶ The ¹H NMR spectra of $1H \cdot PF_6$ and $4H \cdot PF_6$ were measured in the temperature range of 243-293 K in order to evaluate the dependence of the chemical shift of the NH protons on temperature (denoted hereafter as $\Delta\delta/\Delta T$), which is customarily considered as one of the tests for the existence of intramolecular hydrogen bonding.¹⁷ At 243 K the ¹H NMR spectrum of 1H·PF₆ exhibited a signal for the NH protons at 9.34 ppm, whereas the corresponding signal in the ¹H NMR spectrum of **4H**·PF₆ was found to be shifted upfield by ca. 3 ppm. Furthermore, from variable temperature ¹H NMR spectra, $\Delta\delta/\Delta T$ of -0.006 and -0.004 ppm K⁻¹ for **1H**·PF₆ and **4H**·PF₆, respectively, were deduced. Both results are consistent with the existence of weak hydrogen bonding in **1H**·PF₆.

Finally, in order to shed light on the intrinsic strength of hydrogen bonding in $1H \cdot PF_6$ (i.e., in the gas phase) we also calculated the topological properties of the electron density distribution for the N-H···N intramolecular bridges in terms of the Bader theory of atoms in molecules (AIM)¹⁸ for the protonated form of 1 using the B3LYP/6-311+G** method.¹⁹ The minimum energy structure, together with the selected bond distances and bond angles are shown in Figure 2. Before turning to analysis of the calculated topological parameters it is worth noting that, likewise in the crystal state, the optimized structure is close to C_3 -symmetry. It is also interesting to observe that the proton is located unsymmetrically in a non-linear hydrogen bridge (e.g.,



Figure 2. Molecular geometry of $1H^+$ calculated at the B3LYP/ 6-311+G** level. Selected geometrical parameters:¹⁵ C1–N1: 1.344 Å; N1–C2: 1.467 Å; C2–C3: 1.535 Å; C3–C4: 1.532 Å; N2–C4: 1.475 Å; N1'···N2: 2.941 Å; N1'–H: 1.036 Å, H···N2: 1.917 Å; C1–N1–C2: 125.2°; N1–C2–C3: 115.3°; C2–C3–C4: 116.1°; C3–C4–N2: 114.7°; N1'–N2–C4: 96.6°; N1'–H···N2: 168.8°; N1–C1–N1'–N1'': –179.8; N1'–C1–N1–C2: –23.7°; C1–N1–C2–C3: 106.7°; N1–C2–C3–C4: –59.7°; C2–C3–C4–N2: –50.9°.

N1'-H···N2, where N1' and N2 are the donor and acceptor nitrogen atoms, respectively). This is indicated by the short N1'-H bond length of 1.036 Å, a long distance H···N2 of 1.917 Å and an N1'-H···N2 angle of 168.8°. It should also be noted that the distance between the proton and the accepting nitrogen atom of 1.917 Å is shorter by ca. 0.8 Å than the sum of their van der Waals radii,²⁰ implying that the strength of the hydrogen bonds in **1H**⁺ in the gas phase is substantial.^{21a} In agreement with anticipated behaviour, the N-H bond is found to be longer by 0.029 Å than the unperturbed N-H bond in, for example, protonated N,N',N''-trimethylguanidine (calculated at the same level of theory).

In recent years, the topological parameters derived from the Bader theory have often been applied in the analysis of intramolecular hydrogen bonds.²¹ Koch and Popelier proposed eight criteria based on AIM theory to characterize hydrogen bonds.²² Two of them are connected with electron density ρ_{BCP} and Laplacian ($\nabla^2 \rho_{BCP}$) of the electron density at the bond critical point (BCP) of the $H \cdots A$ (proton \cdots acceptor) bond. The ranges of $\rho_{\rm BCP}$ and $\nabla^2 \rho_{\rm BCP}$ are 0.002–0.040 e Å⁻³ and 0.024–0.139 e Å⁻⁵, respectively, if H-bonds do exist. Both of these criteria are found to be fulfilled for the optimized geometry of the **1H** cation: the $\rho_{H...N}$ value is 0.036 e Å⁻³ and for $\nabla^2 \rho_{H...N}$ a value of 0.085 e Å⁻⁵ is obtained. The corresponding values for the N–H bond amount to $0.314 \text{ e} \text{ Å}^{-3}$ and $-1.568 \text{ e} \text{ Å}^{-5}$, which are smaller by 0.027 e Å⁻³ and 0.136 e Å⁻⁵ compared to the unperturbed N-H bond in the previously mentioned protonated N, N', N''-trimethylguanidine. Additional support for the existence of intramolecular hydrogen bridging in $1H^+$ is provided by locating a ring critical point (RCP) in each of the eight-membered rings.

In summary, we have prepared hithertho unknown N, N', N''-tris-(3-dimethylaminopropyl)-guanidine derivative **1**. The X-ray structural analysis of the hexafluorophosphate salt of **1** provided firm evidence for the existence of multiple intramolecular hydrogen bonding in the solid state, in accordance with previous theoretical predictions.⁹ The existence of hydrogen bonding in solution and in the gas phase is also discussed. Our further efforts will involve investigation of the catalytic activity of **1**, as well as a measurement of its basicity.

2. Experimental

 N^1 , N^3 -Bis-(3-dimethylaminopropyl)-thiourea 2 was prepared by reacting CS₂ with 3-dimethylaminopropylamine according to a previously described procedure.²³ N^1 , N^3 -Bis-(3-dimethylaminopropyl)-carbodiimide 3 was prepared by modification of the procedure for the preparation of N^1 -cyclohexyl- N^3 -dimethylaminopropylcarbodiimide.²⁴ It involved treatment of **2** with an equimolar amount of yellow HgO in CH₂Cl₂ for 2 h followed by high vacuum distillation, yielding pure carbodiimide in 80% yield. Crystals of 1H·PF₆·CH₃CN suitable for X-ray analysis are unstable at room temperature and decompose if left in air. To prevent decomposition, a single crystal was mounted on a goniometer head and rapidly cooled in a stream of nitrogen to 100 K, at which temperature full X-ray diffraction experiments were performed. Full data sets were collected using the ω scan mode over the 2θ range of 4–60°. The structures were solved and refined using the SHELXS package.14b Structure solution was accomplished using direct methods followed by differential Fourier syntheses using the WINGX program package.^{14c}

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Supplementary data

Cartesian coordinates for the optimized structure of **1** and its protonated form are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.035.

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- 10. N, N', N''-Tris-(3-dimethylaminopropyl)-guanidine 1: A solution of carbodiimide 3 (7.33 g, 0.035 mol) and 3dimethylaminopropyl-1-amine (8.70 g, 0.070 mol) in 40.0 cm³ of dry THF was stirred under reflux for 24 h. After cooling to room temperature, the solvent was evaporated under vacuum (133 Pa, 1 mmHg) affording guanidine 1 as a colourless viscous oil (10.75 g, 0.034 mol, yield = 99%), which was used for preparation of hexafluorophosphate salt without further purification. An analytically pure sample was obtained by distillation of the crude product at 0.01 Pa $(10^{-5} \text{ mmHg}, \text{ bp} = 132 - 132)$ 136 °C/2 × 10^{-4} mmHg). Selected data: IR (KBr) $(v/cm^{-1} = 1584, 1628; N=C(NH)_2); HR-MS (M-H^+)$ exp.: m/z = 315.322185 (theor. m/z = 315.32307); ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS) δ/ppm: 1.59–1.68 (m, 6H, CH₂), 2.14 (s, 18H, CH₃), 2.25–2.29 (t, ${}^{3}J$ (H,H) = 6 Hz, 6H, CH₂), 3.09–3.13 (t, ${}^{3}J$ (H,H) = 6 Hz, 6H, CH₂), ¹³C NMR (75.5 MHz, CDCl₃, 25 °C, TMS) δ/ppm: 27.5, 39.3, 45.2, 57.3, 159.2.
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- 12. Guanidine 1 was converted to hexafluorophosphate salt by mixing equimolar amounts of 1 and NH₄PF₆ in dry acetonitrile, followed by the filtration through a Celite pad and evaporation of the filtrate. Guanidinium salt was crystallized from acetonitrile by slow addition of diethyl ether and cooling below 0 °C yielding 75% of 1H·PF₆. A crystal of 1H·PF₆ suitable for X-ray analysis was obtained by slow diffusion of diethyl ether into a solution of hexafluorophosphate salt in acetonitrile at room temperature. The crystal incorporates one molecule of solvent in the unit cell. Selected data: Mp = 111–112 °C (from

acetonitrile). ¹H NMR (300 MHz, CD₃CN, 25 °C, TMS) δ /ppm = 1.94 (m, 6H, CH₂), 2.43 (s, 18H, CH₃), 2.57 (t, ³*J*(H,H) = 6 Hz, 6H, CH₂), 3.46 (t, ³*J*(H,H) = 6 Hz, 6H, CH₂), 9.00 (br s, 1H, NH); ¹³C NMR (75.5 MHz, CD₃CN, 25 °C, TMS) δ /ppm = 27.31, 40.44, 44.76, 55.29, 159.55.

- 13. Crystal data: Crystal dimensions: $0.4 \text{ mm} \times 0.3 \text{ mm} \times$ 0.3 mm; crystal system: cubic; space group: P213; unitcell dimensions (pm): a = 1382.5(1); volume (Å³) = 2643; $\rho_{\text{calcd}} = 1.269; \quad 2\theta_{\text{max}} = 30.11; \text{ radiation and wave-}$ length = Mo K α /71.073, scan mode = omega scan; temperature = 293 K; no. of measured and independent reflections = 2558/1124; no. of reflections included in refinement = all; Lorenzian polarization and absorption correction = analytical; method of structure solution and program = direct method in SHELXS-97;^{14a} method of refinement and program = SHELXL-97;^{14a} no. of parameters = 110; the position of hydrogen atoms bound to the N1, N1' and N1" atoms were located in the final stage of the refinement, while H atoms bonded to the carbon atoms were introduced at calculated positions and treated as riding, with $U_{iso}(H)$ values equal to $1.2U_{eq}(C)$ and C-H distances of 0.93 Å. $R = 0.0589 \ (F^2 > 2\sigma(F^2)); \ wR =$ 0.1345; refinement based on $|F^2|$; residual ρ (max/ \min) = 0.251/-0.199; database: Cambridge Crystallographic Data Centre (CCDC, 12 Union Road, Cambridge CB2 1EZ, UK); CCDC reference number: 236453.
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