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Communication

The Synthesis and Structural Characterization of Peralkylated Triguanide Superbases

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Organic superbases derived from a peralkylated triguanide framework have been synthesized in a coupling reaction between monosubstituted guanidines and a Vilsmeier salt. Single crystal X-ray diffraction analysis of the chloride salt allowed the structural characterization of the benzyl derivative for the first time and revealed an effective delocalization of the positive charge despite significant distortion of the triguanide cation planarity. With the calculated gas phase basicity ranging from 262 to 265 kcal mol⁻¹ and pK_a values in acetonitrile between 28 and 30, these compounds have been evaluated as potential organocatalysts in the transesterification reaction of vegetable oil.

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Guanidine moiety plays a prominent role in the theoretical design of strong non-ionic organic bases, which significantly contributed to the expansion of known basicity scales.^[1] Special attention in this regard has been paid to guanidines substituted with flexible heteroalkyl chains capable of forming intramolecular hydrogen bonds,^[2] forcing structural rigidity in proton sponges^[3] and enlargement of the guanidine framework leading to polyguanides.^[4]

However, the progress of the in silico design of guanidine superbases,^[5] especially polyguanide based ones (e.g. tri-, tetra-, and heptaguanide),^[4] has not been followed by an equally successful development of synthetic methods in the field. While preparative chemistry of biguanides is well documented and spans from conventional procedures^[6] to more environmentallyfriendly methods,^[7] reports on the synthesis of higher analogues such as triguanides^[8a] and tetraguanides still remain scarce with only a few examples found in the patent literature.^[8b-f] Our group has recently made a contribution towards the synthesis, structure, and reactivity of pentasubstituted triguanide derivatives.^[9] These compounds have been prepared in a one-pot reaction between monosubstituted guanidines and a carbodiimide, followed by a tedious workup involving preparative HPLC. The protocol additionally suffered from the formation of several by-products as a result of diverse and hard to control reactivity of monosubstituted guanidines and pentasubstituted triguanides.

The difficulties associated with the isolation and reactivity of substituted triguanides described earlier impose the need to develop a method that would circumvent these issues and allow easier access to this class of compounds. In this communication, we wish to report on the use of a coupling reaction between monosubstituted guanidines and a Vilsmeier salt as a new strategy for the preparation of peralkylated triguanide derivatives with high basicity. Our approach utilizes the nucleophilic character of the monosubstituted guanidines, and the strong electrophilicity of the carbon atom in the Vilsmeier compound (Fig. 1). Whereas Vilsmeier salt such as 2-chloro-1,3-dimethylimidazolinium chloride, introduced by Ishikawa's group, has already found applications as a strong electrophile in guanidine chemistry,^[10] it was not until recently that this approach was also used for the synthesis of strong bases derived from imidazole and guanidine.^[11] Except for this example, there are no other literature precedents for its use in the synthesis of polyguanides.

In this way, a peralkylated triguanide backbone whereby the terminal nitrogen atoms are not part of a closed system (e.g. imidazole)^[11] could be constructed, allowing the study of basicity that originates solely from the triguanide moiety. We also hypothesized that the absence of nitrogen-bonded hydrogen atoms in such a structure should contribute to the overall stability of the triguanide backbone, thus preventing further side reactions, e.g. cyclization to 1,2-dihydrotriazines.^[9,12] Additionally, the larger number of alkyl groups in the structure has a positive effect on the basicity since the corresponding cation is stabilized by the polarizability effect exerted by the alkyl substituents.^[13]

In our first trial, a stoichiometric reaction involving one equivalent of guanidine and two equivalents of Vilsmeier salt **2** was conducted (Fig. 1b). The procedure is made up of two steps, namely the synthesis of an electrophilic species (salt **2**) and the base-assisted nucleophilic addition of a monosubstituted guanidine **3a** ($\mathbf{R} = \mathbf{Bn}$) or **3b** ($\mathbf{R} = 4$ -OMeBn).

The Vilsmeier salt 2 was prepared from tetramethylurea 1 using oxalyl chloride in a suitable solvent, which had to be exchanged for the next step while taking care of the moisture sensitivity of 2.^[14] The solvent was removed by distillation at



Fig. 1. (a) The disconnection approach for the synthesis of peralkylated triguanides. (b) A two-step synthesis of triguanides 4a (R = Bn) and 4b (R = 4-OMeBn).

reduced pressure followed by pressure equalization under an argon atmosphere, which prevented the hydrolysis of the Vilsmeier salt 2 (see Fig. SM1 in the Supplementary Material). In the second step, 2 was dissolved in dry acetonitrile or dichloromethane and reacted with benzylguanidine 3a in the presence of N,N-diisopropylethylamine (DIPEA). Although the HPLC analysis of the crude product revealed that the target peralkylated benzyl triguanide [4aH]Cl was present in the reaction mixture (Fig. SM10), the final isolated product turned out to be the intermediate biguanide salt [5aH]Cl. Repeating the reaction using four equivalents of Vilsmeier salt 2 significantly reduced the amount of biguanide **5a** in the mixture (Fig. SM11), affording the triguanide salt [4aH]Cl in satisfactory 63 % yield after workup. By analogy with the reported procedure,^[15] we attempted the synthesis of 2 in chloroform followed by guanidine addition in dichloromethane. While the Vilsmeier product 2 formed as expected, the second step in CH₂Cl₂ did not result in full conversion of guanidine 3a resulting in a mixture of 4a and 5a, as revealed by ¹H NMR and HPLC analysis (Table 1 and Fig. SM13). Also, we tested different bases such as 1,5diazabicyclo[4.3.0]non-5-ene (DBN), DIPEA, and potassium fluoride. The results show that DBN was not a good choice of base in this reaction, and neither was potassium fluoride. Although KF worked well when 2-chloro-dimethylimidazolium was used as an electrophile,^[11] in our case with the 1,1,3,3tetramethyl analogue of 2, only a small amount of triguanide 4a was formed with biguanide 5a being the major product. However, after the addition of DIPEA to the KF-mediated reaction mixture, the triguanide formation readily took place providing [4aH]Cl in 69 % isolated yield (Fig. SM12). The same behaviour was observed during the synthesis of 4-methoxybenzyl derivative 4b. Interestingly, HPLC analyses suggest that KF plays an important role in the quantitative conversion of guanidine 3a-b to biguanide 5a-b, while DIPEA is essential for the formation of triguanides **4a–b** in the final step.

With the optimized conditions in hand, the 4-methoxybenzyl derivative [**4b**H]Cl was synthesized and isolated in 62 % yield. It should be noted that HPLC and NMR analyses of the reaction

 Table 1. Optimization of the reaction conditions^A

Solvent	Base	Yield of [4a H]Cl [%]
1. Toluene	DIPEA	63
2. Acetonitrile		
1. Toluene	DBN	No reaction ^B
2. Acetonitrile		
1. Toluene	KF	$< 5^{\circ}$
2. Acetonitrile		
1. Toluene	KF then DIPEA	69
2. Acetonitrile		
1. Chloroform	DIPEA	29 ^D
2. Dichloromethane		

 $^{A}n(1): n(3a) = 4:1.$

^BAccording to ¹H NMR analysis, a complex mixture with possible opening of the DBN structure.

^CHPLC analysis.

^DBased on ¹H NMR analysis.

mixtures did not show the formation of triazine-like byproducts, as it was the case with pentasubstituted triguanides.^[9] Also, the isolated triguanide salts are stable under standard conditions and do not seem to decompose further. This observation supports the hypothesis that the elimination of hydrogen atoms (which allows the existence of a single tautomer) from the triguanide structure increases its chemical stability.

We next resorted to density functional theory (DFT) and polarisable continuum model (PCM) quantum chemical calculations to estimate the gas phase basicities (GB_{gas}) of peralkylated triguanide derivatives **4a**–**b** and biguanides **5a**–**b**. Also, their p K_a values, as listed in Table 2, were calculated using the linear equation (Eqn 1)^[12,16]:

$$pK_a = 0.617 \times GB'_{AN}(B) - 155.585$$
 (1)

where $GB'_{AN}(B)$ stands for the 'reduced basicity' of the neutral base B in acetonitrile.^[17]

Table 2. Gas phase and solution basicities (in acetonitrile) of peralkylated triguanides 4a-b and biguanides 5a-b calculated using the IEFPCM/B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) approach^[12]

Molecule	GB _{gas} (B)	$GB_{gas}^{\prime}(B)$	$\Delta G(\mathbf{X})_{\mathrm{AN}}$ [kcal mol ⁻¹]		$GB'_{AN}(B)$	pK ^A a
	$[\text{kcal mol}^{-1}]$		$X\!=\!B$	$X\!=\!BH^+$	$[\text{kcal mol}^{-1}]$	
4a	262.2	268.5	16.91	-12.75	298.2	28.4
4b	264.5	270.8	16.52	-12.58	299.9	29.4
5a	253.1	259.3	6.95	-27.11	293.4	25.4
5b	255.3	261.6	6.73	-26.65	295.0	26.4

^ACalculated using Eqn 1.

The intermediate biguanides **5a–b** have gas phase basicities of 253.1 and 255.3 kcal mol⁻¹ and p K_a values of 25.4 and 26.4 in acetonitrile (**Table 1**), respectively, making them ~6-7 p K_a units stronger base than 2-tolylbiguanide (pK_a^{AN} 19.66).^[18] Concomitantly, it was expected that **5a–b** would form the corresponding chloride salts under the applied reaction conditions. Since protonated guanidines and biguanides are poor nucleophiles, the need for an external base to drive the reaction towards a polyguanide product is obvious. The pK_a value of DIPEA in acetonitrile, which was used here as a base, was estimated to be 19.4 employing Eqn 1. Although the equilibrium between [**5a–b**]H⁺ and DIPEA is shifted towards the biguanide bases, DIPEA effectively deprotonates [**5a–b**]H⁺ because the following formation of triguanides **4a–b** as the strongest bases in the system act as the driving force for the reaction.

The introduction of the second guanidine subunit in **5a–b** to yield **4a–b** increased the basicity by ~10 kcal mol⁻¹ and the p K_a value by three units. This follows the general principle of building up basicity in polyguanides where the extension by a C(NR'R'')₂ fragment, coupled with a proper choice of substituents, leads to stronger bases.^[4] For example, the order of GB_{gas} values going from 1,1,3,3-tetramethylguanidine (TMG, 240.7 kcal mol⁻¹) to biguanides **5a–b** and triguanides **4a–b** fully conforms to this principle. Based on the GB_{gas} and p K_a values, both **4a–b** and **5a–b** can be considered as organic superbases.^[1] Furthermore, unlike **5a–b** which undergo deprotonation during the synthesis, triguanides **4a–b** after being formed remain in the form of chloride salts, witnessing the inability of DIPEA to effectively deprotonate such strong bases.

Single crystals of the benzyl triguanide chloride salt [4aH]Cl were grown by slow evaporation of ethyl acetate-ethanol mixture over a few days. The title compound crystallizes in orthorhombic Pbca space group with unit cell parameters a 15.9304 (4) Å, b 14.0589(3) Å, and c 19.0244(4) Å. In the crystal structure, the triguanidium cation is heavily distorted (Fig. 2) as evidenced by N1-C1-N3-C2 (149.86(2)°) and C2-N5-C3-N6 $(60.84(2)^{\circ})$ dihedral angles. Despite such a pronounced nonplanarity, the bond lengths within the triguanide core lie in the range from 1.3204(2) to 1.3584(2) Å (Table SM4 in the Supplementary Material). Since a typical carbon-nitrogen double bond is 1.27 Å and a single C-N bond is 1.47 Å, all the bonds in the triguanide framework are highly delocalized, confirming that the resonant stabilization of the positive charge in 4aH⁺ is not affected by its twisted geometry. This observation is in line with the reported crystal structure of pentasubstituted triguanide sulfate salt.^[9] The three guanidine subunits containing C1, C2, and C3 atoms are essentially planar, where the carbon atoms are displaced by 0.010-0.053 Å from the mean plane defined by the



Fig. 2. A distorted triguanide cation in the crystal structure of the chloride salt **[4aH]**Cl. The displacement ellipsoids are drawn at the 40 % probability level, while the hydrogen atoms are omitted for clarity.

corresponding nitrogen atoms. The pyramidalization for atoms N1, N2, N4, N6, and N7 amounts to 5.1, 0.5, 1.1, 4.1, and 1.0%, respectively, and is consistent with the protonated state of **4a**. The gas phase structure of **4a**H⁺ optimized with B3LYP/6–31G (d) is also in agreement with the solid-state one, with dihedral angles of 146.0 and 49.1°, respectively, and bond lengths of 1.326 to 1.374 Å in the triguanide (Fig. SM14 and Table SM2). Upon protonation, the three double bonds in **4a** (C1–N3, C2–N4, and C3–N5) undergo an increase in length, and the distances of the remaining triguanide core bonds slightly decrease.

The only proton in the molecule is involved in a hydrogen bond to a neighbouring chloride anion (N4-H1N4...Cl13.184(1) Å). The chloride anion also interacts with the surrounding methyl, benzyl, and phenyl protons (3.514(2)-3.706(2) Å), while the triguanidium cations interact with each other through weak van der Waals contacts between methyl groups, as well as between the benzene C–H proton and adjacent CH₃ group. This arrangement gives rise to a two-dimensional array of triguanide cations bridged by chloride anions, as shown in Fig. SM17 in the Supplementary Material.

The calculated basicity of peralkylated triguanides from 262 to 265 kcal mol⁻¹ in the gas phase and pK_a values in acetonitrile between 28 and 30 render these compounds as candidates for base-catalyzed reactions, such as the transesterification of vegetable oil^[14,19] which is an important transformation in the biodiesel production.^[20] For this purpose, we followed a standard procedure and tested the benzyl triguanide derivative **4a** in a transesterification reaction with methanol (see the Supplementary Material for details). Although the synthesized triguanides are predicted to be very strong bases, the catalytic activity of **4a** in the transesterification reaction is lower than, for example N^I, N^2 -dicyclohexyl- N^4, N^4, N^5, N^5 -tetramethylbiguanide (DCTMB) or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD),^[7] which are weaker bases (Fig. 3).

Nevertheless, 33 % conversion at 0.5 mol-% loading, 53 % at 1.0 mol-%, and 61 % at 2.0 mol-%, respectively, places triguanide **4a** above TMG (pK_a^{AN} 23.3), PMG (pK_a^{AN} 25.0), or P₁-phosphazene (pK_a^{AN} 28.27) as organocatalysts in this type of transformation.^[14] Whereas catalyst **4a** lacks protons directly attached to nitrogen atoms, DCTMB and TBD possess one such proton. In the protonated form, they are capable of forming



Fig. 3. (a) Reaction scheme for the transesterification reaction of vegetable oil. (b) Structures of the catalysts. (c) Catalytic performance of catalysts at 0.5, 1.0, and 2.0 mol-% loading. Values for DCTMB and TBD taken from Ref. [7].

hydrogen-bonded complexes with the substrate molecules (the fatty acid carbonyl group and methanol) through the $-[NH-C=NH]^+$ structural fragment.^[21] Obviously, the basicity is not the only determining factor for the successful catalytic performance of these compounds as steric hindrance and the ability to form intermolecular hydrogen bonds may also play an important role in the catalysis of transesterification reaction.

In conclusion, the strategy for the synthesis of peralkylated triguanides, based on the coupling reaction between a Vilsmeier salt and a monosubstituted guanidine has been described. Two novel triguanide derivatives **4a–b** were prepared in good yields and the molecular structure of the benzyl derivative chloride salt [**4a**H]Cl was determined by single crystal X-ray diffraction allowing access to structural features of peralkylated triguanide backbone for the first time. DFT calculations predict these compounds to be classified as superbases with estimated pK_a values in acetonitrile 28.4 (for **4a**) and 29.4 (for **4b**). Bearing this in mind, the presented peralkylated triguanide scaffold has a potential to be further transformed by substitution to enable the design of possibly stronger polyguanide bases.

Experimental

Solvents and glassware were dried before use to ensure minimal exposure of the reagents to moisture. All manipulations were carried out under an argon atmosphere. In a typical experiment, one equivalent of *N*-benzylguanidine **3a** was reacted with four equivalents of Vilsmeier salt **2** in dry acetonitrile in the presence of KF at 60°C for 20 h, followed by the addition of DIPEA, and refluxed for another 24 h. After workup, triguanide **4a** was isolated in the form of chloride salt **[4aH]**Cl. For details, see the Supplementary Material. Recrystallization of the product from ethyl acetate/ethanol (1/1) mixture afforded single crystals suitable for structure determination by X-ray diffraction. Details

of structure refinement are given in the Supplementary Material. CCDC-995347 contains the crystallographic data which can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

All computational work was done using *Gaussian* 03 package.^[22] The geometries were optimized at the B3LYP/6–31G(d) level of theory and were verified to be minima by the vibrational analysis at the same level of theory. The electronic energies and Gibbs energy corrections (E_{Gibbs}) were calculated by the B3LYP/6–311+G(d,p) and B3LYP/6–31G(d) methods, respectively. Zero point vibrational energies were used unscaled. Solvation energies ($\Delta G(X)_{\text{AN}}$) of the neutral (X = B) and protonated (X = BH⁺) species were calculated using the IEF-PCM/HF/6–31G(d) approach with Klamt radii optimized for COSMO-RS.^[23]

Supplementary Material

A detailed description of experimental procedures for the synthesis of [4aH]Cl and [4bH]Cl, a procedure for the transesterification of vegetable oil using 4a as a catalyst along with ¹H and ¹³C NMR spectra, HPLC chromatograms, crystallographic data for [4aH]Cl, electronic energies, zero-point vibrational, enthalpy, and Gibbs energy corrections, and the Cartesian coordinates for 4a–b and 5a–b are available on the Journal's website.

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