J. Chem. Sci., Vol. 122, No. 2, March 2010, pp. 157–167.

Synthesis and conformational features of *sym N,N′,N″*-triarylguanidines

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MS received 27 August 2009; revised 28 January 2010; accepted 5 February 2010

Abstract. A one pot reaction involving *sym N,N′*-diarylthiourea and the respective arylamine in the presence of aq. KOH in nitrobenzene at ≥105°C afforded *sym N,N′,N″*-triarylguanidine in fair to good yield and the products have been characterized. *Sym N,N′,N″*-tri(4-tolyl)guanidine possesses (**7**) *anti–anti* conformation, *sym N,N′,N″*-tri(2-tolyl)guanidine (**8**) and *sym N,N′,N″*-tris(2,4-xylyl)guanidine (**11**) each possess *anti–anti* $\alpha\beta\alpha$ conformation whereas *sym N,N′,N″*-tris(2-anisyl)guanidine possesses (**9**) *syn–anti* $\alpha\beta\beta$ conformation as determined by single crystal X-ray diffraction data. The observed conformations appear to result from a subtle balance between steric factor associated with the aryl substituent and multiple electronic factors namely $n-\pi$ conjugation/negative hyperconjugation and non-covalent interactions in the crystal lattice.

Keywords. *Sym N,N′,N″*-triarylguanidines; organocatalysts; *N*-donor ligands; conformations; non-covalent interactions; AM1 calculations.

1. Introduction

Guanidine, $(NH_2)_2C(=NH)$ (**A**) is a CN_3 core containing compound that possesses a central carbon atom to which one imino group (NH) and two amino groups (NH_2) are covalently bonded. *N*–Substituted guanidines have attracted attention recently due to their multiple role as non-ionic bases, organocatalysts, and as *N*-donor ligands for metal ions.[1–6] *Sym N,N′,N″*-trisubstituted guanidines **1**–**3** were shown to act as *N*-donor ligands in their monoanionic (guanidinate(1-), **B**) and dianionic (guanidinate(2-), **C**) forms and in such forms the guanidinate backbone exhibits bridging bidentate and chelating bidenate coordination modes with various metal ions.[4–6] In addition, *sym N,N′,N″*-triphenylguanidine (**1**) was also shown to coordinate to the metal ions through the imine nitrogen in its neutral form. Compounds **2** and **3** owing to their high basicity were shown to act as non-ionic bases/superbases in organic transformations.[7–9] Recently, *sym N,N′,N″*-trialkylguanidines, **4**–**6** were shown as a highly basic compounds with pK_a values 24·92, 27·15, and, 24·74, respectively in acetonitrile and the pK_a value of **5** is ca 4 units higher than that of the commercially available *N,N,N′,N′*-tetramethylguanidine (pK_a = 23·4).[10]

N-Substituted guanidines can be prepared either by *guanylation* (i.e. the conversion of an amine to a guanidine, where the amine nitrogen is incorporated into the newly formed guanidine functional group) of amine with a guanylating reagent[11] or *guanidinylation* (i.e. functionalization of a pre-existing guanidine core).[12] *Sym N,N′,N″*-tri-substituted guanidines (**1**–**6**) were prepared by guanylation reaction involving the primary amine and the respective *sym N,N′*-di-substituted carbodiimide at elevated temperatures depending upon the substrate.[8,10b,13] Guanylation of aryl amines with unsymmetrically substituted *N,N′*-diarylcarbodiimides catalysed by Bu_4NF was shown to afford unsymmetrical guanidines of the type **D** in moderate to good yield.[14] However, guanylation of aryl amine with *sym N,N′*-dialkylcarbodiimide catalysed by metal amides, half-sandwich rare earth metal complexes, and Al-$ClMe_2$ at relatively mild reaction conditions were shown to afford unsymmetrical guanidines of the type **E** in high yield.[15]

We have been interested in developing a one-pot synthesis for *sym N,N′,N″*-triarylguanidines such as **7**–**12** in high yield with a view to investigate the conformational features of this class of compounds

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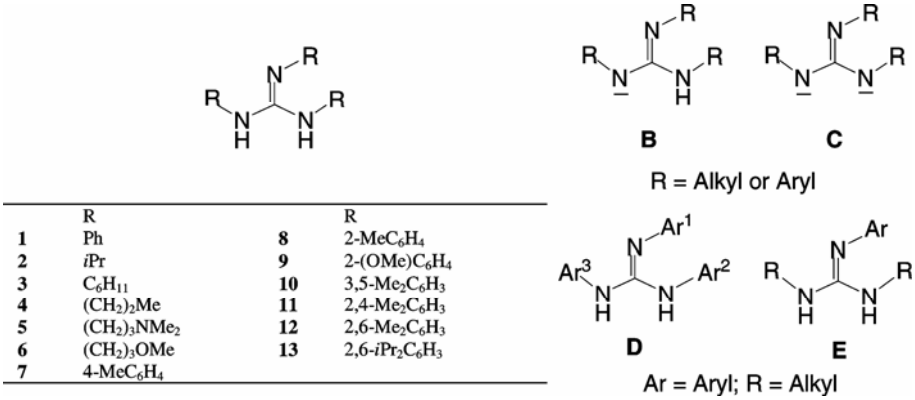


	R		R
1	Ph	**8**	2-MeC_6H_4
2	*i*Pr	**9**	2-$(OMe)C_6H_4$
3	C_6H_{11}	**10**	3,5-$Me_2C_6H_3$
4	$(CH_2)_2Me$	**11**	2,4-$Me_2C_6H_3$
5	$(CH_2)_3NMe_2$	**12**	2,6-$Me_2C_6H_3$
6	$(CH_2)_3OMe$	**13**	2,6-$iPr_2C_6H_3$
7	4-MeC_6H_4		

and subsequently utilize these compounds as organocatalysts and as *N*-donor ligands for metal ions. The electron releasing Me/OMe substituents in **7**–**12** were anticipated to exhibit a distinct reactivity pattern with metal ions as compared with **1** and could serve as NMR spectroscopic handle during the course of the reactions of **7**–**12** with metal ions.[16–20] Further, *sym N,N′,N″*-triarylguanidinium cations of **7**–**12** could be a promising scaffold to stabilize reactive anions of unusual structure given the extraordinary stability of guanidinium cations due to Y-aromaticity.[21] One of the convenient routes envisaged for **7**–**12** would be guanylation of aryl amine with the respective *sym N,N′*-diarylcarbodiimide as previously reported for **1**.[13] Unfortunately, this route is limited by *sym N,N′*-diarylcarbodiimides source. *Sym N,N′*-diarylcarbodiimides necessary for **7**–**12** are difficult to prepare because the reactions require additional reagents, toxic substances, catalysts and sometimes involve more than two-step syntheses followed by rigorous purification procedure.[22–25] Some of the *sym N,N′*-diarylcarbodiimides are difficult to isolate from the reaction mixture due to solubility issues. We describe here guanylation reactions of arylamine with the easily accessible *sym N,N′*-diarylthiourea in a single-step to afford **7**–**12** in good yield and in large quantities. Further, the procedure reported here is convenient to perform. The newly prepared *sym N,N′,N″*-triarylguanidines were characterized by micro analytical data, spectroscopic methods and representative products characterized by X-ray diffraction data. The steric and electronic factors responsible for the observed conformations of *sym N,N′,N″*-triarylguanidines were analysed.

2. Experimental

Sym N,N′-diarylthiourea $(ArNH)_2CS$ (Ar = C_6H_4Me-4, C_6H_4Me-2, $C_6H_4(OMe)$-2, $C_6H_3Me_2$-3,5, $C_6H_3Me_2$-2,4 and $C_6H_3Me_2$-2,6) were prepared from the corresponding arylamine (430 mmol) and CS_2 (660 mmol) in absolute ethanol (63·5 mL) in presence of KOH (20 wt% with respect to CS_2) following the literature procedure reported for *sym N,N′*-diphenylthiourea[26] and purified by crystallization from hot ethanol at ambient temperature. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a spectrometer with field strengths 300 and 75·5 MHz, respectively. Chemical shifts are reported in ppm and were referenced to the solvent resonance as internal standards. TOF-Mass and EI-Mass spectra were obtained on a mass spectrometer with a mass range of 1000.

2.1 *Synthesis of sym N,N′,N″-tri(4-tolyl)guanidine* $(ArNH)_2C{=}NAr$ *(Ar =* C_6H_4Me*-4)* (**7**)

A 500 mL round bottom flask was charged with *sym N,N′*-di(4-tolyl)thiourea (30·96 g, 120 mmol), 4-toluidine (12·96 g, 120 mmol), 70 wt% aq. KOH solution (27·60 g), and nitrobenzene (7·44 g). The contents of the RB flask were gradually heated up to 105°C and maintained at the same temp for 6 h, while being stirred with a mechanical stirrer. The reaction mixture was allowed to attain ambient temperature to leave an orange residue. The residue was diluted with distilled water (100 mL) and the contents of the flask were set to stir with a mechanical stirrer. Water soluble portion was decanted and the remaining residue was triturated with water (3 × 100 mL) to obtain a free flowing solid which was subsequently filtered and washed with distilled water (5 × 200 mL). The solid was transferred into a RB flask (250 mL) that contained *n*-hexane (2 × 150 mL) and the contents of the flask were set to stir with a mechanical stirrer for 15 min and allowed to stand. *n*-Hexane soluble aliquot was discarded and the insoluble solid was again dispersed in *n*-hexane (150 mL), stirred with a mechanical

stirrer for 15 min and allowed to stand. The solid was filtered in small portions and washed with *n*-hexane (4 × 200 mL), dried on a hot-plate at 70°C for 6 h to furnish **7** in 83% yield (32·71 g, 99·30 mmol). The solid was dissolved in hot ethanol (250 mL) and left at room temperature for 12 h to afford **7** (22·0 g) as colourless crystals. The mother liquor was concentrated on a rotary evaporator and left at room temperature for 12 h to afford second crops of **7** (5·01 g). The aforementioned concentration and crystallization procedure was repeated to obtain third crops of **7** (4·00 g). Total yield: 31·01 g (94·12 mmol), 78%; m.p. (DSC): 116·6°C (lit., m.p.: 118–123°C).[27] IR (KBr): 3371, 3320 (NH), 1641 (C=N) cm^{-1}. ^1H NMR: δ 2·29 (*s*, 9 H, CH_3), 5·80 (*br*, 2H, NH), 7·09 (*br*, 12H, ArH). ^{13}C NMR: δ 20·8 (CH_3), 121·7, 129·8, 132·5, 140·0, 145·5 (ArC and C=N). TOF MS ES^+, *m/z* (%): 330·9995 (83) $[M + H]^+$, 329·4692 (92) M^+, 223·6710 (45) $[ArNCNAr + H]^+$, 222·6423 (100) $[ArNCNAr]^+$. Anal. Calcd. for $C_{22}H_{23}N_3$: C, 80·20; H, 7·04; N, 12·75. Found C, 79·87; H, 6·97; N, 12·42.

2.2 *Synthesis of sym N,N′,N″-tri(2-tolyl)guanidine $(ArNH)_2C{=}NAr$ (Ar = C_6H_4Me-2)* (**8**)

Compound **8** was prepared and purified by a procedure analogous to that mentioned previously for **7**. The quantity of starting materials is given below. *Sym N,N′*-di(2-tolyl)thiourea (22·80 g, 88·90 mmol), 2-toluidine (9·52 g, 88·90 mmol), 70 wt% aq. KOH (18·00 g) and nitrobenzene (6·00 g). Yield: 82% (24·0 g, 72·85 mmol). Compound **8** was dissolved in hot ethanol (150 mL) and stored at 10°C to furnish **8** as colourless crystals in 75% yield (22·0 g, 66·78 mmol) (lit. yield: 60%).[17a] M.p. (DSC): 133·3°C. IR (nujol): 3372 (NH), 1658 (C=N) cm^{-1}. ^1H NMR: δ 2·19 (*br*, 9H, CH_3), 5·60 (*br*, 2H, NH), 7·00 (*br*, 3 H, ArH), 7·18 (*br m*, 9H, ArH). ^{13}C NMR: δ 17·8 (CH_3), 121·5 (*br*), 122·5 (*br*), 126·8, 129·0, 130·6, 144·7 (ArC and C=N). MS EI^+, *m/z* (%): 329·3 (82) $[M^+]$, 314·2 (33) $[M–Me]^+$, 222·2 (75) $[ArNCNAr]^+$, 107·1 (100) $[ArNH_2]^+$. Anal. Calcd. for $C_{22}H_{23}N_3$: C, 80·20; H, 7·04; N, 12·75. Found C, 80·31; H, 6·98; N, 12·71.

2.3 *Synthesis of sym N,N′,N″-tris(2-anisyl) guanidine $(ArNH)_2C{=}NAr$ [Ar = $C_6H_4(OMe)$-2]* (**9**)

Sym N,N′-bis(2-anisyl)thiourea (20·00 g, 69·30 mmol), 2-anisidine (8·40 g, 74·40 mmol), 70 wt% aq. KOH (14·00 g) and nitrobenzene (5·00 g) were charged into a 250 mL RB flask. The RB flask was fitted with a mechanical stirrer and gradually heated up to 105°C, while being stirred for 8 h. The reaction mixture was cooled to ambient temperature and diluted with water (150 mL). The organics were extracted with chloroform (3 × 200 mL) and the extracts were dried over anhydrous Na_2SO_4 for an hour, filtered, concentrated under vacuum to obtain an orange solid. The orange solid was dissolved in diethyl ether (150 mL) and stored at 10°C to afford a colourless powder (17·00 g). Mother liquor was concentrated and stored at 10°C to secure colourless powder (2·50 g) and this purification procedure was repeated to obtain more of **9** (1·50 g). Total yield: 80% (21·0 g, 55·64 mmol). Compound **9** (21·00 g) was dissolved in hot ethanol (150 mL) and stored at 10°C for several hours to furnish colourless crystals of **9** in 71% yield (18·50 g, 49·01 mmol), (lit., yield: 25%).[28] M.p. (DSC): 119·6°C. IR (nujol): 3407 (NH), 1655 (C=N) cm^{-1}. ^1H NMR: δ 3·80 (*s*, 9H, OCH_3), 6·35 (*br*, 1H, NH), 6·70–7·10 (*br m*, 12H, ArH), 8·50 (*br*, 1H, NH). ^{13}C NMR: δ 55·5 (OCH_3), 110·6 (*br*), 120·9 (*br*), 122·5 (*br*), 129·1 (*br*), 144·5, 149·6 (Ar*C* and C=N). TOF–MS ES^+, *m/z* (%): 380·7336 (78) $[M + 3H]^+$, 379·8248 (92) $[M + 2H]^+$, 378·1553 (83) $[M + H]^+$, 254·9967 (91) $[ArNCNAr]^+$, 242·1596 (100) $[ArNCNAr–Me + 3H]^+$. Anal. Calcd. for $C_{22}H_{23}N_3O_3$: C, 70·00; H, 6·14; N, 11·13. Found C, 69·60; H, 6·06; N, 10·75. The value of δ_C 55·5 ppm for OCH_3 was independently confirmed with the aid of two-dimensional HMQC NMR data (see supporting information).

2.4 *Synthesis of sym N,N′,N″-tris(3,5-xylyl) guanidine $(ArNH)_2C{=}NAr$ (Ar = $C_6H_3Me_2$-3,5)* (**10**)

The RB flask was charged with *sym N,N′-bis*(3,5-xylyl)thiourea (10·00 g, 35·10 mmol), 3,5-xylidine (4·25 g, 35·10 mmol), 100 wt% aq. KOH (4·33 g) and nitrobenzene (10·00 g) and fitted with a mechanical stirrer. The contents of the flask were slowly heated up to 105°C, while being stirred at the same temperature for 15 h. The reaction mixture was cooled to ambient temperature and diluted with distilled water (400 mL). The organics from the above solution were extracted with chloroform (3 × 300 mL) and the extract was subsequently dried over anhydrous Na_2SO_4. The volatiles from the extract were removed under vacuum to obtain a brown solid. The solid was dissolved in *n*-hexane (150 mL)

and left at ambient temperature for several hours to furnish **10** as crystals in 73% yield (9·50 g, 25·57 mmol). Compound **10** was dissolved in hot ethanol (150 mL) and stored at 10°C to furnish **10** as colourless crystals (5·00 g). Mother liquor was concentrated and stored at 10°C to secure more of **10** (2·00 g) and this purification procedure was repeated to obtain more of **10** (1·0 g). Total yield: 61% (8·00 g, 21·53 mmol). M.p. (DSC): 184·7°C. IR (KBr): 3387 (NH), 1648 (C=N) cm^{-1}. ^1H NMR: δ 2·27 (*s*, 18H, CH_3), 5·80 (*br*, 2H, NH), 6·67, 6·84 (*br*, 9H, Ar*H*). ^{13}C NMR: δ 21·3 (CH_3), 119·1 (*br*), 124·4 (*br*), 138·8 (*br*), 144·0 (*br*), 144·7 (Ar*C* and *C*=N). TOF–MS ES^+, *m/z* (%): 373·0528 (39) $[M + H]^+$, 372·0259 (100) $[M^+]$. Anal. Calcd. for $C_{25}H_{29}N_3$: C, 80·82; H, 7·86; N, 11·31. Found C, 80·41; H, 7·81; N, 11·36.

2.5 *Synthesis of sym N,N′,N″-tris(2,4-xylyl) guanidine $(ArNH)_2C{=}NAr$ (Ar = $C_6H_3Me_2$-2,4)* (**11**)

Compound **11** was prepared and purified by a procedure analogous to that described previously for **10** with the reaction period being 10 h. The quantity of starting materials is given below. *Sym N,N′*–bis(2,4-xylyl)thiourea (20·00 g, 70·30 mmol), 2,4-xylidine (8·51 g, 70·30 mmol), 100 wt% aq. KOH (15·79 g), and nitrobenzene (10·00 g). Yield: 77% (20·00 g, 53·83 mmol). The sample was further purified by crystallization from *n*-hexane at ambient temperature for several hours to furnish **11** in 69% yield (18·00 g, 48·44 mmol). Crystals suitable for single crystal X-ray diffraction data were grown from *n*-heptane at ambient temperature over the period of several hours. M.p. (DSC): 100·8°C. IR (nujol): 3396 (NH), 1659 (C=N) cm^{-1}. ^1H NMR: δ 2·16 (*br*, 9H, CH_3), 2·27 (*s*, 9 H, CH_3), 5·40 (*br*, 2H, N*H*), 6·95, 6·98 (*br*, 9H, Ar*H*). ^{13}C NMR: δ 17·7, 20·7 (CH_3), 122·2 (*br*), 127·3, 128·9, 129x4 (*br*), 131·2 (*br*), 145·5 (Ar*C* and C=N). TOF MS ES^+, *m/z* (%): 374·66 (48) $[M + 2H]^+$, 373·14 (55) $[M + H]^+$, 372·10 (100) M^+, 344·14 (24) $[(M–2Me) + 2H]^+$, 251·07 (22) $[ArNCNAr + H]^+$. Anal. Calcd. for $C_{25}H_{29}N_3$: C, 80·82; H, 7·86; N, 11·31. Found C, 80·73; H, 7·85; N, 11·28.

2.6 *Synthesis of sym N,N′,N″-tris(2,6-xylyl) guanidine $(ArNH)_2C{=}NAr$ (Ar = $C_6H_3Me_2$-2,6)* (**12**)

Sym N,N′–bis(2,6-xylyl)thiourea (10·00 g, 35·10 mmol), 2,6-xylidine (4·26 g, 35·10 mmol), 100 wt% aq. KOH (12·02 g) and nitrobenzene (10·00 g) were charged into a 250 mL RB flask and the flask was fitted with a water condenser. The contents in the flask were gradually heated up to 138°C and maintained at the same temperature for 24 h, while being stirred. The reaction mixture was cooled to ambient temperature and diluted with water (200 mL). The organics from the above solution were extracted with chloroform (3 × 200 mL) and dried over anhydrous Na_2SO_4. The volatiles from the extract were removed under vacuum to furnish an orange residue. The residue was washed with ethanol (80 mL) and filtered to secure **12** as a colourless solid in 69% yield (9·00 g, 24·22 mmol). The sample was further purified by crystallization from hot ethyl acetate at ambient temperature. Yield after crystallization: 65% (8·50 g, 22·88 mmol).[29,30] M.p. (DSC): 243·4°C. ^1H NMR: δ 2·33, 2·39 (*br*, 18H, CH_3), 4·76, 5·01 (each *s*, 2H, NH), 6·82 (*br*, 1H, ArH), 7·04 (*br*, 8H, ArH). ^{13}C NMR: δ 18·7 (CH_3), 121·9, 126·8, 128·1 (*br*), 128·6, 130·9, 134·7, 135·7, 136·6, 137·7, 145·3, 146·5 (ArC and C=N). IR (KBr): 3377 (NH), 1639 (C=N) cm^{-1}. TOF–MS ES^+, *m/z* (%): 373·1153 (18) $[M + H]^+$, 372·1628 (50) $[M]^+$, 371·6063 (93) $[M–H]^+$, 370·5751 (100) $[M–2H]^+$. Anal. Calcd. for $C_{25}H_{29}N_3$: C, 80·82; H, 7·86; N, 11·31. Found C, 80·63; H, 7·90; N, 11·22. The values of δ_H 4·76 and 5·01 ppm for NH protons and the value of δ_C 18·7 ppm for CH_3 were independently confirmed with the aid of two-dimensional HMQC NMR data (see supporting information).

2.7 *Crystal structure determinations*

Suitable crystals of **1**, **7**–**9**, **11** and **12** for X-ray diffraction study were carefully selected after examination under an optical microscope and mounted on the goniometer head with a paraffin oil coating. The unit cell parameters and intensity data were collected at room temperature using a Bruker SMART APEX CCD diffractometer equipped with a fine focus Mo-Kα X-ray source (50 kV, 40 mA). The data acquisition was done using SMART software, and SAINT software was used for data reduction.[31] The empirical absorption corrections were made using the SADABS program.[32] The structure was solved and refined using the SHELXL-97 program.[33] Hydrogen atoms were fixed in idealized positions and refined in a riding model. The X-ray crystallographic parameters and the details of data collection and structure refinement are presented in table S1

(see supporting information). The crystallographic data for **1** and **12** are reported in the supporting information to better analyse the non-covalent interactions though crystal structure data of **1**[34] and very recently that of **12**[30] are reported in the literature. CCDC-723582 (**1**), CCDC-723583 (**7**), CCDC-723584 (**8**), CCDC-723585 (**9**), CCDC-723586 (**11**), and CCDC-723587 (**12**) contain the supplementary crystallographic data for this paper. Copies of these data can be obtained free of charge from the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/data_request/cif).

3. Results and discussion

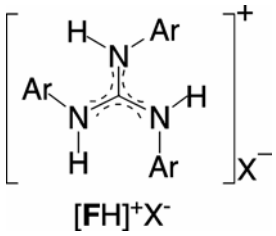
3.1 *Synthesis*

The reaction of *sym N,N′*-di(2-tolyl)thiourea with four fold excess of KO_2 in acetonitrile was shown to afford **8** in 60% yield along with trace amount of *sym N,N′*-di(2-tolyl)urea.[17a] Compounds **7**,[27,35,36] **9**[28] and **12**[30] are known in the literature but details pertinent to their synthesis and complete characterization have not been described clearly. The one pot reaction involving *sym N,N′*-diphenylthiourea and aniline in the presence of 35 wt% aq. NaOH reported for **1**[37] appeared to be the most convenient procedure for **7**–**12** because this procedure does not require *sym N,N′*-diarylcarbodiimide and hence the number of steps is reduced. We decided to prepare **7**–**12** in a single-step from the reaction involving *sym N,N′*-diarylthiourea and the corresponding arylamine following the procedure reported for **1** given the possible role of **7**–**12** as *N*-donor ligands for metal ions, and as organocatalysts. The patent procedure reported for **1** did not work for **7**–**12** and hence we substantially modified the patent procedure and the results obtained in our hands are listed in table 1. The reactions of *sym N,N′*–diarylthiourea with the respective arylamine in the presence of aq. KOH of varying strengths in nitrobenzene afforded **7**–**11** in good yield. Compounds **7** and **8** were isolated as colourless solid by simple work procedure (see experimental). Compounds **9**–**11** were isolated as colourless solid after removal of nitrobenzene by vacuum distillation. Using this procedure, **7**–**11** can be isolated on multigram scale conveniently.

The reaction of bulkier $(ArNH)_2CS$ with $ArNH_2$ (Ar = 2,6-$Me_2C_6H_3$) under the condition identical to that adopted for **10** and **11** produced **12** in low yield and the same reaction carried out at 150 °C produced largely insoluble material. Thus, the aforementioned reaction was carried out in the presence of 100 wt% aq. KOH in nitrobenzene at 138°C for 24 h to afford a mixture from which **12** was isolated as colourless crystalline material in 69% yield. Conceivably, **12** can also be prepared from the reaction involving ArNCNAr, and ArNHLi (Ar = 2,6-$Me_2C_6H_3$) as previously reported for **13**.[38] However, the method reported here for **12** does not require ArNCNAr, a reagent hard to prepare[39–41] and hence less cumbersome and more convenient to perform. The probable mechanism of formation of *sym N,N′,N″*-triarylguanidine from the reaction of *sym N,N′*-diarylthiourea and the respective arylamine in the presence of a base is believed to proceed through a tetrahedral intermediate that could collapse to form the product as outlined in scheme 1.

3.2 *Spectroscopic studies*

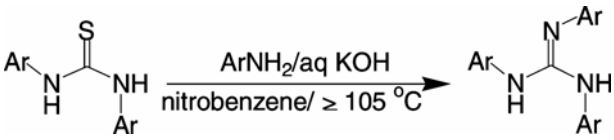
The TOF-mass spectrum of **7** revealed peaks at *m/z* = 329·4692 and 330·9995 assignable for M^+, and $[M + H]^+$, respectively whereas that of **9** revealed peaks at *m/z* =378·1553, 379·8248, and 380·7336 which are assigned for $[M + H]^+$, $[M + 2H]^+$, and $[M + 3H]^+$, respectively. The highly intense peaks observed for $[M + H]^+$ ion of **7** and **9** are attributed to the formation of a stable guanidinium cation of the type $[\mathbf{F}H]^+$. The EI-mass spectrum of **8** revealed a peak at *m/z* = 329·3 assignable for M^+. Compounds **10**–**12** revealed peaks at *m/z* = 372·0259, 372·10, and 372·1628, respectively assignable for M^+ of the respective guanidine moiety.



$[\mathbf{F}H]^+X^-$

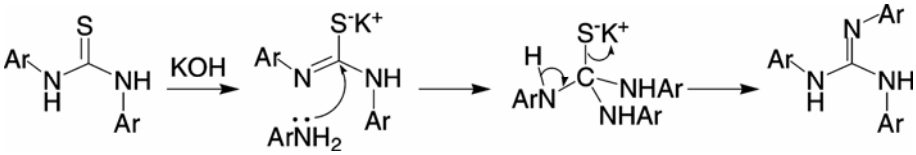
Compound **7** revealed two IR bands at 3371, and 3320 cm^{-1} assignable for ν(NH) and a single band at 1641 cm^{-1} assignable for ν(C=N) as analogously reported for **1** (ν(NH): 3387 and 3373 cm^{-1}, and ν(C=N): 1629 cm^{-1})[42] whereas the IR spectrum of **8**–**12** each revealed a single ν(NH) band at 3372, 3407, 3387, 3396, and 3377 cm^{-1} and a single ν(C=N) band at 1658, 1655, 1648, 1659, and 1639 cm^{-1}, respectively. Two ν(NH) bands observed for **1** and **7** compared with one ν(NH) band observed for **8**–**12**

Table 1. Syntheses of *sym N,N′,N″*-triarylguanidines (**7**–**12**).



Ar	Strength of aq KOH (wt%), time (h)	Compound	Yield (%)
4-MeC_6H_4	70, 6	**7**	83
2-MeC_6H_4	70, 6	**8**	82[a]
2-(OMe)C_6H_4	70, 8	**9**	80[b]
3,5-$Me_2C_6H_3$	100, 15	**10**	73
2,4-$Me_2C_6H_3$	100, 10	**11**	77
2,6-$Me_2C_6H_3$	100, 24[c]	**12**	69

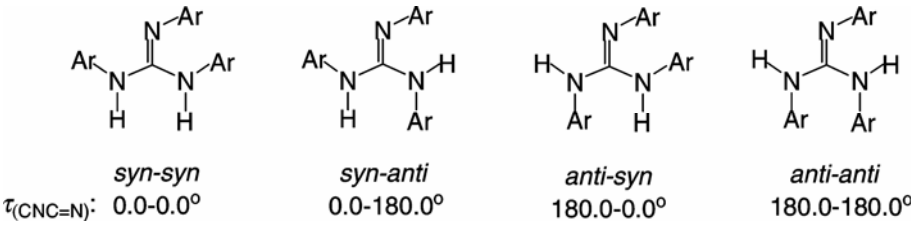
[a]Lit., yield: 60%;[17a] [b]Lit., yield: 25%;[28] [c]Temp: 138°C



Scheme 1. Probable mechanism of formation of *sym N,N′,N″*-triarylguanidines.

may be attributed to an intermolecular medium strength N–H···N hydrogen bonding present in the formerly mentioned compounds as will be discussed in the following section.

^{1}H NMR spectra of **7**, **8**, and **10** revealed a broad peak at δ_H = 2·29, 2·19, and 2·27 ppm for CH_3 protons whereas the ^{1}H NMR spectrum of **9** revealed a downfield shifted peak at δ_H = 3.80 ppm; two singlets were observed at δ_H = 2·16 and 2·27 ppm for **11** which are assignable for *o*- and *p*-CH_3 protons of the aryl moieties. In addition, compounds **7**, **8**, **10**, and **11** exhibited a broad peak in the range δ_H = 5·40–5·80 ppm whereas **12** exhibited two upfield shifted singlets at δ_H = 4·76 and 5·01 ppm for the NH protons. Compound **9** exhibited a broad peak at δ_H = 6·35 ppm and a significantly down field shifted broad peak at δ_H = 8·50 ppm for the NH protons. The ^{13}C NMR spectra of **7**, **8**, **10**, and **12** revealed a singlet at δ_C = 20·8, 17·8, 21·3, and 18·7 ppm for CH_3 carbon while **9** exhibited a downfield shifted singlet at δ_C = 55·5 ppm for O*C*H$_3$ carbon. On the other hand, two distinct singlets are observed at δ_C = 17·7 and 20·7 ppm for **11** which are ascribed to the *o*- and *p*-CH_3 carbon of the aryl rings. *Sym N,N′,N″*-triarylguanidines **1**, **7**, **10**, **12** and **13** can have four extreme C–N rotameric conformations namely, *syn–syn*, *syn–anti*, *anti–syn,* and *anti–anti* with $\tau_{CNC=N}$ torsion angles of 0·0–0·0, 0·0–180·0, 180·0–0·0 and 180·0–180·0°, respectively as illustrated in scheme 2. The number of conformer increases to a minimum of sixteen if the aryl substituents are unsymmetrically substituted as those present in **8**, **9** and **11** as listed in table 2. In solution, the conformers shown in scheme 2 and table 2 may equilibrate among themselves due to (i) rapid N–Ar bond rotation if the aryl substituents are less bulky and (ii) a relatively fast prototropic amine–imine tautomerism[43] arising from shift of the NH protons across the C=N bond as shown in scheme 3. Compounds **9** and **12**, analogous to **13**[38] appear to retain *syn–anti* conformation in solution as inferred from two separate signals observed for the NH protons. A broad peak observed for the NH protons of **7**, **8**, **10** and **11** in conjunction with a highly symmetrical ^{1}H and ^{13}C NMR spectra suggest that there exist perhaps both prototropic amine–imine tautomerism as well as N–Ar bond rotation due to less bulky aryl moieties in these compounds on a time scale faster than NMR time scale (3×10^7 s^{-1}).

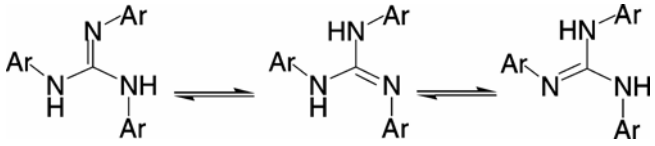


Scheme 2. Possible conformations of **1**, **7**, and **10**–**13**.

Table 2. Various possible tautomers of **8**, **9**, and **11**[a].

syn–syn $\alpha\alpha\alpha$	*syn–anti* $\alpha\alpha\alpha$	*anti–syn* $\alpha\alpha\alpha$	*anti–anti* $\alpha\alpha\alpha$
syn–syn $\alpha\alpha\beta$	*syn–anti* $\alpha\alpha\beta$	*anti–syn* $\alpha\alpha\beta$	*anti–anti* $\alpha\alpha\beta$
syn–syn $\alpha\beta\alpha$	*syn–anti* $\alpha\beta\alpha$	*anti–syn* $\alpha\beta\alpha$	*anti–anti* $\alpha\beta\alpha$
syn–syn $\alpha\beta\beta$	*syn–anti* $\alpha\beta\beta$	*anti–syn* $\alpha\beta\beta$	*anti–anti* $\alpha\beta\beta$

[a] α and β indicate upward and downward orientation of *o*-substituent on the aryl ring with respect to the CN_3 plane. The nomenclature begins from the aryl substituent attached to the imine nitrogen in a clock-wise direction



Scheme 3. Prototropic amine-imine tautomerism in *sym N,N′,N″*-triarylguanidines.

3.3 *Structural investigations*

3.3a *Crystal structures:* Compounds **7**–**9** were crystallized from ethanol and **11** was crystallized from *n*-heptane at ambient temperature and single crystals were subjected to X-ray diffraction studies. The ORTEP representations of **7**–**9** and **11** are depicted in figure. 1. Selected bond distances and bond angles are listed in table 3. Compound **7** possesses *anti–anti* conformation as indicated by $\tau_{CNC=N}$ values (–146·7(2) and –128·1(2)°) that contrast with *syn–syn* conformation revealed by **1** ($\tau_{CNC=N}$ 12·4(4) and 37·2(4)°). 4-Toluidine is more basic than aniline (pK_a = 5·08 vs 4·87) and this trend could possibly be maintained in **1** and **7**. Such difference in basicity and different types of non-covalent interactions in the crystal lattice could probably dictate the conformations of **1** and **7**. The C1–N3 distance, 1·391(3) Å in **7** is slightly longer than the analogous distance found in guanidine, **A** [1·3663(10) Å (molecule 1), and 1·3635(9) Å (molecule 2)],[44] co-crystals of $\mathbf{A}\cdot C_5H_8N_4$ (1·366(2) Å) and $\mathbf{A}_2\cdot C_5H_8N_4$ [1·359(3) Å (molecules 1 and 2)],[45] and **1** (1·363(3) Å). The salient structural parameters of **A**,[44] $\mathbf{A}\cdot C_5H_8N_4$, $\mathbf{A}_2\cdot C_5H_8N_4$[45] and related *sym N,N′,N″*-triarylguanidines are collected in table 4. The parameter Δ_{CN} defined in table 4 was used to measure the extent of delocalization of the lone pair on the amino nitrogen with the C=N bond of amidines ($n-\pi$ conjugation).[46] Δ_{CN} value range from 0 Å in fully delocalized system up to 0·10 Å in a fully localized system retaining C–N and C=N groups. We introduce an additional parameter $\Delta_{CN'}$ in table 4 to better understand the bonding situation in *sym N,N′,N″*-triarylguanidines. The Δ_{CN} 0·077(4) Å value in **7** is shorter than the $\Delta_{CN'}$ 0·106(4) Å value. The amino nitrogen in **7** are planar ($\Sigma N = 360°$) that contrasts with the significantly pyramidilised amino nitrogens in **A**,[44] $\mathbf{A}\cdot C_5H_8N_4$, $\mathbf{A}_2\cdot C_5H_8N_4$.[45] The aforementioned structural variation may be explained by invoking (i) $n-\pi$ conjugation or negative hyperconjugative interaction involving the lone pair on the amino nitrogen with C=N π^* orbital,[47] (ii) the interaction of the lone pair on the amino nitrogen with the antibonding orbital of the aryl substituent[48,49] and intermolecular N–H···N hydrogen bonding (see below).

Sym N,N′,N″-tri(2-tolyl)guanidine (**8**) possesses *anti–anti* $\alpha\beta\alpha$ conformation as inferred from the $\tau_{CNC=N}$ values (134·4(3) and 145·4(3)°) and from the orientation of *o*-Me substituents with respect to the planar CN_3 unit (see table 2). In contrast, *sym N,N′,N″*-tris(2-anisyl)guanidine (**9**) possesses *syn–anti* $\alpha\beta\beta$ conformation as revealed by $\tau_{CNC=N}$ values (–11·6(5) and 154·0(3)°) as well as from the orienta-

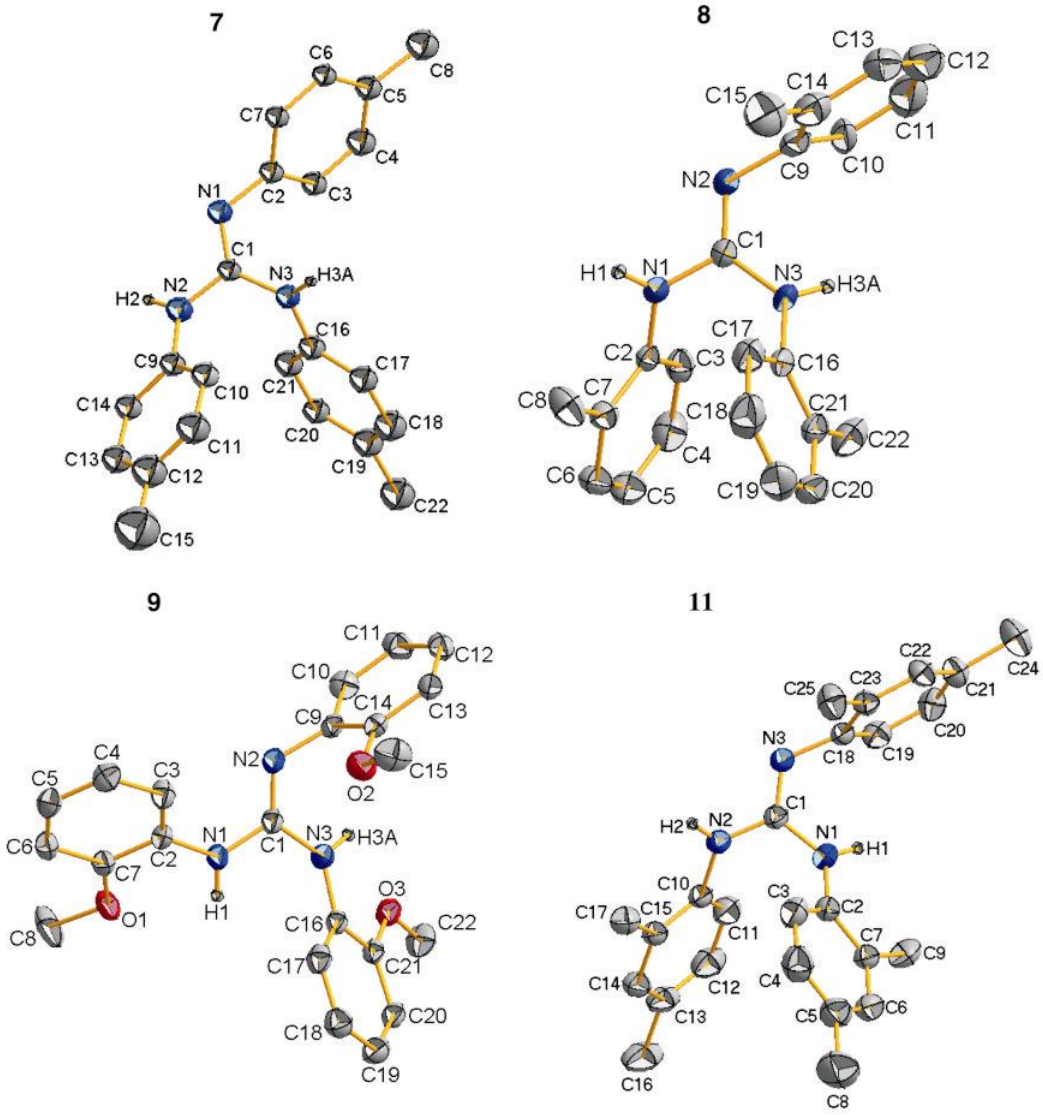


Figure 1. The ORTEP representations of **7–9** and **11** at 30% probability level. NH hydrogen atoms drawn as circles of arbitrary size and the remaining hydrogen omitted for clarity.

tion of *o*-OMe substituents with respect to the planar CN_3 unit. Thus, a subtle variation of the substituents in the *o*-position of the aryl moiety results in different conformation namely, *anti–anti* $\alpha\beta\alpha$ for **8** *versus* *syn–anti* $\alpha\beta\beta$ for **9**. The values of Δ_{CN} 0·100(6) and $\Delta_{CN'}$ 0·111(6) Å in **9** are significantly higher than those observed for **1** (Δ_{CN} 0·086(5), and $\Delta_{CN'}$ 0·078(4) Å) and these values are the highest among *sym N,N′,N″*-triarylguanidines studied.

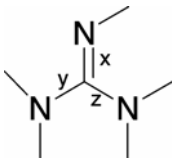
Sym N,N′,N″-tris(2,4-xylyl)guanidine (**11**) possesses *anti–anti* $\alpha\beta\alpha$ conformation as inferred from $\tau_{CNC=N}$ values (130·8(2) and 148·9(1)°) as well as from the orientation of *o*-Me substituents as analogously found in *o*-tolyl derivative, **8**. The Δ_{CN} value, 0·091(3) Å in **11** is comparable to that observed for **8** (Δ_{CN} 0·095(6) Å) but higher than that observed for **7** (Δ_{CN} 0·077(4) Å) probably owing to the steric hindrance associated with the *o*-Me substituent in **8** and **11**. Compounds **12** and **13** were shown to possess *syn–anti* conformation as revealed by $\tau_{CNC=N}$ values [$\tau_{CNC=N}$: 1·0(2) and 178·5(1)° (**12**); –11·0(2) and 172·5(2)° (**13**)].[30,38]

3.3b *AM1 Calculations:* In order to gain an insight regarding conformational features of *sym N,N′,N″*-triarylguanidines, we carried out semi-empirical AM1 energy calculations for *syn–syn*, *syn–anti*, *anti–syn,* and *anti–anti* conformations for **7** and the optimized energies for these conformers are 6·52, 0·00, 2·46 and 5·75 kcal/mol, respectively.

Table 3. Selected bond distances (Å) and bond angles (deg) for **7**–**9**, and **11**.

7		**8**		**9**		**11**	
C1–N1	1·285(3)	C1–N1	1·377(4)	C1–N1	1·372(4)	C1–N1	1·384(2)
C1–N2	1·362(3)	C1–N2	1·282(4)	C1–N2	1·272(4)	C1–N2	1·367(2)
C1–N3	1·391(3)	C1–N3	1·380(4)	C1–N3	1·384(4)	C1–N3	1·276(2)
C2–N1	1·427(3)	C2–N1	1·421(4)	C2–N1	1·408(4)	C2–N1	1·416(2)
C9–N2	1·411(3)	C16–N3	1·432(4)	C9–N2	1·413(4)	C10–N2	1·427(2)
C16–N3	1·421(3)	C9–N2	1·432(4)	C16–N3	1·400(4)	C18–N3	1·428(2)
N1–C1–N2	119·1(2)	N1–C1–N2	119·8(3)	N1–C1–N2	121·1(3)	N1–C1–N2	116·5(2)
N1–C1–N3	124·4(2)	N1–C1–N3	115·2(3)	N1–C1–N3	113·8(3)	N1–C1–N3	123·2(2)
N2–C1–N3	116·5(2)	N2–C1–N3	125·0(3)	N2–C1–N3	125·0(3)	N2–C1–N3	120·3(2)
C1–N1–C2	119·8(2)	C1–N1–C2	120·9(3)	C1–N1–C2	126·6(3)	C1–N1–C2	126·8(2)
C1–N2–C9	127·3(2)	C1–N1–H1	119·5(3)	C1–N1–H1	116·7(3)	C1–N1–H1	116·6(2)
C1–N2–H2	116·3(2)	C2–N1–H1	119·5(3)	C2–N1–H1	116·7(3)	C2–N1–H1	116·6(2)
C9–N2–H2	116·4(2)	C1–N2–C9	119·8(3)	C1–N2–C9	120·2(3)	C1–N2–C10	121·9(2)
C1–N3–C1	123·9(2)	C1–N3–C16	123·2(3)	C1–N3–C16	129·0(3)	C1–N2–H2	119·1(2)
C1–N3–H3	118·0(2)	C1–N3–H3A	118·4(3)	C1–N3–H3A	115·5(3)	C10–N2–H2	119·1(2)
C16–N3–H3A	118·0(2)	C16–N3–H3A	118·4(3)	C16–N3–H3A	115·5(3)	C1–N3–C18	119·4(2)

Table 4. Salient structural parameters of guanidine and its derivatives.



$\Delta_{CN} = y–x$; $\Delta_{CN'} = z–x$

Compound	Δ_{CN} (Å)	$\Delta_{CN'}$ (Å)	Angle sums around the amino nitrogen (deg)
A[a]			
Molecule 1	0·0616(9)	0·0661(10)	347, 356
Molecule 2	0·0733(9)	0·0611(9)	345, 350
A·$C_5H_8N_4$[b]	0·060(2)	0·071(2)	351, 356
$\mathbf{A}_2$·$C_5H_8N_4$[b]			
Molecule 1	0·047(4)	0·056(4)	359, 350
Molecule 2	0·060(4)	0·059(4)	348, 353
1	0·086(5)	0·078(4)	359, 355
7	0·077(4)	0·106(4)	360, 360
8	0·095(6)	0·098(6)	360, 360
9	0·100(6)	0·111(6)	360, 360
11	0·091(3)	0·108(3)	360, 360
12	0·083(6)	0·090(6)	360, 360
13[c]	0·041(3)	0·032(3)	358, 355

[a]Temp: 270 K,[44] [b]Ref. 45; [c]Ref. 38

Hence, *syn–anti* conformation appears to be the most stable conformer of **7**. However, compound **7** revealed *anti–anti* conformation in the solid-state. The energy penalty of 5·75 kcal/mol associated with **7** is perhaps partly compensated by crystal structure stabilization due to the N–H···N and C–H···π interactions (see supporting information). It has been demonstrated that organic compounds with flexible torsion angles are prone to exhibit conformational polymorphism.[50] The solid–state conformation of **7**

is probably kinetic in origin. Additional experiment such as variable temperature ^{1}H NMR and DFT/*ab initio* calculations would probably yield better information regarding the conformational features of *sym N,N′,N″*-triarylguanidines.

4. Conclusions

A one pot synthesis was developed for *sym N,N′,N″*-triarylguanidines in moderate to good yield without recourse to the isolation of *sym N,N′*-diarylcarbodiimide, one of the commonly used and difficult to isolate guanylating reagents. We believe that the present method is beneficial especially when *sym N,N′,N″*-triarylguanidines are required in large amounts. The observed conformations of *sym N,N′,N″*-triarylguanidines appears to be dictated by multiple factors, i.e. *steric* factor associated with the aryl rings and *electronic* factors that maximizes the conjugative interaction involving the lone pair on the amino nitrogen with C=N* orbital (negative hyper conjugation) or the antibonding orbitals of the aryl ring. The energy associated with non-covalent interactions are low (i.e. <5 kcal/mol) nonetheless these forces when act together could also play a significant role in deciding the shape/conformation of *sym N,N′,N″*-triarylguanidines.

Acknowledgements

The authors acknowledge the Department of Science and Technology, New Delhi (SR/S1/IC-22/2004) and University of Delhi for financial support. Dr M Nethaji, Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore is gratefully acknowledged for his assistance in solving the crystal structures reported in this manuscript. Pierre Charless Hirson is acknowledged for his experimental assistance in isolating compound **10**.

Supplementary information

The supplementary information can be obtained/viewed on www.cdcc.comac.uk/data_request/cif.

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