Acidity and *N*-methylation of *N*-aryl-*N′*-cyanoguanidines †

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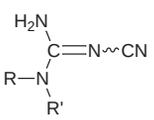
Acid dissociation constants in water have been determined for proton loss from a series of *N*-aryl-*N′*-cyanoguanidines **1**. Treatment of the same compounds with a strong base, butyllithium, followed by excess methyl iodide leads to successive *N*-methylation to yield mono-, di- and tri-methylated *N*-aryl-*N′*-cyanoguanidines. The mechanism of the methylation is discussed.

Guanidines are traditionally viewed as strong organic bases with the pK_a for guanidinium $(H_2N)_2C{=}NH_2^+$ being 13.6 in water.[1] However, *N*-substitution by a strongly electron-withdrawing group such as nitro (*e.g.* **2** (R = H)) or cyano (*e.g.* **1**



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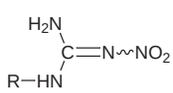

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(R = R′ = H)) dramatically reduces the basicity such that the pK_a values for the corresponding nitro- and cyano-guanidinium ions in water are quoted as -0.89 ± 0.04 and -0.63 ± 0.23, respectively.[2] The consequences of this low basicity for these and related molecules include a lack of prototropic tautomerisation in DMSO,[3] an unusual electron distribution[4] and neutrality in the solid state.[5] Moreover, nitroguanidine **2** and its amino-*N*-substituted derivatives are found to be relatively *acidic* with pK_a values for *proton loss* in water ranging from 12.80 (**2**, R = H) to 7.5 (**2**, R = H_2NCO);[2a,6] these values are comparable with those of phenols! Given this, we were interested in determining pK_a values for the cyanoguanidines and our results for the series **1** (R = various substituted phenyl; R′ = H, Me) are reported in this paper. In addition, we assess the reactivity of the cyanoguanidine conjugate anion as a nucleophile towards methylation.

Experimental

General

Chemicals for the pK_a experiments were of AR or similar grade where possible. For preparative work, except where indicated, GPR reagents were used.

Values of pH were determined using a Hanna Instruments H18417 microprocessor bench pH meter with a Russell combination electrode calibrated with solutions made from Russell pH buffer capsules.

Products were microanalysed using a Leeman Labs Inc. CE 440 elemental analyser or by high resolution mass spectroscopy using a Finnigan MAT 8400 High Resolution Spectrometer in EI mode. Melting points were determined using a Kofler apparatus. NMR experiments were carried out at 298 K using a Bruker AC300 300 MHz FTNMR spectrometer. The solvent was acetone-d_6; the reference for ^{1}H NMR was added TMS, and for ^{13}C NMR was the centre peak of the acetone multiplet at 29.8 ppm.

Preparation of *N*-aryl-*N′*-cyanoguanidines

N-Aryl-*N′*-cyanoguanidines were prepared from sodium dicyanamide and the corresponding aniline in hydrochloric acid according to a previously published procedure.[3]

Measurement of pK_a

Aqueous sodium hydroxide solutions for the pH range 11–14 were prepared by appropriate dilution of a 1.0 mol dm^{-3} solution prepared from a BDH 'convol' ampoule. The ionic strength was brought to 1.0 if necessary by the addition of an amount of sodium chloride (Rose Chemicals, 99.9%) calculated according to the equation $\mu = \frac{1}{2}\Sigma c_i z_i^2$ where c_i is the concentration of ion of charge z_i. The pH was assumed to be the calculated value. Aqueous carbonate buffers for the pH range 8.5–11 were prepared by mixing 50 cm^3 of 0.1 mol dm^{-3} sodium bicarbonate solution (prepared from BDH solid sodium bicarbonate, >99.9%) and an amount (<50 cm^3) of 0.1 mol dm^{-3} aqueous sodium hydroxide calculated to approximate to a buffer of the desired pH, along with water to make up a volume of 100 cm^3. Measurement of the exact pH by meter allowed calculation of the exact carbonate, CO_3^{2-}, and bicarbonate, HCO_3^-, concentrations which in turn allowed calculation of the amount of sodium chloride required to bring the ionic strength μ up to 1.0. The final pH value was determined by pH meter.

Samples for UV–vis analysis were prepared by pipetting 0.5 cm^3 of a stock solution of cyanoguanidine in ethanol (*ca.* 4 mmol dm^{-3}) into a 25 cm^3 volumetric flask and then making up to the mark with the appropriate buffer solution; final concentrations of cyanoguanidine, identical across the range of buffers for any individual cyanoguanidine, were typically *ca.* 0.8×10^{-4} mol dm^{-3}. The value of pH was assumed unchanged by the addition of the ethanol. Sample solutions were prepared in duplicate and for each a 'blank' was prepared using ethanol instead of cyanoguanidine in ethanol.

Spectra were run in the region 190–600 nm for each cyanoguanidine in buffer solution and duplicate, and, after subtraction of the spectrum of the 'blank', absorbances were determined at a fixed wavelength. The mean absorbance values were plotted against pH and the pK_a values determined graphically at the half-neutralisation point to give the values in Table 1.

† Full microanalytical/MS, ^{1}H NMR and ^{13}C NMR data for all products are given as supplementary information (SUPPL. NO. 57504, 9 pp.). For details of the Supplementary Publications Scheme see '*Instructions for Authors*', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC web page (http://www.rsc.org/authors).

Methylation of *N*-aryl-*N′*-cyanoguanidines—typical procedure

N-(4-Chlorophenyl)-*N′*-cyanoguanidine **1d** (0.0014 moles) was placed in a round-bottomed flask sealed with a rubber septum. The vessel was purged with dry nitrogen before addition of THF (distilled from potassium and benzophenone, 11 cm^3) and cooling to −10 °C using an ice-salt bath. *n*-Butyllithium in hexane (Janssen Chimica, 1.6 mol dm^{-3}, 1 cm^3, 0.0016 moles) was added and the mixture stirred for 30 minutes before addition of iodomethane (Aldrich, 99.5%, 0.87 cm^3, 0.014 moles). The resulting mixture was stirred at room temperature for 24 hours before addition of water (3 cm^3) and then extraction by ethyl acetate (70 cm^3). After washing of the organic layer with brine (10 cm^3) and water (3 × 10 cm^3), it was dried over magnesium sulfate, filtered and concentrated *in vacuo* to leave the crude product. This was analysed by TLC to show five components (one starting material) and when subjected to silica gel column chromatography (Acros Organics, 0.035–0.70 mm particle size, pore diameter 6 nm) using chloroform–ethanol (3% ethanol) the five components eluted in the order, *N*-aryl-*N*-methylcyanamide, trimethylated cyanoguanidine, dimethylated cyanoguanidine, monomethylated cyanoguanidine and unreacted starting material. Upon concentration *in vacuo*, samples were seen to be homogeneous by TLC and ^{1}H NMR, and following recrystallisation from chloroform–hexane, were sent for microanalysis or HRMS.

N-(4-Chlorophenyl)-*N*-methylcyanamide **6d**, 29%, mp 79–80 °C (Found: C, 57.75; H, 4.05; N, 16.78. $C_8H_7N_2Cl$ requires C, 57.67; H, 4.23; N, 16.81%); δ_H (acetone-d_6) 3.41 (3 H, s, ArNCH_3), 7.18 (2 H, d, Ar-H), 7.45 (2 H, d, Ar-H); δ_C (acetone-d_6) 37.36 (ArNCH_3), 114.26 (C_{cyano}), 117.26 (C2, C6), 128.55 (C4), 130.30 (C3, C5), 140.88 (C1). *N*-(4-Chlorophenyl)-*N′*-cyano-*N*,*N″*,*N″*-trimethylguanidine **14d**, 17%, mp 135–137 °C (Found: C, 55.79; H, 5.48; N, 23.60. $C_{11}H_{13}N_4Cl$ requires C, 55.91; H, 5.55; N, 23.73%); δ_H (acetone-d_6) 2.94 (6 H, s, $(CH_3)_2$N), 3.37 (3 H, s, ArNCH_3), 7.05 (2 H, d, Ar-H), 7.38 (2 H, d, Ar-H); δ_C (acetone-d_6) 38.40 (ArNCH_3), 39.47 ($(CH_3)_2$N), 116.48 (C_{cyano}), 120.93 (C3, C5), 128.09 (C4), 130.27 (C2, C6), 144.28 (C1), 165.09 (C_{imino}). *N*-(4-Chlorophenyl)-*N′*-cyano-*N,N″*-dimethylguanidine **10d**, 6%, mp 161–163 °C (Found: C, 53.32; H, 4.87; N, 24.42. $C_{10}H_{11}N_4Cl$ requires C, 54.04; H, 4.99; N, 25.22%); δ_H (acetone-d_6) 2.92 (3 H, d, CH_3HN), 3.36 (3 H, s, ArNCH_3), 6.30 (1 H, br s, CH_3HN), 7.35 (2 H, d, Ar-H), 7.45 (2 H, d, Ar-H); δ_C (acetone-d_6) 38.40 (ArNCH_3), 39.48 (CH_3HN), 116.45 (C_{cyano}), 120.93 (C3, C5), 128.00 (C4), 130.29 (C2, C6), 144.31 (C1), 165.11 (C_{imino}). *N*-(4-Chlorophenyl)-*N′*-cyano-*N*-methylguanidine **7d**, 28%, mp 171–173 °C (Found: C, 51.42; H, 4.16; N, 26.41. $C_9H_9N_4Cl$ requires C, 51.91; H, 4.34; N, 26.92%); δ_H (acetone-d_6) 3.29 (3 H, s, ArNCH_3), 6.32 (2 H, br s, NH_2), 7.42 (2 H, d, Ar-H), 7.51 (2 H, d, Ar-H); δ_C (acetone-d_6) 39.27 (ArNCH_3), 117.85 (C_{cyano}), 130.02 (C2, C6), 130.84 (C3, C5), 133.84 (C4), 142.37 (C1), 162.02 (C_{imino}).

All compounds gave satisfactory microanalyses/MS and the same pattern of ^{1}H and ^{13}C NMR spectra as listed for the 4-chloro series.†

Table 1 pK_a Values for *N*-aryl-*N′*-cyanoguanidines **1** in 2% ethanol–aqueous buffer at 25 °C

Compound	R rubstituent	pK_a [a]	σ [b]
1a	4-MeOC_6H_4	12.7	−0.28
1b	4-MeC_6H_4	12.6	−0.14
1c	Ph	12.0	0.0
1d	4-ClC_6H_4	12.0	0.24
1e	4-BrC_6H_4	11.9	0.26
1f	3-ClC_6H_4	11.7	0.37
1g	3-$NO_2C_6H_4$	11.3	0.71
1h	4-NCC_6H_4	11.2	0.7
1i	4-$NO_2C_6H_4$	10.9	0.81
1j	Ph [c]	*d*	

[a] The estimated precision is ±0.1 units except for **1a** and **1b** where it is ±0.2. [b] Values taken from J. March, *Advanced Organic Chemistry*, 4th edn., Wiley, New York, 1991. Most of these values are in turn from O. Exner, *Correlation analysis in Chemistry: Recent Advances*, ed. Chapman, Plenum, New York, 1978. [c] R′ = Me. [d] Not observed below pH 14.0.

X-Ray crystallography

Details of the crystal data, data collection and processing, and structure analysis and refinement for **7a** are summarised in Table 2. The structure solution was by direct methods and non-default use of MULTAN78[7] with refinement by full matrix least squares and SDP.[8] The H-atoms attached to carbon were placed in geometrically calculated positions. The value of $(\Delta/\sigma)_{max}$ was 0.08 for all atoms *except* the single-bonded N12, N22 and their attached hydrogen atoms (see Fig. 1) where the maximum was 0.45. The asymmetric unit comprised two molecules of **7a** shown in Fig. 1.

Results and discussion

Acidity of *N*-aryl-*N′*-cyanoguanidines

The pK_a values for the *N*-aryl-*N′*-cyanoguanidines **1** were determined by a UV–vis spectroscopic method in aqueous buffer solutions containing 2% ethanol. Carbonate and hydroxide buffers (0.05–1.0 mol dm^{-3}) in the pH range 8–14 were used and the ionic strength, μ, was made equal to 1.0, by addition of NaCl if necessary. The values are collected in Table 1.

In contrast to the situation for cyanoguanidines **1a**–**1i**, no curvature of the absorbance *vs*. pH plot for the *N*-methyl compound **1j** was observed below pH 14. This confirms that the site

Table 2 Crystal data for *N*-cyano-*N′*-(4-methoxyphenyl)-*N′*-methylguanidine **7a**

Formula	$C_{10}H_{12}N_4O$	μ(Mo-Kα)/cm^{-1}	0.83
Formula weight	204.23	*T*/K	298
Dimensions/mm	0.6 × 0.2 × 0.2	$2\theta_{max}$/°	52
Crystal system	Triclinic	Range of *h*, *k* and *l*	0 to 12, −12 to 12, −14 to 14
Space group	$P\bar{1}$	Scan technique	$\omega/2\theta$
Z	4	Scan rate/°(2θ) min^{-1}	6.6 (max)
a/Å	9.806(2)	Independent reflections	4091
b/Å	10.494(4)	Observed reflections	3530
c/Å	12.044(2)	Criterion	$I > 3\sigma(I)$
α/°	70.18(20)	*R*(*F*)	0.045
β/°	68.36(17)	*wR*(*F*)	0.069
γ/°	69.70(25)	*S*	1.061
V/Å^3	1048.3(5)	Extinction coefficient	none
D_x/g cm^{-3}	1.296	$(\Delta/\sigma)_{max}$	0.45
Diffractometer	Enraf-Nonius CAD4	$\Delta\rho/e$ Å^{-3}	+0.25, −0.3
Radiation	Mo-Kα		
λ/Å	0.71073		

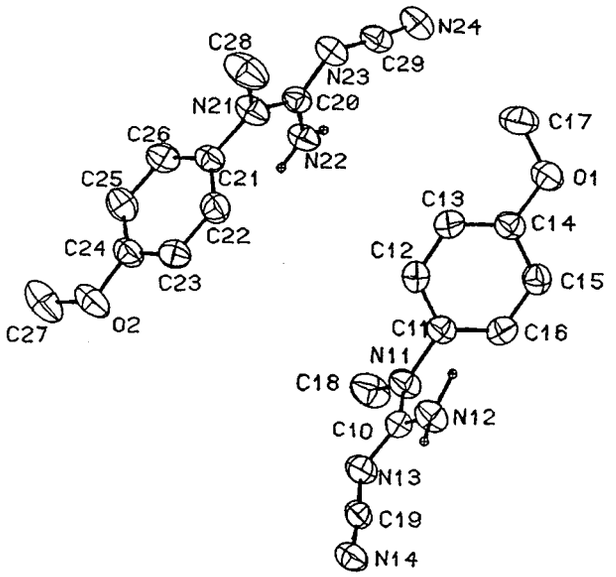


Fig. 1 The asymmetric unit of *N*-cyano-*N*′-(4-methoxyphenyl)-*N*-methylguanidine **7a** (arbitrary numbering).

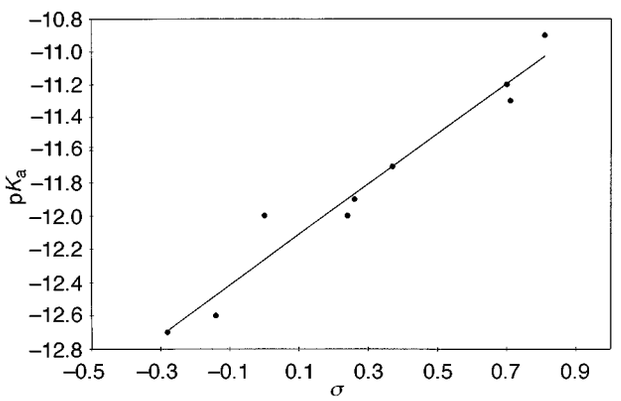


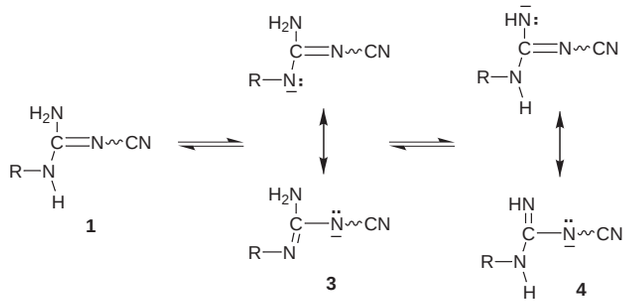
Fig. 2 LFER plot of $-pK_a$ values *vs.* σ for *N*-aryl-*N*′-cyanoguanidines **1**.

of deprotonation is the aryl-substituted N–H. In addition, no significant changes in the spectra were observed during the 'equilibration' period of several minutes or on standing for up to an hour. This indicates a rapid (on this time-scale) equilibrium deprotonation from H–N and negligible hydrolysis of the conjugate base.

A LFER plot of $-pK_a$ *vs.* σ is shown in Fig. 2. The correlation with σ ($r = 0.98$) is only slightly better than with σ^- ($r = 0.97$), although the closeness in the pK_a values for the key 3-NO_2, 4-CN and 4-NO_2 substituted compounds **1g–i** would appear to weigh more in favour of the former. The ρ value of +1.53 compares with one of +1.9 for the nitroguanidines.[6] The delocalisation of the negative charge formed on deprotonation predominantly involves the cyanoguanidine unit rather than the aryl group. This can be seen by comparing the ρ value of +1.53 for the series **1** with that of *ca.* +8 calculated for aniline deprotonation ($ArNH_2 \leftrightarrow ArNH^- + H^+$). In effect, the relatively high acidity of **1** is due to the cyanoguanidine part, with the fine variation being due to the varying aryl substituent.

Methylation of the conjugate base

The ready formation of the stable conjugate base **3** from deprotonation of **1** (Scheme 1) allows the possibility of alkylation of **3** as an alternative route to *N*-alkylated cyanoguanidines. Such compounds are traditionally prepared from reaction of the appropriate *N*-alkylated amine as for the preparation of *N*-cyano-*N*′-methyl-*N*′-phenylguanidine **1j**

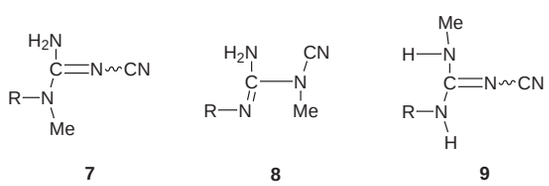


Scheme 1

above.[3,10] However, despite the fact that the aryl-substituted NH is clearly the site of first deprotonation, identifying the preferred alkylation site is not a trivial matter. The conjugate base **3** is resonance stabilised (Scheme 1) with a (−) delocalised across the guanidine system. Furthermore, there is the potential for prototropic tautomerisation to yield the tautomeric form **4** along with its resonance form. While an anion such as **4** is clearly much less stable than **3** the likelihood of its correspondingly greater nucleophilicity means that it must be considered as a potential alkylation site.[11]

Treatment of **1a**,**b**,**c**,**d**,**g** with 1.15–1.2 equivalents of butyllithium in hexane–THF followed by 2–10 equivalents of MeI gave (TLC and ^1H NMR) for each (irrespective of the amount of base and/or MeI used) the *N*-aryl-*N*-methylcyanamide **6** (see Scheme 3), *recovered starting material* **1** and three further products. These were identified from their microanalytical/MS data and from general aspects of their ^1H and ^{13}C NMR spectra as a monomethylated, a dimethylated and a trimethylated product.

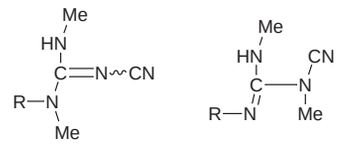
Given the likely resonance and/or tautomerisation behaviour of the anion **3** (Scheme 1), there are three reasonable candidates for the structure of the monomethyl product, **7**, **8** and **9**.[12]



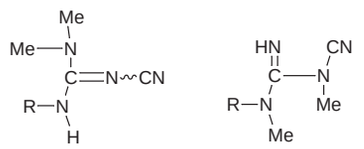
The phenyl-substituted monomethylated product (derived from **1c**) was assigned structure **7c** (R = Ph) since it was found to be identical to *N*-cyano-*N*′-methyl-*N*′-phenylguanidine, **1j**, prepared unambiguously from *N*-methylaniline and dicyanamide (**7c** ≡ **1j**).[13] An X-ray crystal structure was obtained for the 4-methoxyphenyl derivative (Fig. 1 and Table 2) showing it be **7a**.

The remaining monomethylated products were also assigned structure **7** on the basis of the similarity in the ^1H and ^{13}C NMR patterns (*e.g.* methyl singlet 3.2–3.4 ppm and a broad NH_2 peak 5.7–6.6 ppm) for these compared with the unambiguously assigned structures **7a** and **7c**.[14]

There are four likely dimethylated products **10**–**13** and in the absence of X-ray crystal structures or unambiguously prepared reference samples, NMR evidence is used to assign the correct structures. The ^1H NMR spectra of the dimethylated products all show two methyl signals, *one a singlet and one a doublet*. This excludes **12** which would be expected to show either one singlet (if rotation about the Me_2N–C bond is rapid) or two singlets (if rotation is slow). Furthermore, unambiguously prepared structures corresponding to **12a**,**b** and **c** are known in the literature with melting points of 178–180,[15] 190–192[15] and 178–180 °C,[16] respectively, sufficiently different to those for the dimethylated compounds here (those derived from **1a**, **1b** and **1c** are 135–137, 155–157 and 161–163 °C, respectively). Structure **13** can be discounted since it would not show a methyl doublet. Of the



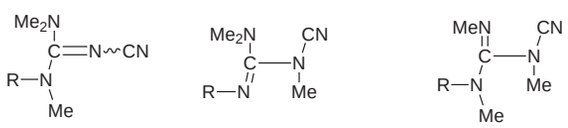
10 **11**



12 **13**

remaining two, structure **10** is preferred since it is clearly derived from the monomethylated product **7** and no evidence for a monomethylated precursor to **11** (*e.g.* **8**) is seen.

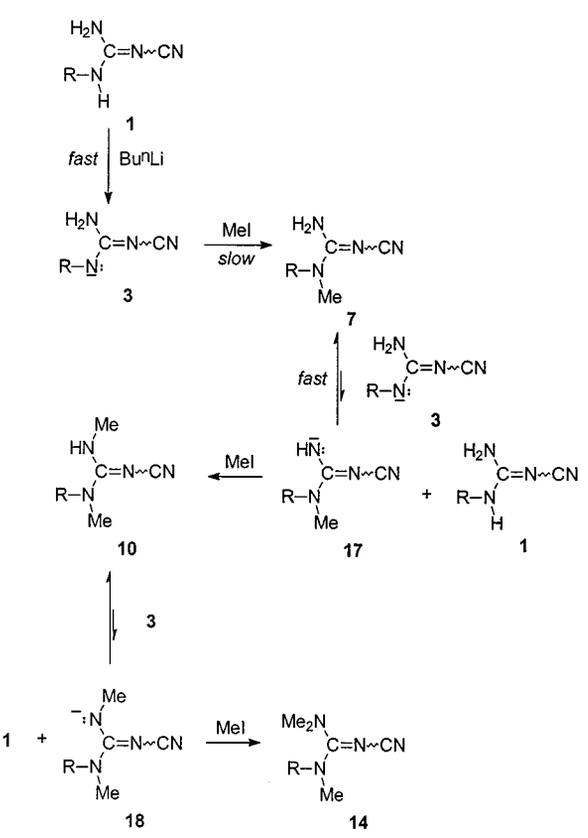
Of the three likely trimethylated products **14**–**16**, the presence



14 **15** **16**

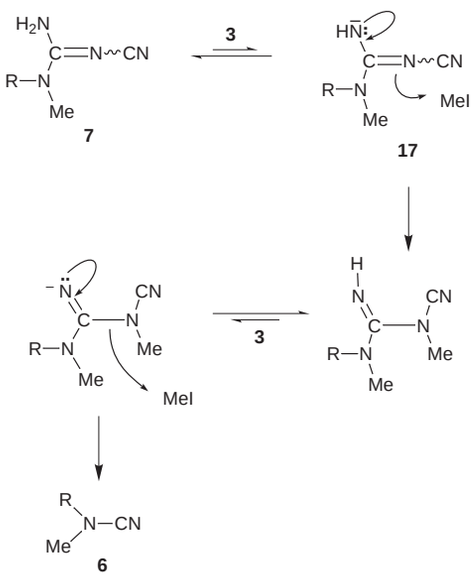
of a six-proton singlet (2.8–3.1 ppm) in the ^{1}H NMR and of only two methyl peaks (one of intensity approximately twice that of the other) in the ^{13}C NMR excludes **16**. For the chlorophenyl product (derived from **1d**) the X-ray crystal structure is available and shows this product to have structure **14d**.[17] The similarity of the ^{1}H and ^{13}C NMR spectra for all the trimethylated products supports assignment of **14** to all.

In considering a mechanism of methylation two relevant observations are worth emphasising: *i*) the relatively large amounts of unreacted starting material despite the use of *ca.* 1.2 equivalents of butyllithium and *ii*) the relatively high yield of di- and tri-methylated material. These observations we explain by the mechanism shown in Scheme 2. Rapid, irreversible and quantitative deprotonation at the Ar–NH group of the cyanoguanidine **1** is followed by a slower reaction of the conjugate base **3** with MeI. However, as the product **7** builds up, in the presence of still unreacted **3**, a proton-transfer equilibrium is set up between **3** and **7** to yield **1** and **17**, this last being the conjugate acid of **7** (**3** + **7**↔**1** + **17**). The anion **17**, being clearly less stable than **3**, is likely to be present in only small amounts, but its likely greater nucleophilicity towards MeI would be expected to 'pull' the equilibrium towards **17** giving a greater yield of dimethylated product **10** than would be expected on the basis of the relative acidity **1** and **7**.[18] A similar process (see Scheme 2) would explain the trimethylated product **14**.



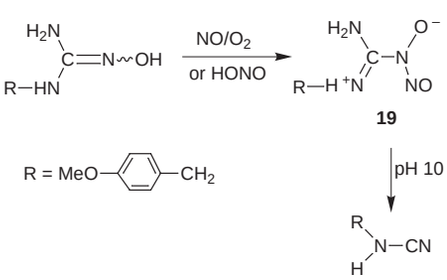
Scheme 2

In addition to the cyanoguanidines **1**, **7**, **10** and **14** were found quantities of the *N*-aryl-*N*-methylcyanamides **6**. These were identified from microanalytical/MS and spectroscopic data.[19] We propose the mechanism shown in Scheme 3 to account for the formation of these materials.



Scheme 3

The proposition of base-catalysed elimination of the imino-N and its substituent following deprotonation of the NH_2 group has some precedent. A product analogous to **6**, *N*-(4-methoxybenzyl)cyanamide, was found when the product **19** resulting from NO/O_2 or HONO treatment of *N*-(4-methoxybenzyl)-*N′*-hydroxyguanidine was dissolved in aqueous alkali (Scheme 4).[20]



Scheme 4

In conclusion, we have determined pK_a values for proton loss from *N*-arylcyanoguanidines to be in the range 10.9–12.7 and have identified the site of first deprotonation. We have also shown that alkylation of the conjugate base is relatively slow, and that proton transfer takes place between the conjugate base and the methylated product leading to di- and then trimethylated products. In addition, deprotonation can lead to elimination of the =N–CN fragment.

Acknowledgements

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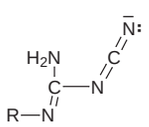
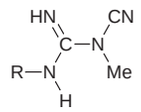
11 Other forms such as **5** where resonance involves the cyano group are much less likely to be involved given the known propensity of the cyano group to behave as a π-inductive group in cyanoguanidines; see ref. 4 and G. R. Bedford, P. J. Taylor and G. A. Webb, *Magn. Reson. Chem.*, 1995, **33**, 383.

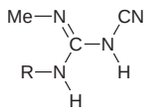


5

12 Structures such as **8′** and **9′** can be dismissed since it is well established that prototropic tautomerism favours the imino double bond towards the more electron-withdrawing cyano group (as in **9**) or if the cyano-substituted nitrogen is methylated towards the aryl group (as in **8**).



8′



9′

13 *N*-Cyano-*N′*-methyl-*N′*-phenylguanidine **1j** from *N*-methylaniline and dicyanamide, mp 139–141 °C (lit. 135–136 °C, see ref. 10).
14 In addition to the above arguments, structure **9** can almost certainly be excluded since *two* NH signals would be expected (as is seen for the parent cyanoguanidines **1**) and furthermore, the methyl signals from the CH_3NH group would appear as a doublet.
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16 M. Fedtke, F. Domaratius, K. Walter and A. Pfitzman, *Polym. Bull.*, 1993, **31** 429.
17 This compound shows unusual crystallisation behaviour and will be the subject of a separate paper. The X-ray crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre. For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/162.
18 The pK_a for **1c** (R = Ph, R′ = H) is 12. 0 in water while that for the *N*-methylated **1j** (R = Ph, R′ = Me) is >14; this suggests a difference in stability in the anions **3** *vs.* **17** of at least 2 log units.
19 Several of the products **6** are known literature compounds. The low mp values quoted (see Supplementary material for refs.) and the fact that some were obtained here in only trace amounts makes identification by mp comparison difficult. However, NMR spectra, where published, are in good agreement with those here (see Supplementary material) (see A. Alemagna, P. Del Buttero, E. Licandro and A. Papagni, *Gazz. Chim. Ital.*, 1988, **118**, 249 and R. Radeglia, W. Storek, G. Engelhardt, F. Ritschi, E. Lipmaa, T. Pehk, M. Magi and D. Martin, *Org. Magn. Reson.*, 1973, **5**, 419).
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