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Kinetic study of nitrosation of guanidines

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The kinetics of the nitrosation reaction of three guanidines, dicyandiamide, *N,N′*-dimethyl-*N″*-cyanoguanidine and guanidine have been studied. The nitrosation rate is first order with respect to both the guanidine and acid concentration. The absence of catalysis by nucleophilic anions, the observed general acid–base catalysis and the observed deuterium isotope effect lead us to propose mechanism for the nitrosation of guanidines similar to that which operates in the case of the amides and ureas, in which a slow proton transfer is the rate determining step. From this mechanism we were able to obtain the values of the rate constants for the nitrosation and denitrosation processes. The catalytic constants in presence of buffers were also obtained and the analysis of the Brönsted slopes suggests a process with a transition state more similar to reactants than products. Copyright © 2008 John Wiley & Sons, Ltd.

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Keywords: nitrosation; guanidines

INTRODUCTION

The chemistry of nitroso compounds has attracted considerable research effort mainly due to their important biological relevance. A wide variety of structurally related compounds possessing the *N*-nitroso-*N*-alkyl functionality have demonstrated a cancer chemotherapeutic potential.[1,2] However, perhaps the greatest interest in nitrosation reactions, and nitroso transfer, arises from the important role that nitric oxide plays in regulating several important physiological functions[3–6] such as the widening of blood vessels. Due to this widespread significance of nitrosation reactions, knowledge of their mechanisms and kinetics[7] is of much importance.

The mechanisms of nitrosation of amides and ureas in an acidic medium have been exhaustively investigated[8–14] and a large number of differences have been found between nitrosation of these compounds and amines. In the case of amines the attack of the nitrosating agent on the free amine is rate determining, while for amides and ureas this first step is fast, the slow step being a proton transfer from an intermediate to the reaction medium. In the latter case the reaction seems to occur initially on the oxygen atom, and a fast internal rearrangement leads to the thermodynamically more stable *N*-nitrosoamide. The reason for this seems to be related to the much lower basicity of amides, compared to amines.

Guanidines (Gs) can be considered nitrogenated analogues of ureas. However, their peculiar structure makes them compounds of great basicity, and in this sense, more similar to amines than ureas. This situation makes the kinetic study of the nitrosation of Gs, molecules that combine characteristics of both functional groups, very interesting and provides a bridge between amines and ureas. In fact a study of the nitrosation of clonidine[15] (a guanidine with hypotensive properties) has shown than in acid medium, the mechanism shows parallels with that found for ureas. However, in basic medium, the kinetic behaviour is similar to that exhibited by amines. In the present work we report the results of a kinetic investigation in acid media of the nitrosation of three Gs (as shown in Chart 1), dicyandiamide (DCDA), *N,N′*-dimethyl-*N″*- cyanoguanidine (CG) and guanidine (G).

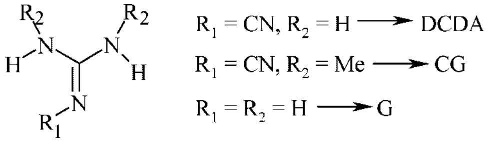

Chart 1.

EXPERIMENTAL

CG and *N,N′*-dimethyl-*N*-nitroso-*N″*-cyanoguanidine (NCG) were obtained from the Zeneca laboratories (UK). DCDA and G (as guanidine hydrochloride) were Fluka products. All other reagents (from Fluka or Sigma) were of the highest available grade and used without further purification. Nitrosation of CG gives only one product as observed by HPLC. This was shown to be identical to the sample of NCG, which was prepared and authenticated independently.[16] Kinetic runs were monitored following the change in absorbance ($\lambda = 250$–280 nm) due to the formation of the *N*-nitroso compound using a Agilent 8453 Diode-Array UV–Vis spectrophotometer equipped with a multiple cell carrier

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Table 1. Values of the kinetics parameters for the nitrosation and denitrosation of guanidines

Guanidine	pK_a	$k_n = k_3K_2$ ($M^{-1}\,s^{-1}$)	$k_d = k_{-3}$ ($M^{-1}\,s^{-1}$)	K_{NO}	$K = K_1K_{NO}$ (M^{-1})	α	β
DCDA	−0.73	5.0×10^4	2.1×10^{-3}	2.4×10^7	7.2	0.82	0.16
CG	−0.25	8.0×10^5	1.6×10^{-3}	5.0×10^8	150	0.77	0.25
G	13.6	5.5×10^3	9.2×10^{-4}	5.9×10^6	1.8	0.78	0.23

thermostatted by circulating water. All experiments were carried out at 25.0 °C. In all kinetic experiments $NaClO_4$ was used to fix the ionic strength of the medium at 1.0 M. All kinetic experiments were performed under pseudo-first-order conditions keeping in deficit the nitrite concentration ($[NO_2^-] = 2 \times 10^{-4}$ M in the experiments with CG and $[NO_2^-] = 3 \times 10^{-3}$ M when we used G or DCDA). In all cases the absorbance-time data fitted accurately the corresponding first-order integrated rate equations. The observed first-order rate constants, k_{obs} were reproducible within 5%. In the experiments to study the effect of buffers, different amounts of buffer solutions were added to mixtures that already contained the amount of acid required to achieve the desired pH.

RESULTS

Gs are traditionally viewed as strong organic bases with the pK_a for guanidinium $(H_2N)_2C{=}NH_2^+$ being 13.6 in water.[17] However, *N*-substitution by a strongly electron withdrawing group such as cyano dramatically reduces the basicity such that the pK_a value for the corresponding cyano-guanidinium ions of DCDA in water[18,19] is −0.63. We have measured the pK_a (BH^+) of CG and DCDA using a spectrophotometric method.[20] The values obtained for DCDA – similar to literature values[18,19] – and CG (as shown in Table 1) indicate to us that these compounds are in their neutral form while the G exist mainly in the protonated form under the experimental conditions used in this study ($H^+ = 2.5 \times 10^{-3} - 0.5$ M).

The influence of the concentration of the Gs on k_{obs} was studied at three different constant H^+ concentrations (0.1, 0.2 and 0.3 M) and Gs concentrations ranging from 0 to 0.5 M. Figure 1 shows the influence of the [DCDA] concentration on the observed rate constant. The plots are all good straight lines with significant positive intercepts. The values of both the slopes and intercepts increase with increasing [H^+]. This behaviour is indicative of a first order term with respect to [DCDA] and shows that the nitrosation of DCDA is an equilibrium reaction. Similar behaviour was observed for CG and G (shown in Figures S1 and S2 of supplementary material)

$$HNO_2 + \text{guanidine} \overset{K}{\rightleftarrows} NO - \text{guanidine} + H_2O \qquad (1)$$

Figure 2 shows the influence of acidity upon the reaction rate at constant concentration of Gs. The plot is a good straight line that passes through the origin for the three Gs studied, indicative of a first order dependence on the concentration of H^+.

In order to explore the apparent differences between amines and Gs, we studied the influence of the usual catalysts of the nitrosation process on the rate of the reaction. These catalysts (halides, thiocyanate, etc.) considerably accelerate the rate at which the amines[7] and amino acids[21] nitrosate by providing important concentrations of new and effective nitrosating agents (ONCl, ONBr, ONSCN, etc.). However, nitrosation of amides and related compounds[7] is not susceptible to this type of catalysis. Table 2 show the effect of the addition of X^- to the reaction media on the rate constant for the nitrosation of G. As can be observed, there is no trace of catalysis (similar results were observed for the other Gs studied, as shown in Table S1 of supplementary material). Halide ions at these concentrations produce substantial catalytic effects in the nitrosation or diazotisation of amines. This result seems to rule out a mechanism for the nitrosation of Gs similar to that which operates in the case of the amines, that is, a mechanism whose slow step is reaction between the nitrosable substrate and the nitrosating agent. Thus, towards nitrosation, Gs behave much more like an amide or urea.

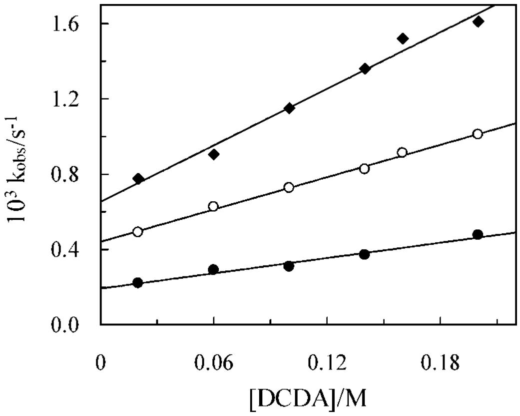


Figure 1. Influence of dicyandiamide concentration upon k_{obs}, (●) $[H^+] = 0.1$ M, (○) $[H^+] = 0.2$ M, (■) $[H^+] = 0.3$ M

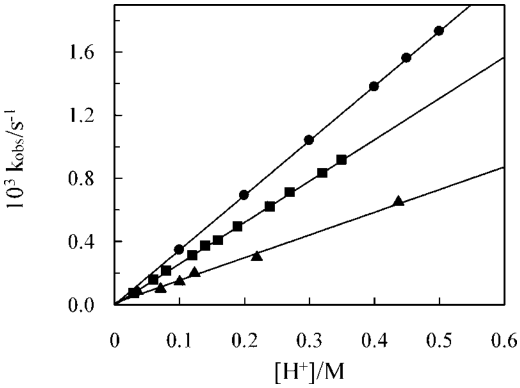
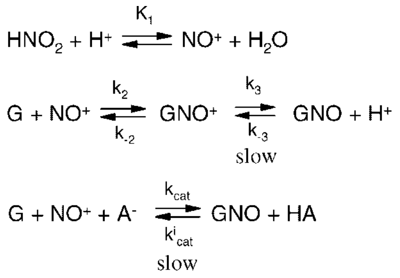


Figure 2. Influence of [H^+] upon k_{obs} in the nitrosation of (▲) [G] = 0.1 M, (■) $[CG] = 3.3 \times 10^{-3}$ M and (●) [DCDA] = 0.1 M

Table 2. Influence of X^- concentration on k_{obs} for the nitrosation of guanidine $[H^+] = 0.1$ M (NaCl) and $[H^+] = 0.44$M (NaBr), $[G] = 0.1$ M

10^2[NaCl] (M)	10^4 k_{obs} (s^{-1})	10^2[NaBr] (M)	10^4 k_{obs} (s^{-1})
0	1.45	0	6.50
5	1.14	19	6.77
7	1.67	21.75	6.92
9.75	1.52	37	6.61
25	1.33		



Scheme 1.

The mechanism for the nitrosation of Gs is show in Scheme 1. The first step, the pre-equilibrium formation of the nitrosating agent (NO^+) through protonation of nitrous acid (K_1), is followed by a fast equilibrium reaction between the nitrosating agent and the G (K_2), leading to the formation of a protonated intermediate (GNO^+). The final step is a reversible rate limiting transfer of a proton from (GNO^+) to the reaction medium to give the nitrosoguanidine (GNO). This mechanism leads to the next expression for the observed first-order rate constants (Eqn 2) which explain the influence of concentration of G and $[H^+]$ on the reaction rate, and the absence of catalysis by X^- (the derivation of this equation has been included in the supplementary material)

$$k_{obs} = k_3 K_2 K_1 [\text{guanidine}][H^+] + k_{-3}[H^+] \qquad (2)$$

The value of the overall equilibrium constant (K) for the nitrosation reaction can be obtained from the relation between the slopes and the intercepts of each straight line of Fig. 1 and Figures S1 and S2 of supplementary material. The values of K are showed in Table 1.

The observed rate equation (Eqn 2) is similar to that found in the nitrosation of amides and ureas.[9,10,13,14] The values of the bimolecular rate constant were calculated taking a value of $3 \times 10^{-7}\,M^{-1}$ for K_1,[22] (although there is considerable uncertainty over the correct value of this equilibrium constant, with measured values ranging[23,24] from this value and $1.2 \times 10^{-8}\,M^{-1}$). The values obtained for the nitrosation process $k_n = k_3 K_2$, and for the denitrosation process $k_d = k_{-3}$ for the three Gs studied are showed in Table 1. In all cases the values for the nitrosation process are lower than that found in the nitrosation of urea[25] and very far from the encounter controlled limit ($7 \times 10^9\,M^{-1}\,s^{-1}$ for neutral substrates).[7] This behaviour differs from that of most amines, whose basicity causes them to be mostly protonated and react with nitrosating agents through the free base, more nucleophilic than neutral Gs, leading to much higher values for the nitrosation bimolecular rate constants and close to the diffusion controlled limit. G is in solution in the protonated form, but the observed rate equation indicates that protonated G, of very low basicity, is the reactive species. This situation, which is impossible in the case of amines, becomes possible for G because it has more than one nuclephilic centre. The reaction via neutral G cannot be detected because its concentration is so low that the reaction rate of this process is much lower than that resulting from the less basic and less reactive, but more abundant protonated G.

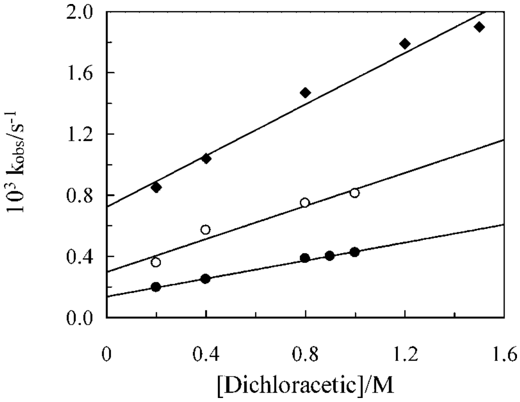


Figure 3. Influence of the total concentration of buffers dichloroacetic acid – dichloroacetate on k_{obs}, for the nitrosation of dicyandiamide [DCDA] = 0.1 M (●) pH = 1.50, (○) pH = 1.16, (■) pH = 0.71

In order to confirm the proposed mechanism and studied the process in more detail, the possibility of the existence of general base catalysis, of the type found in the nitrosation of amides and ureas, was investigated. For this, buffers of monochloroacetic, dichloroacetic and trichloroacetic acid were employed. Figure 3 shows the influence of the total concentration of dichloroacetic acid on the observed rate constant, k_{obs}, for the nitrosation of (DCDA). We can see as the reaction rate increases as increase the concentration of the buffer at all pH studied (similar results were obtained with the other buffers and the others Gs studied, as shown in Tables S2–S4 of supplementary material). The results obtained are indicative of significant buffer catalysis that indicates that the reaction is subject to a general base–acid catalysis, and strongly support the mechanism outlined in Scheme 1, in which a slow proton transfer is the rate determining step, as occurs in the nitrosation of amides and ureas. From Scheme 1, it is easy to obtain the following rate equation (Eqn 3) in presence of buffers, where k_{cat} and k'_{cat} are the catalytic constants for the nitrosation and denitrosation of Gs, respectively. In absence of buffers Eqn (3) can be simplified to Eqn (2):

$$\begin{aligned} k_{obs} &= k_n K_1 [\text{guanidine}][H^+] + k_{cat} K_1 [\text{guanidine}][H^+][A^-] \\ &\quad + k_d [H^+] + k'_{cat}[AH] \end{aligned} \qquad (3)$$

From Eqn (3) and taking into account that K_a is the dissociation constant of the buffers used, we obtain Eqn (4), which is in terms of the total concentration of buffer and explain the experimental behaviour observed in Fig. 3:

$$\begin{aligned} k_{obs} &= (k_n K_1 [\text{guanidine}] + k_d)[H^+] \\ &\quad + \left(\frac{k_{cat} K_a K_1 [\text{guanidine}] + k'_{cat}}{K_a + [H^+]}\right)[H^+][\text{Buffer}]_T \end{aligned} \qquad (4)$$

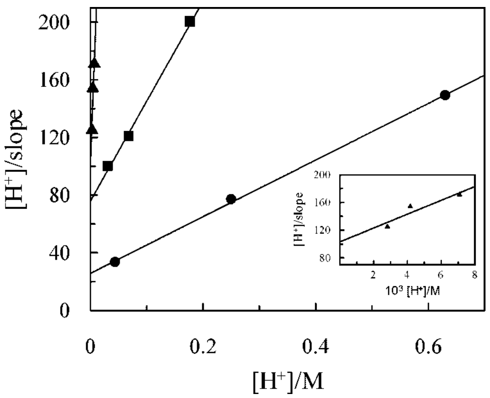


Figure 4. Fit of Eqn 5 to experimental results for the nitrosation of DCDA. (▲) MCA, (■) DCA and (●) TCA. The inset shows a blow-up of MCA data

In accordance with this equation, reciprocals of the slopes from Fig. 3 (and Tables S2–S4) have to show a linear dependence on concentration of H^+, as predicted

$$\frac{[H^+]}{\text{slope}} = \frac{K_a}{k_{cat}K_aK_1[\text{guanidine}] + k'_{cat}} + \frac{[H^+]}{k_{cat}K_aK_1[\text{guanidine}] + k'_{cat}} \tag{5}$$

In Fig. 4 we show the result obtained for the three buffers studied in the nitrosation of DCDA. From this plot the values for the dissociation constants of mono-, di- and trichloroacetic acids were obtained ($pK_a = 2.36$, 1.32, 0.70, respectively) in good agreement with literature values at this ionic strength. These results indicate the validity of the model being applied.

Catalytic constants ($k_{cat}$and k'_{cat}) for the three buffers for the nitrosation and denitrosation of Gs were obtained from Eqn (5), and taking into account the values of the equilibrium constant for the nitrosation process K_{NO}, (as shown in Table 1) defined by

$$K_{NO} = \frac{k_3K_2}{k_{-3}} = \frac{k_n}{k_d} = \frac{[\text{GNO}][H^+]}{[\text{guanidine}][NO^+]} \tag{6}$$

and its relationship with the acidity constant of the buffers used:

$$\frac{k_{cat}}{k'_{cat}} = \frac{[\text{GNO}][\text{AH}]}{[\text{guanidine}][NO^+][A^-]} = \frac{K_{NO}}{K_a} \tag{7}$$

Table 3 summarises the catalytic constants for nitrosation and denitrosation of the Gs for all buffers used and Fig. 5 shows the Brönsted plots relating the catalytic efficiency and the pK_a of the catalysts for all Gs studied. It is clear that these plots are essentially straight lines. From the slopes of the plots we can calculate the values of the Brönsted exponents (α and β) for the three Gs studied, (as shown in Table 1). These values are very similar for our Gs and we can see that $\alpha + \beta$ is approximately the unit for all cases, as correspond to a reversible process. The practice of identifying the degree of proton transfer in the transition state with the value of the Brönsted slope allow us to estimate that the transition state of the slow process for the nitrosation occurs early along the reaction coordinate ($\beta \approx 0.20$) and late for the denitrosation reaction ($\alpha \approx 0.80$), it means that protonation of nitrosoguanidine is nearly complete in the transition state.

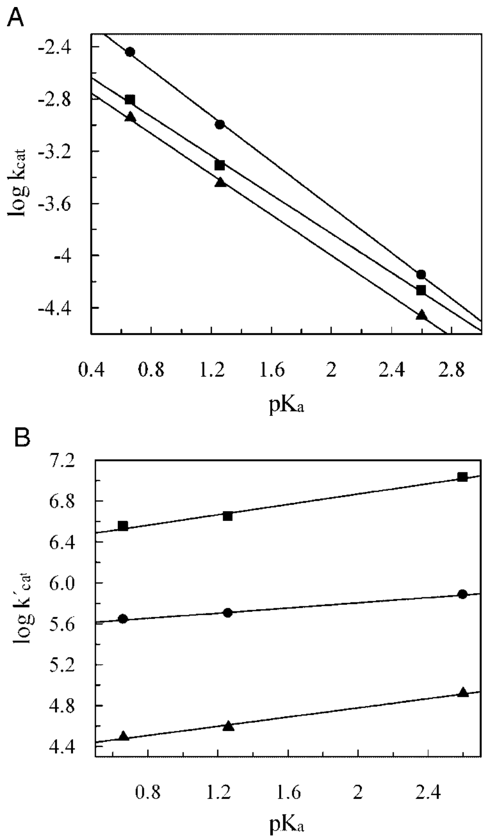


Figure 5. Brönsted plot for (A) base catalysed nitrosation and (B) acid catalysed denitrosation of (●) DCDA, (■) CG and (▲) G

One last indication that the slow step is a proton transfer was obtained when the reaction was carried out in D_2O and the corresponding solvent isotope effect was measured. The results obtained and its comparison with the reaction in presence

Table 3. Values of the catalytic constants for nitrosation and denitrosation of the guanidines for all buffers used

	CG		G		DCDA	
	k_{cat} ($M^{-2}s^{-1}$)	k'_{cat} ($M^{-1}s^{-1}$)	k_{cat} ($M^{-2}s^{-1}$)	k'_{cat} ($M^{-1}s^{-1}$)	k_{cat} ($M^{-2}s^{-1}$)	k'_{cat} ($M^{-1}s^{-1}$)
MCA	1.07×10^7	5.37×10^{-5}	8.30×10^4	3.47×10^{-5}	7.65×10^5	7.12×10^{-5}
DCA	4.44×10^6	4.88×10^{-4}	3.91×10^4	3.58×10^{-4}	5.03×10^5	1.02×10^{-3}
TCA	3.54×10^6	1.55×10^{-3}	3.12×10^4	1.14×10^{-3}	4.46×10^5	3.62×10^{-3}

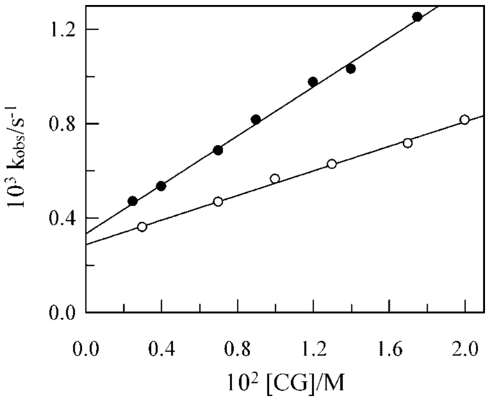


Figure 6. Influence of CG concentration upon k_{obs} $[H^+] = 0.204$ M, (●) in H_2O, (○) in D_2O

of H_2O is shown in Fig. 6 for the case of CG. The observed deuterium isotope effect for the nitrosation reaction $k_nK_1(H)/k_nK_1(D)$ is 1.6 (1.7 for G) and for the denitrosation reaction, $k_d(H)/k_d(D)$ is 1.2. Once again, these results confirm that Gs behave like an amide or urea and not like an amine, which should show inverse solvent isotope effects (typically 0.3).[26] Besides, taking into account the mechanism outlined in Scheme 1, the observed value for the isotope effect for the nitrosation reaction includes the influence of the isotopic substitution on the equilibrium constants K_1 and K_2 and on the rate constant for the slow step k_3. Replacement of water by deuteriated water increases the value of K_1 2.55 times.[26] Assuming that there is a negligible isotope effect upon K_2, because it does not involve a proton transfer, then the value of the kinetic isotope effect on the slow step, $k_3(H)/k_3(D)$, can be estimated as 4.1. This result is consistent with the proposed step being a slow proton transfer from an acidic species to the water. The magnitude of the isotope effect can be related to the degree of symmetry of the transition state.[27] Thus, both the values of the Brönsted slopes and of the solvent isotope effect on the slow step suggest a process with a transition state more similar to reactants than products.

In spite of the restricted set of Gs used in this study we can try to analyse the substituent effects on the nitrosation process. The presence of an electron-withdrawing group on the iminic nitrogen of Gs (as cyano group), increases the reaction rate. The value of k_n (as shown in Table 1) for DCDA is around 10 times higher than for G. Electron withdrawing groups increase the rate of nitrosation process because of enhanced acidity of the protonated *N*-nitroso guanidine (GNO^+) and then increase the value of k_3. The value of the nitrosation rate constants k_n for CG is also 10 times higher than for DCDA. In this case the presence of electron donating groups also increases the reaction rate. The substituent effects can be understood keeping in mind the mechanism proposed in Scheme 1. Electron donating groups will favour the formation of the protonated nitrosoguanidine (K_2) and disfavour the proton transfer from this intermediate to the medium (k_3). Opposite effects will exert electron withdrawing groups. Substituent effects will arise from the balance between these two processes.

The study of the nitrosation reaction of these Gs lead us to confirm that kinetic behaviour is similar to that exhibited by amides and ureas, the slow step is a proton transfer from an protonated intermediate to the reaction medium. It can be concluded that the basicity of the reactive form is the main factor determining the mechanistic behaviour of Gs towards nitrosating agents. In our acidic medium, DCDA and CG react through the neutral form, whose basicity is low and similar to that of ureas and amides. In the case of G, it is the protonated form of G, of very low basicity, which reacts. This fits in to the pattern of behaviour found for other nitrogen nucleophiles of low basicity, such as ureas and amides, which is quite different to that found for the much more basic amines. Interestingly the much less basic 2,4-dinitroaniline[25] behaves more like an amide or urea. Finally, the analysis of the Brönsted slopes suggest that in the transition state the protonation of nitrosoguanidine is nearly complete.

Acknowledgements

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