# Kinetics and Mechanism of Nitrosation of *N,N′*-Dimethyl-*N″*-cyanoguanidine†

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The nitrosation reaction of *N,N′*-Dimethyl-*N″*-cyanoguanidine is reversible and the mechanism is similar to that found for the nitrosation of amides and ureas.

The nitrosation of amines, ureas, amides has received much attention, owing in large part to the potential carcinogenic properties of the *N*-nitroso products formed. Nitrosation of amines in acidic medium occurs with rate limiting attack of the nitrosating agent on the free base form of the substrate,[1] while that of amides and ureas involves fast *O*-nitrosation followed by slow proton transfer from the substrate and a fast internal rearrangement to yield the N-nitroso products.[1–4] Guanidines can be considered nitrogenated analogues of ureas. However, their peculiar structure makes them compounds of great basicity, and in this sense, are more similar to amines than ureas. This situation makes the kinetic study of the nitrosation of guanidines, molecules that combine characteristics of both functional groups, very interesting and provides a bridge between amines and ureas.[5]

In the present work we report the results of a kinetic investigation in acid media ($1.6 \times 10^{-3}$–0.3 mol dm$^{-3}$ $H^+$) of the nitrosation of *N,N′*-dimethyl-*N″*-cyanoguanidine (CG).

## Experimental

CG and *N,N′*-dimethyl-*N*-nitroso-*N″*-cyanoguanidine (NCG) were obtained from Zeneca laboratories (UK). $D_2O$ was supplied by CIEMAT (Spain). All other reagents were Merck products and were used as received. Kinetics studies were carried out at 25 °C and at a constant ionic strength of 0.5 mol dm$^{-3}$. The analyses of the kinetic data were performed using the integration method following the formation of NCG spectrophotometrically at 280 nm.

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.

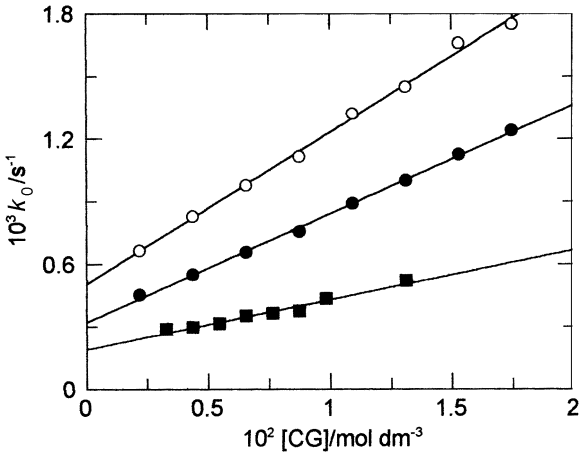


**Fig. 1** Influence of CG concentration on $k_o$; (○) $[H^+] = 0.30$ mol dm$^{-3}$, (●) $[H^+] = 0.204$ mol dm$^{-3}$, (■) $[H^+] = 0.102$ mol dm$^{-3}$

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## Results and Discussion

The p$K_a$ of CG was measured potentiometrically, and a value of 7.9 was obtained, similar to literature values.[6] This means that at the working acidities, CG will exist mainly in the protonated form.

The influence of the concentration of the CG on $k_0$, the measured pseudo first order constant, was studied at three different constant $H^+$ concentrations (0.1, 0.2 and 0.3 mol dm$^{-3}$) and CG concentrations ranging from 0 to $2.0 \times 10^{-2}$ mol dm$^{-3}$. The plots (see Fig. 1) 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 [CG] and, shows that the nitrosation of CG is an equilibrium reaction [eqn. (1)]. The value of the equilibrium constant can be obtained from the relation between the slopes and the intercepts of each straight line. A value of $K = 150 \pm 20$ dm$^3$ mol$^{-1}$ was obtained.

$$HNO_2 + CG \overset{K}{\rightleftharpoons} NCG \qquad (1)$$

Fig. 2 shows the influence of acidity upon the reaction rate at constant concentration of CG. The plot is a good straight line that passes through the origin, indicative of a first order dependence on the concentration of $H^+$. The data obtained in the studies of the influence of [CG] and $[H^+]$ can be fitted to eqn. (2).

$$k_o = k_n[CG][H^+] + k_d[H^+] \qquad (2)$$

The value of the third order rate constant $k_n$ for the nitrosation of CG obtained from the different experiments was $0.24 \pm 0.01$ dm$^6$ mol$^{-2}$ s$^{-1}$, and the value of $k_d$, the second order rate constant for the denitrosation of NCG, obtained was: $(1.6 \pm 0.2) \times 10^{-3}$ dm$^3$ mol$^{-1}$ s$^{-1}$.

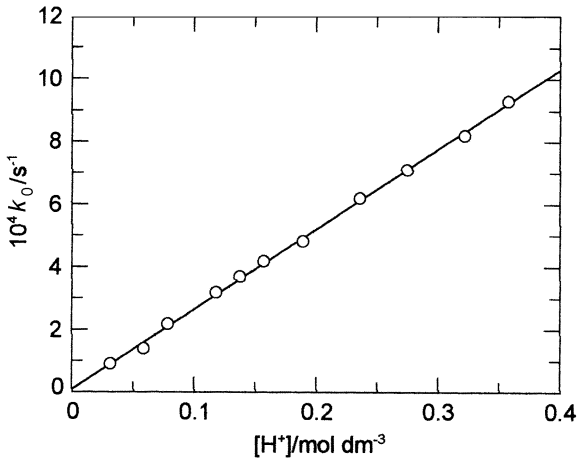



**Fig. 2** Influence of acidity on the reaction rate; $[CG] = 3.3 \times 10^{-3}$ mol dm$^{-3}$

In order to explore the apparent differences between amines and cyanoguanidine, we studied the influence of halide ions on the reaction rate. These ions catalyse the nitrosation of amines (by way of nitrosyl halides generated *in situ*) but not of amides and ureas. Table 1 shows the effect of the addition of $X^-$ to the reaction media on the rate constant. As can be observed, there is no trace of catalysis. Thus, towards nitrosation, CG behaves much more like an amide or urea. Halide ions at these concentrations produce substantial catalytic effects in the nitrosation or diazotisation of amines.

**Table 1** Influence of the concentration of $X^-$ on the pseudo first order constant, $k_o$; $[CG] = 8.8 \times 10^{-3}$ mol dm$^{-3}$, $[H^+] = 0.20$ mol dm$^{-3}$

| $10^2$ [NaCl]/mol dm$^{-3}$ | $10^2$ [NaBr]/mol dm$^{-3}$ | $10^4$ $k_o$/s$^{-1}$ |
|---|---|---|
| — | — | 7.70 |
| 2.39 | — | 7.73 |
| 5.59 | — | 7.57 |
| 11.2 | — | 7.53 |
| — | 1.2 | 7.70 |
| — | 2.8 | 7.91 |
| — | 5.6 | 7.72 |

To study the mechanism of 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, a buffer of monochloroacetic acid (MCA) was employed. The results obtained (Table 2) are indicative of significant buffer catalysis. This indicates that the reaction is subject to a general base catalysis, and implies a slow proton transfer in the rate determining step, as occurs in the nitrosation of amides and ureas.

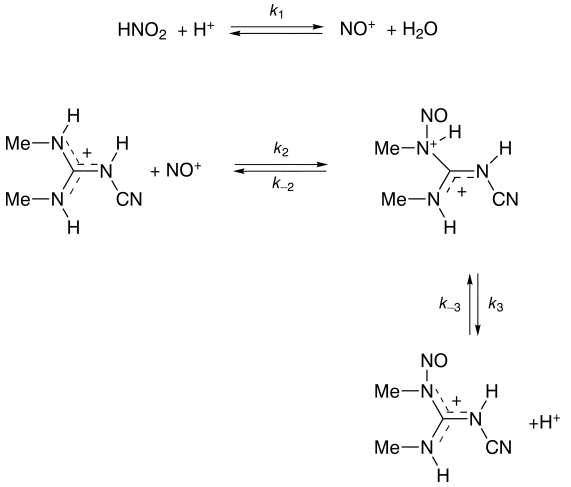
**Table 2** Effect of MCA buffer on $k_o$; $[CG] = 8.8 \times 10^{-3}$ mol dm$^{-3}$, pH = 2.10

| [MCA]/mol dm$^{-3}$ | $10^5$ $k_o$/s$^{-1}$ |
|---|---|
| 0.051 | 3.55 |
| 0.101 | 4.31 |
| 0.152 | 5.13 |
| 0.203 | 5.78 |
| 0.253 | 6.47 |
| 0.306 | 7.01 |

The mechanism for the nitrosation of CG is shown in Scheme 1. The first step, the pre-equilibrium formation of the nitrosating agent ($NO^+$ or $H_2NO_2^+$) through protonation of nitrous acid ($K_1$), is followed by a fast equilibrium reaction between the nitrosating agent with and the protonated CG ($K_2$), leading to the formation of an intermediate. The final step is a reversible rate limiting transfer of a proton from the intermediate to the reaction medium. This mechanism leads to the rate eqn. (3) which coincides with the experimental one [eqn. (2)]. This mechanism explains the experimental rate equation, the absence of catalysis by $X^-$, and the existence of general base catalysis.

$$k_o = k_3 K_2 K_1 [GC][H^+] + k_{-3}[H^+] \quad (3)$$

One other experimental 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 observed deuterium isotope effect for the nitrosation reaction $k_n(H)/k_n(D)$ is 1.6 and for the denitrosation reaction, $k_d(H)/k_d(D)$ is 1.2. Once again, these results confirm that CG behaves like an amide or urea and not like an amine, which should show inverse solvent isotope effects




**Scheme 1**

(typically 0.3).[7] 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.[7] Assuming that there is a negligible isotope effect upon $K_2$ (since 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 is consistent with the proposed step being a slow proton transfer from an acidic species to the water.

It can be concluded that the basicity of the reactive form is the main factor determining the mechanistic behaviour of CG towards nitrosating agents. In acid media, it is the protonated form of CG, 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 shows no halide ion catalysis,[8] and so behaves more like an amide or urea.

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