Mechanism of Reactions of Some N^1-Substituted Biguanides with Chromium(VI) in Aqueous Sulphuric Acid Media

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N^1-Phenylbiguanide RHN–C(=X)NH–C(=NH)NH_2 (R = Ph, X = NH) reacts quantitatively in aqueous sulphuric acid media with Cr^{VI} and Ce^{IV} to produce 1,4-benzoquinone, carbamimidoylurea (R = H, X = O), and ammonium ion. N^1-(4-Methoxyphenyl)biguanide (R = 4-$MeOC_6H_4$, X = NH) reacts similarly except that, instead of a quinone, more extensively oxidized products are produced. Phenylbiguanide (pbg) itself, in acid solution, undergoes slow hydrolysis, and anilinium ion is one of the products. The hydrolyzed solution reacts rapidly with Cr^{VI} and Ce^{IV}. None of the other six biguanides investigated and three other structurally related compounds reacts with Cr^{VI} under the experimental conditions. The kinetics of the reactions is in accord with the rate law (i). A typical

$$\frac{-d[Cr^{VI}]}{dt} = -\frac{4}{3}\frac{d[pbg]}{dt} = k[pbg] \qquad (i)$$

value of k is $(0.25 \pm 0.03) \times 10^{-5}\ s^{-1}$ at 20 °C, $[H^+] = 1.0$ mol dm^{-3}, and $I = 2.0$ mol dm^{-3}, and when determined from experiments with an excess of Cr^{VI} (first-order kinetics observed) agrees closely with that determined in the presence of an excess of pbg (zero-order kinetics) and also that determined for reactions with Ce^{IV}. These results have been interpreted in terms of a mechanism involving the acid-promoted hydrolysis of phenylbiguanide [and (4-methoxyphenyl)biguanide], the oxidant functioning as an analytical assay of the anilinium product.

Biguanides are useful materials for the treatment of hyperglycaemia,[1,2] malaria,[3,4] fileria,[5] and influenza.[6] Thus for example, phenformin [N^1-(2-phenylethyl)biguanide], metformin (N^1,N^1-dimethylbiguanide), and proguanil [N^1-(4-chlorophenyl)-N^5-(1-methylethyl)biguanide] are familiar medicines for diabetes. Recently, the anticarcinogenic effect of at least two substituted biguanides has been established.[7]

Biguanide is a strong base (pK = 13)[8] having an exceptionally high heat of neutralization. Biguanide and substituted biguanides form stable metal[9] and non-metal[10] chelate compounds with extensive π delocalization[8b,11] and stabilize unusual oxidation states of metals.[12] Due to their pseudo-aromatic nature[13] such chelates undergo electrophilic substitution[14] reactions. In addition, biguanides are starting materials for a variety of triazines[15] and heterocyclic compounds[15a] of medicinal value and take part[16] either in the free state or in the complexed form in Schiff-base type reactions giving rise to a wide range of products.

However, except for metal ion–biguanide interactions (*e.g.* formation,[17] dissociation,[18] and intramolecular[19] redox decomposition of biguanide complexes), the mechanisms of the reactions with biguanides have rarely been investigated systematically. The present study involving Cr^{VI} was therefore undertaken. Reactions with Ce^{IV} were also investigated to a limited extent for comparison.

Experimental

Materials and Reagents.—Biguanide[20] RHN–C(=X)NH–C(=NH)NH_2 (X = NH, R = H), N^1-substituted biguanides[21] (X = NH, R = Me, Ph, $PhCH_2$, 4-ClC_6H_4, 4-$MeOC_6H_4$, or 4-$HO_3SC_6H_4$), carbamimidoylurea[22] (X = O, R = H), and N^1-phenylcarbamimidoylurea[23] (X = O, R = Ph) were prepared by usual procedures in the form of their sulphate salts, except for phenylbiguanide for which the hydrochloride salt was prepared for convenience. Guanidine hydrochloride H_2N–C(=NH)–NH_2·HCl was used as received (Koch-Light). All other chemicals used were of reagent grade. Distilled water, freshly redistilled from alkaline permanganate solution in an all-glass still, was used to prepare the solutions.

Procedure and Kinetic Measurements.—The kinetics, under various reaction conditions, were monitored through the loss of oxidant measured spectrophotometrically or titrimetrically at 20, 60, 65, and 70 °C. The absorbance per cm was measured against a reagent blank using a Shimadzu Graphicord (UV-240) spectrophotometer at 320 nm for Ce^{IV} and 370 nm for Cr^{VI}. The oxidant concentration was evaluated from these absorbances and the ε values measured using Beer's law curves. For titrimetric assay of Cr^{VI}, known aliquots of reaction mixtures containing Cr^{VI} were periodically withdrawn and run into an excess of Mohr salt [$FeSO_4 \cdot (NH_4)_2SO_4 \cdot 6H_2O$] solution, then back titrated with standard $K_2Cr_2O_7$ using barium diphenylamine sulphonate as indicator. Under the experimental conditions, the amount of Cr^{VI} reacting with chloride was negligible.

Kinetic runs were performed in the presence of a large excess of acid, of a large excess of substrate over the oxidant, and of an excess of oxidant over the substrate. In a few experiments the reaction mixture was deliberately doped with an excess of carbamimidoylurea to check the effect of a by-product on the reaction rate (as suggested by one of the referees). Ionic strength was usually maintained at 2.0 mol dm^{-3} by adding Na_2SO_4; some experiments were carried out at $I = 1.0$ mol dm^{-3}. The free $[H^+]$ in the media was calculated using appropriate values[24a] for the first protonation constant of SO_4^{2-} (K = 4.7 $dm^3\ mol^{-1}$ at 25 °C, I = 2.0 mol dm^{-3}) and assuming that ion-pair formation between Na^+ and HSO_4^- or SO_4^{2-} is negligible.[24b] Cerium(IV) was added in the form of its sulphate salt, Cr^{VI} as $K_2Cr_2O_7$.

In a large excess of phenylbiguanide over the oxidant, the zero-order rate constants, k^0 = −slope ([oxidant]$_t$ *vs.* t), were evaluated. The first-order rate constant, $k^1 = -\text{slope}\ \{\ln([\text{oxidant}]_t - [\text{oxidant}]_\infty)\ vs.\ t\}$, was determined with an excess of oxidant over the substrate; $[\text{oxidant}]_\infty$ was calculated from the measured stoicheiometry for the respective reaction. For evaluating rate constants and also activation parameters, using the Eyring equation, a linear least-squares technique was adopted.

Product Analysis.—1,4-Benzoquinone was detected as its 2,4-dinitrophenylhydrazone derivative and by comparison of the m.p. of the derivative with the literature value[25] (185 °C). Carbamimidoylurea was determined at the $\lambda_{\text{max.}}$ of the *d–d* spectra of its copper(II) complex. The reported value[26] for $\lambda_{\text{max.}}$ at pH 7.0 is 540 nm. This is noticeably different from the $\lambda_{\text{max.}}$ (560 nm) for the corresponding complex with phenylbiguanide. Aniline was characterized through the formation of a red azo-dye, as usual. In all these cases test solutions were prepared from completely reacted solutions which were made alkaline, filtered to remove $Cr(OH)_3$, if present, and then extracted with diethyl ether. Ammonia was detected by Nessler's reagent directly in the reacted solution after making alkaline with NaOH.

Stoicheiometry.—This was determined only in the presence of an excess of oxidant. Unchanged oxidant was quantified titrimetrically or spectrophotometrically. The reaction was assumed to be complete when the titre attained essential constancy over a sufficiently long period of time.

Results and Discussion

Biguanide, seven N^1-substituted biguanides, carbamimidoylurea, N^1-phenylcarbamimidoylurea, and guanidine were digested with a slight excess of $K_2Cr_2O_7$ in aqueous H_2SO_4 solution at 60—70 °C for 8—10 h. Among these, only phenyl- and 4-methoxyphenyl-biguanide reacted with the Cr^{VI}. For comparison, the action of Ce^{IV} on phenylbiguanide was also investigated. It was observed that 0.75 ± 0.02 mol dm^{-3} and 0.25 ± 0.1 mol dm^{-3} of phenylbiguanide are consumed per mol of Cr^{VI} and Ce^{IV} respectively. Each mole of 4-methoxyphenylbiguanide consumes a much larger quantity (1.7 ± 0.1 mol dm^{-3}) of Cr^{VI} under these conditions. In acidic media, Ce^{IV} as well as Cr^{VI} transforms phenylbiguanide into 1,4-benzoquinone (m.p. of isolated 2,4-dinitrophenylhydrazone derivative 183 °C), carbamimidoylurea [$\lambda_{\text{max.}}$ of copper(II) complex 540 nm], and ammonium salt. In the case of 4-methoxyphenylbiguanide, instead of quinone, some more extensively oxidized products are indicated by the higher stoicheiometric consumption of Cr^{VI}. However, carbamimidoylurea and ammonia were the common products. Stoicheiometric measurements could not be done in an excess of substrate. However, ammonia and 1,4-benzoquinone were detected as the reaction products with phenylbiguanide present either in excess or deficit. Therefore, the same reaction products and stoicheiometry are highly probable for phenylbiguanide under either of these conditions.

In perchloric acid media both phenyl- and 4-methoxyphenylbiguanide gave strongly coloured (probably polymeric), ill defined products. Such reaction media, therefore, were avoided.

In sulphuric acid media, equations (1) and (2) [R′=NHC(=NH)NH$_2$]

$$\begin{aligned}3\text{PhHNC(=NH)R}' + 4\text{Cr}^{\text{VI}} + 9\text{H}_2\text{O} &\longrightarrow 3\text{C}_6\text{H}_4\text{O}_2 + \\ 3\text{NH}_3 + 4\text{Cr}^{3+} + 12\text{H}^+ &+ 3\text{H}_2\text{NC(=O)R}' \quad (1)\end{aligned}$$

$$\begin{aligned}\text{PhHNC(=NH)R}' + 4\text{Ce}^{\text{IV}} + 3\text{H}_2\text{O} &\longrightarrow \text{C}_6\text{H}_4\text{O}_2 + \\ \text{NH}_3 + 4\text{Ce}^{3+} + 4\text{H}^+ &+ \text{H}_2\text{NC(=O)R}' \quad (2)\end{aligned}$$

thus appear to be the main routes for the reaction of phenylbiguanide with Cr^{VI} and Ce^{IV} respectively (protonation of substrate, oxidant, and products is omitted). In a large excess of phenylbiguanide over the oxidant, plots of $[\text{oxidant}]_t$ *vs.* t were linear for more than 70% completion of reaction (see Figure 1) indicating zero-order kinetics. The zero-order rate constants, k^0, are first order in [pbg] (pbg = phenylbiguanide) and zero order in [Cr^{VI}] (see Table 1). However, in an excess of oxidant over the substrate [pbg or 4-methoxyphenylbiguanide (mpbg)] first-order kinetics are observed. Table 1 shows that the first-order rate constants, $k^1 = -d\ln[\text{pbg}]/dt$, are independent of the concentrations [pbg] and [Cr^{VI}] over five- and two-fold ranges.

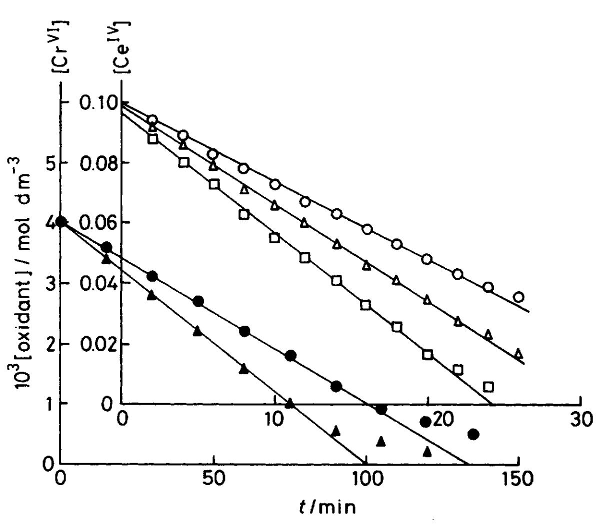

Figure 1. Graphical evaluation of k^0 for the oxidation of pbg. Oxidant 0.004 mol dm^{-3} Cr^{VI}: [pbg] = 0.04 (●) and 0.06 (▲), [H$^+$] = 0.1, I = 2 mol dm^{-3} at 65 °C. Oxidant 10^{-4} mol dm^{-3} Ce^{IV}: [pbg] = 0.015 (○), 0.02 (△), and 0.025 (□), [H$^+$] = 1, and I = 2 mol dm^{-3} at 20 °C

The kinetics are reasonably well represented over the whole range of [pbg] and [Cr^{VI}] by the rate law (3) This on integration leads to expressions (4) and (5). Under comparable

$$\frac{-d[\text{Cr}^{\text{VI}}]}{dt} = -\frac{4}{3}\frac{d[\text{pbg}]}{dt} = k[\text{pbg}] \quad (3)$$

$$k^0 = k[\text{pbg}] \quad (4)$$

$$k^1 = \tfrac{3}{4}k \quad (5)$$

conditions of temperature and acidity, the k values determined from the experiments in an excess of [pbg] ($k = k^0/[\text{pbg}]$) agree within 10% of that determined in an excess of oxidant ($k = \frac{4}{3}k^1$). Such k values are also independent of the identity of the oxidant. Thus, for example, $k = 0.25 \times 10^{-5}$ s^{-1} for Cr^{VI} at 20 °C, [H$^+$] = 1.0 mol dm^{-3}, and I = 2.0 mol dm^{-3}. Under similar conditions, but with Ce^{IV} as the oxidant, $k = (0.27 \pm 0.03) \times 10^{-5}$ s^{-1}.

These results may be interpreted in terms of mechanism (A).

$$\left.\begin{aligned}&\text{pbg} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{aniline (B)} + \\ &\qquad\qquad \text{carbamimidoylurea (cu)} \\ &\text{B} + \text{oxidant} \xrightarrow{k_2} \text{products}\end{aligned}\right\} \quad \text{(A)}$$

For mpbg, a similar scheme is applicable, where B is 4-methoxyaniline. Stationary-state analysis of (A) for d[B]/dt = zero readily gives the rate law (6). This reduces to the observed

$$\frac{-d[\text{oxidant}]}{dt} = \frac{k_1k_2[\text{pbg}][\text{oxidant}]}{k_{-1}[\text{cu}] + k_2[\text{oxidant}]} \quad (6)$$

Table 1. Some representative rate constants[a] for the reactions of phenylbiguanide (pbg)

Temperature °C	$[H]^+$	10^2[pbg]	10^2[oxidant]	10^7k^0	10^5k^1	10^5k
	mol dm^{-3}			$dm^3\ mol^{-1}\ s^{-1}$	s^{-1}	
Oxidant = Cr^{VI}						
20	1.0	4.0	0.4	1.0	—	0.25
65	0.1	4.0	0.4	5.0	—	1.2
	0.1	4.0	0.2	4.9	—	1.2
	0.1	5.0	0.4	6.0	—	1.2
	0.1	6.0	0.4	6.7	—	1.1
	0.1	7.0	0.4	8.5	—	1.2
	0.1	8.0	0.4	9.6	—	1.2
	0.1	8.0	0.8	10.0	—	1.2
	0.1	4.0	0.6	4.5	—	1.1
	0.5	4.0	0.4	9.2	—	2.3
	0.5	5.0	10.0	—	1.8	2.4
	0.6	5.0	10.0	—	2.0	2.7
	0.7	5.0	10.0	—	2.2	3.0
	0.8	5.0	10.0	—	2.4	3.2
	0.9	5.0	10.0	—	2.6	3.5
	1.0	5.0	10.0	—	2.8	3.7
	1.0	5.0	15.0	—	2.9	3.9
	1.0	5.0	20.0	—	2.9	3.9
	1.0	3.0	10.0	—	2.9	3.9
	1.0	2.0	10.0	—	2.8	3.7
	1.0	1.0	10.0	—	2.9	3.9
70	0.5	5.0	10.0	—	2.8	3.7
70[b]	0.5	5.0	10.0	—	5.6	7.5
Oxidant = Ce^{IV}						
20	1.0	1.5	0.01	0.43	—	0.28
	1.0	2.0	0.01	0.54	—	0.27
	1.0	2.5	0.01	0.67	—	0.27
	1.0	1.0	0.015	0.30	—	0.30
	1.0	1.0	0.02	0.28	—	0.28

[a] Maximum error ± 8%; $I = 2.0$ mol dm^{-3} unless otherwise mentioned. [b] $I = 1.0$ mol dm^{-3}.

form zero order in [oxidant] and first order in [pbg] for the condition (7).

$$k_{-1}[cu] \ll k_2[Cr^{VI}] \quad (7)$$

In effect mechanism (A) represents the acid-promoted hydrolysis of the substituted biguanide, the oxidant being employed as an analytical assay of the anilinium (or 4-methoxyanilinium) product. The kinetics and the measured $k(= k_1)$ values are thus for the hydrolysis not the oxidation. This is further supported by the following observations. (*a*) In the absence of the oxidant, pbg itself is hydrolyzed in acidic media where aniline has been identified as one of the products. Such an acid-digested solution of pbg immediately reacts with Ce^{IV} and Cr^{VI}, although neither of the oxidants reacts with an unhydrolysed solution of pbg. (*b*) A mixture of $K_2Cr_2O_7$ and H_2SO_4 immediately oxidizes a solution of anilinium sulphate even in the cold. Although, to our knowledge, the kinetics of this process is not known, the above observation indicates that k_2 is large and it is likely that condition (7) holds. (*c*) Carbamimidoylurea, the hydrolysis by-product, is resistant to oxidation by Cr^{VI} as demanded by scheme (A).

The second and fifth kinetic runs of Table 1 were repeated in the presence of added carbamimidoylurea (0.1 mol dm^{-3}). This had practically no effect on the reaction rate, and may be interpreted if k_2 is large enough so that, even in the presence of 0.1 mol carbamimidoylurea, condition (7) holds under the experimental conditions. This, however, does not lend any independent support to scheme (A). Unfortunately carbamimidoylurea had only a limited solubility in the reaction media and we could not verify whether product inhibition of the rate becomes observable at even higher concentrations of added carbamimidoylurea.

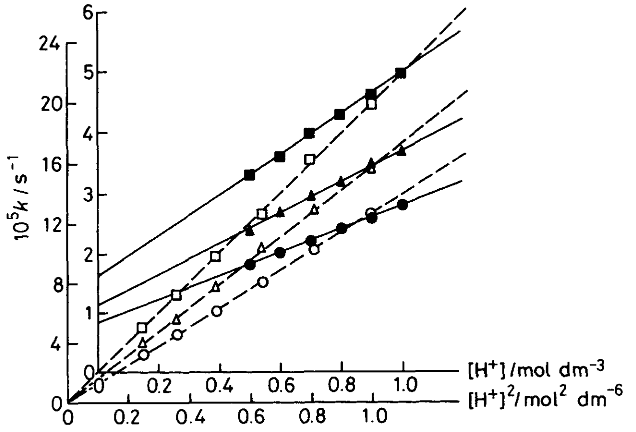

Figure 2. Acid dependence plot: k *vs.* $[H^+]$ (full lines, for pbg) at 60 (●), 65 (▲), and 70 °C (■); k *vs.* $[H^+]^2$ (broken lines, for mpbg) at 60 (○), 65 (△), and 70 °C (□). [pbg] = 0.05, [mpbg] = 0.01, $[Cr^{VI}]$ = 0.1, and $I = 2$ mol dm^{-3}

Slow acid-promoted hydrolysis of various biguanides substituted both at N^1 and N^5 has already been demonstrated.[27–29] Thus for example, N^1-(4-chlorophenyl)-N^5-isopropylbiguanide quantitatively hydrolyses to *p*-chloroaniline and $H_2NC(=O)$-$NHC(=NH)NHPr^i$ by heating with 0.25 mol dm^{-3} HCl under

Table 2. Kinetic parameters[a] for reactions of phenylbiguanide with Cr^{VI}

Temperature °C	10^5k_0 s^{-1}	10^5k_H $dm^3\ mol^{-1}\ s^{-1}$	$10^5k_H'$ $dm^6\ mol^{-2}\ s^{-1}$
60	0.79 ± 0.04	2.0 ± 0.1	12.6 ± 0.5
65	1.12 ± 0.06	2.6 ± 0.2	15.8 ± 0.6
70	1.6 ± 0.1	3.4 ± 0.2	20 ± 1
70[b]	1.7 ± 0.1	7.7 ± 0.3	
$\Delta H^{\ddagger}$/kJ mol^{-1}	64 ± 1	48 ± 2	40 ± 1
$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	−153 ± 5	−193 ± 6	−203 ± 5

[a] Errors quoted are standard deviations from the least-squares line. [b] I = 1.0 mol dm^{-3}. In all other cases I = 2.0 mol dm^{-3}.

pressure. However, no kinetic investigation of these processes is available that may be compared with the present one.

As shown in Table 1, k for pbg increases with media $[H^+]$; mpbg behaves analogously except that while for pbg equation (8) applies, for mpbg equation (9) is appropriate (see Figure 2). Pre-equilibrium protonation of the substrate may be responsible for the observed acid dependences. An increase in ionic strength decreased k_H but did not affect k_0 (Table 2). Added $[Cr^{3+}]$ has no effect on k.

$$k = k_0 + k_H[H^+] \qquad (8)$$

$$k = k_H'[H^+]^2 \qquad (9)$$

Except for pbg and mpbg, none of the other nine compounds consumed in solution any appreciable amounts of the oxidants. This is true even for N^1-(benzyl), N^1-(4-sulphophenyl), and N^1-(4-chlorophenyl)-biguanide. It was verified that in acidic media, benzylamine, sulphanilic acid, and *p*-chloroaniline are all rapidly oxidized by Cr^{VI}. The observed non-reactivity of the corresponding biguanides therefore arises from their resistance to hydrolysis to the parent amines. The nature of the substituents thus appears to be an important factor in determining the mode and feasibility of biguanide hydrolysis. This was noted previously.[27–29] However, the present investigation is the first recorded example of hydrolysis of biguanides having substitution only at N^1. Phenyl- and 4-methoxyphenyl-biguanide are also examples of the least-substituted biguanides so far known to undergo hydrolysis.

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