[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

THE STRUCTURE OF NITROGUANIDINE AND NITROAMINOGUANIDINE

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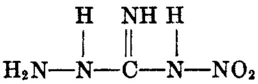
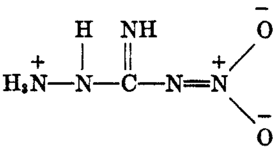
The structures of nitroguanidine and nitroaminoguanidine have been studied for a number of years (1–12). While working with a number of nitroguanylhydrazones (13), it occurred to us that the structure of the reagent nitroaminoguanidine used in their preparation could be elucidated from a knowledge of the dipole moment, dissociation constant, and ultraviolet absorption spectra. The structure commonly accepted for nitroaminoguanidine is I and that for nitroguanidine is VI.



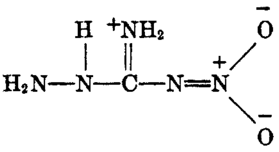
$H_2N-\overset{H}{\overset{|}{N}}-\overset{NH}{\overset{\|}{C}}-\overset{H}{\overset{|}{N}}-NO_2$

I



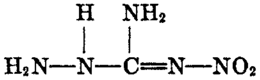
$H_3\overset{+}{N}-\overset{H}{\overset{|}{N}}-\overset{NH}{\overset{\|}{C}}-N{=}\overset{+}{N}{<}^{\bar{O}}_{\bar{O}}$

II



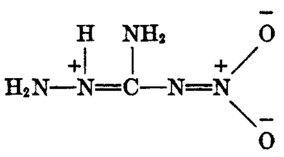
$H_2N-\overset{H}{\overset{|}{N}}-\overset{^{+}NH_2}{\overset{\|}{C}}-N{=}\overset{+}{N}{<}^{\bar{O}}_{\bar{O}}$

III



$H_2N-\overset{H}{\overset{|}{N}}-\overset{NH_2}{\overset{|}{C}}{=}N-NO_2$

IV

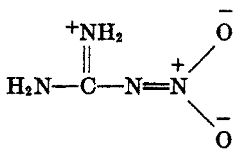


$H_2N-\overset{H}{\overset{+|}{N}}{=}\overset{NH_2}{\overset{|}{C}}-N{=}\overset{+}{N}{<}^{\bar{O}}_{\bar{O}}$

V

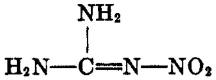
$H_2N-\overset{NH}{\overset{\|}{C}}-\overset{H}{\overset{|}{N}}-NO_2$

VI



$H_2N-\overset{^{+}NH_2}{\overset{\|}{C}}-N{=}\overset{+}{N}{<}^{\bar{O}}_{\bar{O}}$

VII



$H_2N-\overset{NH_2}{\overset{|}{C}}{=}N-NO_2$

VIII

However, since this work was under way and the first manuscript submitted (14) a paper has appeared (11) in which the "zwitterion" structure II is proposed for nitroaminoguanidine. Another paper has appeared (12) in which a structure for nitroguanidine has been proposed consisting of a resonance hybrid of zwitterion structures such as VII. A third paper has appeared (9) in which evidence is presented that nitroguanidine has a nitrimine structure VIII. Our work indicates that these compounds are best represented by a nitrimine structure with small contributions from forms with a separation of charge.

NITROAMINOGUANIDINE

Dissociation constants. If the structure usually written for nitroaminoguanidine (I) is correct, the compound would be a comparatively strong acid with

pK_a 2–4. This is deduced from the pK_a 6.1 (15) for $\mathrm{CH_3{-}\overset{\overset{H}{|}}{N}{-}NO_2}$ and the electronegativity of nitrogen. We have determined the dissociation constants of nitroaminoguanidine in solutions approximately 0.03 *molar* by titration with both acid and base using a glass electrode. The purity of the compound was checked by following the ultraviolet spectrum after repeated recrystallizations. The titration was carried out immediately after dissolving the compound in water to reduce the possibility of a rearrangement. Fig. 1 shows the titration curve of the compound together with the curve for water. The pK_a and pK_b were calculated using exact equations and were found to be pK_a 10.47 and pK_b 12.98. The observed pK_a of 10.47 definitely rules out structure I.

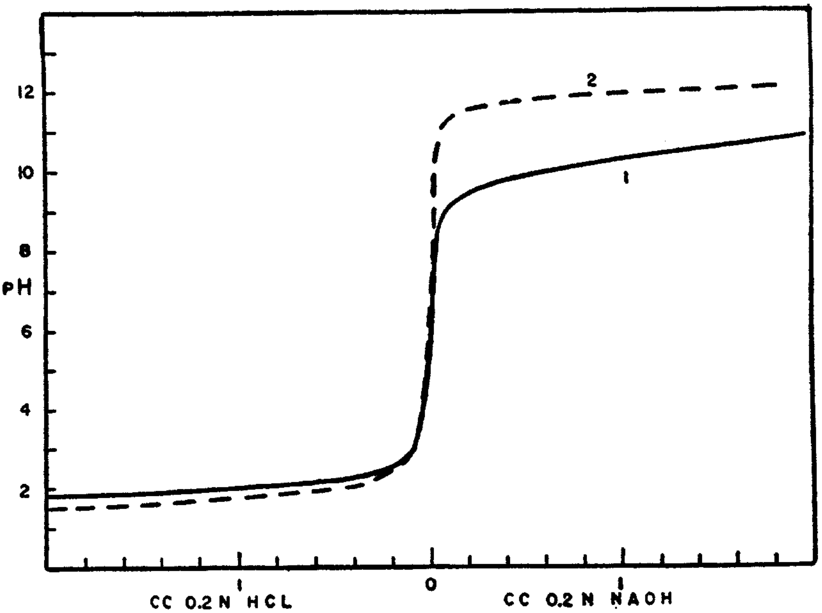


FIG. 1. CURVE 1 ——— is the titration of a solution of nitroaminoguanidine with acid and base at approximately 0.03 *molar* concentration. CURVE 2 - - - is the curve obtained by adding acid and base to the same volume of distilled water.

Dipole moment. Of the two "zwitterions" the one II proposed by Lieber *et al.* (11) with a $\overset{(+)}{\mathrm{H_3N}}$— group is improbable compared with the structure III because of the resonance stabilization in the latter. If the compound is a "zwitterion" of either type it would have a high dipole moment. The value would range from 25 D if the calculation is made assuming no mutual induction of the polar groups to 15 D if considerable mutual induction is assumed. The dipole moment was measured in dioxane at 30°. The dioxane was purified as before (16). In Fig. 2 the plot of ϵ_{12} against ω_2 is a straight line. The value of ϵ_1 was obtained by extrapolation, and the dipole moment was calculated using the method and equation of Halverstadt and Kumler (17).

$$p_{2_0} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\,\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$P_{2_0} = p_{2_0} M_2$$

$$\mu = 0.01281\sqrt{(P_{2_0} - P_{E_2})T}$$

The following values were found: ϵ_1 2.2027; v_1 0.97393; α 38.0; β −0.460; P_{E_2} 27; P_{2_0} 783; μ 6.13.

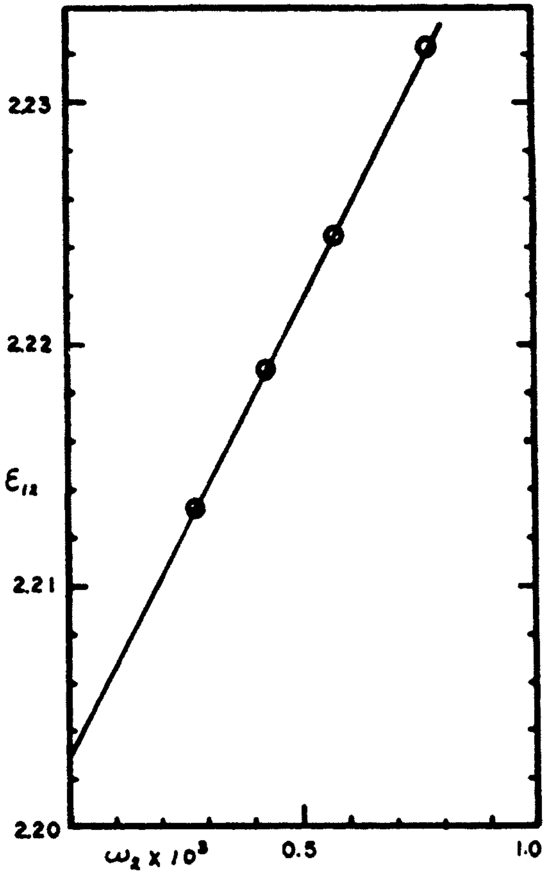
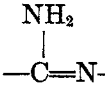


FIG. 2. PLOT OF ϵ_{12} *versus* ω_2 FOR NITROAMINOGUANIDINE

The observed dipole moment of 6.13 D is definite evidence that the compound is not a "zwitterion" or a resonance hybrid, with "zwitterions" as the main contributing structures.

The nitroimine structure IV is a resonance hybrid of the "zwitterion" structures III and V and would be more stable than either of the latter because it has no separation of charge. This structure is consistent with a dipole moment of 6.13 D.

The nitroimine structure IV is also consistent with the observed dissociation constants. The acidic hydrogen is the one attached to nitrogen to which the amino group is attached. As an acid this compound can be considered an analog of acetamide, pK_a 14, in which the =O is replaced with the slightly more electronegative $=N—NO_2$; the CH_3 with the more electronegative $—NH_2$ and a hydrogen on a nitrogen with the more electronegative NH_2. All of these changes are acid strengthening and are adequate to account for the increase of acidity from pK_a 14 in acetamide to 10.47 in nitroaminoguanidine.

The amino group attached to nitrogen is the most basic group in the molecule since the basicity of its nitrogen is neither weakened by double bonds nor contributions of forms placing a plus charge on it. The compound may be considered a derivative of hydrazine pK_b 5.8 (15) in which one hydrogen has been replaced by the very electronegative  $—\overset{\overset{NH_2}{|}}{C}=N—NO_2$ group. This would reduce the basicity by a large amount but in addition small contributions from the form placing a plus charge on the adjacent nitrogen V would reduce the basicity still further. Both of these effects appear capable of reducing the basicity to pK_b 12.98 from the pK_b value of hydrazine.

Ultraviolet spectrum. Nitroaminoguanidine, ϵ_{max} 14,000 and λ_{max} 267 mμ (18) absorbs with considerably higher extinction and at longer wavelengths than either an N-nitroamine ϵ_{max} 7,000, λ_{max} 230 mμ (19), or guanidine hydrochloride (20) which has an ϵ_{max} of less than 15 above 230 mμ. The bathochromic and hyperchromic effect resulting from combining these two groups in nitroaminoguanidine is accounted for by a structure in which a double bond is conjugated with the nitro group. This is the situation in the nitroimine structure.

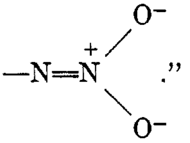
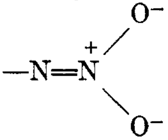
NITROGUANIDINE

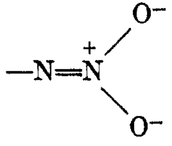
Dissociation constants. The titration curve for nitroguanidine was found to be indistinguishable from the titration curve of the same volume of distilled water. This is in agreement with the titration data of Barton, Hall, and Wright (9) and clearly rules out the usually written nitramine structure for the compound which would have pK_a 3–5.

It is interesting that nitroaminoguanidine, pK_a 10.47, with an additional amino group is a stronger acid than nitroguanidine, with pK_a of about 14. This is another illustration of the not too generally appreciated fact that an amino group is an acid-strengthening and base-weakening group. Two factors are involved in this case, the electronegativity of the nitrogen, and the fact that the introduction of the additional amino group makes the resonance forms with a separation of charge of the undissociated molecule of nitroaminoguanidine not equivalent, which makes it less stable than nitroguanidine with regard to their respective anions. Both of these factors cause nitroaminoguanidine to be a stronger acid than nitroguanidine.

Dipole moment. The dipole moment of nitroguanidine was measured in dioxane at 30° and the moment calculated by the method used above for nitroaminoguanidine. The following values were found: ϵ_1 2.2122; v_1 0.97413; α 72.3; β − 1.37; P_{E_2} 24; P_{2_∞} 995; μ 6.95. The dipole moment of 6.95 D definitely rules out the possibility of the compound existing mainly in the form of a "zwitterion" or a resonance hybrid of "zwitterions." Clearly the compound must consist chiefly of VIII with only small contributions from the "zwitterion" forms, VII etc. It is to be noted that the dipole moment of nitroguanidine, 6.95 D, is larger than that of nitroaminoguanidine 6.13 D, in spite of the fact that the latter has an additional  $-\overset{\overset{H}{|}}{N}-$ group. This is accounted for on the basis of the "zwitterion" forms making a greater contribution to nitroguanidine than they make to nitroaminoguanidine because the forms are equivalent in the first case but not in the second. However, the total contribution of the "zwitterion" forms is small in both cases.

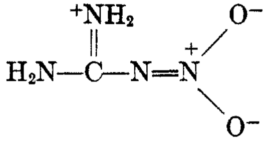
Ultraviolet absorption spectra. The spectrum of this compound has been reported by others (12, 18, 21), and our values for two peaks at 265 and 218 mμ with extinction coefficients of 13,100 and 5,530 respectively are in essential agreement with the previous work. This compound like nitroaminoguanidine shows considerably more absorption and at longer wavelengths than the sum of the absorption of an alkyl-N-nitroamine and guanidine hydrochloride thus giving evidence that the nitro group is conjugated. This condition is fulfilled by the nitrimine structure VIII but not by the nitroamine structure VI.

In a recent paper McKay, Picard, and Brunet (12) have interpreted the fact that nitroguanidine and some related compounds have more absorption than some similar compounds as showing that in nitroguanidine and related compounds "the nitramino group exists mainly in the form  $-N{=}\overset{+}{N}\genfrac{}{}{0pt}{}{\diagup O^-}{\diagdown O^-}$." This necessitates that the compounds exist mainly in the form of zwitterions as they themselves so state on page 754 "a dilute acid solution of nitroguanidine might be expected to consist mainly of a hybrid of 'zwitterion' structures . . . along with, possibly, very little of cation . . ." And again on page 758 they state, "These compounds in which the chromophore group  $-N{=}\overset{+}{N}\genfrac{}{}{0pt}{}{\diagup O^-}{\diagdown O^-}$ is present should not be classed as nitrimines,"—which definitely indicates they believe the form VIII makes only a minor contribution, since it *is* a nitrimine.

We differ also with McKay, *et al.* (12), in regard to their interpretation that the ultraviolet spectra data give evidence that nitroguanidine is a "zwitterion." If the compound in its normal state were mainly a "zwitterion" the differences in energy between the ground state and the first excited state would be expected to be more and not less, and thus the absorption would be at shorter wavelengths and with less extinction. There are numerous cases in the literature where the ability of a normal structure to resonate with a form with a separation of charge causes a bathochromic and hyperchromic shift but in such cases the contribution of the form with a separation of charge is small in the ground state but larger in the excited state. If the form with a separation of charge makes the main contribution to the ground state, there is not likely to be a very stable excited state with further separation of charge to which it can go. The observation then of McKay, *et al.* in regard to the bathochromic and hyperchromic shifts in the spectrum of nitroguanidine and similar compounds instead of being evidence for these molecules being mainly in "zwitterion" forms with the nitramino group in the form  $-\mathrm{N}{=}\overset{+}{\mathrm{N}}\begin{array}{l}/\mathrm{O}^-\\ \backslash \mathrm{O}^-\end{array}$ actually is evidence that these compounds are mainly *not* in these forms.

Conclusion. The acid dissociation constants of nitroguanidine pK_a 14 and nitroaminoguanidine pK_a 10.47 rule out the possibility of the molecules being nitramines. The dipole moment of 6.95 D for nitroguanidine and 6.13 D for nitroaminoguanidine rule out the possibility that these compounds exist mainly as resonance hybrids of "zwitterions." The nitrimine structure with small contributions from forms with a separation of charge is consistent with the dissociation constants, dipole moments, and ultraviolet spectra of the compounds.

SUMMARY

The dipole moment of nitroguanidine is 6.95 D and that of nitroaminoguanidine is 6.13 D. These values indicate that the compounds are not "zwitterions" or resonance hybrids of "zwitterions" as has been proposed by McKay, *et al.* (12), and by Hahn, *et al.* (6). Nitroguanidine has acidic and basic properties very similar to those of water. Nitroaminoguanidine has pK_a 10.47 and pK_b 12.98. The observed acid dissociation constants of these compounds are inconsistent with their existence as nitramines. The dipole moment, dissociation constant, and ultraviolet absorption spectra data indicate that the structure of these compounds is best represented as a resonance hybrid with the main contribution from the nitrimine structure  $\mathrm{H_2N{-}\overset{\overset{\textstyle NH_2}{|}}{C}{=}N{-}NO_2}$ and small contributions from forms with separation of charge  $\mathrm{H_2N{-}\overset{\overset{\textstyle ^+NH_2}{\|}}{C}{-}N{=}\overset{+}{N}}\begin{array}{l}/\mathrm{O}^-\\ \backslash \mathrm{O}^-\end{array}$ etc. This is in essential agreement with the conclusions of Barton, Hall, and Wright (9) but in general contrary to those of McKay, *et al.* (12).

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