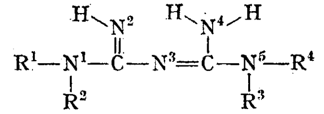
Structure of Mono-, Di-, and Tri-protonated Biguanides

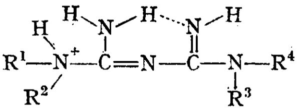
By KEITH M. WELLMAN* and DAVID L. HARRIS
(*Department of Chemistry, State University of New York at Buffalo, Buffalo, New York* 14214)
and PATRICK J. MURPHY
(*San Diego State College, San Diego, California*)

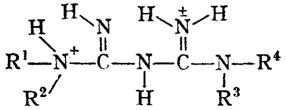
THE intriguing structural problem arising from protonation of the physiologically important biguanides has been the subject of several investigations. Shapiro and his co-workers have interpreted spectral and chemical evidence in favour of (IId) and (IIId) as the mono- and di-protonated species.[1] These conclusions have been criticised,[2] and ultraviolet (u.v.) spectroscopic data have been interpreted[3] as indicating that protonation does not occur on the N^1-nitrogen in either 5N- or concentrated sulphuric acid. The present Communication provides definitive support for structures (IV–VI) as the sequence of biguanide conjugate acids.

The n.m.r. spectrum[†] of N^1-n-butylbiguanide (Ia) as the hydrochloride in Me$_2$SO shows the CH$_2$N^1 protons as a broadened quartet (δ = 3·48 p.p.m., $J \sim 6$ c./sec.) coupled to the N^{1}H and adjacent CH$_2$ protons. The N^{1}H proton correspondingly appears as a badly broadened triplet (8·02 p.p.m., $J \sim 6$ c./sec.). The six remaining NH protons appear as a singlet (7·33 p.p.m., $w_{\frac{1}{2}}$ = 5 c./sec.). The multiplicity of the CH$_2$N protons clearly rules out protonation on N^1. Further evidence against (IIa) is the lack of a low-field proton signal expected[4] for the hydrogen-bonded proton; whereas, the similar chemical shifts of the NH protons appearing at 7·33 p.p.m. support structure (IVa).

The u.v. spectrum of (Ia) as the hydrochloride in water exhibits a strong band at 236mμ (ϵ 14,800) which is reasonably assigned as the monocation.[2] In 3–18N-sulphuric acid the 236mμ band is absent, and only end-absorption is observed. These observations are consistent with formation of the biguanide dication even in mildly acidic solutions as suggested previously.[2,3] In the n.m.r. spectrum, the NH protons of the dication of (Ia) are obscured by the solvent (18N-H$_2$SO$_4$), but they could be detected in trifluoroacetic acid


(I)


(II)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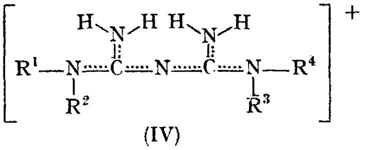
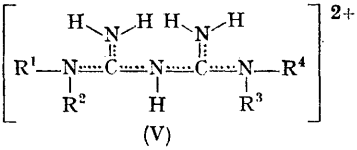
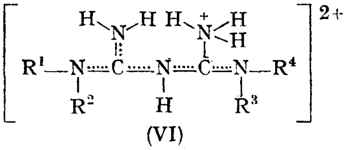

(IV)


(V)


(VI)

(a) R^1=Bu^n, R^2=R^3=R^4=H; (b) R^1=R^2=Me, R^3=R^4=H;
(c) R^1=R^2=R^3=R^4=Me; (d) R^1=PhCH$_2$·CH, R^2=R^3=R^4=H

[†] N.m.r. spectra were determined with a Varian A60 using reagent grade solvents: dimethyl sulphoxide, trifluoroacetic acid (T.F.A.), or concentrated sulphuric acid. External tetramethylsilane was taken as δ = 0 p.p.m.

(T.F.A.) which has a comparable Hammett acidity constant.[5] Surprisingly, the spectrum in T.F.A. bore a striking similarity to that of the monocation in Me_2SO showing a two-proton quartet at 3·55 p.p.m. (CH_2N^1), a broad triplet at 8·10 p.p.m. (N^1H) and a singlet ($w_{\frac{1}{2}}$ = 3 c./sec.) at 7·75 p.p.m. for the remaining NH protons. The total NH proton integral corresponds to seven protons rather than the eight expected for the dication. Analogous results were obtained for (Ib) and (Ic) in T.F.A. which integrated for six (expect seven) and four (expect five) NH protons, respectively. These results demand that protonation of the monocation (IV) occur selectively, and reversibly, at N^3 to give the dication (V). Support for this hypothesis was gained from the spectra of (Ia—c) in concentrated sulphuric acid which show a new, low-field singlet ($w_{\frac{1}{2}}$ = 3 c./sec.) at 9·18, 9·03, and 8·22 p.p.m. for (Ia), (Ib), and (Ic), respectively. This new signal, which integrates for a single proton in all cases, must be the proton at N^3 in (V). The other NH protons of (Va) and (Vb) give exchange-broadened signals. The imino-protons of (Vc) in concentrated H_2SO_4 were completely time-averaged with solvent at room temperature; however, correct area integrals for all protons corresponding to (Vc) were obtained using 10% T.F.A. in concentrated H_2SO_4 at 0°. Thus, it appears that the mode of proton exchange in concentrated sulphuric acid is *via* attack of the proton on the π-electron system of (V) at N^1, N^2, N^4, and N^5. It follows that the biguanide trication has one of several possible prototropic structures such as (VI).

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