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SPECTROPHOTOMETRIC (UV) INVESTIGATION ON BIGUANIDE AND SUBSTITUTED BIGUANIDES

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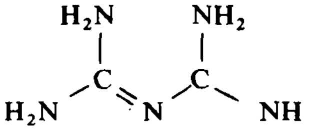
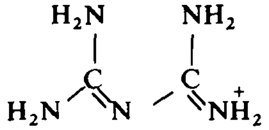
Abstract—Biguanide base and its monosalts have absorption maxima at 230 mμ which has been attributed to π-π^* transition. The spectral effect on replacement of a carbon π centre by a heteroatom nitrogen centre is discussed and attempt has been made to predict the spectral shifts in biguanide base and normal salts due to the substitution heteronitrogen atom in place of its carbon analogue in the substituted butadine. The effect of substitution on the N atom of biguanide molecule by various alkyl groups has been considered and results correlated with analogous alternant hydrocarbon. The findings confirm the suggested structure of biguanide base and its normal salts with alternate single and double bond.

INTRODUCTION

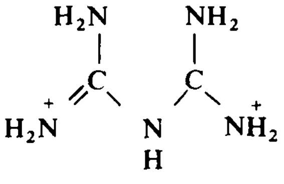
The UV spectral studies and its pH dependence indicated the presence of three distinct forms of biguanide.



Base



Normal salt



Acid salt

It is seen from the structure that both in the basic and normal salt forms biguanide possesses a conjugate single and double bond system. In these two forms biguanide is capable of complex formation with transitional elements. The base can be isolated in nonaqueous solvents such as methanol, ethanol etc. In aqueous solution the base will be protonated following the scheme:

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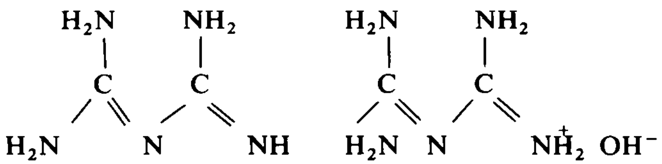
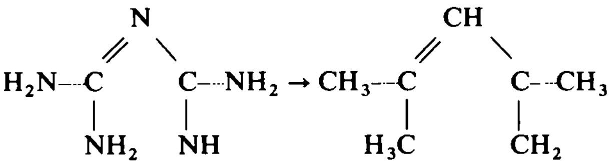


so that the molecule behaves structurally almost like the normal salt. Hence normal salt was used for the UV spectral studies. Both these forms of biguanide have absorption maxima at 230 mμ, which has been attributed to π–π* transition.

Biguanide normal sulphate may therefore be considered as a conjugated system containing the heteroatom, nitrogen. It is well known that —CH= may be considered to be equivalent to =N— or =O, $=CH_2$ as =NH, and $—CH_3$ as $—NH_2$. Substituting the corresponding groups in the biguanide molecule, the following hydrocarbon, 1-dimethyl-3-methylbutadiene, can be constructed.



Attempt will now be made to predict the spectral bands in biguanide base and its normal salt due to the substitution of hetero nitrogen atoms in place of carbon analogues in the substituted butadiene.

The spectral effect of replacement of a carbon π centre, say, the *i*th π centre in a carbon π system by a heteroatom π-centre and the effect of introduction of a non-mesomeric substituent on to the *i*th C atom can be treated within the frame work of simple LCAO-MO method to a first approximation by assigning an appropriate altered value of the coulomb integral, $\alpha_i = \alpha + h_i\beta$ to the *i*th πAO of the parent π system. The value of the parameter h_i is positive for the heteroatoms which are more electronegative than the carbon and for electron attracting substituents. The change in the energy separation between MO's $\psi_n$and ψ_m, $\Delta E_{m\to n}$ $(= W_n - W_m)$, associated with the change in the coulomb integral for π AO at the *i*th atom from $\alpha + h_i$ can be expressed approximately as follows:

$$\begin{aligned}\delta\Delta E_{m\to n} &= -(C^2_{n,i} - C^2_{m,i})\,h_i\\ &= -(p_{ii}{}^{(n)} - p_{ii}{}^{(m)})\,h_i\\ &= -\Delta p_{ii}h_i.\end{aligned}$$

where $C_{n,i}$ is the co-efficient of the *i*th π AO in MO ψ_n of the parent π system, $p_{ii}{}^{(n)}$ is the partial π electron density of ψ_n at the *i*th atom associated with one electron transition from ψ_m to ψ_n. Although this expression is of rough approximation, this is useful to some extent for obtaining a qualitative or semiquantitative explanation of the effects of the foregoing structural changes on the spectra of the π-system. In even alternant hydrocarbons, $C^2_{-n,i}$ and $C^2_{+n,i}$ are identical, therefore in such system, it is expected that the replacement of the carbon π centre by a heteroatom π centre and introduction of a non-mesomeric substituent cause no change in the position of the absorption bands due to transitions ψ_{+1} to ψ_{-1}, ψ_{+2} to ψ_{-2}, etc. This explanation is substantiated by the following examples.

Compound	Solvent	max mμ	ε_{max}
$CH_3-CH=CH-CH=CH-CH_3$	Hexane	227	25,500
	Ethanol	227	22,500
$CH_3-CH=CH-CH=N-C_4H_9$	Ethanol	220	23,500
$CH_3-CH=CH-CH=O$	Ethanol	217	15,650
$CH_3-CH=CH-CH=CH_2$	Heptane	223	26,000

From theoretical consideration the replacement of $=CH-$ by $=N-$ and by $=O$ causes no substantial change in the first main band of each parent compound. However, consideration of a number of experimental data indicates that such replacement causes a blue shift on the π-π* transition of the parent compound.[1]

The effect of replacing ethylenic by azomethine groups on the UV light absorption of conjugated system has been done by Baranay *et al.*[1] The effect of $-\underset{|}{C}=\underset{|}{C}-$ and $-\underset{|}{C}=N-$ chromophore in linear system of the butadiene and polyene types have been compared. There are five possible azomethine analogues of the butadiene system of which the three, namely the en-imine system $-\underset{|}{C}=\underset{|}{C}-N=$, the di-imine system $-N=\underset{|}{C}-\underset{|}{C}=N-$, and the azine system $-\underset{|}{C}=N-N=\underset{|}{C}-$ were prepared and their analogues of 1 :4 dimethylbutadiene and 1 :4 diphenylbutadiene were used for study of UV spectra. Their absorption data are given below:

Compound	λ_{max}	ε_{max}
$MeCH=CH-CH=CHMe$	227	22,500
$MeCH=CH-CH=NBu$	220	23,500
$BuN=CMe-CMe=NBu$	206	17,000
	209	18,500
$PrCH=N-N=CHPr$	205	13,000
		11,500

The introduction of azomethine group as in crotonylidene butylamine and cinnamylidene aniline results in slight decrease in λ_{max} (7 to 24 mμ), whilst the introduction of two azomethine groups as in diacetyl-di-N-butylimine and diacetylanil, and as in butyraldazine and benzylideneazine, gives rise to somewhat larger blue shift (19 to 28 mμ). In this case it is seen that the effects of replacing the ethylenic by azomethine groups in dimethyl-butadiene and diphenyl butadiene are very similar. It has been observed that the blue shift due to the replacement of $-C=C-$ by $-C=N-$ is more and more as λ_{max} moves more and more towards the visible region in the case of higher polyene system.

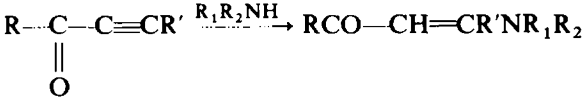
Compound	X = —CH=CH—		X = —CH=N—	
	λ_{max} mμ	ε_{max}	λ_{max} mμ	ε_{max}
$(\text{MeCH=X})_2$	227	25,000	208	10,000
$(\text{MeCH=CH–CH=CH–CH=X})_2$	360	70,000	338	73,000
$(\text{MeCH=CH–CH=CH–CH=CH–CH=X})_2$	420	36,000	385	84,000

The blue shift produced by replacing ethylenic by azomethine groups may be compared with the corresponding effects observed in cyclic conjugated systems as shown below:

Compound	λ_{max}(mμ)	ε_{max}
Benzene	255	250
Pyridine	250	2,000
Pyramidine	243	3,000

From this data, it is concluded that the replacement of —CH= by =N— will produce a blue shift both in aliphatic as well as aromatic system. The effect produced in alicyclic system is far greater in magnitude than that produced in aromatic system. From the above data it may be concluded that the replacement of —CH= by —N= will cause a blue shift of λ_{max} to the extent of (20–28 mμ) and in case of butadiene it may be approximated to 22 mμ taking into consideration the fact that the properties of the chromophore —C=C—C=N— would be intermediate between —C=C—C=C— and —C=C—C=O groups.

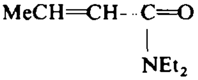
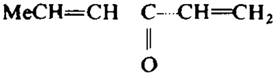
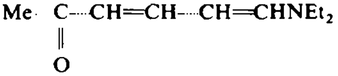
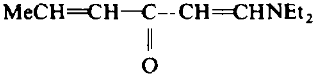
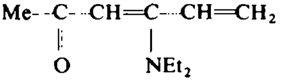
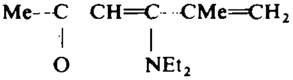
It is also known[2] that the introduction of an —NH_2 group at the terminal carbon atom in a conjugated system of the butadiene or methyl vinyl ketone type results in pronounced red shift and hyperchromic displacements of the maximal absorption ($\Delta\lambda = +50$ to 100 mμ) and ($+\Delta\varepsilon = 2500$ to 20,000). These are even considerably greater in magnitude than those displacements normally produced and well exemplified in the literature by substitution with additional ethylenic or other unsaturated groups. Moreover, even the conjugation of a single ethylenic bond with an amino group, results in light absorption equivalent to that exhibited by conjugated systems such as butadiene:

(1) 

$$\text{R—}\underset{\displaystyle \text{O}}{\underset{\displaystyle \|}{\text{C}}}\text{—C≡CR}' \xrightarrow{R_1R_2NH} \text{RCO—CH=CR}'\text{NR}_1\text{R}_2$$

The amino group when substituted to the aromatic ring, red shift is observed. In aliphatic system, the auxochromic effects of the amino group have been much less clearly established, although it has recently been shown that the increase in λ_{max} must be ascribed to the conjugating power of the >NH group and not to the extension of conjugation.

TABLE 1.

Compound	λ_{max}(mμ)	ε_{max}
(1) $\mathrm{CH_2{=}CH{-}CH{=}CH_2}$	217	21,000
(2) $\mathrm{CH_2{=}CH{-}CH{=}CHNEt_2}$	281	23,500
(3) $\mathrm{MeCH{=}CH\ \ CH{=}O}$	217	
	215	11,000
(4)  $\mathrm{MeCH{=}CH{-}\underset{NEt_2}{\underset{\vert}{C}}{=}O}$	242	6,500
(5)  $\mathrm{MeCH{=}CH\ \ \underset{O}{\underset{\Vert}{C}}{-}CH{=}CH_2}$	236	
(6) $\mathrm{CHMe{=}CH\ \ C\ \ CH{=}CHNHPh}$	240 (165)	
	377 (295)	
(7)  $\mathrm{Me\ \ \underset{O}{\underset{\Vert}{C}}{-}CH{=}CH{-}CH{=}CHNEt_2}$	227	3,500
(8)  $\mathrm{MeCH{=}CH{-}\underset{O}{\underset{\Vert}{C}}{-}CH{=}CHNEt_2}$	242·5	10,500
	315·0	
(9)  $\mathrm{Me{-}\underset{O}{\underset{\Vert}{C}}{-}CH{=}\underset{NEt_2}{\underset{\vert}{C}}{-}CH{=}CH_2}$	308	18,500
(10)  $\mathrm{Me{-}\underset{O}{\underset{\Vert}{C}}\ \ CH{=}\underset{NEt_2}{\underset{\vert}{C}}{-}CMe{=}CH_2}$	310	30,500

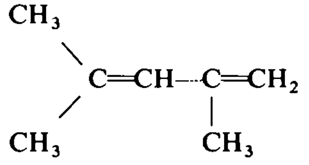
The result of the spectral study given in the table indicates in a more direct and conclusive manner that the amino group in aliphatic system possesses conjugating power similar to that of an ethylenic bond in many respects. This property is clearly to be ascribed to the presence of the unshared pair of electron on the nitrogen atom and its capacity to provide a seat for a positive charge. Fixation of this free electron pair by quaternary salt formation completely destroys the powerful auxochromic properties. Substitution of the diethylamino group into butadiene results in displacements of λ_{max} of 430 to 640A (ε_{max} remaining practically constant). In purely ethylenic systems, the tertiary amino group has thus a bathochromic effect rather greater than that observed with an ethylenic double bonds[4, 5] ($\Delta\lambda$ = 30 to 40 mμ), but no hyperchromic effect is observed· Attachment of dialkyl amino group to the terminal carbon atom of triply conjugated systems[6, 7] results in still larger red shift ($\Delta\lambda \approx 110$ mμ) than that observed on substitution of αβ ethylenic ketones. The bathochromic effect of the amino group, unlike that of the ethylenic bond appears to be enhanced with the increasing conjugated system to which it is attached. As would be expected, however, if the amino group forms a branch of the conjugated system (cross conjugation), the bathochromic effect is much smaller.

From the above table 1 (3 and 4) it is concluded that the attachment of NEt_2 group in place of hydrogen in a double conjugated system containing one heteroatom will shift the λ_{max} to about 25 mμ. When the number of heteroatoms will be more, the $\Delta\lambda$ will be smaller. It may be assumed that in systems containing two heteronitrogen atoms, the bathochromic effect will be in the range 20–25 mμ.

RESULTS AND DISCUSSION

It is concluded from observations that the replacement of C=C by C=N will have a blue shift and the attachment of $-NH_2$ group at the terminal C atom of the doubly conjugated system will have a red shift. As a result of these two effects, the determination of the actual position of λ_{max} for the simultaneous substitution of these two factors will be difficult. An attempt has been made to predict the value of λ_{max} for the biguanide molecule.

It has been shown that the following hydrocarbon



1-dimethyl-3-methylbutadiene

can be visualised as being formed by suitable replacement of heteroatoms by their carbon analogues in the biguanide molecule. Let us now consider butadiene as our reference substance having λ_{max} 217 mμ. We can now construct biguanide molecule by suitable substitution and calculate the probable λ_{max} for biguanide. In compounds 3 and 4 in the Table 1, the red shift produced by introduction of $-NEt_2$ group is 25 mμ. This happens in compounds containing heteroatom oxygen in the conjugated system. In biguanide, the effect of replacing two hydrogens of $-NH_2$ group by ethyl group is found to be 4 mμ. Hence it is reasonable to assume that in butadiene if two hydrogen atoms of the terminal C atoms be replaced by $-NH_2$ group, the red shift associated with each replacement will amount to near about 21 mμ. Computed λ_{max} value for biguanide is given below:

Compound	λ_{max}(mμ)
$CH_2=CH-CH=CH_2$	217
$CH_2=N-CH=NH$	217 − (22 × 2) = 173
$H_2N-\underset{H_2N}{\underset{\vert}{C}}=N-CH=NH$	173 + (2 × 21) = 215
$H_2N-\underset{H_2N}{\underset{\vert}{C}}=N-\underset{NH_2}{\underset{\vert}{C}}=NH$	215 + 21 = 236

Considering various uncertainties involved in this type of qualitative evaluation, the the predicted value tallies reasonably well with the experimental value of 230 mμ for biguanide.

Let the effect of substitution on the N atom of biguanide molecule be considered. Methyl and other alkyl groups attached to the π centre are usually considered to exert hyperconjugative and electron donating inductive effects. The hyperconjugative effect usually reduces the energies of electron transitions in both alternant and non-alternant hydrocarbons by extending the conjugated system. In alternant hydrocarbons, the inductive effect is of subsidiary importance owing to the pairing property of π orbitals and the hyperconjugative small bathochromic effect is dominant. The red shifts of π–π^* transition of alternant hydrocarbons by an alkyl substituent are usually small and rarely exceed 10 mμ. For example as is seen from the table, the first S—S band of butadiene undergoes a red shift of about 6 mμ on introduction of one methyl group and further a red shift of about 4 mμ on introduction of a second methyl group. Furthermore, as is seen in the following table, the first main band of styrene undergoes a red shift of about 2 mμ on methyl substitution at β position. In addition to the bathochromic effect, introduction of a methyl group exerts usually a hyperchromic effect on π–π^* band, that is, it intensifies π–π^* transition.

Compound	Solvent	λ_{max}	ε_{max}
$C_6H_5CH{=}CH_2$	Heptane	248	14,760
	Ethanol	248	16,620
C_6H_5 $CH{=}CH{-}CH_3$	Ethanol	250	17,300

However, biguanide is a compound containing heteroatom nitrogen in a conjugated system, the red shift due to substitution at the π centre atom will be about 5–6 mμ and this is in accordance with the Woodward's rule[8] which is stated below.

(1) Each alkyl substituent or ring residues attached to the diene system chromophore displaces the λ_{max} by 5 mμ towards longer wavelengths.

Thus the calculated and observed values for the substituted butadienes are given below:

Compound	λ_{max} (observed)	λ_{max} (calculated)
$CH_2{=}CH{-}CH{=}CH{-}CH_3$	223 mμ	217 + 5 = 222 mμ
$CH_2{=}C(CH_3){-}C(CH_3){=}CH_2$	226 mμ	217 + 10 = 227 mμ
$CH_3{-}CH{=}CH{-}CH{=}CHCH_3$	227 mμ	217 + 10 = 227 mμ

where butadiene has $\lambda_{max} = 217$ mμ.

Biguanide base and its normal salts have a conjugate —C=N—C=N— chromophore and N atoms having lone pairs capable of forming a delocalized π electron system. Even the electrons attached to $-NH_2$ have π character due to various resonating forms in which the ligand is capable of remaining in aqueous solution. The red shift due to the alkyl groups attached to these N atom will be smaller than that of a regular π centre according to Woodward's rule.[8]

In the case of butadiene, the red shift is, in general, 5 mμ for an alkyl group, and in biguanide the substitution of an alkyl group is expected to have a red shift of 3 to 4 mμ for the first alkyl group. The introduction of a second alkyl group may have a shift of 1 mμ or nothing at all. In addition to this effect, there is expected a similar hyperchromic effect, smaller for the first alkyl group and still smaller for the second alkyl group. Phenyl biguanide shows the λ_{max} at 245 mμ. At this λ_{max} a broad band is observed and perhaps it is a resultant of two λ_{max}'s, one due to the phenyl ring which is expected to be about 250 mμ and the other due to biguanide molecule, expected to be at about 230 mμ.

TABLE 2.

Compound	λ_{max}(mμ) (experimental)	λ_{max}(mμ) (calculated)	ε
Biguanide mono-hydrochloride	230	—	11,000
N′-methyl-biguanide mono-hydrochloride	233	230 + 3 = 233	12,000
N′-ethyl-biguanide mono-hydrochloride	233	230 + 3 = 233	13,110
N′,N′-diethyl-biguanide mono-hydrochloride	234	230 + 3 + 1 = 234	14,500
N′,N′-dimethyl-biguanide mono-hydrochloride	234	230 + 3 + 1 = 234	12,500
N′-phenyl-biguanide mono-hydrochloride	245	—	16,010
N′-benzyl-biguanide mono-hydrochloride	233	233	16,390

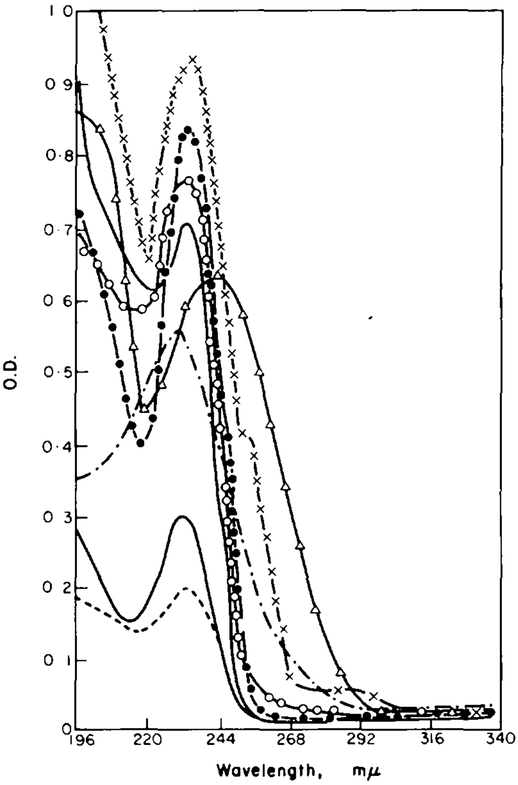


FIG 1. Ultra violet absorption spectral curves of biguanide and substituted biguanides.

- · – ·· – ·· Biguanide mono-hydrochloride
——— ——— Methyl biguanide mono-hydrochloride
- ● · ●- · Ethyl biguanide mono-hydrochloride
– – – ·· – – – Di-methyl biguanide mono-hydrochloride
- ○- ○ · Di-ethyl biguanide mono-hydrochloride
△ · △ · Phenyl biguanide mono-hydrochloride
- × · × · Benzyl biguanide mono-hydrochloride

In benzyl biguanide, the λ_{max} is expected to be the same as the methyl biguanide, because the total effect of hyperconjugation and electronic inductive effect of $C_6H_5CH_2$ will be almost the same as the alkyl group and hence the result $\lambda_{max} = 233$ mμ is the predicted value.

TABLE 3. ANALYSIS (%), WITH CALCULATED VALUES IN PARENTHESES

Compound	C (%)	N (%)	Anion (%)	Ref.	Fig. No.
1. $C_2H_7N_5$.HCl	17·42 (17·58)	51·38 (51·28)	25·93 (26·01)	9	1
2. $CH_3.C_2H_6N_5$.HCl	23·71 (23·76)	46·18 (46·20)	23·39 (23·41)	10	1
3. $C_2H_5.C_2H_6N_5$.HCl	28·87 (29·00)	42·21 (42·30)	21·37 (21·45)	11	1
4. $(CH_3)_2.C_2H_5N_5$.HCl	29·10 (29·00)	41·91 (42·30)	21·38 (21·45)	12	1
5. $(C_2H_5)_2.C_2H_5N_5$.HCl	37·08 (37·20)	36·10 (36·17)	18·17 (18·34)	13	1
6. $C_6H_5.C_2H_6N_5$.HCl	44·94 (44·96)	32·68 (32·78)	16·60 (16·63)	14	1
7. $C_6H_5.CH_2.C_2H_6N_5$.HCl	47·18 (47·46)	30·66 (30·77)	15·49 (15·61)	15	1

EXPERIMENTAL

The UV absorption data presented here were obtained in a Beckman DB automatic recording spectrophotometer using fused quartz cells. The compounds (Table 3) were prepared by the methods given in the references. They were all recrystallized and their purity checked by elemental analysis.

Acknowledgement I thank Professor Dr. D. Sen for valuable suggestions and thanks are also due to Ministry of Education, Govt. of India for financial assistance.

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