Physico-chemical Behaviour of Sulpha Drugs. Spectroscopic Trends and Conjugation in Phenylsulphonylguanidine Derivatives

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The stretching frequencies of the sulphonyl group and the u.v. spectra of phenylsulphonylguanidine, and its *ortho-*, *meta-*, *para*-amino, -methyl, -chloro, and -nitro-derivatives have been measured. For *p*-aminophenylsulphonamidoguanidine which, as well as the ring *N*-methyl derivatives of *p*-aminophenylsulphonamido-pyridine (SP) and -thiazole (ST), shows electronic properties intermediate between those of the *neutral* [*N*(1)-methyl derivatives of SP and ST] and of the *anionic* species (sodium salts of SP and ST), the occurrence of the imide or zwitterion structure was confirmed. The i.r. results indicate that no effective conjugation occurs between the aryl and the S–O bonds, while the u.v. spectra give evidence of the interaction between the two chromophores bonded to the SO_2 group. The experimental data seem to support a previously postulated model for conjugation where (a) the conjugation between the two chromophores can occur *via* an empty *d* orbital of the expanded valence shell of the sulphur atom not entering the SO_2 π-system, and (b) a further interaction operates between the SO_2 π-system and the guanyl portion of the molecule.

SPECTROSCOPIC evidence has been produced [1-5] for the presence of different forms of sulpha drugs in different solvents and in aqueous solutions at different acid concentrations. For example 2-*p*-aminophenylsulphonamidopyridine consists mostly of the neutral form (1) in ethanol, and of the imide (2a) or zwitterion (2b) form in water (pH *ca.* 5), whereas *p*-aminophenylsulphonamidopyrimidine does not show any appreciable concentration of the imide or zwitterion form in water; this was demonstrated by comparison with the u.v. absorption spectra of the methyl derivatives which are fixed in form (1) [*N*(1)-methyl] or form (2) (ring *N*-methyl).[1,2,6] Usually sulpha drugs have acid properties and give the anion form (3) in alkaline, aqueous solutions. The existence of several species in aqueous neutral solutions is relevant to the problem of the relationship between the electronic structure and the bacteriostatic activity of these drugs, because the different forms must have widely differing electronic properties as shown by the u.v. absorptions. Bell and Roblin,[7] who took into account only the neutral and the anion forms and established the well known correlation between the *in vitro* activity and the pK_a values of a large series of sulphonamides, assigned to the anion a far greater activity than the neutral form; Shepherd *et al.*[1] showed that the *N*(1)-methyl derivatives of *p*-aminophenylsulphonamido-pyridine and -thiazole

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[5] T. Uno, K. Machida, K. Hanai, M. Ueda, and S. Sasaki, *Chem. Pharm. Bull. (Japan)*, 1963, **11**, 704.
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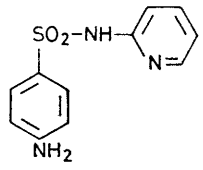
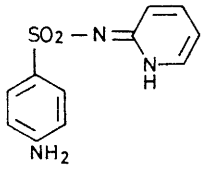
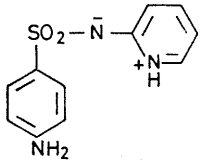
exhibit very low activity. In the light of these results it is rather surprising that correlations only between the biological activity and the electronic structural indices of the molecules in their neutral forms have been sought [8-13] and that the electronic structures of



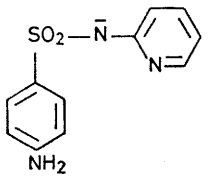
(I)



(2a)



(2b)



(3)

the anion and zwitterion (or imide) forms have been paid very little attention. Although, in principle, the electronic structure of the neutral molecule should determine both the amount and the electronic structure of the ionic and zwitterionic species, the relation appears to be too indirect to be of practical use; for example the SO_2 and NH_2 stretching frequencies of a large series of neutral sulphonamides [12] are identical within experimental error, whereas their pK_a values, tautomeric equilibria in water and the solid state, and bacteriostatic activities are markedly different. For these reasons we deemed it useful to undertake experimental and theoretical work on the anionic [14] and zwitterion [6] forms in order to obtain information on their electronic structures, starting from the problem of conjugation between the various chromophores. According to many authors [15-17] resonance occurs between the *p*-amino and the SO_2 groups and it is considered the main factor affecting activity; the resonance hypothesis has been alternately disproved [18-20] and confirmed,[11,21] and clear conclusions have not been reached.[22] Care should be taken to differentiate among the individual possibilities because the neutral, imide, and anion forms can furnish different answers both regarding the kind and the extent of conjugation, and the bacteriostatic activity. In this respect *p*-aminophenylsulphonylguanidine (sulphaguanidine) is an interesting case; it lacks acid properties and exists as a single form, *i.e.* the imide [16,20] or zwitterion. The fairly high bacteriostatic activity must be due to that form alone, as must any experimental trend that can be explained through a conjugation model which depicts the resonance of the form.

A collection of *ortho*-, *meta*-, and *para*-derivatives of sulphaguanidine were prepared and their SO_2 stretching frequencies and u.v. absorptions were considered in order to investigate whether trends exist that can be assigned to conjugation effects.

I.r. and U.v. Spectra.—In Table 1 the asymmetric (ν_{as}) and the symmetric (ν_s) stretching frequencies of the SO_2 group, both in Nujol and in dimethyl sulphoxide (DMSO) solution, are reported for phenylsulphonylguanidine (I), and the amino- (II)—(IV), methyl (V)—(VII), chloro- (VIII)—(X), and nitro-derivatives (XI)—(XIII); the averaged frequencies ($\bar{\nu}$) have also been included. The $\bar{\nu}$ values can be considered as more representative of the S–O bond electronic environments than the single symmetric or asymmetric stretching frequencies,[23] and so more useful for discussing the trends in series of molecules. The stretching frequency of an isolated diatomic molecule A–B is approximately equal to the weighted average of the symmetric and asymmetric stretching frequencies of the corresponding AB_x molecule calculated according to $\bar{\nu}(A\text{–}B) = \{[\nu^2_s + (x-1)\nu^2_{as}]/x\}^{\frac{1}{2}}$ and the average rule has been shown also to hold when AB_x is a component group of

TABLE 1

Asymmetric (ν_{as}), symmetric (ν_s), and average ($\bar{\nu}$) SO_2 stretching frequencies (cm^{-1}) of phenylsulphonylguanidine derivatives, $RC_6H_4SO_2NHC(:NH)NH_2$

		Solid state (Nujol) [a]			In solution (DMSO)		
Number	R	ν_{as}	ν_s	$\bar{\nu}$	ν_{as}	ν_s	$\bar{\nu}$
(I)	H	1240	1136	1189	1271	1142	1208
(II)	*o*-NH_2	1255	1131	1194·5	1264	1135	1201
(III)	*m*-NH_2	1263	1139	1202·5	1269	1133	1203
(IV)	*p*-NH_2	1235	1130	1183·5	1264	1135	1201
(V)	*o*-CH_3	1254	1143	1200	1266	1146	1207·5
(VI)	*m*-CH_3	1253	1132	1194	1271	1135	1205
(VII)	*p*-CH_3	1240	1133	1187·5	1270	1141	1207
(VIII)	*o*-Cl	1264	1143	1205	1266	1146	1207·5
(IX)	*m*-Cl	1259	1146	1204	1274	1145	1211
(X)	*p*-Cl	1243	1135	1190	1268	1143	1207
(XI)	*o*-NO_2	1282	1154	1219·5	1282	1149	1217
(XII)	*m*-NO_2	1272	1152	1213·5	1277	1150	1215
(XIII)	*p*-NO_2	1268	1139	1205	1280	1144	1214

[a] All compounds were crystallized from methanol.

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[16] W. D. Kumler and T. C. Daniels, *J. Amer. Chem. Soc.*, 1943, **65**, 2190.
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[23] W. J. Lehman, *J. Mol. Spectroscopy*, 1961, **7**, 261.

larger molecules, provided that there is no mixing of the vibrations of the AB_x group and those of the rest of the molecule.

From the results of Table 1 we notice that the $\bar{\nu}$ values fall in a small range ($\Delta\bar{\nu}$ 36 cm^{-1} in Nujol and 16 cm^{-1} in DMSO), $\Delta\nu_{as}$ usually being larger than $\Delta\nu_s$. On passing from the crystalline to the solution state the frequency values usually shift towards higher wavenumbers; some of the shifts undergone by $\bar{\nu}$ [19 cm^{-1} for (I), 17·5 cm^{-1} for (IV)] are of the same order as the frequency range covered by the compounds studied. In the Nujol spectra the groups of isomers have $\Delta\bar{\nu}$ values of 19, 12·5, 15, and 14·5 cm^{-1} for NH_2, CH_3, Cl, and NO_2 derivatives respectively, the *para*-derivative always showing the lowest value in the group. On the other hand, in solution the frequency changes within each group of isomers are very small (2—4 cm^{-1}): the only clear trend is that the introduction of NH_2, whatever the position, lowers the frequency values, whereas NO_2 raises them, and CH_3 and Cl leave them nearly unchanged.

U.v. band maxima and molar extinction coefficients are reported in Table 2 for compounds (I)—(XIII) and a number of reference compounds.

TABLE 2

Band maxima and intensities of u.v. absorptions

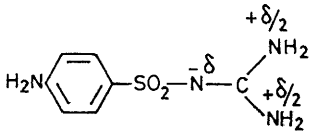
Compound	α Band $\lambda_{max.}$/nm (ε)	*p* Band $\lambda_{max.}$/nm (ε)	Compound	α Band $\lambda_{max.}$/nm (ε)	*p* Band $\lambda_{max.}$/nm (ε)
(I)	264·5 (900)	222 (12,400)	Nitrobenzene [a]		268·5 (7800)
Aniline [a]	280 (1430)	230 (8600) [b]	(XI)	~ 260 (3300) [c]	
(II)	297 (2150)	239 (7000) [b]	(XII)		260 (7500)
(III)	297 (2300)	239 (6500)	(XIII)		268 (10,830)
(IV)		258·5 (16,250)	Sulphonamide	264·5 (950)	218 (9600)
Toluene [a]	261 (225)	206·5 (7000)	*o*-Amino-	303 (3300)	242 (6900)
(V)	269 (1200)	226 (9000)	*m*-Amino-	296 (2250)	240 (6900)
(VI)	270 (1100)	227 (9700)	*p*-Amino-	286 (4000) [b]	258 (22,000)
(VII)	262·5 (1100)	229 (15,500)	Anion	270 (400)	224 (4700)
Chlorobenzene [a]	263·5 (190)	209·5 (7400)	*p*-Amino-anion	280 (3000) [b]	251 (21,200)
(VIII)	272 (1150)	227 (7700) [b]	*p*-Nitro-		261 (11,300)
(IX)	272·5 (1000)	228 (7500) [b]			
(X)	265 (650)	232 (17,150)			

All data refer to water solutions; the spectra of anions were recorded at pH 12.

[a] Reference compound. [b] Shoulders. [c] Not assigned.

DISCUSSION

In a recent paper [24] on the electronic structure of the SO_2 group in benzenesulphonamide, *o*-, *m*-, and *p*-aminobenzenesulphonamides, their salts, and a number of related compounds ranging from sulphate to sulphonate ion and to crystalline sulphuric acid, we were able to show that the $\bar{\nu}$(S–O) values fell in three well separated frequency ranges corresponding to neutral molecules ($\bar{\nu}$ 1226—1271 cm^{-1}), to univalent anions ($\bar{\nu}$ 1152—1163 cm^{-1}), and to the divalent sulphate ion ($\bar{\nu}$ 1087 cm^{-1}); for a number of sulpha drugs, in their neutral forms, $\bar{\nu}$ had a mean value of 1242 cm^{-1} in the solid state and 1243 cm^{-1} in methanol solution. The $\bar{\nu}$ values for a collection of sulpha drugs in their anion form,[14] decrease to 1160—1186 cm^{-1} in Nujol and to 1174—1195 cm^{-1} in DMSO solution, whereas the corresponding imide or zwitterion methyl derivatives [6] have the intermediate values 1188—1209 and 1205—1230 cm^{-1} in Nujol and solution respectively. The $\bar{\nu}$ value of sulphaguanidine (both in the solid state and in solution) put this molecule in the group of ring *N*-methyl derivatives, thus providing an additional proof of the structure proposed by Kumler and Daniels [16] and demonstrated through i.r. and n.m.r. studies on the NH_2 groups.[20,25] The imide and zwitterion formulae are the limits of the actual structure of these molecules: a hybrid structure wherein a partial negative formal charge is assumed by the nitrogen atom bonded to the sulphur atom seems to account well for the result that the $\bar{\nu}$ values are intermediate between those of the neutral and the anionic molecules.



This can also explain the bacteriostatic activity of sulphaguanidine (minimum inhibitory concentration, m.i.c. 62 μmol l^{-1} against *E. coli* [26]) which is intermediate, for example, between that of the neutral sulphanilamide (m.i.c. 128 μmol l^{-1}, pK_a 10·43) and that of *p*-aminophenylsulphonamidopyrimidine (m.i.c. 1·02 μmol l^{-1}, pK_a 6·35) whose activity is essentially due to the proportion of the anionic form (*ca.* 75% at pH 7). Further proof comes from the result that *N*-ring derivatives of *p*-aminophenylsulphonamido-pyridine and -thiazole, exhibit activities that are one fourth and one sixteenth respectively of those of the parent compounds,[1] which are mixtures of zwitterion and anionic forms, under the experimental conditions of measurement of activity. According to the i.r. results all the sulphaguanidine derivatives of Table 1 can be assigned similar zwitterion structures.

The $\bar{\nu}$(S–O) stretching frequencies and the π(S–O)

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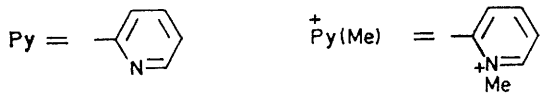
bond orders calculated by means of a semiempirical LCAO–SCF procedure, have been found [24] to be linearly correlated. The calculation was based on a theoretical model, derived from Koch and Moffitt,[27] where the main simplification consisted in neglecting the effects of aryl substituents on the electronic environment of the S–O bond. The chosen approximation that excluded direct conjugation between the aryl and the SO_2 π-systems, seems to be a good one in the light of the results collected in Table 1. In fact, no definite trend can be found within each group of isomers which can be clearly assigned to conjugation; in any case the extent of conjugation must be so feeble as to be screened by intermolecular effects. The conclusion that there is no effective conjugation between the aryl group and the S–O bonds, does not mean that there is no interaction between the two chromophores bonded to the SO_2 group; in fact the u.v. spectra of *o*-, *m*- and *p*-aminophenylsulphonylguanidine, as well as those of *o*-, *m*-, and *p*-aminobenzenesulphonamide and their salts show (Table 2) the typical spectroscopic trend of disubstituted benzene derivatives.[28,29] Clear evidence of interaction can be obtained by comparing the u.v. results of a group of compounds where both chromophores give absorption bands easy to measure and

$H_2N-C_6H_4-SO_2-N(Me)-Py$	λ_s 264nm	
$H_2N-C_6H_4-SO_2-\bar{N}-\overset{+}{P}y(Me)$	λ_s 260nm	λ_{Py} 245nm
$H_3\overset{+}{N}-C_6H_4-SO_2-\bar{N}-\overset{+}{P}y(Me)$		λ_{Py} 240nm
$H_2N-C_6H_4-SO_2-\bar{N}-Py$	λ_s 256nm	λ_{Py} 243nm
$Ph-SO_2-\bar{N}-Py$		λ_{Py} 240nm



SCHEME

assign (see Scheme). The λ_s maxima refer to conjugation bands mainly localized on the first chromophore ($H_2NC_6H_4$), whereas λ_{Py} relate to conjugation bands mainly localized on the second. The Scheme gives evidence of the shifts undergone by the absorption maxima of one chromophore when the other changes. Here again sulphaguanidine (λ_s 258·5 nm) shows a strict similarity to the ring *N*-methyl derivative, and the zwitterion structure is half-way between the neutral and the anionic forms. The blue shifts undergone by the band of the first chromophore on passing from neutral to zwitterion and anion forms reveal that $\bar{N}-\overset{+}{P}yMe$ and $\bar{N}-Py$ are less favourable than N(Me)–Py for the conjugation with the *p*-amino-group and possibly hamper it. This conclusion is the opposite of that reached by Kumler and Daniels.[16]

The i.r. and u.v. results seem to corroborate a theoretical model [24,27] of the model where (a) conjugation between the two chromophores, bonded to the SO_2 group, can occur *via* an empty *d*-orbital of the (expanded valence shell of the) sulphur atom not entering the SO_2 π-system, and (b) a further coupling operates [mainly in the forms (2) and (3)] between the SO_2 π-system and the N–R group; interaction (a) mainly accounts for the u.v. spectral trend in the sulphamoyl system, whereas interaction (b) is the determining factor for the changes undergone by the SO_2 stretching frequencies on passing from neutral to zwitterion and anionic forms. According to this simplified picture the two interactions give concomitant but roughly independent contributions to the overall electronic structure. The quantitative aspects of this model are now being considered by means of MO calculations.

EXPERIMENTAL

Compounds (I), (III), and (V)—(XIII) were prepared as described in the literature.[30–35] Compound (IV) was a commercial product, crystallized from methanol. 2-Aminophenylsulphonylguanidine (II) was synthesized by reduction of the corresponding 2-nitro-derivative (XI) with $Fe–FeCl_2$, following Haworth *et al.*[35] After neutralizing the reaction mixture with $NaHCO_3$ the insoluble material was filtered, dried, and extracted with boiling acetone. The acetone solution was cooled and concentrated *in vacuo* at room temperature: the crude product was collected and recrystallized from methanol (60%). *2-Aminophenylsulphonylguanidine* is a crystalline solid, m.p. 203—204°.

I.r. measurements were taken with a Perkin-Elmer 257 spectrophotometer for Nujol mulls and for DMSO solutions (C. Erba RPE) (0·05 mm thickness).

[4/1571 *Received*, 29*th July*, 1974]

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