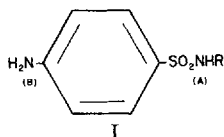


Molecular Orbital Calculations on Some Sulfanilamides

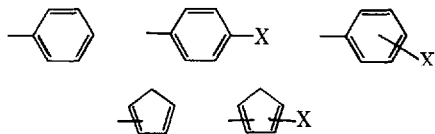
By A. CAMMARATA

Simple HMO-calculations on three sulfanilamides have been done using semi-empirical parameters for the SO_2 group which intrinsically take into account the effects of d -orbital overlap. Charge variations at the sulfonamido and at the aromatic p -amino position are noted which are in qualitative agreement with expectations.

RECENTLY a number of quantum chemical calculations on substituted sulfanilamides have been reported (1, 2). These calculations indicated that a variation in R in structure I results in a variation



of the positive formal π -electronic charge on nitrogen A whereas the positive formal π -electronic charge on nitrogen B remains unaffected. When these compounds were classified into groups depending on the nature of R, where R was

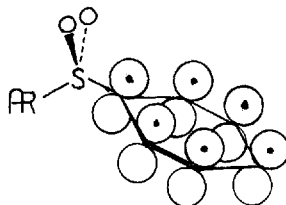


and where any of these R may contain heteroatoms (2), it was found that the variation in formal charge on nitrogen A was consistent with their pK_a 's, *i.e.*, higher formal charge, lower pK_a . Hence, it was concluded that (a) the well known relationship between bacteriostatic activity and pK_a (3) has a quantum chemical foundation; and (b) although a p -amino group may be necessary for activity, the insensitivity of the formal charge on nitrogen B to variations in R did not support the view (4-6) that the bacteriostatic action of the sulfanilamides is primarily associated with the p -amino group.

Since Seydel (5, 6) has presented evidence, based on infrared studies, indicating that substituents placed on the sulfonamido-nitrogen are able to influence the electronic environment of the p -amino group, it is expected that charge variations at the p -amino position should be calculable by making a suitable choice of Hückel parameters for the SO_2 group. Apparently, any choice of parameters which is made for the SO_2 group should somehow include the contribution by the sulfur d -orbitals to the overall conjugation, for neglect of such participation, as found by Martin (1, 2), does not lead to variations in charge at the p -amino position.

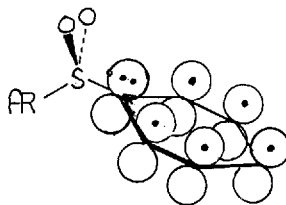
The approach taken here is to utilize semiempirical parameters derived for the SO_2 group from electron paramagnetic resonance (EPR) studies on diphenyl and p,p' -ditolyl sulfone anion radicals (7) in simple Hückel molecular orbital (HMO) calculations on substituted sulfanilamides. While objections may be raised to the application to sulfanilamides, of parameters derived from ESR studies on diarylsul-

fones, a rationalization for their use can be provided. Pictorially, a diarylsulfone may be represented as in II, where only one of the aromatic rings has its π -



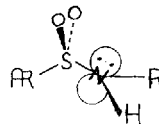
II

network described, and where the dot inside of each p -orbital represents the electron which may be associated with that orbital.¹ Formation of a diarylsulfone anion radical infers that an extra electron is being donated to the π -network. For conjugation to occur across the sulfur atom at some time the p -orbital adjacent to the sulfur atom must contain two electrons (this in keeping with the simple pictorial representation in II), one electron which was originally associated with that orbital and the other the electron which was donated to the π -network. This situation may be represented as in III, which at the atom adjacent to sulfur is



III

formally analogous to a similar representation of sulfanilamide, and presumably its derivatives (IV).



IV

Note, it is also tacitly assumed that the amido-nitrogen is in an sp^2 -hybridized state to enable

¹This type of description appears generally accepted: "For delocalization of π -electron density along the length of a chain or the circumference of a ring, it is necessary that each atom comprising the chain or ring have associated with it at least one p -type electron that is not being employed in formation of single bonds" (11). "Each p_z -electron is paired with its neighbor, and the p -orbitals overlap in the π -manner around the ring" or along the length of a chain (12). The description is equivalent to one in which only molecular orbitals are considered, as in arriving at molecular orbitals one must make linear combinations of these one-electron atomic orbitals.

conjugation through the d -orbitals of the sulfur atom. Such conjugation would require overlap of a sulfur d -orbital with the p -orbital on nitrogen (8, 9).

Using the Hückel parameters $\alpha_{\text{SO}_2} = \alpha_{\text{C}} - 2.60$, $\beta_{\text{C}-\text{C}}$ and $\beta_{\text{C}-\text{SO}_2} = 0.99 \beta_{\text{C}-\text{C}}$ which were derived for the sulfone group in the above-mentioned EPR studies, and which intrinsically take into account d -orbital participation, the formal π -electronic charges of three sulfanilamides were calculated. As these calculations were performed without the aid of a computer the following simplifying assumptions were made for the exchange integrals involving the sulfone group: $\beta_{\text{C}-\text{SO}_2} = \beta_{\text{C}-\text{C}}$ and $\beta_{\text{N}-\text{SO}_2} = \beta_{\text{C}-\text{C}}$.² The Coulomb and exchange integrals used for all other atoms and bonds were those suggested by Streitwieser (10).

The compounds selected were chosen primarily to establish whether, by using this approach, charge variations could be noted at the p -amino position for select sulfanilamide derivatives. Thus, in Fig. 1 there are reported the calculated formal π -electronic charges for: (a) an electron-donating substituent, (b) unsubstituted sulfanilamide, and (c) an electron-withdrawing substituent. Inspection of the calculated formal π -electronic charges on the sulfonamido and on the p -amino position indicate their respective values to be in accord with expectations. The charge at the p -amino position appears to vary in accord with the type of substituent placed on the amido nitrogen, *i.e.*, low for an electron-donating substituent, high for an electron-withdrawing substituent, and the charge at the amido position also appears consistent for the type of group substituted on it. Furthermore, the apparent magnitudes of the charge variation at the amido position (0.07) relative to the p -amino posi-

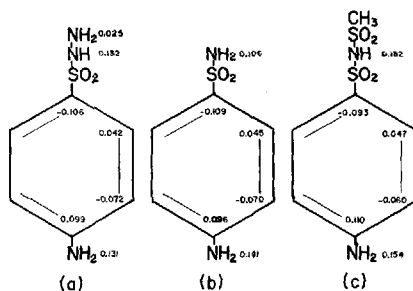


Fig. 1.—Calculated formal π -electronic charges. Key: a, an electron-donating substituent; b, unsubstituted sulfanilamide; c, an electron-withdrawing substituent.

tion (0.02) is consistent with the observation of Bell and Roblin (3) that whereas the pK_a 's of a series of sulfanilamides may vary over a wide range their pK_b 's (for the p -amino group) remain within a very narrow range. It should be emphasized that, at present, these calculations must be considered as being more qualitative than quantitative. Although the trends suggested are in reasonable accord with observation it must yet be demonstrated that these trends provide a correlation. This aspect is currently under investigation. These calculations, however, do suggest that if the effects of d -orbital overlap, due to the sulfur of the SO_2 group, are taken into account, variations in electronic charge at the p -amino position of sulfanilamides could be noted.

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² The error introduced by the approximation $\beta_{\text{N}-\text{SO}_2} = \beta_{\text{C}-\text{C}}$ is expected to be no greater than that introduced in calculations on hydrocarbons in which it is assumed that all β 's are equal. This arises from the following considerations: k is generally assumed to be proportional to the overlap integral, S (13) and is linearly related to the bond distance (Reference 10, pp. 104–105). Aromatic double bonds have lengths 1.33–1.35 Å, while single sp^2 - sp^2 bonds, *e.g.*, the central bond in butadiene, have lengths 1.48–1.50 Å. For precise work with hydrocarbons it is apparent that different β -values should be used depending upon the type of bond. This is seldom done in comparative studies. The S—N and S—C bond distances for sulfanilamides are 1.62 and 1.75 Å, respectively (14, 15). As can easily be seen, the difference in bond distance between aromatic and single sp^2 - sp^2 bonds is approximately equal to the difference in bond distance between the S—N and S—C bonds in sulfanilamide. Thus, since $\beta_{\text{C}-\text{SO}_2} = \beta_{\text{C}-\text{C}}$ is a semiempirically determined quantity, it appears valid to assume $\beta_{\text{N}-\text{SO}_2} = \beta_{\text{C}-\text{C}}$. The approximation is not expected to greatly affect the calculated charge densities (*cf.* Reference 10, p. 106). The largest source of error is expected to be due to the Hückel theory itself, especially when applied to materials containing heteroatoms. However, while the absolute magnitudes of the calculated quantities cannot be considered significant, their values relative to those for other homologs have direct bearing on their physical interpretation.

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