# The Electronic Structures and Pharmacological Activities of Sulfanilamide Derivatives and Carbonic Anhydrase Inhibitors with the Same Sulfonamide Moiety

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SUMMARY

The electronic structures of a series of sulfanilamide and sulfonamide derivatives have been calculated by the Hückel method and also by the extended Hückel method.

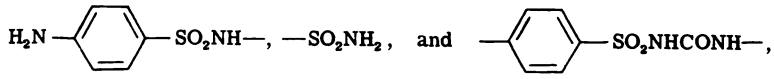
In the case of the sulfanilamide derivatives (sulfa drugs), the electrophilic reactivity indices (superdelocalizability or partial atomic population) at the $N^4$ atom in the molecule are correlated with their relative bacteriostatic activities against *Escherichia coli*. From the results calculated for a dihydropteridine derivative, a possible reaction mechanism is proposed in which the carbonium cation of the compound will attack the $N^4$ atom of the sulfanilamide derivatives electrophilically.

In the case of sulfonamide derivatives (carbonic anhydrase inhibitors), the relative activities as carbonic anhydrase inhibitors are discussed in terms of the electrophilic reactivity indices at the nitrogen atom of the free amino group. A hypothetical reaction model for the interpretation of the inhibitory action for carbonic anhydrase is proposed.

## INTRODUCTION

Recently, many investigations have been carried out to reveal the relation between chemical structure and pharmacological activity. In order to design pharmacologically more effective compounds, it is especially important to study quantitatively the relation between pharmacological activity and electronic structure and to identify the most important and secondary centers in the chemical structures responsible for the activity of various drugs.

Three species of drugs having the same sulfonamide moiety are known to show quantitatively quite different pharmacological activities: sulfanilamide derivatives, sulfonamide compounds, and sulfonylurea compounds. These compounds are the antibacterial sulfa drugs, the carbonic anhydrase inhibitors, and the oral antidiabetic drugs, respectively. Ariëns *et al.* (1) showed that the essential moieties for the bacteriostatic action, the carbonic anhydrase-inhibitory action, and the oral antidiabetic action are




respectively. Various physicochemical properties of these compounds, especially

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of the sulfa drugs (2), have also been studied in relation to their biological activities. In this report, the electronic structures of the former two types of compounds have been calculated by the Hückel method and the extended Hückel method and related to their pharmacological activities.

The changes in electronic structure that some model compounds undergo during a hypothetical reaction have also been studied.

The oral antidiabetic drugs have not been studied here because their mechanism of pharmacological action is not clear.

## THEORETICAL

*The Hückel method.* It is safe to assume that the $\pi$-electrons play particularly important roles in bacteriostatic and carbonic anhydrase-inhibitory action, insofar as these actions of $\pi$-conjugated compounds are exhibited through specified chemical reactions. Consequently the conjugated $\pi$-systems are treated by the Hückel method.

The parameters used in these calculations are the Coulomb integrals, $\alpha_c$, of a carbon atom C; $\alpha_x$, of a hetero atom X; and the resonance integral, $\beta_{c-x}$, between a carbon atom and a hetero atom. These values are shown in Table 1.

The number of $\pi$-electrons in the sulfonyl group is regarded as 4, on the assumption

TABLE 1
*Coulomb and resonance integrals used in the Hückel method*

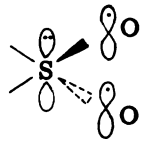
| | a | b | l |
|---|---|---|---|
| =O | 2 | 0.2 | 1.4 |
| -O- | 2 | 0.2 | 0.6 |
| -OH | 0.6 | 0 | 0.7 |
| =N- | 0.6 | 0.1 | 1 |
| $-NH_2$ | 0.4 | 0 | 0.6 |
| >N- | 0.5 | 0 | 0.6 |
| $O_2S$< | 0.2 | 0 | 0.5 |
| =S | 0.2 | 0.1 | 1.2 |
| -S- | 0.1 | 0.1 | 0.5 |
| $-OCH_3$ | 0.5 | 0 | 0.6 |
| $-CH_3$ | 3 | -0.1 | 1 |

| | b |
|---|---|
| NH< (N) | 0.2 |
| NH< (C) | 0.2 |
| NH< (N) | 0.2 |
| (N) | 0.2 |
| NH< (C) | 0.2 |
| N (N) | 0.2 |
| $OCH_3$ | |
| C (N) | 0.1 |
| $OCH_3$ | |

| | l' |
|---|---|
| S=O | 0.8 |
| S-NH | 0.6 |
| N-N | 1 |
| N-O | 1 |

$\alpha_X = \alpha + a\beta$
$\alpha_C = \alpha + b\beta$
$\beta_{C-X} = l\beta$
$\beta_{X-Y} = l'\beta$

that the $\pi$-molecular orbitals for this group are constructed as follows.



Two oxygen atoms of the sulfonyl group are out of plane, and each $\pi$-electron takes part in $\pi$-conjugation (3).

The formal charge $(2 - q_r)$ and the electrophilic or nucleophilic superdelocalizability, $S_r$ (4), are used as reactivity indices.

$$S_r^{(E)} = 2 \sum_j^{\text{occ}} \frac{(C_r^j)^2}{\lambda_j}$$

$$S_r^{(N)} = 2 \sum_j^{\text{unocc}} \frac{(C_r^j)^2}{(-\lambda_j)}$$

where $C_r^j$ is the coefficient of the $r$th atomic orbital in the $j$th molecular orbital, $\lambda_j$ is the coefficient of its energy (given as $\epsilon_j = \alpha + \lambda_j\beta$), and the summations $\Sigma^{\text{occ}}$ and $\Sigma^{\text{unocc}}$ cover occupied orbitals and unoccupied orbitals, respectively.

*The extended Hückel method.* In this method (5) all valence atomic orbitals are taken into account. A molecular orbital $\psi$ can be expressed as a linear combination of all the atomic orbitals $\chi_r$ of the valence electrons of each constituent atom.

$$\psi = \sum_r C_r\chi_r$$

The simultaneous equations are written

$$\sum_s (H_{rs} - \epsilon S_{rs})C_s = 0, \qquad r = 1, 2 \ldots$$

The orbital energies $\epsilon$ are roots of the secular equation

$$|H_{rs} - \epsilon S_{rs}| = 0$$

The $j$th molecular orbital is normalized as

$$\sum_s \sum_r C_r^j C_s^j S_{rs} = 1$$

In these equations $H_{rs}$ and $S_{rs}$ are reso-

nance and overlap integrals, respectively. $C_r^j$ is the coefficient of the $r$th atomic orbital in the $j$th molecular orbital.

The Coulomb integral, $H_{rr}$, of an atomic orbital is taken as $H_{rr} = -I_r$, in which $I_r$ is the modified valence state ionization potential of the $r$th atomic orbital. For the modified valence state ionization potentials, we adopted the approximate values for some related compounds determined by an $\omega$-technique in the extended Hückel method as proposed by Cusachs *et al.* (6–8). These values are shown in Table 2. The Coulomb integrals for the zinc atom were obtained from the estimated values of Ballhausen and Gray (9), and are given in the same table.

The resonance integral, $H_{rs}$, between the $r$th and the $s$th atomic orbitals is given by the following equation:

$$H_{rs} = \frac{KS_{rs}(H_{rr} + H_{ss})}{2}$$

where $K = 1.75$ and $S_{rs}$ is the overlap integral.

The exponent values of atomic orbitals are assessed according to Slater's rule to be 1.00 for the hydrogen atom, 1.625 for the carbon atom, 1.95 for the nitrogen atom, 2.275 for the oxygen atom, and 1.817 for the sulfur atom. The exponent values of the zinc atom are 3.067 for the 3*d* orbital and 1.176 for the 4*s* and 4*p* orbitals.

The steric configurations of the compounds used were obtained from Sutton's Tables (10) and are shown in Fig. 1. Unknown bond lengths and bond angles have been estimated from those of analogous compounds.

We adopted the largest partial atomic population in the highest occupied (HO) or the next HO or the lowest vacant (LV) orbitals, and also these orbital energies, as the reactivity indices in the extended

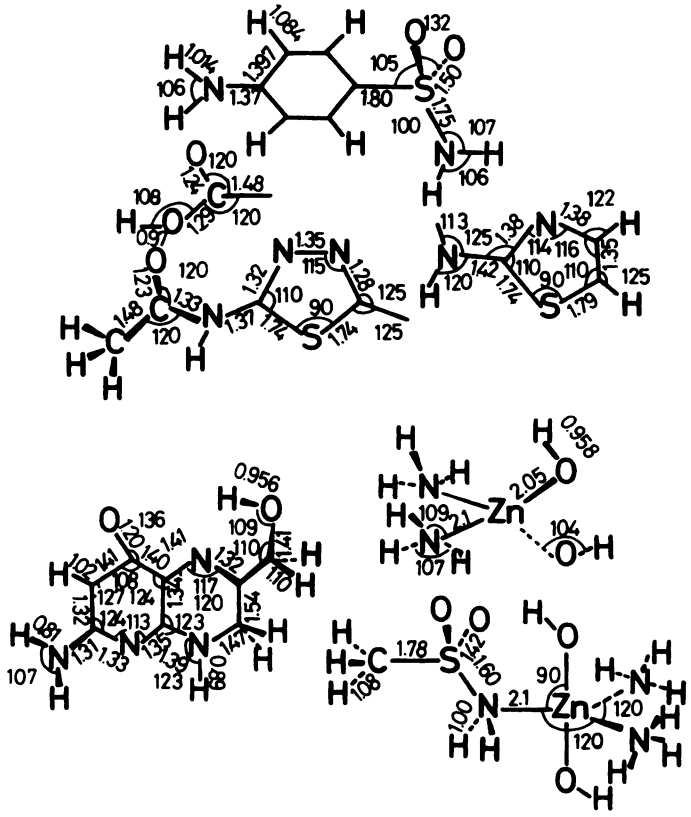


FIG. 1. *Interatomic distances and configurations*

Bond lengths and angles are represented in units of Ångströms and degrees, respectively.

TABLE 2
*Coulomb integrals used in the extended Hückel method*[a]

| | | d | s | p |
|---|---|---|---|---|
| neutral | H 1 | | -13.6 | |
| $-NH_2$ | 2 | | -15.83 | |
| -OH | 3 | | -17.15 | |
| pyridine | 4 | | -14.65 | |
| neutral | C 1 | | -21.43 | -11.42 |
| -COOH | 2 | | -24.47 | -14.85 |
| pyridine | 3 | | -21.01 | -11.52 |
| >CO | 4 | | -21.53 | -12.84 |
| $>SO_2$, O>COH | O 1 | | -30.79 | -14.29 |
| -OH | 2 | | -27.73 | -11.00 |
| >CO | 3 | | -31.29 | -15.02 |
| $-NH_2$ | N 1 | | -23.39 | -10.26 |
| pyridine | 2 | | -23.70 | -10.99 |
| $NH_3$ | 3 | | -23.69 | -10.47 |
| -S- | S 1 | | -22.07 | -11.85 |
| $>SO_2$ | 2 | | -28.6 | -17.4 |
| $Zn^{2+}$ | Zn | -28.00 | -14.49 | - 8.42 |
| | | | | eV |

[a] Data from Yonezawa *et al.* (6), Hinze and Jaffé (7), Cusachs and Reynolds (8), and Ballhausen and Gray (9).

Hückel method. The partial atomic populations are

$$n_r(j) = 2 \sum_{r}^{X} \sum_{s} C_r{}^j C_s{}^j S_{rs}$$

where $C_r{}^j$ is the coefficient of the $r$th atomic orbital belonging to the X atom in the $j$th molecular orbital and $\sum_{,r}^{X}$ covers all the atomic orbitals belonging to the X atom.

The properties of the ionized forms of sulfanilamide derivatives seem to affect indirectly the biological activities, as for instance with respect to membrane permeability. The above treatment of the unionized form, therefore, is considered to be appropriate.

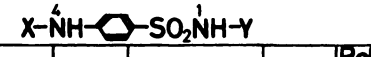
## RESULTS AND DISCUSSION

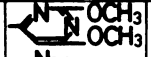
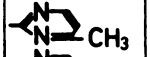
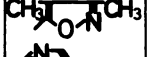
*Chemical reactivity indices obtained by the Hückel method.* In the case of sulfanilamide compounds, X—$N^4$H—  —

TABLE 3
*Chemical reactivity indices calculated by the Hückel method, relative bacteriostatic activities of sulfa drugs against E. coli, and $pK_a$ at the $N^1$ atom*[a]

The empty blocks in the last column indicate no pharmacological activity.

Sulfa Drugs



| No | X | Y | $S_4^{(E)}$ | $S_1^{(E)}$ | $S_S^{(N)}$ | $2-q_1$ | Relative ratio E.coli inhibit. | pKa (1) |
|---|---|---|---|---|---|---|---|---|
| 1 | H |  | 4.911 | 2.141 | 2.330 | 0.445 | 182 | 5.98 |
| 2 | H |  | 4.907 | 2.110 | 2.347 | 0.444 | 142 | 6.85 |
| 3 | H |  | 4.907 | 2.111 | 2.346 | 0.444 | 142 | 6.37 |
| 4 | H |  | 4.871 | 1.865 | 2.659 | 0.473 | 36 | 4.37 |
| 5 | H |  | 4.951 | 2.386 | 2.201 | 0.458 | 80 | 7.23 |
| 6 | H |  | 4.938 | 2.314 | 2.254 | 0.465 | 56 | 4.79 |
| 7 | H |  | 4.919 | 2.192 | 2.281 | 0.442 | 27 | 8.56 |
| 8 | H | -H | 4.951 | 2.498 | 2.013 | 0.428 | 1 | 10.43 |
| 9 | H | $-CONHC_4H_9$ | 4.893 | 1.969 | | | a little | |
| 10 | $(CH_3)_2CO$ | $-CONHC_4H_9$ | 0.705 | 1.953 | | | | |
| 11 | $CH_3CO$ | -H | 2.667 | 2.447 | | | | |
| 12 | $CH_3CO$ |  | 2.657 | 2.076 | | | | |
| 13 |  | | 4.611 | | | | | |

[a] The relative bacteriostatic activities are from Krüger-Thiemer (11), Seydel and Wempe (12), and Ortel and Mohnike (13). The $pK_a$ values are from Bell and Roblin (14) and Yoshioka *et al.* (15).

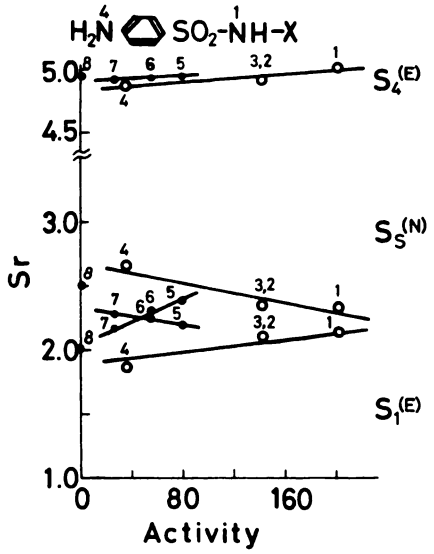



FIG. 2. *Superdelocalizabilities and relative bacteriostatic activities of sulfa drugs*

The numbers over the points in this figure correspond to those of the compounds in Table 3. ●——●, Short-acting sulfa drugs; ○——○, long-acting sulfa drugs.

$SO_2N^1H$—Y, electrophilic superdelocalizability, $S_4^{(E)}$, at the $N^4$ atom; nucleophilic superdelocalizability, $S_s^{(N)}$, at the sulfur atom; and electrophilic superdelocalizability, $S_1^{(E)}$, at the $N^1$ atom are compared with their relative bacteriostatic activities *in vitro* against *Escherichia coli*. These relative activities compared to sulfanilamide are cited from Krüger-Thiemer (11), Seydel and Wempe (12), and Ortel and Mohnike (13).

The formal charge $(2 - q_1)$ at the $N^1$ atom is compared with the $pK_a$ value at the same position, which is obtained from the papers by Bell and Roblin (14) and Yoshioka *et al.* (15).

In Table 3, $N^4$-substituted and $N^1$-substituted sulfanilamides and *p*-aminobenzoic acid are shown. Compounds 1–4 are long-acting and compounds 5–8 are short-acting sulfa drugs. Compounds 9–12 have little or no bacteriostatic activity, and compound 13 is the essential metabolite indispensable for the growth of *E. coli*. It is clear that in each group of long-acting and short-acting sulfanilamide derivatives, the active ones have the largest $S_4^{(E)}$ and comparatively large $S_1^{(E)}$ and $S_s^{(N)}$ in the molecule. In contrast, the same reactivity indices at the same position in the $N^4$-substituted compounds (Nos. 10–12) and carbutamide (No. 9) are extremely small. The nitrogen atom of *p*-aminobenzoic acid (No. 13) has an $S_4^{(E)}$ value comparable to those of active sulfanilamide derivatives. *p*-Aminobenzoic acid, which is the essential metabolite for *E. coli*, appears, therefore, to compete as expected with active sulfanilamides.

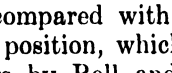
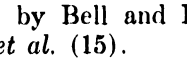
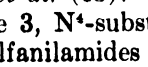
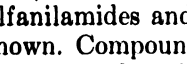
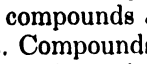
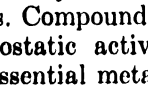
In Fig. 2, electrophilic and nucleophilic $S_r$ values are plotted against the relative bacteriostatic activities of sulfanilamide compounds. Only when these results are divided into two separate categories (i.e., long-acting and short-acting) can a characteristic tendency be visualized. The reason is uncertain. The correlation curve of $S_s^{(N)}$ with bacteriostatic activity has a negative slope, which suggests that large $S_s^{(N)}$ values reflect metabolic instability of the molecular structure or another unknown factor.

It is therefore likely that the electrophilic reactivity of the $N^4$ atom in sulfanilamide compounds may play the principal role in their bacteriostatic action, and that

TABLE 4

*Electrophilic superdelocalizabilities and relative carbonic anhydrase-inhibitory activities of sulfonamide derivatives*

$X\text{-}SO_2NH_2$

| No | X | $S^{(E)}_{\text{-}NH_2}$ $S^{(E)}_{\text{-}S\text{-}}$ | Relative ratio CA inhibition |
|---|---|---|---|
| 1 |  | 2.472 4.405 | 227[a](94%)[b] |
| 2 |  | 2.477 2.857 | 198 |
| 3 |  | 2.438 | (66%) |
| 4 |  | 2.480 3.063 | 59 (11%) |
| 5 |  | 2.380 | (++)[c] |
| 6 |  | 2.498 | 1 (+) |

[a] Data of Wistrand (17).
[b] Data of Tanimukai *et al.* (16).
[c] Data of Burger (19).

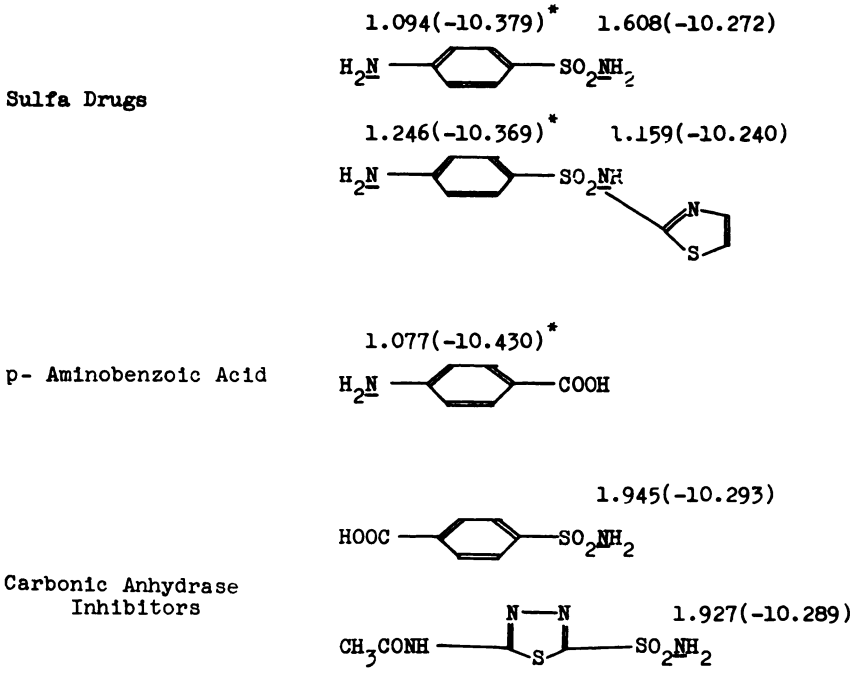



FIG. 3. *The largest partial atomic populations of the HO or the next HO (starred) orbitals at the nitrogen of all component atoms of sulfa drugs, p-aminobenzoic acid, and carbonic anhydrase inhibitors, and their orbital energies (electron volts)*

the sulfur atom and the $N^1$ atom may be of secondary importance with respect to such factors as metabolic instability, solubility, and membrane permeability.

In the case of sulfonamide compounds, electrophilic superdelocalizability, $S^{(E)}_{NH_2}$, at the free amino position is the next largest value in the molecule. The sulfur atoms in the heterocyclic thioether group of compounds 1, 2, and 4 in Table 4 have the largest reactivity indices. These indices are closely correlated with the inhibitory activities on erythrocyte carbonic anhydrase *in vitro*. These values were obtained from Tanimukai *et al.* (16), Wistrand (17), Maren and Wiley (18), and Burger (19). The relative reactivity is expressed by taking that of sulfanilamide as unity. Although compounds 3 and 5 have no heterocyclic thioether group, they have considerable inhibitory activity.

It is therefore suggested that the electrophilic reactivity of the nitrogen atom of the free amino group may be an important factor for carbonic anhydrase-inhibitory activity. In fact, the chemical reactivity indices of the nitrogen atom in Table 4 are much larger than those of the $N^1$ atom of the sulfanilamide derivatives shown in Table 3.

*Chemical reactivity indices obtained by the extended Hückel method.* The compounds for which calculations have been made are sulfanilamide and sulfathiazole as sulfa drugs, *p*-aminobenzoic acid as the essential bacterial metabolite, and *p*-sulfamoylbenzoic acid and acetazolamide as carbonic anhydrase inhibitors. The largest partial atomic populations at the HO or the next HO level (starred) and these orbital energies in units of electron volts in several compounds are shown in Fig. 3.

In the case of the sulfa drugs, the calculated energies of the HO and of the next HO orbitals are nearly degenerate. The partial atomic populations at these levels are largest at the $N^4$ or $N^1$ atom of the two sulfanilamide compounds shown in Fig. 3. The partial atomic populations of the LV orbital in the benzene ring are fairly large.

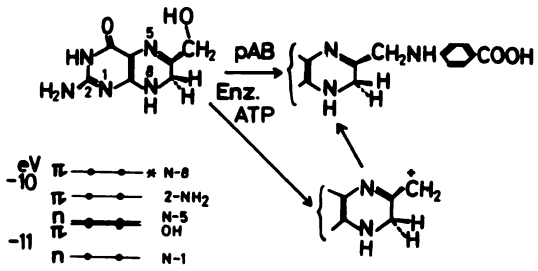



FIG. 4. *Possible biosynthetic path to dihydropteroic acid from 2-amino-4-hydroxy-6-hydroxymethyldihydropteridine and its orbital energies*

Occupied energy levels are represented in units of electron volts, and the HO level is starred. pAB is *p*-aminobenzoic acid.

The nitrogen atom of *p*-aminobenzoic acid has a slightly smaller reactivity index than that of the sulfa drugs, in accordance with the tendency calculated by the Hückel method.

In the case of the carbonic anhydrase inhibitors, the partial atomic populations of the nitrogen atom of the free amino group at the HO level are much larger than those of any other position in the molecule. The largest partial atomic population at the HO level denotes the highest electrophilic reactivity.[1] These results are not compatible with those obtained by the Hückel method. These differences may be attributed to the different evaluations of the Coulomb integrals.

From the results described above, it is generally concluded that the bacteriostatic actions of sulfa drugs are closely related to the electrophilic reactivities at the $N^4$ atom. These reactivities are rather larger than those of *p*-aminobenzoic acid. On the other hand, for carbonic anhydrase-inhibitory action the high electrophilic reactivity of the nitrogen atom of the sulfonamide group seems indispensable.

[1] Some of the present authors have proposed the frontier electron theory, in which the most reactive position in an electrophilic reaction is that of the largest partial electron density of the highest occupied orbital (8). This frontier electron concept in the Hückel calculation is extended to the result obtained by the extended Hückel calculation.

*Possible reaction mechanism of sulfa drugs.* It has been reported that sulfa drugs interfere with the biosynthesis of dihydropteroic acid, either by inhibiting the enzyme system responsible for condensation of *p*-aminobenzoic acid with 2-amino-4-hydroxy-6-hydroxymethyldihydropteridine pyrophosphate (20) or by producing "fraudulent analogues" of dihydropteroic acid (21).

Based on the latter mechanism, the electronic structure of 2-amino-4-hydroxy-6-hydroxymethyldihydropteridine was calculated by means of the extended Hückel method. In this case, the geometrical structure of the compound is assumed to be similar to that of a pteridine, for which experimental data are given in Sutton's Tables (10). In Fig. 4, some of the higher occupied molecular orbitals are shown, as well as the numbering of the position of the largest partial atomic population in certain molecular orbitals.

From these results it is suggested that because of the high electrophilic reactivities (i.e., the largest partial atomic populations in the HO or next HO level, and so on), the N-8 atom, the 2-$NH_2$ group, and the oxygen atom of the hydroxymethyl group will be most easily protonated, since these positions

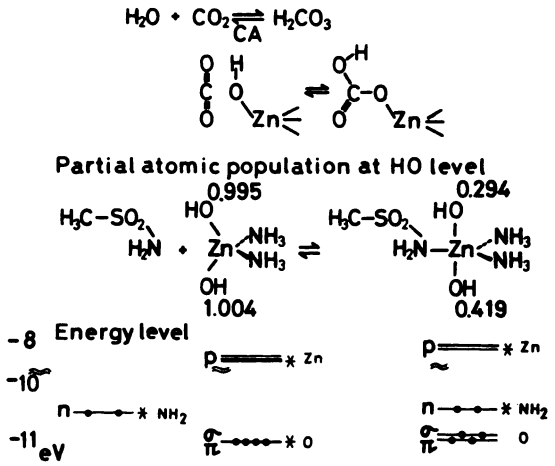



FIG. 5. *Partial atomic populations of the HO level at the oxygen atom in the hydroxyl groups of diammine zinc(II) hydroxide, and their occupied and unoccupied energy levels in the complex formation*

The starred level is the HO or LV level.

have the largest partial atomic populations in higher occupied molecular orbitals, while the formation of intramolecular hydrogen bonds between the hydrogen atom of the 6-hydroxymethyl group and the $N^5$ atom can be expected. In the presence of enzyme and adenosine triphosphate, this compound is considered to lose its hydroxyl group and to become a carbonium cation in the transition state. The carbonium cation may possibly attack electrophilically at the $N^4$ atom of the sulfa drugs or the nitrogen atom of *p*-aminobenzoic acid.

*Possible reaction mechanism of carbonic anhydrase inhibitors.* From the experimental results obtained by differential infrared spectrometry, the following catalytic mechanism, shown in Fig. 5, has been proposed (22). It was suggested that the bicarbonate ion might be coordinated to the zinc(II) atom of the carbonic anhydrase through the negatively charged oxygen atom of the enzyme.

It was also reported that X-ray diffraction analyses of carbonic anhydrase in the presence of acetoxymercurisulfanilamide suggested that the sulfonamide is bound to the zinc atom of the enzyme through the sulfonamide group (23).

From optical rotatory dispersion spectra, it was concluded that when the enzyme containing a cobalt(II) atom or a zinc(II) atom at the active site interacted with optically inactive azosulfonamide, dissymmetry was induced in the originally symmetrical transition (24). Fixation of the molecule in the dissymmetric molecular environment of the protein might occur through interaction with the metal ion in the protein.

We then studied a hypothetical reaction between methanesulfonamide and diammine zinc(II) hydroxide as models of a carbonic anhydrase and its inhibitor, respectively. The assumption was made that when the sulfonamide is coordinated to a zinc(II) atom on the enzyme, the coordination number of the zinc atom changes from 4 to 5 and the original symmetry of the coordination compound, $T_d$, becomes $D_{3h}$. The change in the electrophilic reactivity of the oxygen atom of the hydroxyl group in diammine zinc(II) hydroxide that accompanies a hypothetical reaction was calculated by the extended Hückel method.

In the case of methanesulfonamide, the HO molecular orbital consists mainly of a lone pair-type nitrogen atom orbital; i.e., the partial atomic population of the nitrogen atom at the HO level is the largest in the molecule.

The LV and next LV orbitals of diammine zinc(II) hydroxide are composed of *p*-type zinc atom orbitals, whereas the HO molecular orbital consists of a $\sigma$-type oxygen atom orbital; the partial atomic population of the HO level becomes largest at the oxygen atom, and consequently a high electrophilic reactivity of the oxygen atom is to be expected. On the other hand, the sulfonamide is assumed to coordinate to the diammine zinc(II) hydroxide to become diammine methanesulfonamide–zinc(II) hydroxide, as indicated in Fig. 5; i.e., the unshared electron pair of the nitrogen atom of the free amino group is assumed to become bound to the zinc. It is stressed that in the complex, the partial atomic population of the HO orbital at the oxygen atom in the hydroxyl group decreases markedly in comparison to that in the isolated molecule. This implies a considerable decrease of electrophilic reactivity in the complex. As a result, attack of the oxygen atom of the hydroxyl group coordinated to the zinc atom becomes more difficult, and the action of carbonic anhydrase is blocked.

From these results it may be concluded that the model proposed above is useful for the formulation of a reaction mechanism of carbonic anhydrase-inhibitory action.

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