A Quantum-Biological Study of the Pharmacological Action of Thiazide Diuretics

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Recently, thiazide diuretics found a new application to many diseases especially edema and hypertension through physiological and clinical experiments. But their fundamental pharmacological action still remains obscure, in the presence some hypothesis asserted. The nature of sodium pump of renal tubule which was considered to be the action site of thiazide diuretics does not seem fully clarified. The present study was made to pursue the pharmacological action of thiazide diuretics from the viewpoint of quantum-chemistry.

Calculation Procedures

1) Calculation of electrondensity of the heterocyclic ring part of thiazide

Linear-Combination of Atomic-Orbital and Molecular-Orbital Method (Self-Consistent Field Method; LCAOMO-SCF) was applied in calculating electrondensity of fundamental \( \pi \) electron bonded part of the common structure of thiazide and two related compounds in which the chlorine in the 6th position was replaced by the fluorine and the methyl group respectively.

LCAOMO method which was adopted in the present study was Hückel's method\(^1\)–\(^8\).

For correction in their calculated results, Self-Consistent-Field Method was adopted\(^9\). Practically, from the molecular orbital, the electrondensity \( q \) and net charge \( Q_r \) of each atom \( r \) is calculated. Then, from Pauling's relation\(^4\)

\[
X'_r - X_r = 2/3 \left( X_{r+1} - X_r \right) Q_r,
\]

a new set of COULOMB integrals of heteroatoms \( a'_r \) may be calculated as follows;

\[
a'_r = a_0 + h'_r \beta_0 = a_0 + (X'_r - X_r) \beta_0
\]

\[
= a_0 + \left( (X'_r - X_t) + (X_t - X_r) \right) \beta_0
\]

\[
= a_0 + 2/3 \left( X_{r+1} - X_r \right) Q_r + h'_r \beta_0
\]

where \( X'_r, X_r \) represent the electronegativity of the \( r \) atom corresponding to the cases in which the atom \( r \) has a net charge \( Q_r \) and zero respectively, and \( X_{r+1} \) is the electronegativity value of the atom next to \( r \) in the periodic table. The new set of \( a'_r \) was used to construct a new set secular determinant. These procedures were repeated till good convergence was satisfied by the use of a computer. Generally accepted COULOMB integrals and resonance integrals\(^3\) and corrected COULOMB integrals by SCF method were summarized in Table I. The results of electrondensity and formal charge of each molecule are shown in Fig I.

2) Sulfamyl group on molecular orbital analysis

The carbon in the heterocyclic part attached to sulfamyl group is considered to have a typical s p\(^2\) hybridized orbital and one electron of which orbital is perpendicular to the s p\(^2\) hybridized orbital and conjugated to the adjacent carbon. The sulfur has a (3s)\(^2\) (3p)\(^4\) electron structure in the outer shell and two valences. Acceptance of two valences to the sulfur atom of the sulfamyl group would result in the configuration of Fig. 2(a). The broken line represents van der Waals force and both oxygen atoms are assumed to have negative charges. When the sulfur combines one oxy-
Table I Parameters used in the Calculation

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h means Coulomb integral of each atom cited from Streitwieser's monograph. h* means corrected Coulomb integral by SCP method. k means resonance integral between the adjacent atoms. Then, $\alpha = a_0 + k* \beta_0$ and $\beta = k \beta_0$

$a_0$ and $\beta_0$ mean Coulomb integral and resonance integral of the carbon of benzene respectively.

Fig. 1. Distribution of $\pi$ electron and calculated results of $\pi$ electron density and formal charge of the $\pi$ bonded part of thiadiazole and its related compounds.

The dot in the figure represents electron in the calculating model. Electron density of each atom is described in the parenthesis. Formal charge is described under the parenthesis.

gen by a coordinate link (charge transfer) and to the other by van der Waals force, the configurations of Fig. 2(b) and (c) will be depicted. But, to fulfill the normal valence state of oxygen, double bonds between the sulfur and the oxygens were assumed as Fig. 2(d). In every state, due to a comparable strong electronegativity of the oxygen, it could be assumed that the oxygen had negative charge more or less. Thus, resonance form of sulfamyl part

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was expected as illustrated in Fig. 2.

**DISCUSSION**

Thiazide diuretics which were derived from sulfonamides, have been used in treating hypertensive and edematous patients. The nature of their pharmacological action, as well as their adverse effects seem to have been left unclarified. In early stage of the study, it was generally accepted that their inhibitory effect on carbonic anhydrase was related to their diuretic action\(^\text{[19]}\). But, recently this acceptance has faced some question\(^\text{[20]}\). Benzothiadiazine derived from benzen-disulfonamide has a lower enzyme inhibitory effect but has an advanced diuretic activity. Therefore, aside from the viewpoint of biochemistry, it seems reasonable to make approach from quantum-chemistry. It has long been believed that thiazide diuretics have the following features\(^\text{[21]}\):

1. Attachment of the sulfamyl group to the 7th position of the heterocyclic ring.
2. Attachment of the halogen or its related group to the 6th position of the heterocyclic ring.
3. Diuretic activity is more advanced when the double bond between the 3rd and 4th position is saturated.

4. Diuretic activity is also dependent on the nature of the side chain of the 3rd position.
5. Introduction of lower alkyl group to the 2nd position increases diuretic activity.
6. Both $\text{SO}_2$ and CO in the 1st position have diuretic activity, the former being more active than the latter.

To estimate the effect of the chlorine attached to the 6th position of the heterocyclic ring, the chlorine was replaced by the fluorine or the methyl group in the calculating models. Hyperconjugation was taken into consideration in selecting the parameters of the methyl group\(^\text{[22]}\). But, about $\pi$ electrondensity of the three models, similar results were obtained as shown Fig. 1. Then, it was considered that the effect of the chlorine or the halogen related group was not caused by $\pi$ electrondensity. Then, it seemed necessary to clarify the electronic state of the sulfamyl group. The ordinary sulfur has two valence. But, in this sulfamyl group, to satisfy the valence of the oxygen the sulfur atom has six valences. Then, promotion and hybridization of the sulfur orbital seem to be necessary. In Fig. 2 (a), shows a normal valence state of the sulfur and the two oxygens attached to the sulfur by $\text{van}$
DER WAALS force by a slight interaction. In Fig. 2. (b) and (c), one electron of the sulfur is shifted to one oxygen (coordinate link), the other oxygen being attached to the sulfur by VAN DER WAALS force. In Fig. 2 (d), where the sulfur is described as having six valences, d s p^6 hybridization is reasonably assumed\textsuperscript{(13)}. In depicting the hybridized orbital of this d s p^6 sulfur, the planar-tetrahedral (s p^3 d^2) hybridized orbital which was proposed by CRAIG et al.\textsuperscript{(23)} was assumed, when the two d-\pi orbitals (two double bonds) were added\textsuperscript{(13)}. Its six orbitals were crossed together as in Fig. 2 (e). As a result of the various electronic states of the sulfur, resonance forms would be expected. (refer to the resonance forms of the phosphate part of ATP.)\textsuperscript{(14,15)}. It was considered that the electronic state of the phosphorus resembled that of the sulfur because the phosphorus is adjacent to the sulfur in the periodic table. The configurations in Fig. 2. had negative charges in the oxygens as in the phosphate part of ATP. The configuration (d) in Fig. 2. the p-\sigma-d-\pi bond between the sulfur and the oxygens seem to be similar to that of p-\sigma bond of the phosphate part of ATP. Considering the nature of this bond, it seemed reasonable to assume the metal chelating effect of sulfamyl part of thiazide because it was already reported theoretically and experimentally that the phosphate part of ATP could chelate both Mg\textsuperscript{++} and Zn\textsuperscript{++}. YAMABE\textsuperscript{(22)} reported the chelate formation of the sulfamyl part of sulfanilamide with Ni\textsuperscript{++} in the alcohol solution. It seems to be very interesting that both Mg\textsuperscript{++} and Zn\textsuperscript{++} have a close relation to the function of renal tubules because Mg\textsuperscript{++} is one of the important cofactors of membranous ATPase\textsuperscript{(20-22)} which was considered to be important among the driving forces of the sodium pump in renal tubules. A number of reports\textsuperscript{(27-28)} have been made of a high content of Zn\textsuperscript{++} in carbonic anhydrase. On a theoretical assumption that the sulfamyl part of thiazide diuretics chelates both Mg\textsuperscript{++} and Zn\textsuperscript{++}, pharmacologically that part is likely to entrap certain metal cofactors of enzymes in renal tubules. It has been long accepted that a long-term administration of thiazide diuretics easily provoked diabetes mellitus. Studies on diabetogenic agents seem to imply that Zn\textsuperscript{++} chelating agents have a close relation to diabetes mellitus developing in experimental animals\textsuperscript{(20)}. ROBIN\textsuperscript{(30)} proposed that the sulfamyl part of thiazide diuretics would attach to the active center of carbonic anhydrase by competing with carbonic acid (Fig. 3). But, his proposition was not without some oppositions from the viewpoint of quantum-chemistry. Because, it was believed that carbonic acid has four resonance forms and moving intramolecular charge\textsuperscript{(31)} (Fig. 4).

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Moreover, it was considered that the carbon in carboxylic acid had a p^2 hybridization whose three orbitals crossed together at an angle 120°. But six sulfur orbitals of the sulfamyl part, i.e., d s p^2 hybridization including two d-orbitals, cross to each other as shown in Fig. 2 (e). Except for π electron orbitals, four bond orbitals cross at an angle about 60° or 120° and such a triangular orbital figure as the carbon in carboxylic acid do not seem to take a configuration of the sulfur orbitals in the sulfamyl part. Only in the forms of Fig. 2 (b) and (c), some resemblance in figure to the carbon and the sulfur may be expected. Some investigators assumed that the bond angle of C=O was nearly equal to that of S=O. But a significant difference of the bond length between the atoms in carboxylic acid and the sulfamyl part would be expected.

For example, the bond length of C=O was assumed as 1.29Å and that of the S=O as 1.56Å in a complete double bond. Therefore, ROBLIN's model does not seem to be adequate from the viewpoint of quantum-chemistry. Though the effect which was proposed by ROBLIN may partly have a role of inhibition of carboxylic anhydrase activity, the metal chelating action of sulfamyl part of thiazide diuretics should be further studied.

**SUMMARY**

The metal chelating action of the S=O part of sulfamyl part was assumed on the basis of studies of the electronic state of the sulfamyl part of thiazide diuretics because of its similarity to the phosphate part p of ATP.

The diuretic activity and inhibitory effect of thiazide on carboxylic anhydrase may be explained as resulting from Mg^{2+} and Zn^{2+} chelating. ROBLIN's model explaining the inhibitory effect of the sulfamyl part on carboxylic anhydrase activity did not seem adequate from the viewpoint of quantum-chemistry.

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33) Cited from reference No. 32 p. 183.