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77. Fumio Yoneda and Yoshihiro Nitta : Electronic Structure and Local Anesthetic Activity of 2-Diethylaminoacetanilide Derivatives.

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The essential processes that induce local anesthetic effects remain unsolved, though several conceptions on functions of local anesthetics are proposed in connection with many physicochemical facts. Recently Galinsky, *et al.*[1] have investigated about influence of *para*-substituted 2-diethylaminoethyl benzoate derivatives on their local anesthetic activities and found that their potencies as local anesthetics were generally related to the bond order of the carbonyl portion of their ester group. They thought that those compounds whose *para*-substituents gave rise to a lower carbonyl bond order might be expected to have a higher affinity for the receptor and therefore compete more favorably for it than acetylcholine.[*2]

By extending these results Hansch and Fujita[2] have suggested that the local anesthetic activities of 2-diethylaminoethyl benzoate derivatives are related to the Hammett's substituent constants and partition coefficients.

Muralt[3] has recognized the formation and participation of thiamine in nervous conduction, although it is impossible for the present to state exactly the function of thiamine in case of nervous stimulation. He has proposed a notable hypothesis that one of the essential active substances in nervous stimulation is thiamine and its phosphoric ester.

Eckert[4] has investigated reactions between local anesthetics and thiamine in accordance with this hypothesis and proved by the absorption spectrography that local anesthetics and thiamine formed charge transfer complexes. He deduced that under physiological conditions such a reaction inhibited biochemical reaction of thiamine and induced the blocking of nervous conduction, namely the local anesthesia.

In the present paper the authors have investigated the relation between the electronic structures and local anesthetic activities of 2-diethylaminoacetanilide derivatives, in order to contribute to the solution of the mechanism of local anesthetics.

In the first place the net charge and bond order of carbonyl portion in acid amide groups were calculated, in consideration of the competetion of local anesthetics with acetylcholine at the receptor mentioned above. Next, the stabilization energy between local anesthetics and thiamine, and in addition the quantity of charge transfer which has been defined recently by Nagata, *et al.*[5] were calculated, when regard was paid especially to the thiamine theory of Muralt. As a result a correlation of the local anesthetic activity was found with the stabilization energy by charge transfer between the local anesthetics and thiamine.

Method of Calculation and the Structure of the Charge Transfer Complex

Calculations were made by means of the simple linear-combination-of-atomic-orbitals molecular orbital (LCAO-MO) method neglecting overlap. The parameters of

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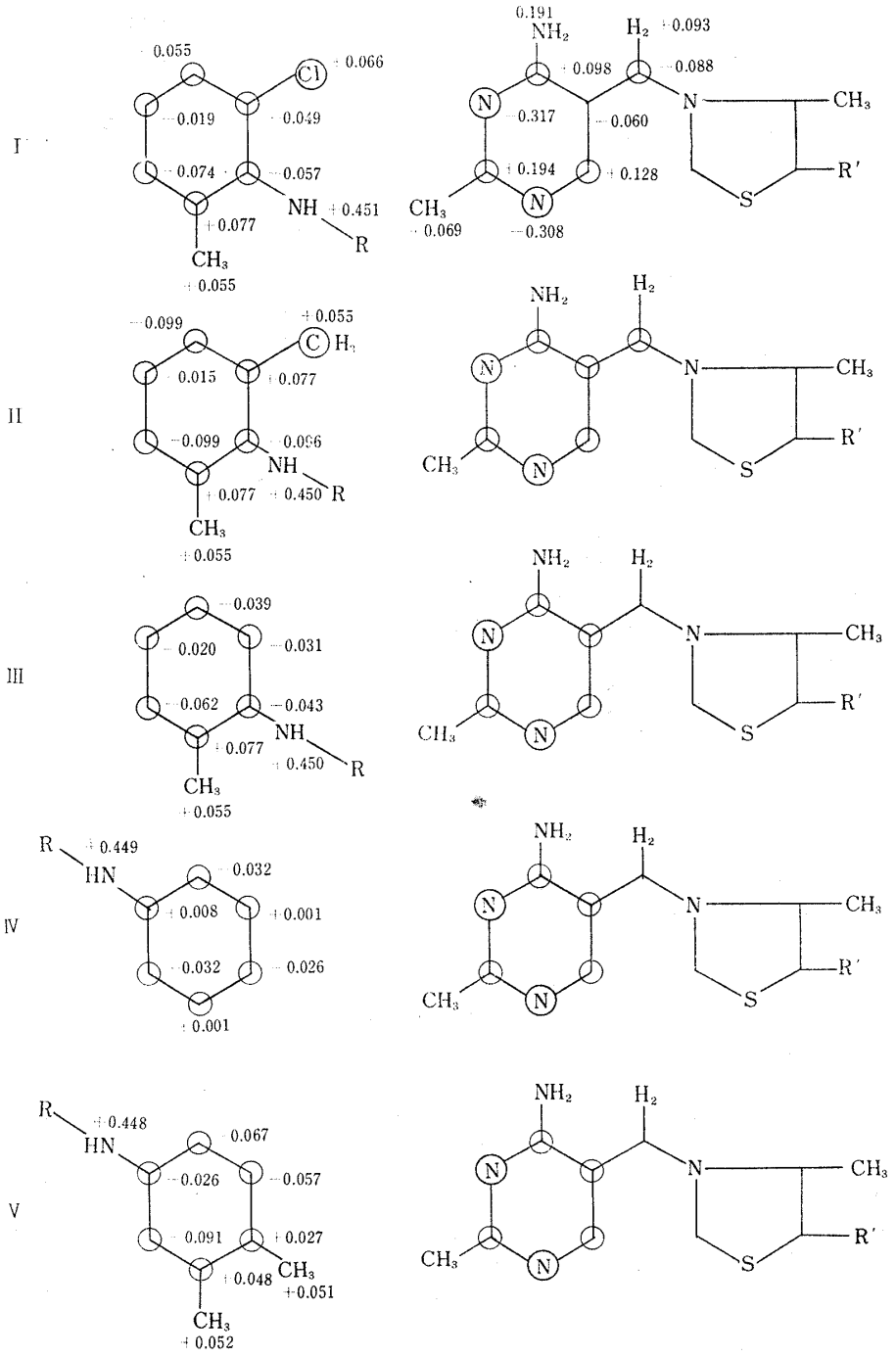
*2 As suggested by Nachmansohn (D. Nachmansohn : "Chemical and Molecular Basis of Nerve Activity," Academic Press, New York, N.Y., 1959.), the local anesthetic effect occurs by a competition with acetylcholine for an enzyme site.

1) A.M. Galinsky, *et al.* : J. Med. Chem., **6**, 320 (1963).
2) C. Hansch, T. Fujita : J. Am. Chem. Soc., **86**, 1616 (1964).
3) A. von Muralt : "Neue Ergebnisse der Nervenphysiologie" Springer, 1958.
4) T. Eckert : Arzneimittel-Forsch., **12**, 8 (1962).
5) C. Nagata, *et al.* : Gann, **54**, 401 (1963).

the coulomb and resonance integrals for substituent groups are the same as the values adopted in our previous papers.[6] Parameters of substituent groups that were not used before are as follows :

Substituent X	a_X[a]	a_r[b]	l[c]
–Cl	1.8	0.18	0.8
–S–	0.9	0.1	0.5
$-CH_3$	3	−0.1	1

a) coulomb integral of the substituent X : $\alpha_X=\alpha+a_X\beta$
b) coulomb integral of the carbon atom adjacent to X : $\alpha_{adj}=\alpha+a_r\beta$
c) resonance integral between that carbon atom and X : $\beta_{C-X}=l\beta$



6) F. Yoneda, Y. Nitta : This Bulletin, 12, 1264 (1964).

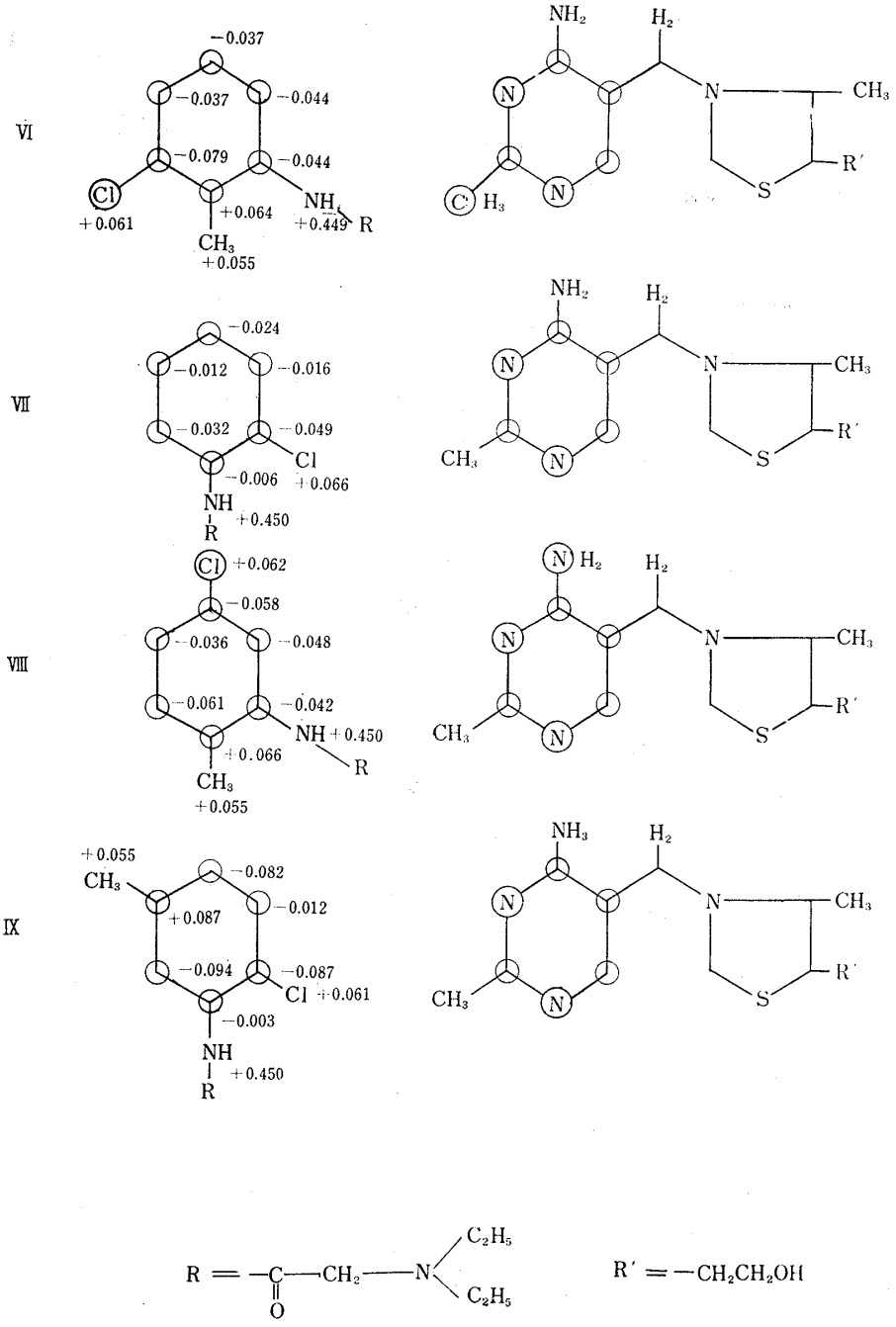


Fig. 1. The most probable orientation between 2-diethylaminoacetanilide derivatives and thiamine determined from consideration of an electrostatic interaction

Concerning the charge transfer between 2-diethylaminoacetanilide derivatives and thiamine, the authors paid special attention to the benzene portion of these local anesthetics and the pyrimidine portion of thiamine in consideration of their similar chemical structures and investigated the charge transfer between them. As was pointed out by Karreman[7] the structure of a charge transfer complex may be predominantly determined by the electrostatic interactions. The sterical orientation of the benzene portion of 2-diethylaminoacetanilide derivatives and the pyrimidine portion in thiamine

7) G. Karreman : Ann. N.Y. Acad. Sci., **96**, 1029 (1962).

were determined in such a way that the electrostatic force between them became the greatest. Thus, the most probable orientation between 2-diethylaminoacetanilide derivatives and thiamine was determined as shown in Fig. 1. The atoms with circles indicate the position where the overlap of the molecular orbital is assumed to occur. Numerals in Fig. 1 are the net charges of the molecules. If 2-diethylaminoacetanilide derivatives and thiamine are assumed to be orientated as shown in Fig. 1, the force of the charge transfer (δE) and the quantitiy of that (δQ) are easily obtained.

If the charge-transfer complex formation is represented schematically as shown in Fig. 2, the force and the quantity of the charge transfer will be given by the formula (1) and (2), respectively.

$$\delta E = -2\left[\sum_{j}^{occ}\sum_{k}^{vac} - \sum_{j}^{vac}\sum_{k}^{occ}\right]\frac{(C_r^j C_s^k I_1 + C_t^j C_u^k I_2 + \cdots\cdots)^2}{\varepsilon_{1j} - \varepsilon_{2k}}(\beta')^2 \qquad (1)$$

$$\delta Q = 2\left[\sum_{j}^{occ}\sum_{k}^{vac} - \sum_{j}^{vac}\sum_{k}^{occ}\right]\frac{(C_r^j C_s^k I_1 + C_t^j C_u^k I_2 + \cdots\cdots)^2}{(\varepsilon_{1j} - \varepsilon_{2k})^2}(\beta')^2 \qquad (2)$$

Where C_r^j is a coefficient of the rth atomic orbital in the jth molecular orbital, ε_{1j} is the energy of the jth molecular orbital of molecule 1 (see Fig. 2), and $\sum^{occ}$ and $\sum^{vac}$ are respectively the summation of the occupied and vacant orbitals. $I_1\beta'$ is the resonance integral between the orbital at the rth atom of molecule 1 and the sth atom of molecule 2 as schematically shown in Fig. 2, where β' is the magnitude of resonance integral between two carbon atom orbitals of the charge transfer complex, the relative magnitude of resonance integrals can approximately be shown by the relative ratio of I_1 etc, and they are indicated in the third column of a Table I. The second column shows the σ-σ type overlap integrals obtained from a Mulliken's table.[8]

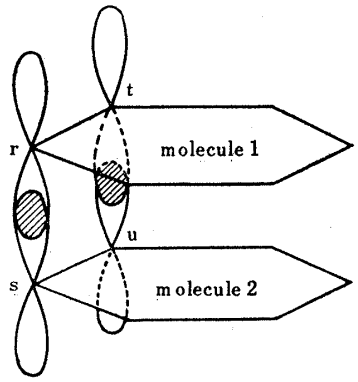


Fig. 2. Schematic representation of σ-σ type overlap of the atomic orbitals

Table I.[5] σ-σ Type Overlap Integrals between Overlapped Atoms X-Y and Relative Ratio of I

Overlapped atoms, X-Y	σ-σ Type overlap integral[a] $S^{\sigma-\sigma}$	I_{x-y}/I_{c-c}	Overlapped atoms, X-Y	σ-σ Type overlap integral[a] $S^{\sigma-\sigma}$	I_{x-y}/I_{c-c}
C-C	0.0561	1	C-Cl	0.0296	0.53
C-N	0.0340	0.61	C-Br	0.0287	0.51
C-O^-	0.0264	0.47	C-I	0.0399	0.71
C-N^+	0.0260	0.46	O-F	0.0030	0.05
C-O	0.0201	0.36	O-Cl	0.0087	0.16
N-N	0.0183	0.32	O-Br	0.0084	0.15
N-N^+	0.0131	0.23	O-I	0.0131	0.23
N-O	0.0098	0.17	N-F	0.0061	0.11
N^+-N^+	0.0097	0.17	N-Cl	0.0157	0.28
N^+-O	0.0071	0.13	N-Br	0.0150	0.27
C-F	0.0134	0.24	N-I	0.0203	0.36

a) Obtained from Mulliken's table[8] assuming that the distance between the two molecules is 3 A.

Results and Discussion

In Table II nine compounds were selected from 2-diethylaminoacetanilide deriva-

8) R.S. Mulliken, *et al.*: J. Chem. Phys., **17**, 1248 (1949).

tives*3 and those net charges at carbon and oxygen atoms in carbonyl radical and amido radical, the bond orders of carbonyl portion, the forces of charge transfer between those compounds and thiamine, and the quantities of charge transfer between them were calculated. These results will be mentioned in two sections as follows:

a) Net Charge at Acid Amide Group and Bond Order of Carbonyl Portion

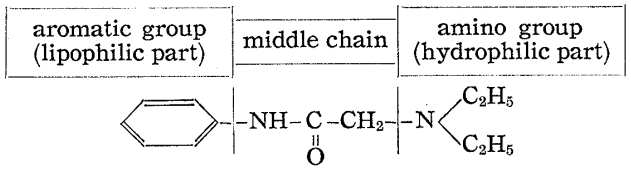


Fig. 3. Chemical Structural Elements of Local Anesthetics

As pointed out by Löfgren,[10] most local anesthetics consist of three components: aromatic group, middle chain and amino group. They are variable to some extent in chemical structure and among them the middle chain the most variable.

It is characteristic that middle chains always contain the functional radicals such as amide, carbonyl, alcohol, and ether. These facts cause us enough to suppose that these functional radicals might interact with the receptor. If 2-diethylaminoacetanilide derivatives are also assumed to combine with the receptor and accordingly to compete with acetylcholine, the electrostatic interaction of the middle chains with the receptor should be considered in the first place. From this consideration, the authors calculated the net charges of amino- and carbonyl portions in acid amido groups. Next, the bond orders of carbonyl portions were calculated in order to study the existence of such correlation in 2-diethylaminoacetanilide derivatives that Galinsky noted in 2-diethylaminoethyl *p*-substituted benzoates. From the result of calculation as shown in the Table II, the net charges and bond orders of these compounds indicated almost the same values. Hence it seems reasonable to conclude that there is no relation between these indices and the local anesthetic activities.

Table II. Relation between Reactivity Indices and Local Anesthetic Activity of 2-Diethylaminoacetanilide Derivatives

No.	δE in units of $-(\beta')^2/\beta$	δQ in units of $(\beta'/\beta)^2$	Net charge at the C in C=O radical	Net charge at the O in C=O radical	Net charge at the N in NH radical	Bond order of C=O radical	Anesthesia duration of 1% sol. min.	Concentration with 1 hour's anesthesia duration (%)
I	0.4350	0.0816	+0.279	−0.703	+0.451	1.613	70	0.8
II	0.5397	0.0954	+0.272	−0.706	+0.450	1.607	58.1	1.05
III	0.4000	0.0776	+0.284	−0.701	+0.450	1.607	40.5	1.4
IV	0.3706	0.0765	+0.296	−0.696	+0.449	1.623	34.6	1.8
V	0.4117	0.1077	+0.286	−0.700	+0.448	1.617	32	2.1
VI	0.3531	0.0796	+0.284	−0.701	+0.449	1.615	11	2.7
VII	0.3689	0.0720	+0.291	−0.697	+0.450	1.621	0	2
VIII	0.3341	0.0764	+0.284	−0.701	+0.450	1.616	0	3.25
IX	0.4254	0.1196	+0.291	−0.697	+0.450	1.621	0	2.3

b) Force and Quantity of Charge Transfer

If it is assumed that thiamine is the essential substance in nervous stimulation as pointed out by Muralt and the charge transfer complex between local anesthetics and thiamine occurs *in vivo* actually, inducing local anesthetic activity, the potency of local

*3 These compounds were synthesized by Koelzer and Wehr[9] and also those local anesthetic activities were measured by them.

9) P. P. Koelzer, K. H. Wehr: Arzneimittel-Forsch., 8, 270 (1958).
10) N. Löfgren: "Studies on Local Anesthetics. Xylocaine, a New Synthetic Drug," J. Haeggström, 13 (1948).

anesthetics might have relations with the stabilization energy (δE)*4 and charge transfer quantity (δQ)*5 between local anesthetics and thiamine. δE and δQ were calculated from the equation (1) and (2), respectively. The result of calculation as shown in Table II seems to indicate that δQ has no evident correlation with the local anesthetic activity. However, it was found, that δE was correlated closely with the local anesthetic activity. As is clearly seen in Table II δE of the substances I~V having strong activity is greater than that of the substances VI~VIII having weak activity. Of course it is unreasonable to say that local anesthetic activity will be determined only by the values of δE. Of these compounds, only IX deviates from the activity that might be predicted from its δE. This reason might originate in the other physicochemical properties, although it can not be explained so far.

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Summary

The relation between the electronic structure and the local anesthetic activity of 2-diethylaminoacetanilide derivatives was investigated by a molecular orbital method and it was found that the stabilization energy due to the charge transfer complex formation between these compounds and thiamine has something to do with their local anesthetic activities.

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*4 Stabilization energy (δE) is a measure of the charge transfer force.

*5 When it must be considered that the electronic structure of thiamine undergoes a remarkable change owing to the formation of the charge transfer complex with local anesthetics, the quantity of charge transfer (δQ) comes into question.