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Molecular Orbital Interpretations for Cholinergic Activities of Some Alkyltrialkylammonium Derivatives[1]

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The electronic structures of alkyltrialkylammonium derivatives were studied by the CNDO/2 method, and cholinomimetic and cholinolytic activities of these compounds were discussed.

The remarkable decrease of the positive charge density of N atom and the raising of the lowest vacant (LV) energy level are theoretically observed with the successive ethylation of tetramethylammonium base (TMA). The stepwise lengthening of an onium group of TMA makes the positive charge density of N atom approach decreasingly to a constant value (+0.60), which corresponds to the range of weak agonist. The lengthening, furthermore, causes the gradual raising of the LV energy, of which the value is expected to approach gradually to the range of antagonistic methyltriethylammonium base (−0.83 eV). From these results, we concluded that the larger than +0.60 the positive charge density of N atom and the lower than −0.83 eV the LV energy are, the more potent agonist the compounds become.

The effect of acetylcholine (ACh), in general, is accompanied by electrophysiological phenomena, namely a decrease in the membrane potential at the site of action, a so-called depolarization. The membrane permeability for cations is then increased. The mimetics cause such a depolarization and the lytics do not. It may be reasonable to assume that the onium group in the cholinomimetic drugs, as in ACh, is primarily responsible for the induction of the electrophysiological events. Thus the correlation of the electric field of the positively charged onium group to that on the negative site of the receptor is supposed to be essential for the induction of the stimulus and the effect.

Studies on the relation between chemical structures and biological activities revealed that the successive substitution by ethyl groups and lengthening of the methyl groups on the onium side of ACh-mimetics caused a regular change of the agonistic action into an antagonistic one, *via* an intermediate dualism in action.[3] Not only the intrinsic activity (α) but also the affinity (*i.e.* the pD_2 or pA_2 values), change in a regular way with the molecular structure for various series of homologous alkyltrialkylammonium derivatives (Table I)[3,4], choline derivatives and other derivatives.

This introduction of larger groups may result in a decrease of the positive charge on the onium group. At the same time, due to the steric hindrance by the larger groups, the approach of the onium group to the receptor, *i.e.* the correlation between the field around this group and the field at the negative site of receptor, may be perturbed. A masking of the charge of the onium group by the larger groups may be involved. The calculations of positive charge densities and the lowest vacant (LV) energy levels of these cholinergic agents are, therefore, really significant pharmacologically.

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3) R.B. Barlow, N.C. Scott, and R.P. Stephenson, *Brit. J. Pharmacol.*, 31, 188 (1967).
4) E.J. Ariëns and A.M. Simonis, *Arch. Intern. Pharmacodyn.*, **CXXVII**, 479 (1960).

TABLE I. Effects (a) on the Frog Rectus and (b) on the Isolated Jejunum of the Rat of a Series of Alkyltrialkylammonium Derivatives

(a)		(b)			
			i.a.[a]	pD_2[b]	PA_2[c]
Agonist: log. equipotent molar ratio relative to Me_4N^+					
Me_4N^+	0.0	Me_4N^+	1	3.0	
Me_3N^+Et	0.437				
$Me_2N^+Et_2$	1.018	Me_3N^+ butyl	1	5.2	
		Me_3N^+ pentyl	1	5.4	
Partial agonist: log. affinity constant					
MeN^+Et_3	2.45	Me_3N^+ hexyl	0.9	5.0	
		Me_3N^+ heptyl	0.1	4.6	
Antagonist: log. affinity constant					
N^+Et_4	2.87	Me_3N^+ octyl	0		5.0
		Me_3N^+ nonyl	0		5.0
		Me_3N^+ decyl	0		5.9
		Me_3N^+ dodecyl	0		6.0
data from Barlow, *et al.*[3]		data from Ariëns, *et al.*[4]			

a) *i.a.*: intrinsic activity
b) $pD_2 = -\log ED_{50}$
c) PA_2 denotes-log dose of the antagonist that requires a doubling of the dose of the agonist to compensate for the action of the antagonist

From plots relating the rate constant of the methanesulfonylation of acetylcholinesterase to the volume of substituents and to ΔH (the van't Hoff enthalpies) binding, Belleau and DiTullio[5] submitted that ΔH binding might reflect the conformational response of the enzyme to quaternary salts differing only in the size and shape of their nonpolar substituents.

The properties of alkylammonium ions in aqueous solutions characterized by their size, shape and charge were reported by Blandamer.[6] With the increase of size of the cation, the viscosities increase and the electrical mobilities decrease. The partial molar volume ($R_4N^+Br^-$) increases through the series (R=) methyl<ethyl. These observations were explained by a structural model in which the alkyl groups enhance water–water interactions and the extent of this enhancement increases with size of the alkyl group.

In the present study, we calculate the positive charge densities of N atoms, and the LV energy levels of molecular orbitals for homologous series of alkyltrialkylammonium salts by the CNDO/2 method.[7,8]

Method of Calculation

In the CNDO/2 method, the Fock operators are written as,[7,8]

$$F_{rr} = -\frac{1}{2}(I_r + A_r) + \left[(P_{AA} - Z_A) - \frac{1}{2}(P_{rr} - 1)\right]\gamma_{AA} + \sum_{B(\neq A)}(P_{BB} - Z_B)\gamma_{AB} \quad (1)$$

$$F_{rs} = \beta_{AB}S_{rs} - \frac{1}{2}P_{rs}\gamma_{AB} \quad (2)$$

The first term in Eq. (1) represents the Mulliken electronegativity of the orbital. The second term of Eg. (1) gives the destabilizing effect of a net excess electrotonic charge on Atom A (if $P_{AA} > Z_{AA}$), and the last term gives the Coulomb potential at the rth AO due to the net excess charges on the other atoms in the molecule. The off-diagonal elements given in Eq. (2) use a semi-empirical resonance integral proportional to overlap

5) B. Belleau and V. DiTullio, *J. Am. Chem. Soc.*, **92**, 6320 (1970).
6) M.J. Blandamer, *Quart. Rev.* (London), **24**, 169 (1970).
7) J.A. Pople, D.P. Santry, and G.A. Segal, *J. Chem. Phys.*, **43**, S129 (1965).
8) J.A. Pople and G.A. Segal, *J. Chem. Phys.*, **43**, S136 (1965); *idem, ibid.*, **44**, 3289 (1966).

and the constant, β_{AB}, depending only on the nature of atoms A and B. The second term in Eq. (2) is a correction to off-diagonal elements due to electron repulsion.

An example of geometry of compound, tetraethylammonium ion, is shown in Fig. 1. Unfortunately we have little information on the equilibrium geometry, especially corresponding to the minimum total energies "in the aqueous solution." We, therefore, referred the configurations found by X ray analysis of their related crystals,[9] assuming that these ammonium groups in the homologous series of alkyltrialkylammonium ions may take tetrahedral forms and the carbon skeletons of alkyl groups take analogously zig-zag forms as shown in Fig. 1.

All the calculations were carried out with the FACOM 230-60 computer (Fujitsu Co.) at Kyoto University.

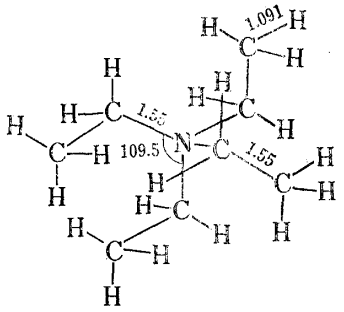

Fig. 1. Interatomic Distances (A) and Angles (degrees) of Ethyltriethylammonium Ion

Result and Discussion

The influence of a stepwise ethylation of the onium groups of TMA, on the positive charge density of the N atom and the LV energy was shown by the CNDO/2 method (Fig. 2). This method indicates that the structural change, from TMA to trimethylethylammonium ion, dimethyldiethylammonium ion, methyltriethylammonium ion and tetraethylammonium ion (TEA) caused the great decrease of the positive charge density of N atom. Pullman, *et al.*[10] with the help of PCILO (perturbative configuration interaction using localized orbitals) reported as follows: In both acetylcholine (ACh) and muscarine the N^+ atom is in fact nearly neutral and a large part (70%) of the formal positive charge is distributed among the three attached methyl groups and these three methyl groups thus form a kind of large ball of spread-out positive charge. Our present calculations in the case of alkyltrialkylammonium ion show almost a similar distribution of the formal positive charge as the report stated above. The gradual decrease of the positive charge density on N atom by the successive ethylation of TMA may correspond to gradual enlargement of such a kind of ball "spread-out positive charge." The LV orbitals of these derivatives consist of σ-type N atomic orbitals, for coefficients of nitrogen atomic orbitals in LV molecular orbital are, for example, TMA (2s: 0.6270, $2p_x$: 0.0000, $2p_y$: −0.0001 and $2p_z$: 0.0) and TEA (2s: 0.6064, $2p_x$: 0.0000, $2p_y$: −0.0001 and $2p_z$: 0.0). When the substituents on the onium groups become bulky, the LV energy increases. Hence the lower LV energy level and the larger the positive charge density mean the higher electron affinity which is closely correlated to the nucleophilic reactivity.

The influence of a stepwise lengthening of an onium group of TMA on the positive charge density of N atom and the LV energy was shown by the CNDO/2 method (Fig. 3). The positive charge densities became approximately constant (+0.060) as to R=propyl, butyl and pentyl, occupying an intermediate position of trimethylethyl derivative and dimethyldiethyl one. The LV orbitals of the series of these derivatives also consist of σ-type N atomic orbitals, for coefficients of nitrogen atom orbitals in LV molecular orbital are, for example, $(Me_3)N^+$propyl (2s: 0.6207, $2p_x$: −0.0129, $2p_y$: −0.0033 and $2p_z$: 0.0) and $(Me_3)N^+$pentyl (2s: −0.6205, $2p_x$: 0.0198, $2p_y$: 0.0035 and $2p_z$: 0.0). The LV energy level with a stepwise lengthening of an onium group increases more gradually in comparison with the cases in ethylation and reaches to a constant (*ca.* −0.83 eV). The LV energies, when R are propyl, butyl and pentyl were calculated, but those for the substituents, hexyl, heptyl and octyl could not be calculated, and were, then, estimated from the slope of the curve shown in Fig. 3.

9) L.E. Suttoned., "Tables of Interatomic Distances and Configuration in Molecules and Ions," The Chemical Society, London, 1958, Suppl., 1956—1959.

10) B. Pullman, Ph. Courrière, and J.L. Coubeils, *Mol. Pharmacol.*, **7**, 397 (1971).

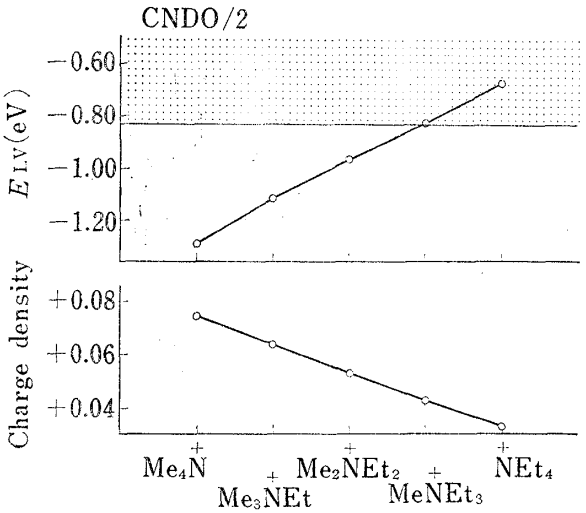

Fig. 2. Positive Charge Densities for the N Atom and the LV Energy Levels of TMA Derivatives with a Gradual Ethylation of the Onium Group by the CNDO/2 Method

The shaded part denotes the range of antagonist.

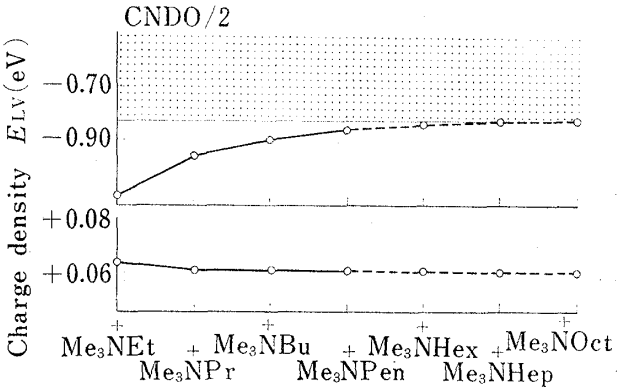

Fig. 3. Positive Charge Densities for the N Atom and the LV Energy Levels of Alkyltrialkylammonium Derivatives with a Stepwise Lengthening of the Onium Group by the CNDO/2 Method

The dotted lines mean extrapolated values, because this method cannot handle compounds of this molecular size. The shaded part denotes the range of antagonist.

Comparing pharmacological activities of alkyltrialkylammonium derivatives shown in Table I with above results, we concluded that the positive charge density of N atom and the LV energy were intimately correlated with the affinity and the intrinsic activity: In the series of ethyl derivatives of TMA, the compound having the positive charge density larger than *ca.* +0.06 may be agonistic and, otherwise antagonistic. Similarly the agonistic derivatives had the LV energy level lower than *ca.* −0.83 eV, and otherwise antagonistic. On the other hand, the further lengthening of the onium group brought the positive charge density of N atom nearly constant. The value remains within that of agonist. The pharmacological activities (in particular, intrinsic activities) of alkyltrimethylammonium derivatives having the substituent bulkier than a pentyl group, sharply decrease and ultimately become zero (*i.e.* antagonistic). By lengthening of the onium group, the LV energy increases more clearly to the direction of the range of antagonist than the trend of positive charge.

An evidence is presented suggesting that ACh receptors possesses two reactive site, an anionic one and an esteratic one. The former site reacts with the quaternary ammonium group of ACh and related compounds. Thus, at pH 9 the contractile effects of a weak base such as ACh are maintained.[11] These experimental facts may imply that the pK_a value of the site are comparatively high and so the site contains a phosphate group or a carboxyl group.[12] The neutralization of such kind of an anionic site of ACh receptor with onium groups having more positive charges and lower LV energies may give the stronger stimulus to the excitable membranes, and induce depolarization.

11) H.O. Schild, *J. Physiol.* 153, 26P (1960).
12) E.J. Ariëns and A.M. Simonis, in "Molecular Pharmacology" (E.J. Ariëns, ed.) Vol. 1, Academic press, New York, 1964, p. 264.