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Half-wave Potentials and LCAO-SCF-MO Calculations for Carcinogenic Benz[*c*]acridines[1)]

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Half-wave reduction potential and half-peak oxidation potential have been measured for 11 methyl-substituted benz[*c*]acridines and unsubstituted benz[*c*]acridine in acetonitrile with tetraethylammonium perchlorate electrolyte. A linear correlation was obtained between the energy of the lowest unoccupied molecular orbital calculated by LCAO-SCF method and the half-wave reduction potential, and also between the energy of the highest occupied molecular orbital and the half-peak oxidation potential. The correlations between carcinogenic activity and both half-wave oxidation and reduction potentials were interpreted in connection with the electron charge density of the K-region. The results of LCAO-SCF calculation for the electron charge density and the electrophilic superdelocalizability index indicated that the electrophilic reactivity of the K-region or the ring nitrogen atom of methyl-substituted benz[*c*]acridines may be essential for their carcinogenic activity.

Keywords——benz[*c*]acridines; chemical carcinogens; polarography; LCAO-SCF-MO calculations; cyclic voltammetry; half-wave potentials; reactivity index; electron density; K-region; superdelocalizability

Several attempts have been made to link the carcinogenic activity of benz[*c*]acridines to their physicochemical properties.[3)] Memory[3b)] reformulated Pullman's theory[4)] and used electrophilic superdelocalizability as a reactivity index for a few methyl-substituted benz-[*c*]acridines, with equal success. Podany *et al.*[5)] suggested that the polarographic behavior and the carcinogenic activity of aza-compounds were related to the number and position of nitrogen atoms in the molecule. Therefore, it may be interest to investigate the relation between the carcinogenic activity and quantum-chemical quantities of methyl-substituted benz[*c*]acridines. In the previous work,[6)] we found the correlation between carcinogenic activity and charge density of the K-region of mono-, di-, and tri-methyl derivatives of benz-[*c*]acridine by use of a simple Hückel calculation. In this paper, we reevaluated the charge density and the energy of molecular orbitals of these derivatives using LCAO–SCF method, and calculated superdelocalizability of the K-region of the derivatives. Half-wave oxidation and reduction potentials were measured and the results were compared with their carcinogenic activity and the energy of molecular orbitals. The results of the present work suggested that the electrophilic reactivity of the K-region or the ring nitrogen atom appeared to be almost essential for carcinogenic activity of benz[*c*]acridine derivatives.

1) This constitutes Part LXV of a series entitled "Electronic Properties of N-Heteroaromatics." Part LXIV: T. Okano, T. Horie, and J. Ohno, *Yakugaku Zasshi*, **98**, 929 (1978).
2) Location: *a) Aobayama, Sendai 980, Japan*; *b) Yato-cho, Tanashi, Tokyo 188, Japan.*
3) *a)* A. Lacassagne, N.P. Buu-Hoi, R. Daudel, and F. Zajdela, *Adv. Cancer Res.*, **4**, 315 (1956); *b)* J.D. Memory, *Int. J. Quantum Chem. Quantum Biol. Symp.*, No. 2, 179 (1975).
4) *a)* A. Pullman and B. Pullman, *Adv. Cancer Res.*, **4**, 117 (1955); *b)* W.C. Herndon, *N.Y. Acad. Sci.*, **36**, 200 (1974).
5) V. Podany, A. Vachalkova, S. Miertus, and L. Bahna, *Neoplasma*, **22**, 469 (1975).
6) T. Okano, T. Horie, M. Iwaizumi, and N. Motohashi, *Gann*, **69**, 109 (1978).

Experimental

Materials——The source of methyl-substituted benz[*c*]acridine derivatives used in this study is the same as that described in the previous paper.[6] Reagent-grade acetonitrile was purified on an activated alumina column, dried over calcium hydride, and then distilled twice. Tetraethylammonium perchlorate (TEAP) was prepared from tetraethylammonium hydroxide and perchloric acid and was recrystallized several times from water.

Polarography and Cyclic Voltammetry——All the electrochemical measurements were performed using acetonitrile containing 0.1 M TEAP as a supporting electrolyte, and pontentials were referenced to a saturated caromel electrode (SCE). Polarographic measurements were carried out on a Yanagimoto polarograph type PA-102 A. Cyclic voltammetry was carried out by use of a Hokuto potentiostat Model HA-104 equipped with an NF Model FG 141 function generator and a Riken Model F-3 DP x-y recorder. Scan rate was 360 mV/sec. The working electrode was a platinum wire with an area of 0.1 cm^2. All the measurements were made at 20°.

Molecular Orbital Calculation——Orbital energies were calculated by the LCAO-SCF method with a π-approximation proposed by Pariser, Parr, and Pople.[7] All the molecules calculated were assumed to be planar π-molecules with bond lengths[5] $r_{C-C}=1.40$ Å and $r_{C-N}=1.36$ Å, and bond angles $\angle CNC=126°$ and $\angle CCN=117°$. Values of the ionisation potential (I_p) and the one center repulsion integrals ($\gamma_{\mu\mu}$) were taken from the reference.[8] A pseudo-heteroatom model was employed for the methyl group in the semi-empirical SCF-MO calculation, and parameters for the carbon atom of methyl group were taken from the literature[9] as follows: $I_p=27.96$ eV, $\gamma_{\mu\mu}=14.20$ eV, $r_{C-CH_3}=1.52$ Å, and Slater effective nuclear charge $Z^*=1.40$. Reactivity indexes were calculated by the simple Hückel method using parameters proposed by Chalvet *et al.*[10]

Results

Half-wave Reduction Potential

According to Koopman's theorem, a linear relationship exists between electron affinity and energy of the lowest unoccupied molecular orbital (ε_{LUMO}), and also between I_p and energy of the highest occupied molecular orbital (ε_{HOMO}). Assuming that no entropic effects occur in the reversible reduction and oxidation processes and the change of solvation energy in this series of molecules remains constant, the electron affinity and I_p may be expressed in terms of half-wave reduction potential ($E_{1/2}^{red}$) and half-wave oxidation potential ($E_{1/2}^{ox}$), respectively. Values of $E_{1/2}^{red}$ were measured for eleven methyl-substituted benz[*c*]acridines and unsubstituted benz[*c*]acridine. All the compounds gave two well-defined reduction waves. The values of $E_{1/2}^{red}$ and ε_{LUMO} calculated are given in Table I. The plot of $E_{1/2}^{red}$ against ε_{LUMO} is shown in Fig. 1. As shown in Fig. 1, a linear correlation was established between $E_{1/2}^{red}$ and ε_{LUMO}, and the method of least squares yielded the correlational equation (1).

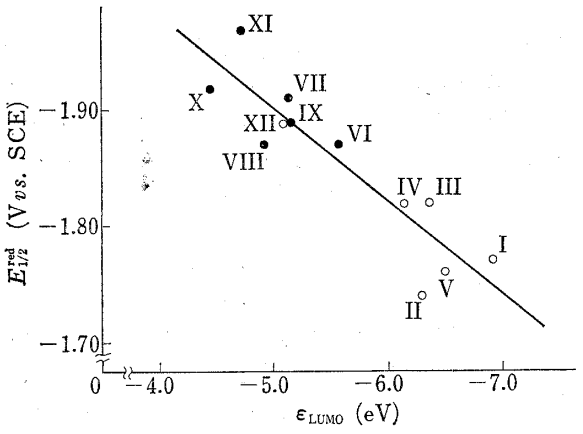

Fig. 1. A Plot of $E_{1/2}^{red}$ against ε_{LUMO} for Benz[*c*]-acridines

●: carcinogenic compound,
○: noncarcinogenic compound.
Compound numbers as in Table I.

$$E_{1/2}^{red}\,(V) = -0.0796\,\varepsilon_{LUMO}\,(eV) - 2.30 \qquad (1)$$

It should be noted in Fig. 1 that the derivatives are grouped in such a way that the compounds which have negative $E_{1/2}^{red}$ values (*i.e.*, higher ε_{LUMO}) are carcinogenic and the derivatives which

7) *a*) R. Pariser and R.G. Parr, *J. Chem. Phys.*, **21**, 767 (1953); *b*) J.A. Pople, *Trans. Faraday Soc.*, **49**, 1375 (1953).
8) J. Hinze and H.H. Jaffe, *J. Am. Chem. Soc.*, **84**, 540 (1962).
9) F. Marschner, *Tetrahedron*, **31**, 2303 (1975).
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have relatively positive $E_{1/2}^{red}$ values (*i.e.*, lower ε_{LUMO}) are noncarcinogenic. 5,7-Dimethylbenz[*c*]acridine was exceptional. The anomalous behavior of this compound will be discussed later.

Cyclic Voltammetric Studies

Cyclic voltammogram in acetonitrile with 0.1 M TEAP electrolyte showed that there were no appreciable background current from −2.5 to +1.8 V *vs.* SCE. Benz[*c*]acridine and all of the methyl-substituted benz[*c*]acridines investigated were found to give rise to an anodic peak current at moderately anodic potentials. However, reduction process was not observed on the return sweep. The anodic oxidation process of these compounds was found to be irreversible. This behavior could be attributed to the dimerization of the cation radicals.[11] The values of half-peak oxidation potentials ($E_{p/2}^{ox}$) and ε_{HOMO} for these compounds are shown in Table I.

Table I. Half-wave Potentials, Orbital Energies, Electron Densities, and Superdelocalizabilities of Benz[*c*]acridines[a]

Compound	No.	ε_{HOMO} (eV)	ε_{LUMO} (eV)	$E_{1/2}^{ox}$ (V *vs.* SCE)	$E_{1/2}^{red}$ (V *vs.* SCE)	q_{5+6}	$S_r(E)_{5+6}$	q_{12}	$S_r(E)_{12}$	Carcinogenic activity[b]
Benz[*c*]acridine	I	−13.833	−6.926	1.59	−1.77	1.9255	2.0242	1.5510	1.1016	−
8-Methylbenz-[*c*]acridine	II	−13.063	−6.315	1.51	−1.74	1.9428	2.0324	1.5716	1.1198	−
9-Methylbenz-[*c*]acridine	III	−13.125	−6.384	1.58	−1.82	1.9373	2.0267	1.5331	1.1027	−
10-Methylbenz-[*c*]acridine	IV	−13.192	−6.148	1.53	−1.82	1.9380	2.0327	1.5738	1.1184	−
11-Methylbenz-[*c*]acridine	V	−12.993	−6.507	1.52	−1.76	1.9341	2.0265	1.5456	1.1045	−
7-Methylbenz-[*c*]acridine	VI	−13.715	−5.583	1.50	−1.87	1.9680	2.0544	1.6199	1.1668	+
7,9-Dimethylbenz-[*c*]acridine	VII	−12.438	−5.134	1.48	−1.91	1.9807	2.0574	1.6118	1.1697	+
7,10-Dimethyl-benz[*c*]acridine	VIII	−12.775	−4.935	1.43	−1.87	1.9765	2.0522	1.6267	1.1571	+
7,11-Dimethyl-benz[*c*]acridine	IX	−12.425	−5.149	1.49	−1.89	1.9780	2.0575	1.6226	1.1721	+
7,9,10-Trimethyl-benz[*c*]acridine	X	−11.825	−4.454	1.39	−1.92	1.9851	2.0651	1.6139	1.1849	+
7,9,11-Trimethyl-benz[*c*]acridine	XI	−11.836	−4.740	1.41	−1.97	1.9885	2.0605	1.6091	1.1748	+
5,7-Dimdthyl-benz[*c*]acridine	XII	−12.016	−5.138	1.46	−1.89	2.0890	2.1636	1.6155	1.1705	−

a) All notations in the text.
b) Skin tumor-producing activity (Ref. 3*a*). +: active, −: inactive.

The plot of $E_{p/2}^{ox}$ against ε_{HOMO} calculated gave a straight line, which is shown in Fig. 2. A least-squares correlation gave equation (2).

$$E_{p/2}^{ox}\,(V) = -0.0859\,\varepsilon_{HOMO}\,(eV) + 0.398 \qquad (2)$$

As will be evident from Fig. 2, carcinogenic compounds gave relatively negative half-peak potentials, or higher ε_{HOMO}, and noncarcinogenic compounds gave relatively positive half-peak potentials, or lower ε_{HOMO}. The plots of $E_{p/2}^{ox}$ against ε_{HOMO}, however, was not divided into carcinogenic and noncarcinogenic groups as clearly as that found in the cathodic process.

11) L. Marcoux and R.N. Adams, *J. Electroanal. Chem.*, **49**, 111 (1974).

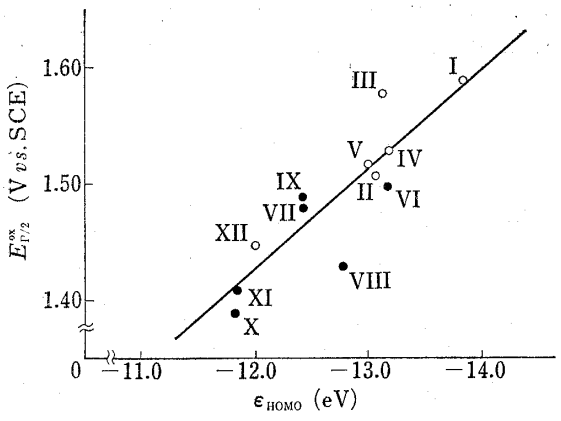

Fig. 2. A Plot of $E^{ox}_{p/2}$ against ε_{HOMO} for Benz[*c*]acridines

●: carcinogenic compound,
○: noncarcinogenic compound.
Compound numbers as in Table I.

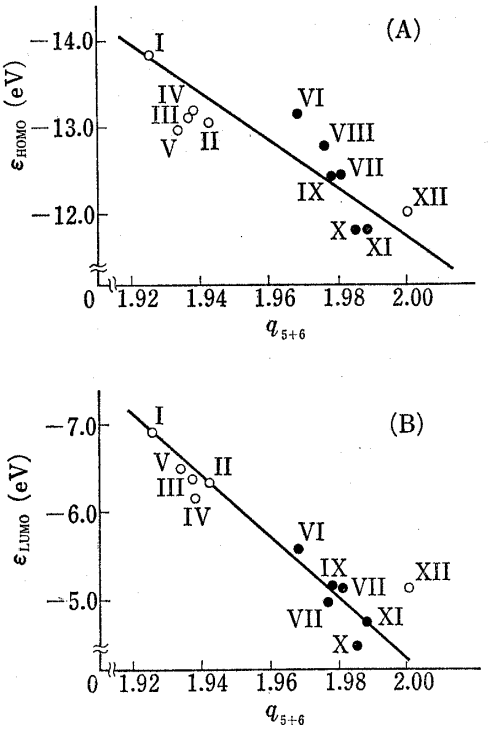

Fig. 3. Plots of ε_{HOMO} against q_{5+6} (A), and ε_{LUMO} against q_{5+6} (B)

●: carcinogenic compound,
○: noncarcinogenic compound.
Compound numbers as in Table I.

Molecular Orbital Calculation and Reactivity Index

The sum of the electron densities for the K-region and that of electron densities for the ring nitrogen atom of benz[*c*]acridines are represented as q_{5+6} and q_{12}, respectively, and are listed in Table I. The reactivity index $S_r(E)_{5+6}$, which was calculated by the simlpe Hückel method, denotes the sum of the electrophilic superdelocalizabilities of the two centers of the K-region. The carcinogenic activity reported by Lacassagne *et al.*[3a] for the twelve compounds used in the present study is also given in the last column of this Table. It will be clear from Table I that the carcinogenic activity of these derivatives is highly correlated with the electron density and also with the electrophilic superdelocalizability of the K-region. There was a similar correlation between carcinogenic activity and both q_{12} and $S_r(E)_{12}$ values of these compounds. However, carcinogenic activity was correlated neither with electron density nor with electrophilic superdelocalizability of other positions of the molecule. Fig. 3 (A and B) show the relationship between ε_{HOMO} and q_{5+6}, and between ε_{LUMO} and q_{5+6}.

It is clear from Fig. 3 (A, B) that a linear correlation exists between q_{5+6} and between q_{5+6} and ε_{LUMO}. The plot of q_{12} against ε_{HOMO} or ε_{LUMO} did not yield straight lines.

Discussion

In the present series of work, oxidation and reduction potentials of methyl-substituted benz[*c*]acridines were studied in acetonitrile with TEAP electrolyte, and the charge density and the energy of molecular orbitals of the derivatives were calculated using LCAO–SCF method. A linear correlation was obtained between the energy of the highest occupied molecular orbital and the half-peak oxidation potential, and also between the energy of the lowest unoccupied orbital and the half-wave reduction potential. Superiority of the SCF method to the Hückel method was evident from the linear relations established between the half-wave potential and the energies of molecular orbital.

We also calculated superdelocalizability of the K-region of benz[*c*]acridine. It has been suggested that the carcinogenicity of benz[*c*]acridine derivatives was closely related to their electron densities at the K-region[3b,10,12] or the ring nitrogen atom[3a] calculated by the simple

12) A. Pullman, *Ann. Chim.*, **2**, 5 (1947).

Hückel method. Our results of SCF calculations instead of the Hückel method for these compounds showed that there was a good correlation between carcinogenic activity and the electron density of the K-region or the ring nitrogen atom. Memory[3b] has demonstrated that the carcinogenic potency of aromatic compounds such as 1,2-benzanthracene, benz[*a*]-acridine, benz[*c*]acridine, and some of their methyl derivatives was highly correlated with the electrophilic superdelocalizability of the K-region. We studied twelve systematically arranged benz[*c*]acridine derivatives and found a good correlation between carcinogenic activity and the electrophilic superdelocalizability of the K-region or the ring nitrogen atom, as is evident from Table I. On the other hand, carcinogenic activity appeared to be also related to the energy of the molecular orbitals. In the plots of $E_{p/2}^{ox}$ against ε_{HOMO} and $E_{1/2}^{red}$ against ε_{LUMO}, benz[*c*]acridine derivatives were divided into carcinogenic and noncarcinogenic groups. The anomalous behavior of 5,7-dimethylbenz[*c*]acridine has been suggested[13] to be caused by steric hindrance due to substitution in the phenanthrenoid bond, which might militate against activity. A question to arise here is whether energies of the molecular orbitals are directly correlated with the carcinogenic activity or not. As previously reported,[6] we found that there was a correlation between the carcinogenic activity of benz[*c*]acridines and the electron spin resonance (ESR) signal intensity of the free radicals produced from the compounds in the presence of protein. Recent studies with benz[*a*]pyrene indicated thet reactive metabolites, such as 4,5-oxide[14] and 7,8-diol-9,10-oxide[15] of benz[*a*]pyrene and 6-hydroxybenz[*a*]pyrene,[16] play an important role in the manifestation of the carcinogenic activity. It may be reasonable, therefore, to consider that the methylated benz[*c*]acridines may undergo an electrophilic reaction in the metabolic system and convert into more reactive intermediate of carcinogenesis. The correlations between carcinogenic activity and $E_{1/2}^{red}$ or $E_{p/2}^{ox}$ in Fig. 1 and 2 can well be explained by the fact that q_{5+6} corresponds to ε_{HOMO} or ε_{LUMO}, as shown in Fig. 3. It is worth noting here that the methyl-substituted benz[*c*]acridines which have higher energy of the highest occupied moleculer orbital and higher energy of the lowest unoccupied energy level, have greater K-region electron density. It is a subject that requires further investigation which of the electron densities, K-region or ring nitrogen atom, is actually correlated with carcinogenic activity. After all, the results of the present work seem to indicate that in the benz[*c*]acridine system carcinogens, the electrophilic reactivity of the K-region or the ring nitrogen atom appear to be almost essential for their carcinogenic activity in the benz[*c*]acridine derivatives.

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16) C. Nagata, Y. Tagashira, and M. Kodama, "Chemical Carcinogenesis," ed. by P.O.P. Ts'o and J.A. Dipaolo, Marcel Deckker, New York, 1974, p. 87.