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Relationship between Carcinogenicity and Electronic Structure of Mononitroquinolines

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It was found that a certain relation seems to exist between the carcinogenic action of mononitroquinoline and the approximate superdelocalizabilities of the carbon atom to which the nitro group is attached. Referring to these results, the approximate superdelocalizabilities of some derivatives of 2- and 4-nitroquinolines were also calculated, and a relationship between the chemical structure and the carcinogenicity was discussed.

That 4-nitroquinoline 1-oxide, synthesized by Ochiai, *et al.*,[2] possesses biological action, especially strong carcinogenic action, was found by Nakahara and his co-workers.[3] 4-Nitroquinoline 1-oxide changes into 4-hydroxyaminoquinoline 1-oxide by chemical reduction,[4] and the present authors have shown that this 4-hydroxyaminoquinoline 1-oxide also possesses a strong carcinogenic action[5] and succeeded in producing stomach cancer in mice and rats by this chemical.[6] The mechanism of the carcinogenesis by 4-nitroquinoline 1-oxide is still not clear, but in this type of compounds, presence of the N-oxide group was said to be indispensable for its carcinogenic action.[7] Referring to this result, Fukui, *et al.*[8] studied the electronic structure of 4-nitroquinoline 1-oxide and its related compounds, and reported that the reaction indices in the nucleophilic reaction of the carbon atom to which the nitro group is attached are intimately connected with the strength of carcinogenicity.

Attempts have been made to produce cancerous change in the internal organs of mice and rats by chemical substances, to find new carcinogenic substances and to clarify the relationship between the chemical structure of carcinogenic substances and their biological actions. It is well knwon that the nitro group in 4-nitroquinoline 1-oxide is active to nucleophilic reactions and can be easily substituted by halogens, alkoxyl, aryloxyl, and hydroxyl groups and, in the case of 2-nitroquinoline and 4-nitroquinoline, the nitro group undergoes a similar substitution with nucleophiles.[9,10] Based on these findings, biological experiments were carried out expecting that these two nitroquinolines might possess a carcinogenic action and it was proved that these two are truely carcinogenic.[11,12] Further, examinations were also made

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2) E. Ochiai, M.O. Ishikawa, and Z. Sai, *Yakugaku Zasshi*, **63** 280 (1943).
3) W. Nakahara, F. Fukuoka, and T. Sugimura, *Gann*, **48**, 129 (1957).
4) *a*) E. Ochiai, A. Ohta, and H. Nomura, *Pharm. Bull.* (Tokyo), **5**, 310 (1957); *b*) E. Ochiai and H. Mitarashi, *Chem. Pharm. Bull.* (Tokyo), **11**, 1084 (1963).
5) Y. Shirasu and A. Ohta, *Gann*, **54**, 221 (1963).
6) K. Mori, A. Ohta, T. Murakami, M. Tamura, M. Kondo, and H. Ichimura, *Gann*, **60**, 627 (1969).
7) W. Nakahara, F. Fukuoka, and S. Sakai, *Gann*, **49**, 33 (1958).
8) K. Fukui, A. Imamura, and C. Nagata, *Gann*, **51**, 119 (1960).
9) E. Hayashi and T. Saito, *Yakugaku Zasshi*, **89**, 108 (1969).
10) I. Nakayama, *Yakugaku Zasshi*, **71**, 1088 (1951).
11) K. Mori, M. Kondo, M. Tamura, H. Ichimura, and A. Ohta, *Gann*, **60**, 609 (1969).
12) K. Mori, M. Kondo, M. Tamura, H. Ichimura, and A. Ohta, *Gann*, **60**, 663 (1969).

on other mononitroquinolines, but at present, none of them showed to have a carcinogenic action. In connection with these carcinogenic experiments, the approximate superdelocalizability of seven mononitroquinolines was calculated by the Hückel method and it was found that these values are related to their carcinogenic action even in the case of mononitro quinolines.

Calculations

Seven kinds of mononitroquinolines were taken up as a system possessing 13 orbitals and 14π-electrons, and their electronic distribution was calculated by the Hückel method. Usually, the Coulomb and the resonance integrals in the Hückel method[13] are given as follows:

$$\alpha_x=\alpha+h_x\beta \qquad \beta_{cx}=l_{cx}\beta$$

where α and β are the Coulomb and resonance integrals of benzene, respectively. The parameters used in this calculation are the same as the values used by Fukui, *et al.*[14] and the nitro group is calculated as follows:

$$\alpha_N=\alpha+\beta \qquad \alpha_0=\alpha+\beta$$

The reaction indices used for comparing the carcinogenic action are the frontier electron density and the approximate superdelocalizability of the carbon atom to which the nitro group is attached. These values can be calculated by using the Hückel method and are shown in Table II. For this calculation, the IBM 1130 computer in the Josai University Calculation Center was used.

The mononitroquinolines which possess a halogen at the 6-position were also treated as the system possessing 14 orbitals and 16π-electrons, and the dinitro compounds as the system possessing 16 orbitals and 18π-electrons.

The parameters used in these calculations are listed in Table I.

Table I. Parameters for Hetero Atoms[13]

X	h_X	l_{CX}	X	h_X	l_{CX}
F	2	1.3	I	1.5	0.5
Cl	2	0.8	NO_2	$\alpha_N=1$	1
Br	1.8	0.7		$\alpha_0=1$	1

Result and Discussion

Relationship between carcinogenic action and approximate superdelocalizability of the carbon atom to which the nitro group is attached in the mononitroquinolines are presented in Table II.

As stated above, Fukui, *et al.*[8] reported that the approximate superdelocalizability $S_r'^{(N)}$ of the carbon atom to which the nitro group is attached in 4-nitroquinoline 1-oxide and its derivatives is related to carcinogenic action. Carcinogenic experiments by Nakahara and his co-workers[7] showed that 6-chloro-4-nitroquinoline 1-oxide (3.361), 4-nitroquinoline 1-oxide (3.113), 4-nitroquinaldine 1-oxide (1.913), and 2-ethyl-4-nitroquinoline 1-oxide (1.894), whose approximate superdelocalizabilities are all larger than 1.894, all possess carcinogenic action, while 4-nitroquinoline (1.579), 4-nitropyridine 1-oxide (1.092) and 6-nitroquinoline (0.173), whose approximate superdelocalizabilities are comparatively small, do not possess carcinogenic action.

13) A. Stereitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N.Y., 1960.
14) K. Fukui, C. Nagata, and T. Yonezawa, *J. Am. Chem. Soc.*, **80**, 2267 (1958).

Table II. Reaction Indices of Mononitroquinolines

No.	Position of nitro group in nitroquinoline	Approximate superdelocaliz-abilities	Frontier electron density	Cancer producing activity
1	2	1.479	0.179	+
2	3	0.178	0.047	
3	4	1.579	0.175	+
4	5	0.440[a]	0.086	
5	6	0.173	0.046	
6	7	0.355	0.077	
7	8	0.258	0.060	

a) This value is corrected here, because the value, which was mentioned in the text of the 2 nd Symposium of the Heterocyclic Chemistry (Nagasaki, 1969), was wrong.

Table II, on the contrary, shows that a certain type of mononitroquilines also possesses carcinogenic action and that the N-oxide group is not always necessary. 2-Nitroquinoline and 4-nitroquinoline, which are carcinogenic, possess approximate superdelocalizabilities of 1.479 and 1.579, respectively, but other mononitroquinolines, which are not found to have carcinogenic action at present, possess smaller approximate superdelocalizabilities. It is clear that there is a fine correlation between carcinogenic action of mononitroquinolines and the value of approximate superdelocalizability. Table II shows that the mononitroquinolines whose values of approximate superdelocalizability of the carbon atom to which the nitro group is attached are at least over 1.479 possess carcinogenic action. It should be noted that this value is qualitative and it is not clear whether or not the carcinogenic power has a linear relation with this value. It shoud be mentioned here that even the substance whose value is smaller than 1.479 has the possibility to be found to possess a carcinogenic action in future.

Table III gives the approximate superdelocalizabilities and the frontier electron densities of 2- and 4-nitroquinolines. Though biological experiments have not been carried out as yet, we can see that a considerable number of substances possess carcinogenic action in view of the values of the approximate superdelocalizability.

Table III. Reaction Indices of Nitroquinoline Derivatives

Quinoline derivatives	Approximate superde-localizabilities $S'^{(N)}$	Frontier electron density
6-Cl-4-NO_2	1.707	0.1805
6-I-4-NO_2	1.673	0.179
6-Br-4-NO_2	1.670	0.179
6-F-4-NO_2	1.384	0.165
6-Me-4-NO_2	1.327	0.163
8-Me-4-NO_2	1.314	0.164
6-Me-2-NO_2	1.228	0.165
8-Me-2-NO_2	1.212	0.166
2-Me-4-NO_2	1.159	0.158
4-Me-2-NO_2	1.055	0.160
2,8-Di-NO_2	2.369[a]	0.180
2,6-Di-NO_2	2.369[a]	0.191
4,8-Di-NO_2	2.458[a]	0.175
4,6-Di-NO_2	2.464[a]	0.186

a) These show the superdelocalizabilities of 2- and 4-positions.

The values of 4-nitroquinoline derivatives which have halogen atoms except fluorine at the 6-position are always greater than 1.579, the value for 4-nitroquinoline. This fact shows

that electron density of the ring tends to be deficient due to the −I-effect of the halogen atom and the fact that only the fluorine compound shows smaller value means that the +E-effect of fluorine is more active. Considering that 6-chloro-4-nitroquinoline 1-oxide has a greater value of approximate superdelocalizability than that of 4-nitroquinoline 1-oxide and that the former actually has a stronger carcinogenic action than the latter, it is expected that the 4-nitroquinoline derivatives possessing chlorine, bromine, or iodine at the 6-position have a stronger carcinogenic action than the original 4-nitroquinoline. Streitwieser, *et al.*[13] used parameters different from that of Fukui, *et al.* When calculated by using this value, we obtained an entirely different results and, therefore, there are much room to study the parameters of halogens.

As far as the methyl replacement is concerned, it is natural that the vlaue of the methyl derivatives will become smaller than the value of the parent compounds due to the +I-effect of the methyl group. It is also natural that the values will become further smaller by the direct effect when the methyl group enters the pyridine ring. Even in the case of 4-nitroquinoline 1-oxide, its carcinogenic action becomes smaller when alkyl groups are introduced into the ring. It will be interesting to see what biological action the alkyl derivatives of 2-nitroquinoline and 4-nitroquinoline will have. Table II showed that the substances having the values over 1.479 possess carcinogenic action. If these alkyl derivatives of 2-nitroquinoline and 4-nitroquinoline were to be carcinogenic, the value of the appropriate superdelocalizability, which shows the presence or absence of carcinogenicity, would have the possibility to become smaller.

Finally, the dinitro derivatives show rather high values, but it is natural in view of the effect of the nitro group. These compounds are all considered to possess a potent carcinogenic action.

As mentioned above, a certain relation seems to exist between the carcinogenic action of mononitroquinolines and the approximate value of superdelocalizability of the carbon atom to which the nitro group is attached, and the approximate superdelocalizabilities values have been presented for several mononitroquinoline derivatives. Carcinogenesis would be caused by the sum of every kind of factors. If cancer is produced by the chemicals possessing a simple structure, this fact will be helpful in clearing the mechanism of carcinogenesis. It is significant to have found out that simple compounds, like mononitroquinolines, possess carcinogenic action which is closely related to the approximate superdelocalizability.