Electronic Structure and Antifungal Activity of Quinoline- and Pyridine-N-oxide Derivatives

By Kenichi FUKUI, Akira IMAMURA and Chikayoshi NAGATA

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Many studies have ever been undertaken in order to elucidate the mechamism of action of fungicides or antifungal substances. Albert et al., through the experiments on 8-hydroxyquinoline, concluded that a chelate formation may be involved in the process of fungicidal action[1]. Ikeda found some parallelism between the reduction potential and the fungicidal activity of 1,4-naphthoquinone derivatives and assumed that the binding ability of fungicides with SH group in the body of fungi may be the main factor determining the fungicidal activity[2].

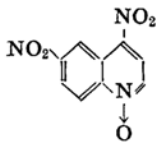
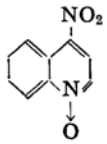
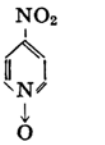
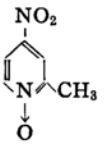
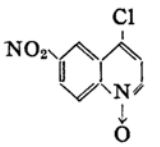
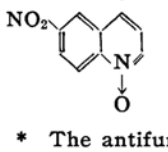
For the purpose of the elucidation of the reaction mechanism involved in the early stage of fungicidal action of quinoline- and pyridine-*N*-oxide derivatives, the present authors have calculated the reactivity indexes, namely, the approximate superdelocalizability (S'_r) which is one of the reactivity indexes used in the frontier electron theory and proved to be a good index for discussing the biological actions of carcinogenic compounds and plant growth compounds[3,4].

Result and Discussion.—In the present paper the authors dealt with *N*-oxides containing the nitro group such as 4-nitroquinoline-*N*-oxide, 6-nitroquinoline-*N*-oxide, 4,6-dinitroquinoline-*N*-oxide, 4-chloro-6-nitroquinoline-*N*-oxide, 4-nitropyridine-*N*-oxide, and 2-methyl-4-nitropyridine-*N*-oxide whose antifungal activities were tested recently by Okabayashi et al.[5]

From an organic chemical point of view, the most probable reaction is the nucleophilic replacement of the nitro group, since this group is very susceptible to the attack by nucleophilic reagent. If any reaction of this type plays a dominant role in the fungicidal action, the order of antifungal activity must be parallel with the reactivity index of the attacked position. The result of the authors' calculation supports this assumption. That is, the order of approximate superdelocalizability for the nucleophilic attack ($S'^{(N)}$) at the most reactive position in the molecule is nearly parallel with antifungal activity as is seen in Table I. The signs + and − indicate the degree of antifungal activity. The larger the number of + sign is, the greater the activity is. The sign − indicates that the compound has no activity. One exception is inactive 4,6-dinitroquinoline-*N*-oxide whose $S'^{(N)}$ value at position 4 is far larger than the most potent fungicide, 4-nitro-quinoline-*N*-oxide. In order to obviate this difficulty, one can assume that the upper threshold value of reactivity index for occurrence of activity as well as the lower one might exist. Such an interpretation has frequently been made in the theoretical study of biological phenomena, for instance, the carcinogenic action of polycondensed aromatic hydrocarbons and azo compounds. Inactiveness of 4,6-dinitroquinoline-*N*-oxide, therefore, may be understood if the authors suppose that this compound is so reactive that it would react with various groups in the body of fungi before it reaches the reaction center connected with the fungicidal action.

1) A. Albert, S. D. Rubbo, R. J. Goldacre and B. G. Balfour, *Brit. J. Exptl. Path.*, **28**, 69 (1947).
2) N. Ikeda, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **75**, 1073 (1955).
3) C. Nagata, K. Fukui, T. Yonezawa and Y. Tagashira, *Cancer Research*, **15**, 233 (1955).
4) K. Fukui, C. Nagata and T. Yonezawa, *J. Am. Chem. Soc.*, **80**, 2267 (1958).
5) T. Okabayashi, *J. Fermentation Technology* (*Hakkô Kôgaku Zasshi*), **31**, 373 (1953).

TABLE I. RELATION BETWEEN REACTIVITY INDEX AND ANTIFUNGAL ACTIVITY OF QUINOLINE- AND PYRIDINE-*N*-OXIDE DERIVATIVES

Compound	Approximate superdelocalizability for nucleophilic ($S_r'^{(N)}$) attack	Antifungal activity*
	1.014(4)**	−
	0.630(4)	+++
	0.297(4)	++
	0.279(4)	+
	0.205(6)	+
	0.168(6)	−

* The antifungal activity was tested for Aspergillus oryzae, Tolura utilis, Saccharomyces sake and Zygosaccharomyces soja by Okabayashi, and the signs + and − are given by the present authors considering the experimental activity.

** The figures in the parentheses indicate the position at which the nucleophilic substitution is assumed to take place.

On the other hand, Okabayashi's *in vitro* experiment showed that the nitro group of 4-nitroquinoline-*N*-oxide was easily substituted by the SH group of cystein and the substituted compound lost its antifungal activity. Bearing this fact in mind together with the theoretical result obtained by the present authors, it may be possible to correlate the easiness of nucleophilic substitution at the carbon atom to which the nitro group is attached with the antifungal activity of nitro group-containing quinoline- and pyridine-*N*-oxides.

Parameters for chloro, methyl and nitro groups used in the calculation are the same as those of a previous paper[4]. Since there seem to exist no unambiguous values used for Coulomb integrals of *N*-oxide, the present authors adopt, according to the result of analyses of the ultraviolet spectrum[6], the values $\alpha+\beta$ and $\alpha+1.8\beta$ for nitrogen and oxygen, respectively.

Faculty of Engineering
Kyoto University
Sakyo-ku, Kyoto

6) M. Ito and W. Mizushima, *J. Chem. Phys.*, **24**, 495 (1956).