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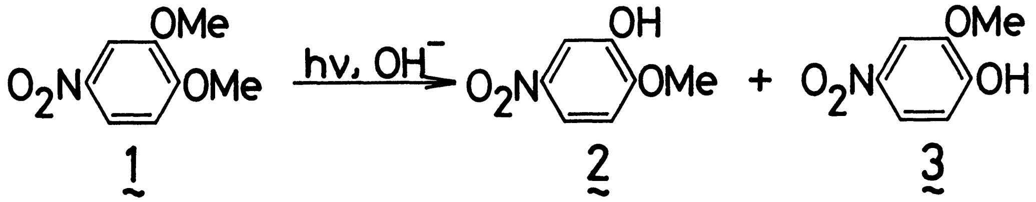
A RATIONALIZATION OF ORIENTATION IN NUCLEOPHILIC AROMATIC PHOTOSUBSTITUTION

Kiyoshi MUTAI* and Ryoichi NAKAGAKI†
Department of Chemistry, College of Arts and Sciences,
The University of Tokyo, Komaba, Meguro, Tokyo 153
†Institute for Molecular Science, Myodaiji, Okazaki 444

For rationalization of regioselectivities observed in nucleophilic aromatic photosubstitutions, two rules discriminating orientation-controlling MO's, based on reaction mechanisms and frontier orbital theory, are proposed.

As a number of examples of photoinduced nucleophilic aromatic substitution accumulate,[1] effects of substituents on the regioselectivity have attracted great interest. Among the substituents, the nitro group is probably the most extensively studied, because of its unusual meta-favoring orientation. A typical example is the photochemical behavior of 3,4-dimethoxynitrobenzene (1); irradiation of 1 in aqueous organic solvents containing sodium hydroxide gives a mixture of 3-hydroxy-4-methoxy- (2) and 4-hydroxy-3-methoxynitrobenzene (3) with a ratio of 370:1.[2]



(1)

On the other hand, thermal hydrolysis of 1 occurs exclusively at the para to the nitro group, affording 3 as a sole product. Thus the orientation of the nitro group in photochemical nucleophilic substitution is in sharp contrast to that in corresponding thermal reactions.

Theoretical interpretations of this perplexing phenomenon have been proposed by Fleming[3] on the basis of frontier orbital theory and by Epiotis[4] in a more sophisticated procedure. Havinga, Cornelisse, and their coworkers have addressed this problem by use of a number of experimental data and MO calculations.[5] Essential part of their conclusions, though some of them are not necessarily explicitly stated, could be summarized in our manner as rule 1.

Rule 1: meta- *or* ipso- *Substitution in nitroaromatics is a HOMO-controlled reaction which involves one-step formation of σ-complex through direct interaction between an excited aromatic substrate and a nucleophile* (Eq. 2 and Fig. 1).

$$\mathrm{ArH} + :\mathrm{Nu} \xrightarrow{h\nu} \mathrm{ArH}^{*} + :\mathrm{Nu} \longrightarrow \sigma\text{-complex} \quad (2)$$

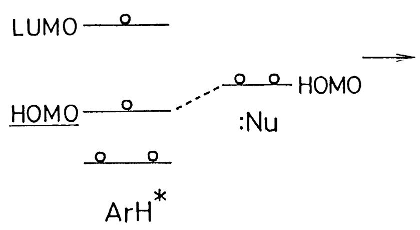


Fig. 1. Schematic illustration of the orientation-determining step, i.e. σ-complex formation via direct interaction of an excited molecule with a nucleophile. A broken line denotes the orbital interaction resulting in bond formation. ArH represents an aromatic substrate and Nu a nucleophile. An asterisk refers to the excited state.

According to frontier orbital theory, the nucleophile should preferably attack the position bearing the highest frontier electron density (FED) in the HOMO. Here, FED is defined as $FED_i = n_i c_{ir}^2$, where n_i is the number of electron(s) occupying the ith MO and c_{ir} the coeffecient of rth atomic orbital in the ith MO. The predominant meta-directing effect of the nitro group observed in Eq. 1 is readily explained by the higher FED at C_3 than at C_4 in the HOMO of 1 (Fig. 2).[6)]

On the contrary, homologs 4 undergo intramolecular nucleophilic photosubstitution (the photo-Smiles rearrangement) to afford 5, exhibiting para-directing effect of the nitro group (Eq. 3).[7)] Despite the participation of a substrate with practically the same chromophore as in Eq. 1, the regioselectivity observed in Eq. 3 is inexplicable by rule 1.

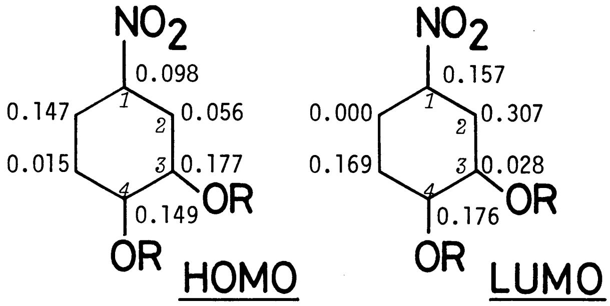
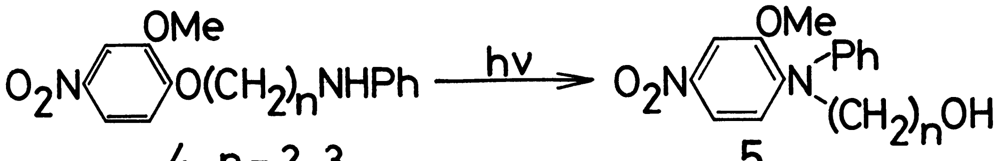


Fig. 2. FED maps of the HOMO and LUMO of 3,4-dialkoxynitrobenzene.

A clue to resolve this conflicting phenomenon lies in the reaction mechanism; 4 undergoes photo-induced electron transfer from the anilino to the nitrophenoxyl moieties, forming a radical ion pair, the components of which are combined into a σ-complex.

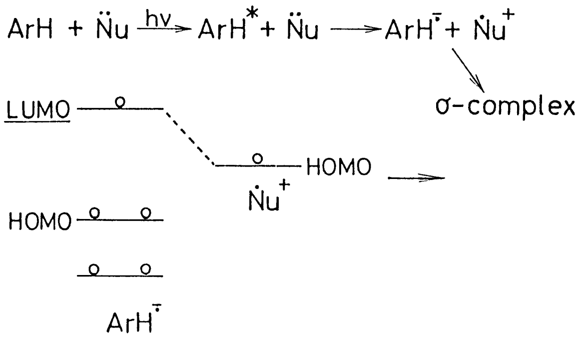


(3)

4, n = 2,3   5

This process has been unambiguously established by laser flash photolysis.[7,8)] The last stage involves strong interaction of a singly occupied MO, which was LUMO in the ground state, with the singly occupied HOMO of nucleophile, as shown in Fig. 3. In the mechanism, this is the key step which raises another type of regioselectivity. Thus, we propose a second rule (rule 2).

Rule 2: para- *or* ortho-*Substitution is a LUMO-controlled reaction in which photoinitiated electron transfer from a nucleophile to a nitroaromatic substrate and subsequent recombination of resultant radical ions are involved* (Eq. 4 and Fig. 3).

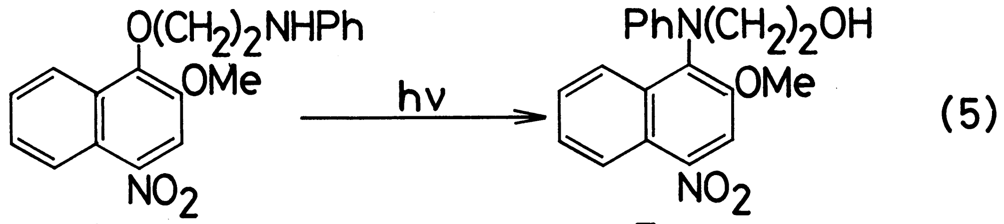


(4)

Fig. 3. Schematic illustration of the orientation-determining step, i.e.σ-complex formation after photoinduced electron transfer. A broken line denotes the orbital interaction resulting in bond formation. ArH represents an aromatic substrate and Nu a nucleophile.

Examination of the FED's of the LUMO of 3,4-dimethoxynitrobenzene (Fig. 2) provides a supporting evidence for the rule; the FED at C_4 is the highest among C_3-C_5 carbons available for intramolecular substitution. No reactivity observed at C_5, in spite of its fairly large FED, is probably due to the absence of a good leaving group at this position.

In order to assess the validity of rule 2 and to obtain further supporting evidence, we have designed **6** as the naphthalene analog of **4**, for the study of photochemical behavior. The compound is chosen with the intention of extending the rule to naphthalene derivatives.



6 **7** (5)

As shown in Eq. 5, the substitution occurred at C_1 or at the "para" position with respect to the nitro group.[9] FED maps of the HOMO and LUMO of the nitronaphthalene moiety (Fig. 4) show that C_1 is favorable for substitution in both MO's. Important difference is the FED's at C_2 which are 0.168 in the HOMO, nearly equal to that at C_1, and 0.011 in the LUMO. Therefore, if the observed reaction is HOMO-controlled, the reaction would have been observed at C_2 as well as C_1. Since no restriction such as steric hindrance is expected for the intramolecular cyclization at C_2, predominant reactivity at C_1 could be best interpreted as LUMO-controlled. Nucleophilic photosubstitutions in a similar nitronaphthalene substrate, exhibiting HOMO-controlled regioselectivity, are also found among intermolecular reactions with anionic nucleophiles.[10]

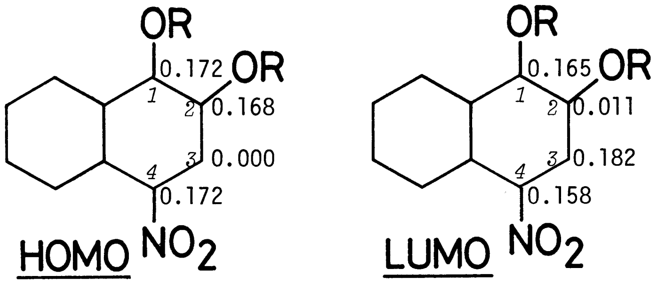


Fig. 4. FED maps of the HOMO and LUMO of 1,2-dialkoxy-4-nitronaphthalene.

Although present approach has neglected other significant factors such as reaction medium, leaving group, or nucleophile, it would provide,as a first approximation, a more comprehensive view on photochemical reaction mechanisms than conventional resonance theory or empirical orientation rules.[12]

References

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5) Ref. 2, and references therein.
6) The present MO calculations were performed with the CNDO/2 program, adapted by replacing the original two-center electronic repulsion integrals with the Nishimoto-Mataga approximation (Z. Phys. Chem. N. F., 13, 140 (1957)), on a Mitsubishi MELCOM COSMO 700 III computer at the University of Tokyo. The program was kindly provided by Prof. Koichi Ohno of the University of Tokyo. Methoxyl or RO group in Figs. 2 and 4 is approximated by a hydroxyl group for convenience of calculation.
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8) K. Yokoyama, R. Nakagaki, J. Nakamura, K. Mutai, and S. Nagakura, Bull. Chem. Soc. Jpn., 53, 2472 (1980).
9) Presented at the 49th National Meeting of the Chemical Society of Japan, Tokyo, 1984; Abstracts 1G35.
10) Although 1,2-dialkoxy-4-nitronaphthalene is an ideal substrate for the present purpose, no reaction of this type of compound has been reported. We adopted 2-fluoro-1-methoxy-4-nitronaphthalene as a substitute, because its FED maps of both HOMO and LUMO show similar patterns with those of the ideal one shown in Fig. 4; for instance, the FED's of the HOMO of this fluoro analog at C_1 through C_4 are 0.142, 0.173, 0.013, and 0.192, respectively. Nucleophilic photoreactions with anionic nucleophiles such as hydroxide, methoxide, and cyanide ions are observed at C_1, C_2, and C_4,[11] as expected for HOMO-controlled regioselectivity.
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12) As other examples showing the applicability of the rules, photocyanation of dimethoxynitrobenzenes[13] (rule 1) and cyanoanisoles[14] (rule 1), and photoamination of chloronitrobenzenes[15] (rule 2) could be cited.
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