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CRYSTALLOGRAPHIC EVIDENCE OF STEREOSELECTIVE EXO-CYCLOADDITION FOR 1,3-DIPOLAR REACTION OF 3,5-DIMETHYLPYRIDINE N-OXIDE WITH N-SUBSTITUTED MALEIMIDES AND SOME COMMENTS

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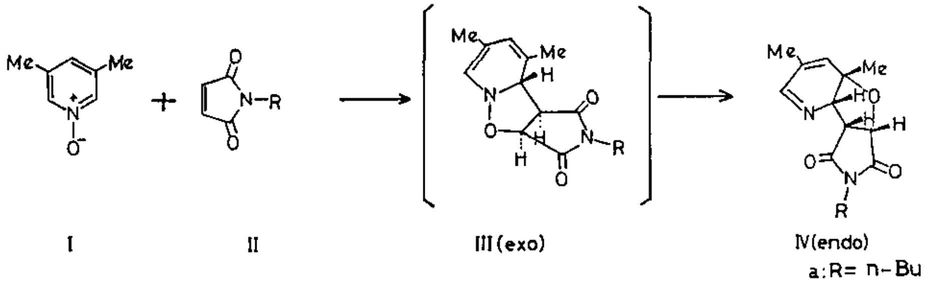
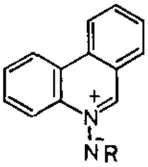
Abstract - The crystal structure of the 1,5-sigmatropic rearrangement product of the cycloadduct of 3,5-dimethylpyridine N-oxide and N-butylmaleimide was elucidated. The result indicates that the cycloaddition proceeds via exo transition state.

We previously reported that the 1,3-dipolar cycloaddition of 3,5-dimethylpyridine (3,5-lutidine) N-oxide (I) with N-substituted maleimides (II) afforded furo[2,3-b]pyridine-type cycloadducts (IV) arising from 1,5-sigmatropic rearrangement of the primary exo cycloadducts (III) (Scheme 1).[1] The exo addition is considered to have resulted from unfavorable secondary orbital interactions between the highest occupied molecular orbital (HOMO) of I and the lowest unoccupied molecular orbital (LUMO) of II.



Scheme 1

In the reaction of N-benzoyliminophenanthridinium betaine (Va) or N-aminophenanthridinium salt (Vb) with N-methylmaleimide, Tamura et al.[2a] isolated the endo primary adducts and suggested that the stereochemical outcome could be rationalized in terms of the attractive secondary molecular orbital interactions between LUMO of V and HOMO of II. A similar endo-cycloaddition was found in the reaction of pyridinium phenacylide with N-methylmaleimide.[2b] These results are in sharp contrast to our result.



Va,b: R=H, COPh

Table I. FMO Energy Levels (eV) and Dominant Interactions

	I	II	Va
π-LUMO	-0.473	-1.156	-0.936
π-HOMO	-8.737	-11.351	-7.676

Based on these backgrounds, an X-ray crystallographic study was undertaken to get a definitive evidence of the molecular structure of IV. Of the various derivatives synthesized, only the N-butyl derivative (IVa) gave single crystals when crystallized from the ethanol-acetone solution by slow evaporation at room temperature. The crystals are monoclinic, space group $\underline{P}2_1/\underline{n}$, which was judged from systematic absence of reflections and there are four molecules in the unit cell of dimensions $\underline{a}$=21.959(22), $\underline{b}$=9.395(6), $\underline{c}$=7.440(8)Å, β=96.53(9)°.[3] The structure was solved by the direct method using the MULTAN78 series of program[4] and refined by the block-diagonal least-squares method using UNICS III program.[5] Hydrogen atoms were fixed at calculated idealized positions keeping their vibrational amplitude fixed (B(H)=B(C)+1.0). The refinement converged to R=0.086. The molecular structure is shown in Fig. 1.

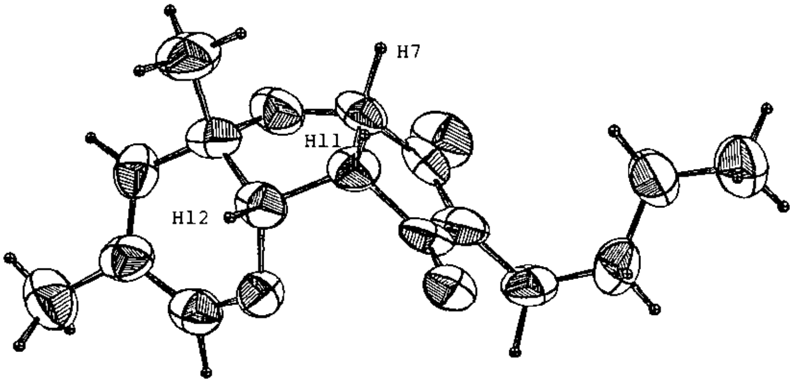
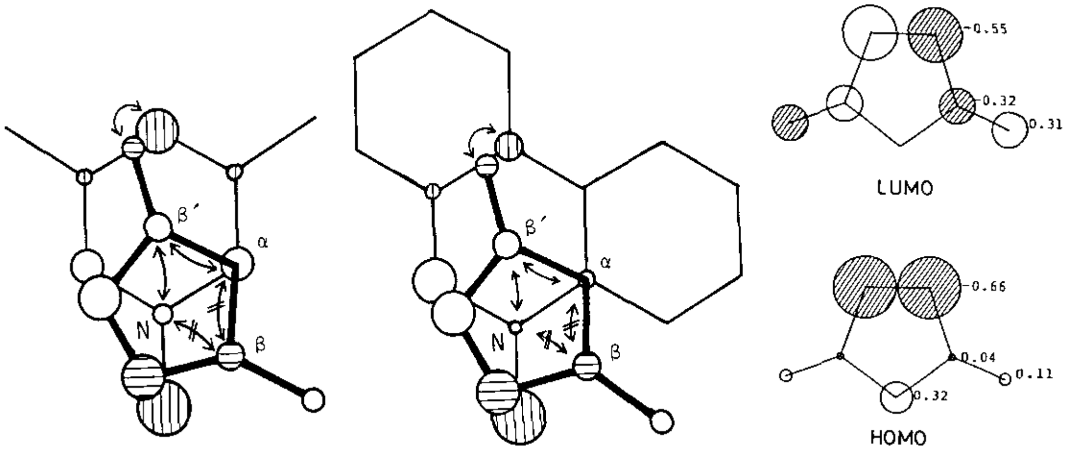


Fig. 1 ORTEP Drawing of IVa

As can be seen in Fig. 1, IVa is the endo 1,5-sigmatropic rearrangement product in which three hydrogens H7, H11 and H12 are all-cis, and therefore the primary cycloaddition product is the exo one. The activation parameters and the substituent and solvent effects are fully in accordance with the concerted reaction behavior.[1,6] So the stereochemistry of the cycloaddition is determined in the early stages of the concerted reaction process. The MNDO calculations suggest the dominant interaction occurring between HOMO of dipoles I and LUMO of II (Table I). The frontier orbital interactions for endo transition state are depicted in Fig. 2a.



a (I+II) b (V+II)

Fig. 2 Frontier Orbitals and Secondary Interactions

In addition to the primary interactions leading ultimately to new bonds, additional nonbonding interactions between the remainder of the diene and dienophile π systems are possible in the endo transition state. Of those, two types of "secondary orbital interactions" between the N atom of dipoles and two carbonyl carbons (C_β and C_β') of maleimides are important.[7] As shown in Fig. 2a, one of the interactions is antibonding. This suggests that the exo transition state is more favorable than the endo one. In the case of V, the frontier electron densities of the N and C_α atoms are smaller than those of I, implying that the antibonding interaction between the N (or C_α) of V and the C_β atom of II is not serious.[8]

This result may provide a useful information on the stereochemistry of 1,3-dipolar cycloaddition reactions of aromatic N-oxides with olefins which is scarcely known in contrast to the extensive data available on the reactions of aliphatic N-oxides (nitrones) and Diels-Alder reactions.

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REFERENCES AND NOTES

1. a) T. Matsuoka, K. Harano, and T. Hisano, *Chem. Pharm. Bull.*, **31**, 2948(1983).
   b) T. Hisano, K. Harano, T. Matsuoka, H. Yamada, and M. Kurihara, *ibid.*, **35**, 1049(1987).
2. a) Y. Tamura, Y. Miki, and M. Ikeda, *J. Chem. Soc. Perkin I*, **1976**, 1702.
   b) O. Tsuge, S. Kanemasa, S. Takenaka, and S. Kuraoka, *Chemistry Letters*, **1984**, 465.
3. Unit cell dimensions were obtained from least squares refinement of the 2θ angles of 20 reflections measured on a RIGAKU AFC-6 diffractometer (Mo, λ = 0.71069Å). Intensity data were collected using the θ scan mode and of the 2114 independent reflections within the range of the diffractometer ($2\theta<50°$), 881 were observed. E maps computed with the 200 normalized structure factors with values of $E>1.6$ revealed the entire structure except hydrogen atoms.
4. P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, "MULTAN78, A System of Computer Programs for the Automatic Solution of Crystal Structure from X-Ray Diffraction Data," Univ. of York, England (1978).
5. All the calculations were performed on the FACOM M-360 computer in the Computer Center of Kumamoto University with the Universal Crystallographic Computation Program System (UNICS) III [T. Sakurai and K. Kobayashi, *Rikagaku Kenkyusho Hookoku*, **55**, 69(1979): S. Kawano, *Koho*, *Comput. Center Kyushu Univ.*, 16, 113(1983)].
6. The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the reaction of I with N-phenylmaleimide in bromobenzene are 20.0 kcal/mol and -35 e.u., respectively (see ref. 1b).
7. I. Fleming, 'Frontier Orbitals and Organic Chemical Reactions,' John Wiley and Sons, Inc., London, 1976, pp. 106-109: M. Burdisso, A. Gamba, R. Gandolfi and R. Oberti, *Tetrahedron*, **44**, 3735 (1988) and references cited therein.
8. The secondary interaction between the LUMO of V and the HOMO of II^2 is unfavorable because the HOMO of II has a nodal property at the carbonyl carbon.

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