REACTION OF AROMATIC *N*-OXIDES WITH DIPOLAROPHILES XIX. PM3 ANALYSIS OF SEQUENTIAL PERICYCLIC REACTIONS BETWEEN PYRIDINE *N*-OXIDES AND ALLENES

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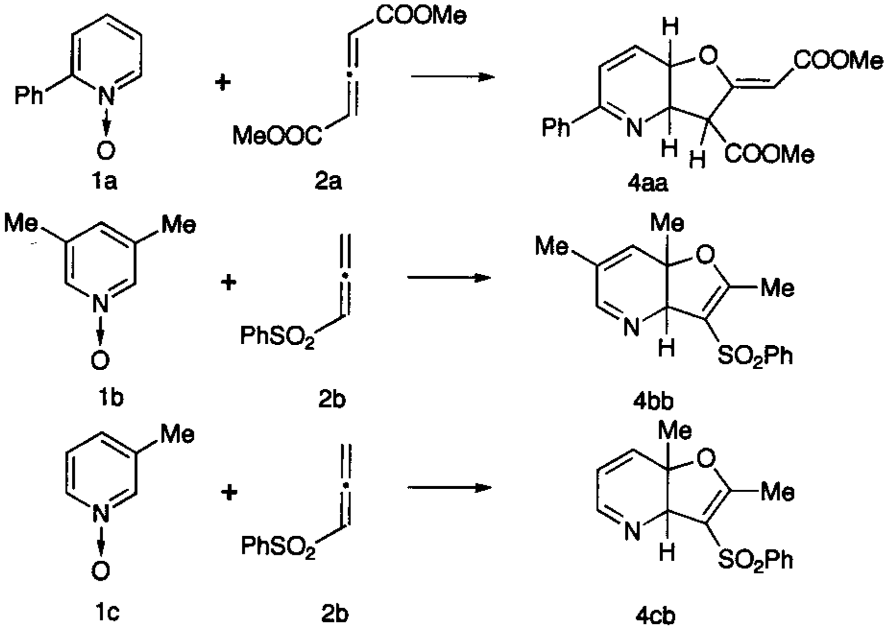
Abstract - Sequential pericyclic reactions between pyridine *N*-oxides and allenes were evaluated in terms of PM3 calculation. Structures corresponding to the perturbating system were calculated by varying the distance of the addends. The cycloaddition occurs *via* π-complex. In the transition structure TS1 of primary cycloaddition, the lengths of the newly created bonds of O-C and C-C are 1.864 and 2.204 Å, respectively. The bond between the O atom of pyridine *N*-oxide and the central carbon of allene is *ca.* 35 % formed at TS1, slightly advanced than the other (*ca.* 30 %). The PM3 calculation at the UHF level predicts that [1,5]-sigmatropic rearrangement of the primary cycloadduct proceeds *via* a transition state with a biradical character.

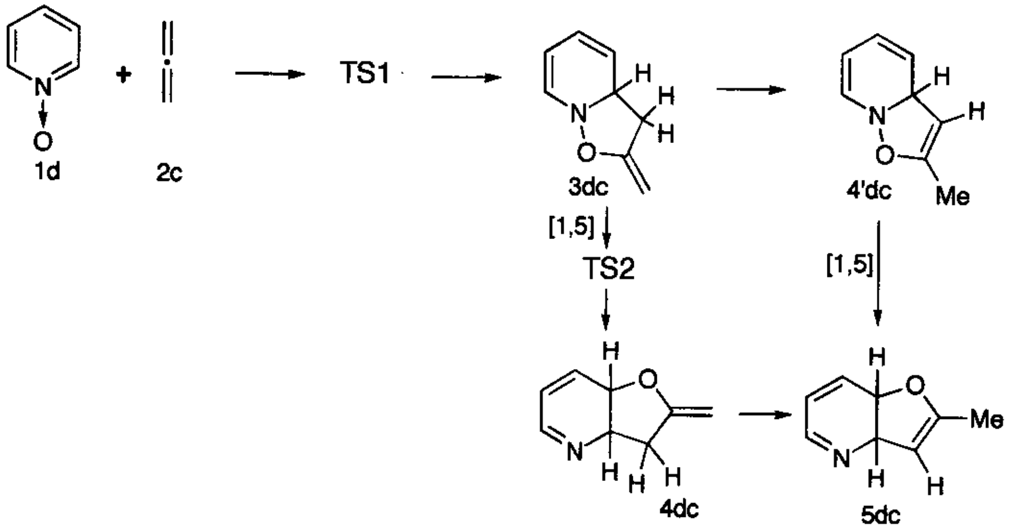
In the course of our study on the 1,3-dipolar cycloaddition between pyridine *N*-oxides 1 and various dipolarophiles, we recently reported that electron deficient allenes 2 showed markedly high cycloaddition reactivity toward 1 to give 2,3-dihydropyridine-type products 4 *via* the primary cycloadducts 3.[1] In the case of the reaction between 2-phenylpyridine *N*-oxide (1a) and dimethyl 2,3-pentadienedioate (2a) afforded 2,3-dihyropyridine-type product 4aa having exocyclic C=C bond. On the other hand, the reaction of 3,5-dimethylpyridine *N*-oxide 1b with phenylsulfonylpropadiene (2b) afforded a 2,3-dihydropyridine-type cycloadduct 4bb having endocyclic C=C bond. The reaction of 3-methylpyridine *N*-oxide (1c) with 2b showed selective cyclization toward 2-position of 1c to give 4cb[1a] (Scheme 1).

As shown in Scheme 2, the reaction involves sequential pericyclic processes and a turning point in the reaction path. Our present interests are: 1) How does the primary cycloaddition proceed? (synchronous or asynchronous); 2) Why does the primary cycloaddition toward 2-position of 1c preferentially occur?; 3) How does the [1,5]-sigmatropic rearrangement of 3 to 4 take place?

The computer simulations are well suited for searching transition-state structures. However, high level *ab initio* calculations with full geometry optimization for the present reaction system are still beyond the capacity of present-day computers. It is well known that the MNDO family has developed with improvement of reproductivity of the physical properties for compounds having N-N or N-O bond and highly strained compounds. In this connection, the present reaction system seems to be very suitable for elucidation of the scope and limitation of PM3[2] method.



Scheme 1



Scheme 2

On the basis of these backgrounds, we performed MNDO-PM3 (PM3)[2] study on the model reaction between pyridine *N*-oxide (1d) and allene 2c to elucidate the mechanistic aspects.

Molecular Orbital Calculations The PM3[2] method was used for the semiempirical SCF MO calculations using the MOPAC[3] (version 6.02) molecular orbital package which was locally modified for Sun FORTRAN 1.2 on a Fujitsu S-4/2 engineering workstation. The starting geometries of 1d, 2c and intermediary structures (3dc and 4dc) were obtained from the corresponding molecular models. The crude structures were then fully optimized using keyword PRECISE. The transition state TS1 for the model primary cycloaddition reaction and the transition state TS2 for conversion of the primary cycloadduct 3dc to the 1,5-sigmatropic rearrangement product 4dc were located using the SADDLE routine[4] implemented in MOPAC and refined with the NLLSQ method.[5]

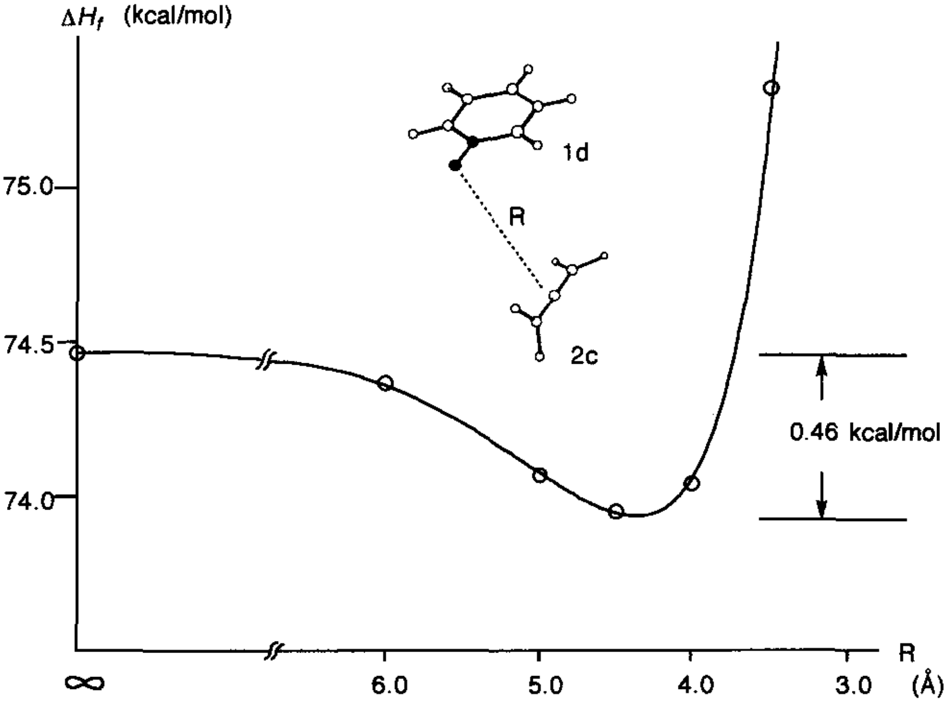


Figure 1 PM3 Results for the Perturbating System.

Primary Cycloaddition between 1d and 2c The PM3 calculated heats of formation of 1d and 2c are 27.38 and 47.06 kcal/mol, respectively. Sum of these values is considered to be the heat of formation of the ground state of the reaction system. The calculation corresponding to the perturbating system was started from the geometry, in which 1d and 2c are located 6 Å apart to give a structure with 74.37 kcal/mol of heat of formation. Then, with varying the distance between the oxygen atom of 1d and the central carbon atom of 2c, similar calculations were performed. As depicted in Figure 1, a 0.46 kcal/mol of shallow minimum was observed at a distance of *ca* 4.5 Å. It is well known that cyclic planar addends are apt to form π,π-complex such as charge-transfer CT complex, which stabilizes the ground-state reaction system, in the early stage on the reaction coordinate prior to cycloaddition.[6] The calculated shallow minimum can be regarded as such a stabilization. At a distance of 4.25 Å, the molecular complex is "uphill" movement to the transition structure.

On the other hand, inspection of the optimized geometry of the primary adduct 3dc revealed that the N-O bond in isoxazoline moiety was calculated to be 1.536 Å, which is somewhat longer than normal N-O bonds.[7] Furthermore, bond order of the N-O bond is only 0.909. These observations suggest that the following [1,5]-sigmatropic rearrangement readily proceeds to give 4dc through TS2. In comparison with the PM3 result, AM1 calculation for 3dc was performed, the N-O bond length was calculated to be 1.367 Å, which is shorter than the standard values.[7]

Transition structure TS1 of the primary cycloaddition was located by SADDLE routine, using the geometries of the ground state and the primary adduct, and fully optimized. The optimized geometry of TS1 in RHF level is shown in Figure 2. The activation enthalpy for the primary cycloaddition was calculated to be 40.22 kcal/mol. In the similar manner, that of the reaction of unsubstituted nitrone 1e with 2c was calculated to be 34.33 kcal/mole.

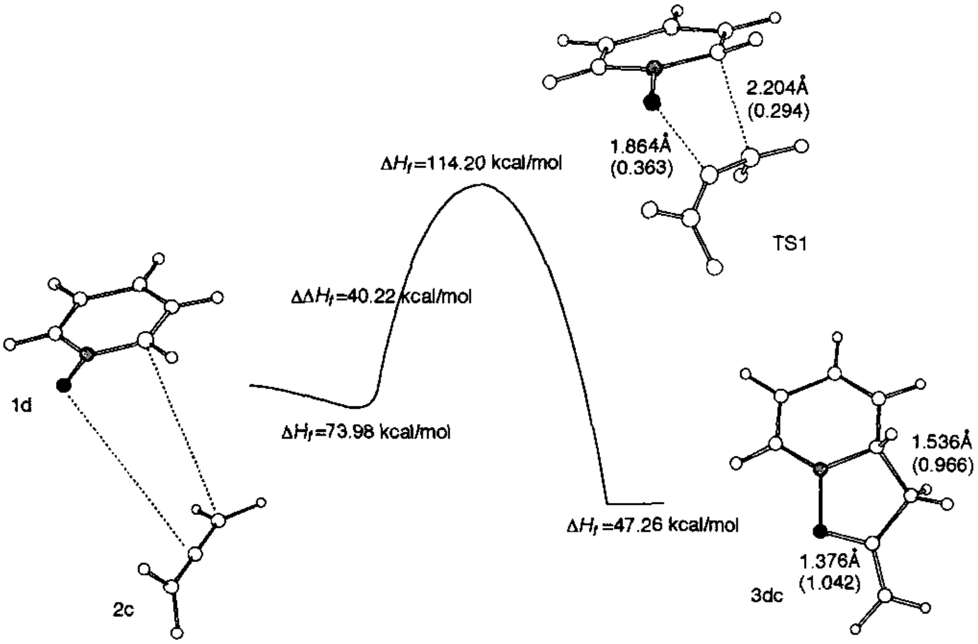


Figure 2 PM3 Results for the Formation of Primary Cycloadduct.
Bond Orders are shown in Parenthesis.

Table 1. Heats of Formation and Dipole Moments of Reactants, Transition Structures, and Intermediary Structures.

Structure	ΔH_f (kcal/mol)	μ (D)	Structure	ΔH_f (kcal/mol)	μ (D)
1d + 2c (4.5 Å)	73.98	3.658	TS2 (RHF)	103.09	4.917
TS1 (RHF)	114.20	2.798	TS2 (UHF)	47.26	2.220
TS1 (UHF)	113.55	2.680	4dc	12.12	1.139
3dc	47.26	2.204	5dc	10.09	1.163

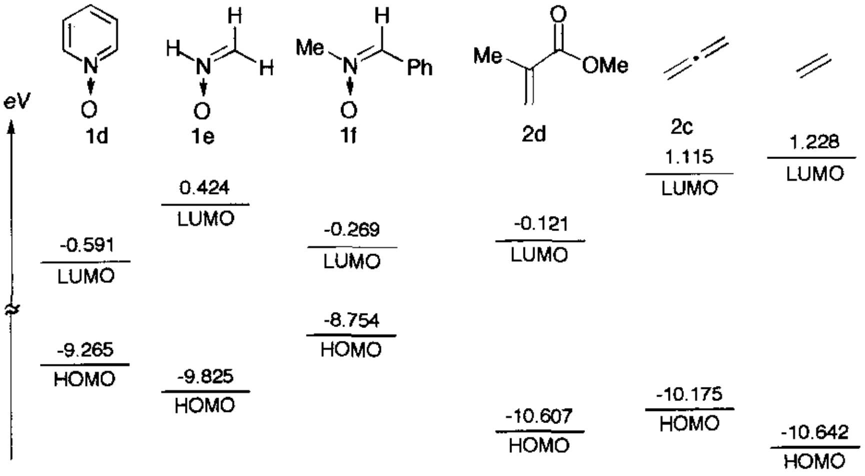


Figure 3 FMO Energy Levels by PM3.

On the basis of the frontier molecular orbital (FMO) theory,[8] the activation enthalpy is inversely proportional to the energy gap between HOMO and LUMO of the addends. The PM3 results for nitrones and dipolarophiles were shown in Figure 3. Huisgen *et al.* reported the kinetic study on the reaction between *N*-methyl-C-phenylnitrone (1f) and methyl methacrylate (2d) and the activation enthalpy was calculated to be 15.7 kcal/mol.[9] Recently, Robb *et al.* reported that the activation enthalpy of the reaction of 1e with ethylene was calculated to be 11.9 kcal/mol by MC-SCF calculation.[10] However, the energy gap between HOMO of 1e and LUMO of 2c or ethylene is very greater than that between 1f and 2d, indicating that the activation enthalpy for 1e plus ethylene should be calculated greater. Therefore, their result is too small and is not immediately convincing from the viewpoint of kinetics and FMO theory, suggesting that high level MO calculations do not always give reasonable results. On the other hand, taking into account the Huisgen's experimental result and our result for 1e plus 2c, the method we employed can fairly reproduce the reaction. The HOMO of 1d is a little higher than that of nitrone, but the calculated activation enthalpy is about 6 kcal/mol greater than the case of nitrone. This can be attributable to the stabilization of ground state by aromaticity.[11]

In TS1, the lengths of the newly created bonds of O-C and C-C are 1.864 and 2.204 Å, respectively. Inspections of the bond orders of TS1 and the primary adduct 3dc reveals that the bond between the O atom of 1d and the central carbon of 2c is *ca.* 35 % formed at TS1, slightly advanced than the other (*ca* . 30 %). The dipole moments of reactants, transition structures, and products are summarized in Table 1. In going from the reactants to TS1, the dipole moment somewhat decreased from 3.658 (4.5 Å) to 2.798 (TS1 (RHF)) Debye, suggesting that no significant charge separation is involved in the transition state. The UHF calculation of TS1 gave no decrease of the activation barrier, indicating that TS1 does not show any biradical character (Table 1). These observations suggest that the primary cycloaddition proceeds with nearly synchronous mechanism. The heat of reaction (ΔH_r) for this step was calculated to be 26.72 kcal/mol. In TS1, the out-of-plane bending of N-O bond is about 15° from the pyridine nuclei. On the other hand, the residual diene moiety in pyridine nuclei is almost in-plane.

Next, mention should be made of periselectivity. As mentioned above, the cycloaddition of 1c with 2b predominantly occurred towards C_2 of 1c, which seems to be sterically unfavorable than the cycloaddition toward C_6 (see also Scheme 1). Similar results were observed in the reaction of 1c with phenyl isocyanates.[9] As the simple FMO consideration did not give a satisfactory prediction, two possible periselections were evaluated based on the calculation data about the transition states for the model primary cycloaddition of 1c with 2c. Inspection of the calculated data revealed that the transition state cyclizing toward C_2 is 0.27 kcal/mol more stable than the other in heat of formation, supporting the experimental results.[11]

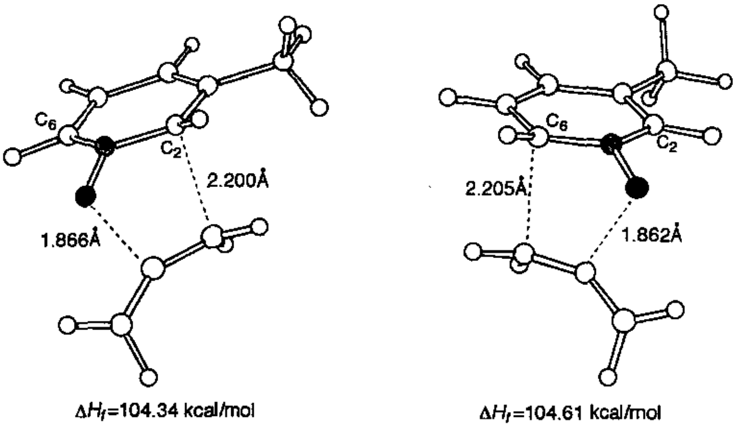


Figure 4 Transition State for the Cycloaddition of 2c toward C_2 and C_6 of 1c.

Formation Pathway of the 5dc from 3dc As depicted in Scheme 2, there are formally two possible pathways for the formation of V from 3dc. However, thermal [1,3]-sigmatropic rearrangement is symmetrically forbidden. Furthermore, taking into consideration that the reaction between 2-phenylpyridine *N*-oxide (1a) and dimethyl 2,3-pentadienedioate (2a) afforded a 2,3-dihydropyridine-type product with an exocyclic C=C bond, the path through [1,5]-sigmatropic transition state TS2 followed by hydrogen shift is more plausible than the other (hydrogen shift → [1,5]) (Scheme 2).

The fully optimized geometry of TS2 is shown in Figure 5. The path from 3dc to 4dc through TS2 was calculated to involve 55.83 kcal/mol of activation enthalpy at the RHF level, significantly greater than that for TS1. However, in the course of our study on the 1,3-dipolar cycloaddition reaction of pyridine *N*-oxides with dipolarophiles, we could not obtain any primary adducts at all, suggesting that the primary adducts are thermally labile and undergo [1,5]-sigmatropic rearrangement.[9] The PM3 calculation of TS2 at the UHF level revealed that the heat of formation of TS2 is 47.26 kcal/mol, comparable to the one for the precursor 3dc. The significant stabilization of TS2 indicates that this step might involve a biradical character. The transition structure optimized at the UHF level is depicted in Figure 5. The N-O and C_3-O bonds are 2.776 Å and 2.705 Å, respectively. During the [1,5]-sigmatropic rearrangement, freedom of motion of the migrating vinyloxy group is sterically restricted because the migrating group is connected to the reaction system and the growing p-orbital is stabilized by resonance with the vinyl group. In such a situation, the thermally allowed orbital interaction may be modified. The weaken N-O bond is considered to be cleaved into biradical to give a more stabilized TS.

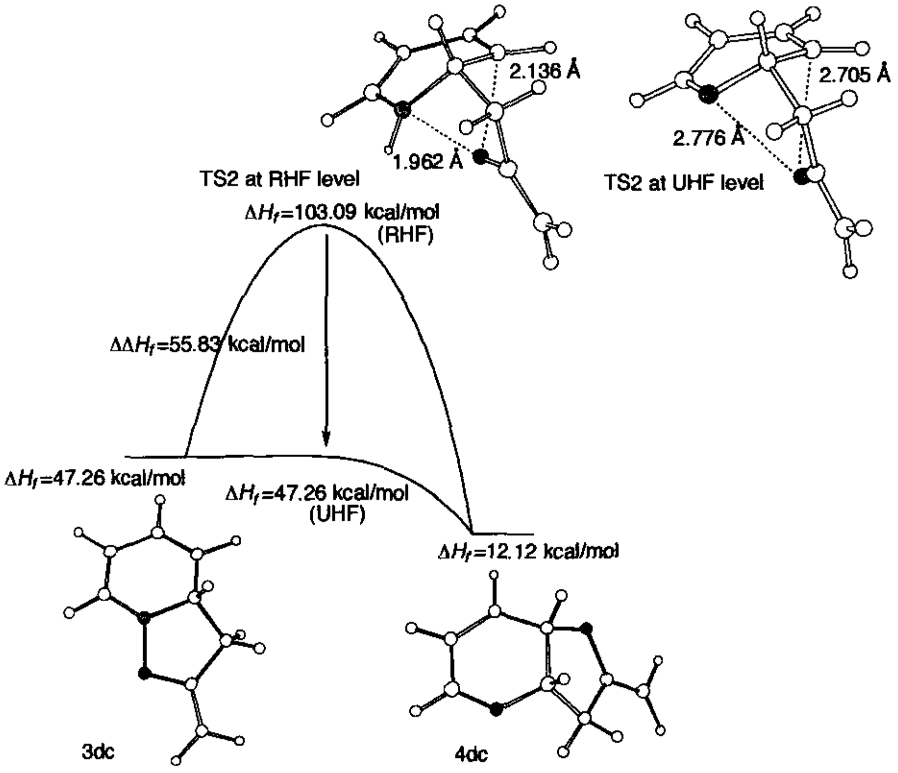


Figure 5 PM3 Results for the Pathway from 3dc to 4dc.

The barrier for the hydrogen shift (3dc → 4'dc) calculated at the RHF level is very high, 76.7 kcal/mol. However, The calculation at the UHF level did not give any stabilization, indicating that the hydrogen shift proceeds *via* a heterolytic reaction pathway.

In conclusion, PM3 calculations suggest that the bond between the O atom of 1d and the central carbon of 2c is formed slightly advanced than the other bond formed. On the other hand, the formation pathway of 5dc from 3dc might have a biradical character, because of the significant stabilization of TS2 at the UHF level calculation.

Cartesian coordinates of the calculated structures are available from the authors upon request.

REFERENCES

1. a) Part XVIII, T. Matsuoka, T. Hasegawa, M. Eto, K. Harano and T. Hisano, *J. Chem. Soc., Perkin Trans. II*, 1993, in press. b) T. Hisano, K. Harano, T. Matsuoka, T. Matsuzaki and M. Eto, *Chem. Pharm. Bull.*, 1991, **39**, 537; T. Matsuoka, T. Hasegawa, K. Harano and T. Hisano, *Heterocycles*, 1992, **33**, 179.
2. J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209, 221: J. J. P. Stewart, *QCPE Bull.*, 1989, **9**, 10.
3. J. J. P. Stewart, *QCPE Bull.*, 1989, **9**, 10: Revised as Ver. 6.02 by present authors for Fujitsu S-4/2 engineering workstation.
4. M. J. S. Dewar, E. F. Healy and J. J. P. Stewart, *J. Chem. Soc., Faraday Trans. I*, 1984, **3**, 227.
5. R. H. Bertels, Report CNA-44, 1972, University of Texas Centre for Numerical Analysis.
6. K. L. Mok and M. J. Nye, *J. Chem. Soc., Perkin Trans. I*, **1975**, 1810.
7. F. H. Allen, O. Kennard and D. G. Watson, *J. Chem. Soc., Perkin Trans. II*, **1987**, S1.
8. K. Fukui, "Chemical Reactions and Electron Orbitals," Maruzen, Tokyo, 1976. (d) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions," John Wiley & Sons, Ltd., London, 1976, pp. 106-109.
9. R. Huisgen, H. Seidl and I. Bruening, *Chem. Ber.*, 1969, **102**, 1102.
10. J. J. W. McDouall, M. A. Robb, U. Niazi, F. Bernardi and H. B. Schlegel, *J. Am. Chem. Soc.*, 1987, **109**, 4642.
11. T. Matsuoka, M. Shinada, F. Suematsu, K. Harano and T. Hisano, *Chem. Pharm. Bull.*, 1984, **32**, 2077 and references cited therein; K. Harano, R. Kondo, M. Murase, T. Matsuoka and T. Hisano, *ibid.*, 1986, **34**, 966; K. Harano, F. Suematsu, T. Matsuoka and T. Hisano, *ibid.*, 1984, **32**, 543; T. Matsuoka, K. Harano and T. Hisano, *ibid.*, 1983, **31**, 2948; T. Hisano, K. Harano, T. Matsuoka, H. Yamada and M. Kurihara, *ibid.*, 1987, **35**, 1049; K. Harano, T. Matsuoka, M. Eto, T. Matsuzaki and T. Hisano, *Heterocycles*, 1989, **29**, 1029.

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