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Ab Initio and PM3 Analysis of 1,3-Dipolar Cycloaddition Reaction between Pyridine *N*-Oxides and Isocyanates. Theoretical Evidence of Concerted and Nonsynchronous Mechanism with Zwitterionic Character

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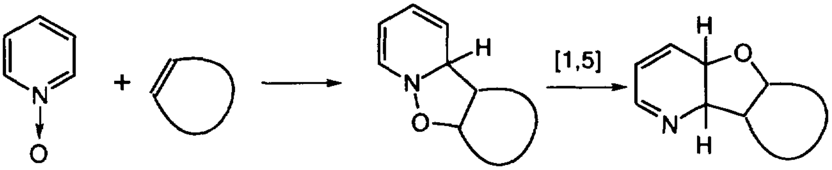
The 1,3-dipolar cycloaddition of nitrone (1a) and pyridine *N*-oxide (1b) with isocyanates (2) was evaluated in terms of *ab initio* and semiempirical PM3 calculations. In the *ab initio* transition structure of 1a with isocyanic acid (2a) by MP2/6-31G* level, the length of the newly forming bonds of O-C and C-N are 1.740 and 2.197 Å, respectively, indicative of the former bond formation being significantly advanced than that of the latter. The PM3 transition structure (TSba) of the cycloaddition between 1b with 2a showed similar result. The O-C bond (1.445 Å) is *ca.* 76 % formed at the transition state, significantly advanced than the C-N bond (2.165 Å, *ca.* 20 %). Moreover, the atoms forming the C-N bond have opposite charge, indicating a zwitterionic character of TSba.

In continuation of our study on the 1,3-dipolar cycloaddition of pyridine *N*-oxides, we have examined the sequential pericyclic reactions of pyridine *N*-oxides with various dipolarophiles such as phenyl isocyanates,[1a-d] *N*-substituted maleimides,[1e-g] 1,4-epoxy-1,4-dihydronaphthalene[1h] and electron deficient allenes[1i-k] and elucidated the mechanistic aspects of the reaction based on the kinetic and frontier molecular orbital (FMO)[2] theoretical points of view.

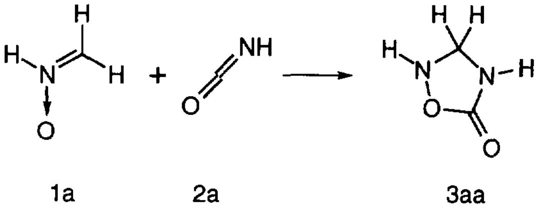


Scheme 1

We recently communicated MNDO-PM3 (PM3)[3] analysis of sequential pericyclic reactions of pyridine *N*-oxide (1b) toward allenes.[1j,k and 4] We thereat showed that the cycloaddition proceeds with nearly synchronous mechanism and the calculation can well reproduce the charge-transfer (CT) complexation observed *priori to* the primary cycloaddition.

We now report the *ab initio* and PM3 study on the reaction of nitrones (1) toward isocyanates (2) to elucidate the mechanistic aspects of the primary cycloaddition.

Molecular Orbital Calculations *Ab initio* calculations were performed with the Gaussian92 program[5] on a Fujitsu S-4/10 engineering workstation. The starting geometries of 1a, 2a and the cycloadduct (3aa) were obtained from the corresponding molecular models, and then were fully optimized with the second-order Mϕller-Plesset wavefunction[6] on the 6-31G* (MP2/6-31G*), 6-31G and 3-21G* basis sets. PM3 and AM1 semiempirical MO calculations were performed by the MOPAC[7] (version 6.02) molecular orbital package which was locally modified for Sun FORTRAN 1.2 on a Fujitsu S-4/2 engineering workstation. The PM3 transition states (TSba) for the primary cycloaddition of 1b with 2a were located using the TS method or SADDLE routine[8] followed by the NLLSQ method[9] implemented in MOPAC and characterized by establishing that the Hessian (force constant) matrix had only one negative eigenvalue.[10]



Scheme 2

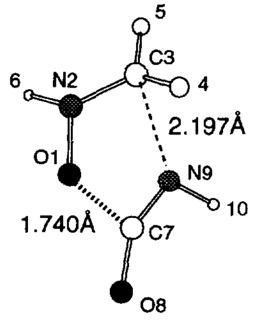


Figure 1 Structure of TSaa by MP2/6-31G*.

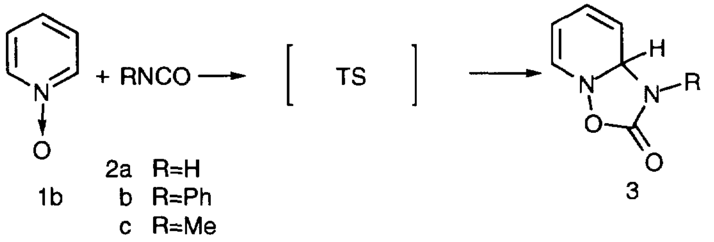
Table 1 Selected Geometries for TSaa, 3aa, 1a and 2a.

Compounds	MP2/6-31G*	HF/6-31G	HF/3-21G*	PM3	AM1
TSaa					
energy(a.u.)	-336.53351	-336.38132	-334.66099	25.24$^{c)}$	37.58$^{c)}$
O1 - C7$^{a)}$	1.740	1.588	1.666	1.459	1.596
C3 - N9$^{a)}$	2.197	2.302	2.388	2.252	2.279
3aa					
energy(a.u.)	-336.63393	-336.46292	-334.75671	-37.55$^{c)}$	-20.12$^{c)}$
O1 - C7$^{a)}$	1.389	1.381	1.391	1.363	1.417
C3 - N9$^{a)}$	1.454	1.453	1.456	1.480	1.458
1a					
energy(a.u.)	-168.80486	-168.73317	-167.85310	11.44$^{c)}$	16.94$^{c)}$
N - O$^{a)}$	1.257	1.328	1.265	1.238	1.220
N - C$^{a)}$	1.322	1.268	1.370	1.315	1.318
2a					
energy(a.u.)	-167.75675	-167.66686	-166.81167	-15.29$^{c)}$	-15.15$^{c)}$
N - C$^{a)}$	1.226	1.176	1.160	1.252	1.232
C - O$^{a)}$	1.185	1.180	1.177	1.189	1.203
∠H-N-C$^{b)}$	125.51	154.23	179.94	123.66	127.18
∠N-C-O$^{b)}$	171.49	175.78	179.95	168.66	166.73

a) Å. b) °. c) Heat of Formation (kcal/mol), 1 a.u.=627.5095 kcal/mol

Cycloaddition between 1a and 2a The fully optimized calculation results by the MP2/6-31G*, HF/6-31G and 3-21G* level for transition structure (TSaa), 1a, 2a and the cycloadduct (3aa) are summarized in Figure 1 and Table 1. In TSaa, the length of the newly forming bonds of O-C and C-N are 1.740 and 2.197 Å, respectively, indicative of the former bond formation is significantly advanced than that of the latter. The activation enthalpy from the reactants (1a +2a) was 17.63 kcal/mol (MP2/6-31G*). Semiempirical calculations such as PM3 and AM1 methods also gave highly unsymmetrical transition structure, suggesting that the reaction proceeds nonsynchronously (Table 1).

Primary Cycloaddition between 1b and 2a Next, we tried to obtain a quantitative clue for the reaction mechanism for the reaction of 1b with 2a. As mentioned above, both the *ab initio* calculations and the semiempirical calculations gave unsymmetrical transition structure, even though the latter somewhat exaggerated the nonsynchoronous character. As the system of interest in this study is too big to perform high level *ab initio* calculations, we applied PM3 calculations for the system of 1b with 2a. The PM3 calculations on the starting system, the transition state (TSa) and the primary cycloadduct (3ba) for the model reaction of 1b with isocyanic acid (2a) were performed. The PM3-calculated heats of formation of 1b and 2a are 27.38 and -15.29 kcal/mol, respectively. Sum of these values (12.09 kcal/mol) is considered to be the heat of formation of the reactants (1b + 2a).



Scheme 3

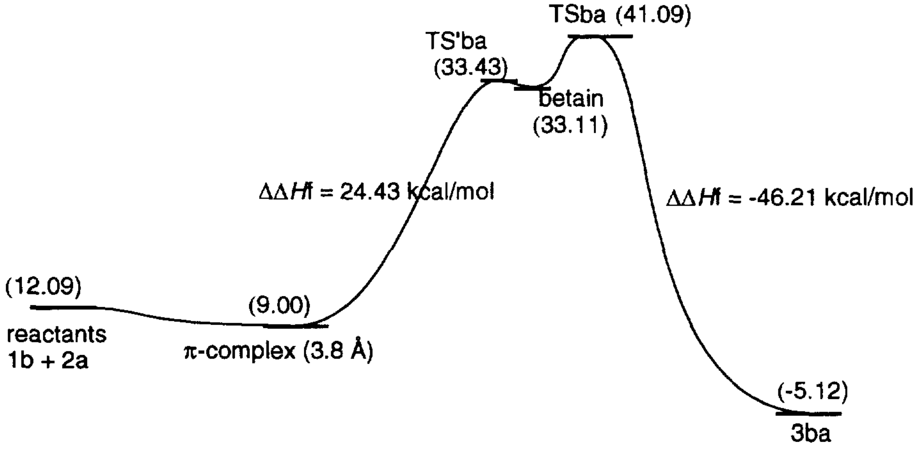


Figure 2 PM3 Calculated Heats of Formation. Δ*Hf* in Parenthesis (kcal/mol).

On the other hand, the heat of formation of the primary cycloadduct (3ba) is -5.12 kcal/mol. Inspection of the fully optimized geometry of 3ba revealed that the isoxazoline N-O bond was 1.541 Å, which is somewhat longer than normal N-O bonds.[11] We obtained similar results in the case of 1 with allene (1.536 Å).[4] The dihydropyridine ring and the oxazolinone ring in 3a are both almost planar, and the dihedral angle between the rings is about 125°. The heat of reaction (ΔHr) for the primary cycloaddition was calculated to be 17.21 kcal/mol.

Based on the geometries of the reactants and the primary adduct, transition structure (TSba) of primary cycloaddition was located using SADDLE calculation followed by the TS refinement. The activation enthalpy for the primary cycloaddition from the reactants to the TSba was calculated to be 29.00 kcal/mol.

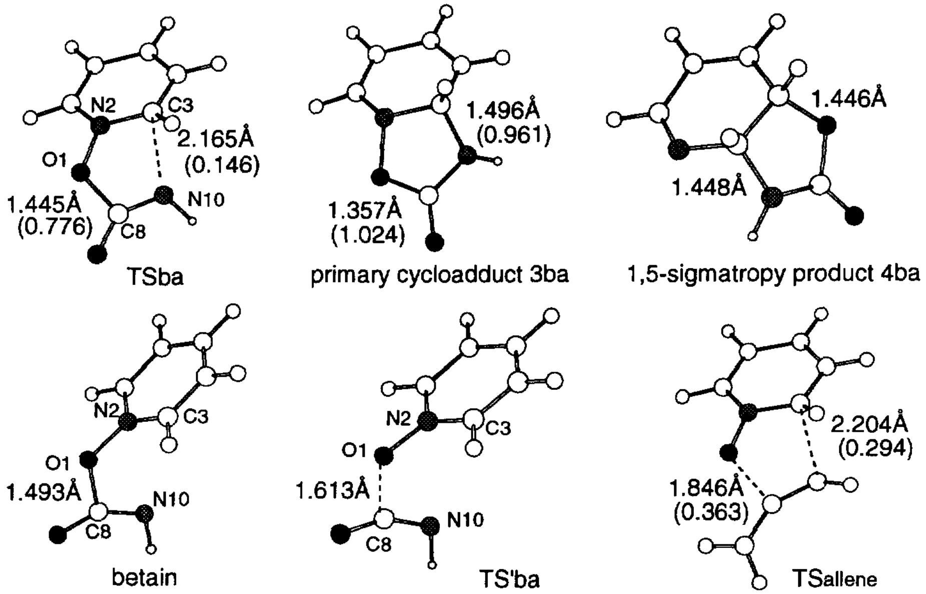
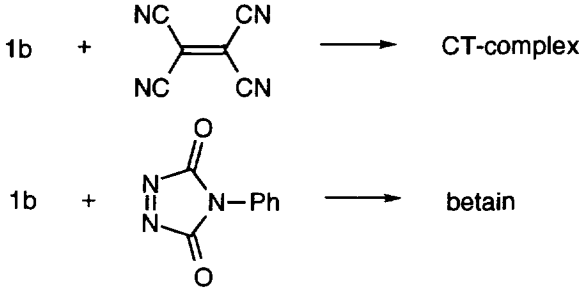


Figure 3 PM3 Optimized Structures of TSba, 3ba, 4ba, betain ,TS'ba and TSallene.
Bond Orders in parenthesis.

In TSba, the lengths of the partial bonding of O-C and C-C are 1.445 and 2.165 Å, respectively. By comparison of the bond orders of O1-C8 and C3-N10 of TSba and 3ba, respectively, the degree of the bond formation can be estimated.[12] The former one was*ca* 76 % formed at TSba, significantly advanced than the latter bond to be formed (*ca* 20 %). N2 is slightly pyramidalized and the out-of-plane bending of N-O bond in TSa is about 25° from the pyridine moiety. On the other hand, the residual diene moiety in pyridine ring is almost planar. These observations are consistent with the *ab initio* calculation results for the reaction of 1a with 2a, as mentioned above.

Even though the SADDLE calculation followed by the refinement with TS routine gave the TSba, some examples affording betain-type intermediates are reported.[13] We also previously reported the reaction behavior of 1b with tetracyanoethylene[1d] or *N*-phenyltriazoline-3,5-dione.[1d] In the former case, the reaction did not occur but gave stable a CT complex and the latter case gave a betain (Scheme 4).



Scheme 4

Therefore, we performed the calculations for a stepwise reaction pathway with elongating the O1--C8 distance of TSba to 1.493 Å to give a betain-type intermediate (ΔHf=33.11 kcal/mol), which requires *ca* 8 kcal/mol of activation energy to reach TSba (see Figure 2). The net charges at N2 and N10 of the betain are 0.767 and -0.551, respectively. An additional slight elongation of the O1--C8 distance of the betain brought about a climb to the low hill (TS'ba, ΔHf=33.43 kcal/mol). In TS'ba, the O1--C8 distance is 1.613 Å and the dihedral angle between the pyridine ring and the isocyanate moiety is nearly 90°. The net charges at N2 and N10 are 0.846 and -0.504, respectively.

Further elongation of the O1--C8 distance, which corresponds to the perturbating system between 1b and 2a, gave a shallow minimum in the vicinity of 3.8 Å, which is 3.09 kcal/mol more stable than the energy of the reactants (1b + 2a). This might be attributable to the π-complex formation *priori to* the cycloaddition, which was experimentally observed in our previous papers.[1b,d] By intrinsic reaction cordinate (IRC) calculation, the transition structures (TSba and TS'ba) and betain were confirmed to be on the same reaction coordinate.[14]

The dipole moments of the reactants, the perturbating system (O1--C8 distance = 3.8 Å), and TSba in the reaction of 1b with 2a are 4.824, 4,402 and 8.473 Debye, respectively. In the "hill climb" movement from the reactants to TSba, the dipole moment significantly increased, suggesting that considerable charge separation is involved in transition state. Moreover, the positive atomic charges for the N2=C3 moiety of the pyridine nuclei in TSba are 0.541 and 0.02, respectively and the one for the nitrogen atom derived from the isocyanate (N10) is -0.565. These results denote that the primary cycloaddition of 1b with 2a proceeds with zwitterionic character, showing a sharp contrast to the reaction of 1 with allene.[4] (see $\mathrm{TS_{allene}}$ in Figure 3)

Though the calculation results above suggest that the reaction rate should be influenced by polarity of solvents, in our kinetic study for the reaction of 1b with 2b,[1b] solvent dependence of reaction rate with increase of the solvent polarity could scarcely be observed. At present, we have no definite interpretation for the results. On the other hand, we previously reported that the site selectivity of the cycloaddition between 3-picoline *N*-

oxide and 1b changes drastically under the influence of the solvent polarity.[1d] We consider that the observation is closely related with the increase of the dipole moment in transition state.

Primary Cycloaddition between 1b and 2b,c Based on the results mentioned above, we tried to obtain a transition structure for the actual reaction system (1b plus 2b,c) examined in our previous papers.[1a-d] The transition structures (TSbb and TSbc) for the cycloadditions of 1b to 2b,c were created by substitution of the H-N proton of TSba with phenyl or methyl group, and the PM3 calculations were performed with the TS routine to give very similar result to that from 1b and 2a. The lone-pair on the isocyanate nitrogen atom of TSb well conjugates with the adjacent phenyl group. The results were summarized in Table 2 and Figure 4. In these cases, shallow minimum corresponding to the π-complexation *priori to* the cycloaddition could not be reproduced.

Table 2. PM3 Calculated Heats of Formation and Dipole Moments.

Reaction	Reactants 1+2	π-Complex at 3.8 Å	TS	Primary Adduct
1b+2a (R=H)			TSba	3ba
ΔHf(kcal/mol)	12.09	9.00	41.09	-5.12
Dipole Moment (Debye)	4.824	4.402	8.473	
1b+2b (R=Ph)			TSbb	3bb
ΔHf(kcal/mol)	39.32	40.12	65.52	25.04
Dipole Moment (Debye)	3.478	4.262	8.866	
1b+2c (R=Me)			TSbc	3bc
ΔHf(kcal/mol)	8.89	9.01	36.26	-7.39
Dipole Moment (Debye)	4.390	4.338	8.423	

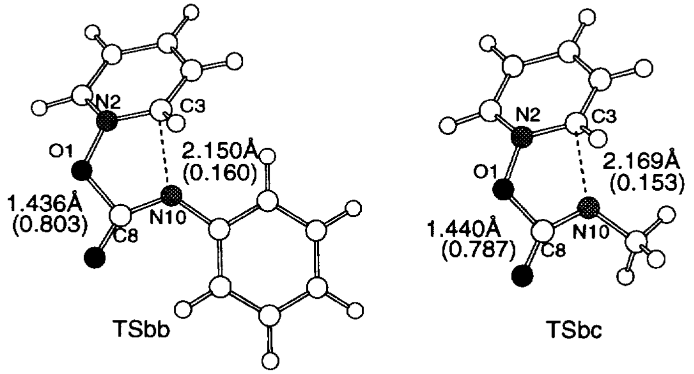


Figure 4 PM3 Optimized Structures of TSbb and TSbc. Bond Orders in Parenthesis.

1,5-Sigmatropic Rearrangement of 3ba to 4ba

Primary adduct 3ba, formed mentioned above, undergoes [1,5]-sigmatropic rearrangement to give 4ba. The transition structure (TS2) of 1,5-sigmatropic rearrangement from 3ba to 4ba was located by saddle calculation between 3ba and 4ba followed by the TS calculation. TS2 at the RHF level involves 47.2 kcal/ mol of activation enthalpy, significantly greater than that of TSba. 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.[1] Therefore, the PM3 calculation for TS2 at the UHF level was performed and revealed that the activation enthalpy of TS2 is 14.45 kcal/mol. 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 distances are 2.384 Å and 3.170 Å, respectively. The heat of formation of 4ba was calculated to be -40.37 kcal/mol, indicating that the [1,5]-sigmatropic rearrangement from 3ba to 4ba readily proceeds with 35.25 kcal/mol of stabilization.

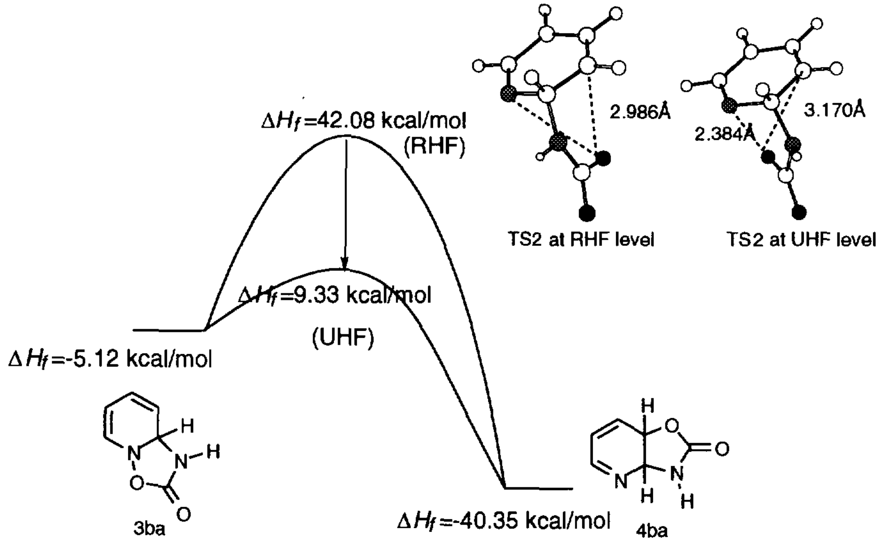


Figure 5 1,5-Sigmatropic rearrangement of 3ba to 4ba.

Conclusion The PM3 calculations for the present reaction revealed that the bond formation between the oxygen atom of 1b and the isocyanate carbon is significantly advanced than the other and the calculated transition structure bears a zwitterionic character. The reaction mechanism of pyridine *N*-oxides with various dipolarophiles varies from concerted to stepwise manner with the change of nature of the dipolarophiles and the polarity of the solvent used. The calculation results in this work do not interpret the small dependence of the reaction rate upon the solvent ionizing power. Therefore, we are now preparing a molecular orbital study including solvent effect and the results will be published separately.

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14. The detailed calculation results are available from the authors upon request.

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