1,3-DIPOLAR CYCLOADDITIONS OF N,α-DIPHENYLNITRONE TO THE 4,5-POSITIONS OF 1H-AZEPINE AND 1H-1,2-DIAZEPINE DERIVATIVES: FORMATION OF ENDO- AND EXO-TYPE CYCLOADDUCTS AND COMPUTER-ASSISTED LINE SHAPE SIMULATION OF THE NMR SPECTRA OF THE ADDUCTS

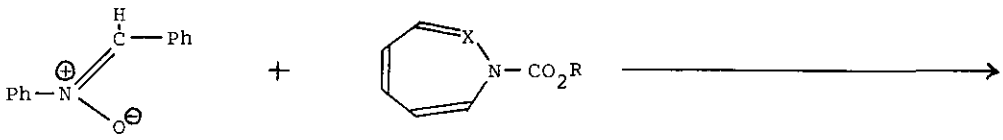
Katsuhiro Saito,* Akihiro Yoshino, and Kensuke Takahashi
Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466, Japan

Abstract —— Reaction of 1-carbomethoxy-1H-azepine with N,α-diphenylnitrone afforded two stereochemical isomers in almost the same ratio. The analysis of the nmr spectra of the cycloadducts were confirmed by good coincidence of the spectra to those obtained by computer assisted line shape simulation. The analogous result was obtained in the reaction using 1-carboethoxy-1H-1,2-diazepine. The reaction is considered to proceed through concerted [4+2]-type 1,3-dipolar cycloadditions of the nitrone to the 4,5-positions of the azepine or diazepine to give endo- and exo-type adducts because of the absence of stabilization effects by secondary orbital interactions in the transition states.

Cycloadditions of azepine and diazepine derivatives have attracted much attention of chemists from the viewpoint of synthetic utility and elucidation of the electronic natures of azepines and diazepines.[1] While the cycloadditions of azepines and diazepines with olefinic compounds of 2π- or 4π-components have been studied extensively to clarify that the azepines can react as 2π-, 4π-, and 6π-components and diazepines can react as 2π- and 4π-components, only a little has been elucidated concerning the 1,3-dipolar additions.[2,3]
1,3-Dipolar additions are known to be one of powerful methods to synthesize heterocyclic compounds and many kinds of reactions have been developed.[4] Nitrones are one of 1,3-dipolar reagents and their reactions with five membered heterocyclic compounds have been researched increasingly.[5] However, we are

unaware of any examples of the reactions of seven-membered heterocycles such as azepines or diazepines with nitrones. As a series of our research on the reactivities of azepines and diazepines,[3,6] we studied the reactions of 1H-azepine and 1H-1,2-diazepine derivatives with N,α-diphenylnitrone to obtain [4+2]-type cycloadducts via the reactions at the 4,5-positions of the azepine and diazepine. Here the results will be discussed.

1-Carbomethoxy-1H-azepine (1) was reacted with 1.5 equimolar amounts of N,α-diphenylnitrone (2) in refluxing toluene for 10 h. Chromatographic separation and purification of the reaction mixture on silica gel afforded products (3) and (4) in almost 1:1 ratio in the total yield of 48%. The similar reaction with 1-carboethoxy-1H-1,2-diazepine (5) gave the corresponding adducts (6) and (7) again in almost 1:1 ratio in 53% of the total yield. No interconversions between the products were observed under the reaction conditions.



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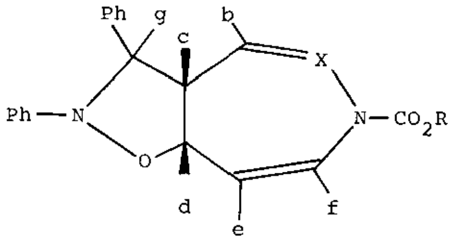
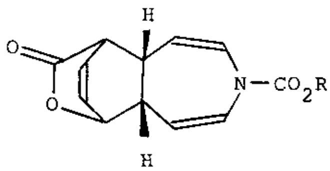
1: X=CH, R=Me
2: X=N, R=Et



3, 4: X=CH_a, R=Me
6, 7: X=N, R=Et



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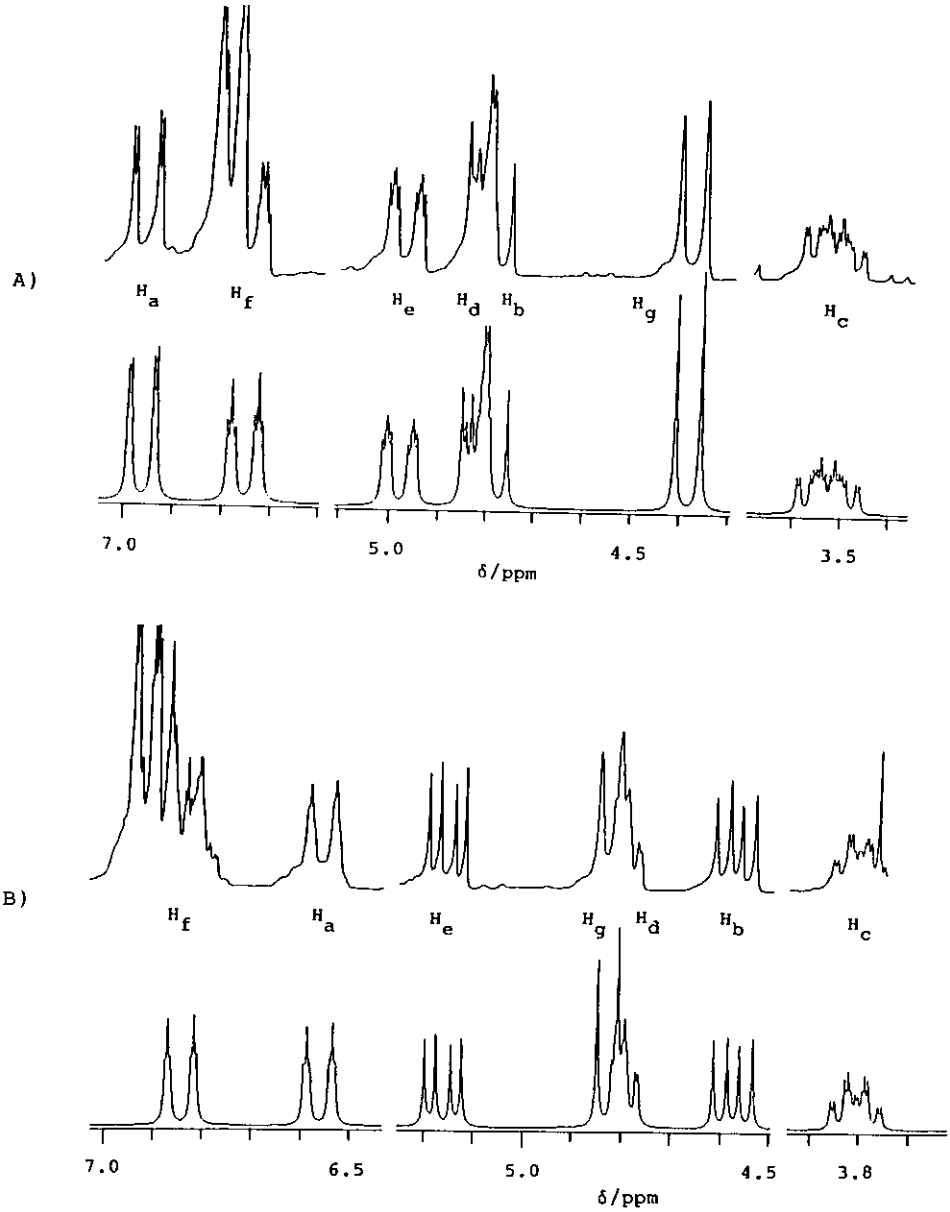
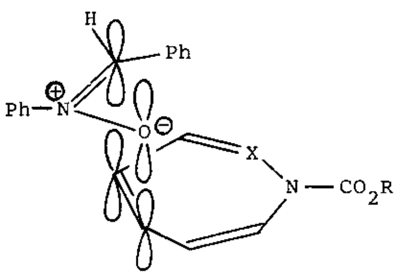
The structures of 3 and 4 were deduced on the basis of their spectral, especially nmr spectral properties as follows:[7] The molecular ion peaks in the mass spectra showed that these products are 1:1 adducts of 1 with 2. The arrangements of the protons (H_a-H_g) were decided using the decoupling technique of ^1H nmr spectra. The cis-configurations of H_c and H_d in both 3 and 4 were supported by the good coincidence of the coupling constant values between these protons to that of the corresponding values of the adduct (8) of azepine and α-pyrone.[3,8]



The observed (upper ones) and the simulated (lower ones) ^{1}H nmr spectra of 3 (A) and 4 (B).

The coupling constant values between the protons except those of the aromatic protons in the ^1H nmr spectra were measured precisely and confirmed by the coincidence with the simulated ones as shown in the figure.[9] The structures of 6 and 7 were also deduced from their spectral properties and the resemblance of them to those of 3 and 4. However, the small differences in the coupling constants J_{cg} between 3 and 4, and 6 and 7 make it hard to decide the full stereochemistries of these compounds.



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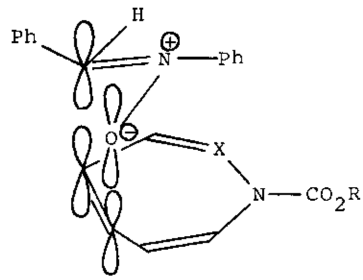

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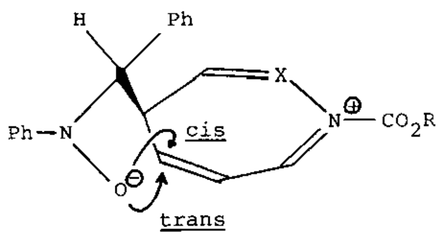
Transition states for concerted [4+2]-type cycloaddition mechanism



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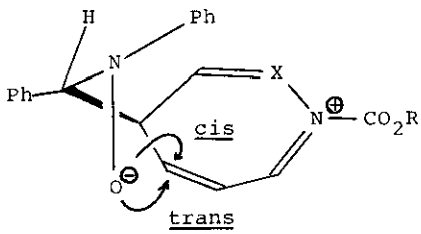

12

Transition states for two step cycloaddition mechanism

Two kinds of paths can be proposed for the reaction as shown in the figure. One is a concerted [$4\pi+2\pi$]-type cycloaddition process through the exo- and endo-type transition states (9) and (10), respectively. The absences of the stabilization effects by the secondary orbital interactions[10] and remarkable steric repulsions both in 9 and 10 allows the formation of the both types of the adducts in almost equal yields. The another path is a two step addition mechanism through ionic intermediates (**11**) and (**12**), each of which can also produce the exo- and endo-adducts, respectively. However, considering that the configurations between H_c and H_d are cis for all of the cycloadducts and that both cis- and trans-addition can proceed through the ionic intermediates (**11**) and (**12**), the concerted [$4\pi+2\pi$]-type cycloaddition process seems to be more plausible.

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7. The characterization data of the products are as follows:

   3: Mass m/z (rel intensity): 348 (M^+, 10), 332 (5), 195 (7), 182 (100). Ir (oil): 3030, 2980, 1720, 1600 cm^{-1}. ^1H Nmr ($CDCl_3$) δ ppm: 6.97 (dd, H_a), 4.80 (m, H_b), 3.53 (m, H_c), 4.81 (m, H_d), 4.98 (ddd, H_e), 6.76 (ddd, H_f), 4.39 (d, H_g), 3.78 (s, 3H, CH_3). Coupling constants in Hz: J_{ab}=10.2, J_{af}=1.5, J_{bc}=8.2, J_{cd}=5.5, J_{ce}=1.5, J_{cg}=10.3, J_{de}=2.4, J_{df}=2.0, H_{ef}=10.9.

4: Mass m/z (rel intensity): 348 (M^+, 33), 240 (24), 180 (65), 151 (100). Ir (oil): 3030, 2980, 1723, 1600 cm^{-1}. ^1H Nmr ($CDCl_3$) δ ppm: 6.56 (ddd, H_a), 4.57 (dd, H_b), 3.80 (m, H_c), 4.79 (ddd, H_d), 5.16 (dd, H_e), 6.84 (ddd, H_f), 4.82 (d, H_g), 3.69 (s, 3H, CH_3). Coupling constants in Hz: J_{ab}=10.3, J_{ac}=1.6, J_{af}=1.3, J_{bc}=5.5, J_{cd}=5.4, J_{cg}=8.2, J_{de}=4.4, J_{df}=1.3, J_{ef}=10.5.

6: Mass m/z (rel intensity): 363 (M^+, 17), 255 (100), 197 (10), 182 (54). Ir (oil): 3040, 1970. 1723, 1600 cm^{-1}. ^1H Nmr ($CDCl_3$) δ ppm: 7.01 (d, H_b), 3.81 (m, H_c), 4.82 (ddd, H_d), 5.08 (ddd, H_e), 7.06 (dd, H_f), 4.72 (d, H_g), 1.37 (t, 3H, CH_3, J=7.2), 4.37 (q, 2H, CH_2, J=7.2). Coupling constants in Hz: J_{bc}=5.9, J_{cd}=6.0, J_{ce}=1.1, J_{cg}=9.0, J_{de}=2.8, J_{df}=1.3, J_{ef}=10.8.

7: Mass m/z (rel intensity): 363 (M^+, 14), 255 (100), 197 (42), 182 (38). Ir (oil): 3030, 2970, 1720, 1650 cm^{-1}. ^1H Nmr ($CDCl_3$) δ ppm: 7.10 (d, H_b), 3.89 (m, H_c), 4.87 (ddd, H_d), 5.19 (ddd, H_e), 7.17 (dd, H_f), 4.94 (d, H_g), 1.31 (t, 3H, CH_3, J=7.1), 4.30 (q, 2H, CH_2, J=7.1). Coupling constants in Hz: J_{bc}=3.4, J_{cd}=3.8, J_{ce}=0, J_{cg}=6.3, J_{de}=4.6, J_{df}=1.6, J_{ef}=10.0.

8. The formation of the endo- and exo-type cycloadducts has been reported in the reaction of **2** with N-phenylmaleimide.
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9. The computer-assisted line shape simulations were run on a Sharp personal computer MZ-80B with a modified LAOCOON III program. The spectra width is 2,000 Hz and the number of the data points are 32,000. Thus the digital resolution is calculated to be 0.125 Hz/point.
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