AZA-AZULANONES AS 4π ELECTRON COMPONENTS IN [4+2] CYCLOADDITION REACTIONS WITH A CYCLIC C_7H_6-SYSTEM

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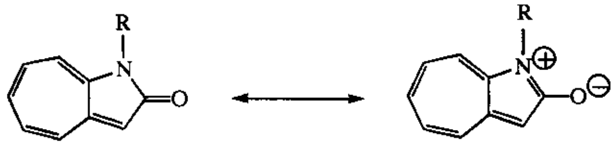
Abstract——Reactions of a cyclic C_7H_6-system, a tautomer of 1,2,-4,6-cycloheptatetraene and 2,4,6-cycloheptatrienylidene, with *N*-(*p*-substituted phenyl)aza-azulanones afforded two types of [4+2] type cycloadducts, where the seven-membered ring moieties of the aza-azulanones played 4 π electrons parts. The reactions were investigated with terms of MO calculations.

Owing to existances of lone pair electrons on the nitrogen atom, aza-azulanones (1) can be considered to be both azulene derivatives (1') and heptafulvene derivatives possessing carbonyl groups at 8-position.[1] The low field resonances of the seven-membered ring protons of 1 in ^1H NMR spectra, compairirng to olefinic protons of cycloheptatrienes, show that the seven-membered ring part possesses positive charge. Azulene derivatives are well known to be typical members of nonbenzenoid aromatic compounds[2] and to resist toward cycloaddition reactions. Heptafulvenes are also members of nonbenzenoid aromatics, but they some times react through cycloadditions.[3,4] While the reaction modes of azulenes and heptafulvenes have been investigated in detail,[1] only a little has been made clear concerning the reactivities, especially for cycloaddition reactions of aza-azulanones.

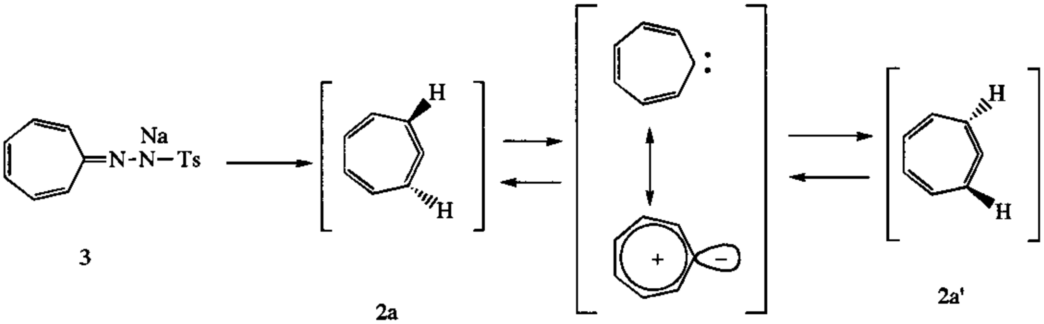
Cyclic C_7H_6-system (2) is known to be a tautomeric mixture of an allene, 1,2,4,6-cycloheptatetraene (2a) and a carbene, 2,4,6-cycloheptatrienylidene (2b), where 2b exists as a transition state of the isomerization between the enantiomeric isomers (2a and 2a'). Because of a contribution of a 6 π electrons aromatic structure, 2b behaves as a nucleophilic singlet carbene to give three-membered cyclic adducts through stereoselective additions. On the other hand 2a plays a role of 2π electrons component in several [2+4] type addition reactions with anthracenes, tropones, and heptafulvenes.[5,6]

The facts that only a small number of documents have been seen on reactions of the C_7H_6-system (2) with heterocyclic compounds[6] and that little is known concerning the reactivities of aza-azulanones (1) prompted us to study the reaction of 1 with 2. Here the results will be discussed.



1a: R= *p*-ClC_6H_4
b: R= *p*-MeC_6H_4

1'

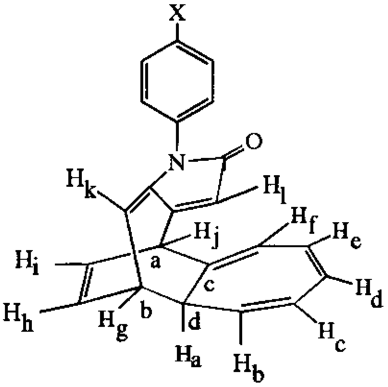


3

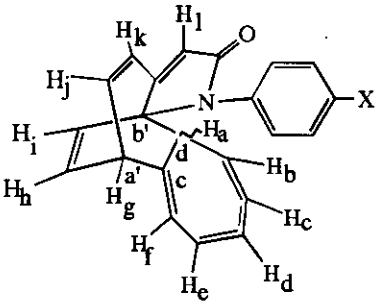
2a

2b

2a'



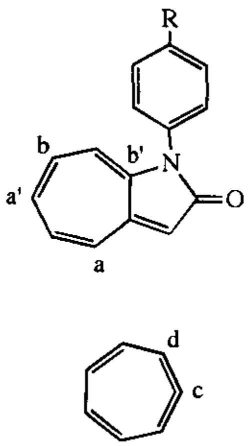
4 a: X= Cl
b: X= Me

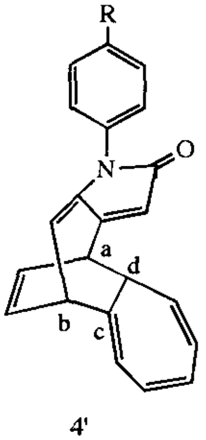


5 a: X= Cl
b: X=Me

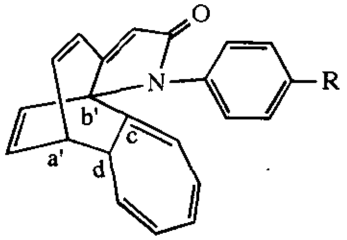
Tropone tosylhydrazone sodium salt (3) was heated at 120°C with two mole equivalent of *N*-(*p*-chlorophenyl)-1-aza-azulanone (1a) in anhydrous diglyme for 15 min to give a complicated mixtures of tarry materials. Repeated separation and purificaion of the reaction mixture with thin-layer chromatography gave two kinds of viscous tarry cycloaddition products (4a) and (5a) in 12 and 7% yields, respectively. The analogous reaction of 3 with *N*-(*p*-methylphenyl)-1-aza-azulanone (1b) gave resinous tars 4b and 5b in 12 and 13 % yields, respectively.

The structures of the adducts were deduced on the basis of their spectral properties as follows. The molecular ion peaks in MS spectra demonstrated that all these products were 1:1 adducts between 1 and 2. The absorptions due to the carbonyl streching in IR spectra showed the existances of the carbonyl groups analogous to those of the starting aza-azulanones. ^{1}H NMR spectra well taught the existances of continued six protons, which were assigned to be the protons of the cycloheptatriene moieties on the basis of their particular splitting pattarns, especailly those of H_a, H_b, and H_c.[4,6,7] The coupling constants between H_a and H_g in 4 showed that the addition occurred in an *exo*- mode in 4.[8] The absence of coupling constants between H_a and H_g in 5 showed that these two protons were located apart from each other suggesting the structure of 5 to be shown in the Figure, and this absence made it impossible to determine the full stereochemistry of 5. Thus it is not clear whether the addition proceeded *via* an *exo*- or an *endo*-mode. The structures were finally confirmed by good resemblances of the NMR spectra of the products to the analogous compounds.[4,5,7,8]



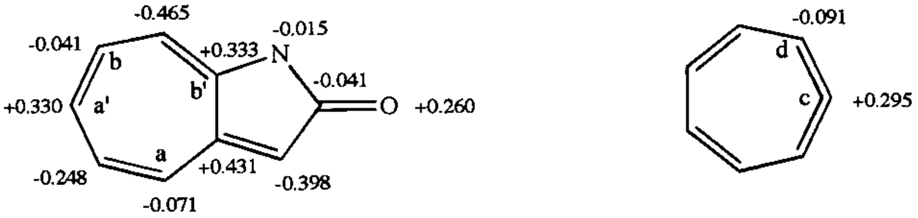


4'



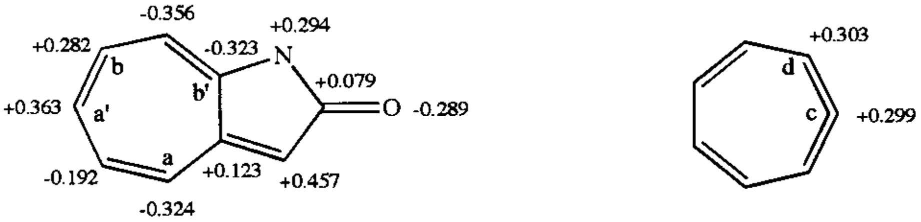
5'

The reaction can be classified to be a [4+2] type cycloaddition reaction where the seven-membered ring of aza-azulanone played a 4π electron part and the allenic bond of the C_7H_6 system played a 2π electron part. There are two sets of 4π electron components in the aza-azulanone's seven-membered ring (a-b and a'-b'). Signs a, b and a', b' are assigned to each reaction points as shown in the Figure. Signs c and d are assigned to the reaction points of the allenic bond of 1,2,4,6-cycloheptatetraene (2a). A combination of the reaction points a-c, b-d affords 4 and a combination a'-c, b'-d produces 5. The another combinations are also considered to be possible and a combination a-d, b-c gives 4' and a combination a'-d, b'-c affords 5'. However, the experiments showed that only the combinations a-c, b-d and a'-c, b'-d were realized.



LUMO -1.047 eV

LUMO -0.147 eV



LUMO -8.423 eV

HOMO -8.736 eV

Orbital Energies and Coefficients

Molecular orbital calculations were carried out on 1 and 2.[9] The energies of the HOMO and the LUMO were −8.423 and −1.047 eV for 1, respectively, and −8.736 and −0.147 eVp for 2, respectively. The coefficients of the HOMO and the LUMO of 1 and 2 on each carbon, nitrogen, and oxygen atoms were as shown in the Figure. The energy gap (ΔE=7.689 eV) between the LUMO of 1 and the HOMO of 2 is smaller than that (ΔE=8.276 eV) between the HOMO of 1 and the LUMO of 2 suggesting that the reaction is controlled by the interaction between the LUMO of 1 and the HOMO of 2.

The regioselectivity is known to be explained by magnitudes of squares of summations of products of molecular orbital coefficients of the reaction sites $(\Sigma \phi_r \phi_s)^2$. The magnitude were calculated for the cases of 4, 4', 5, and 5' to be 2.1229 X 10^{-3}, 1.1405 X 10^{-3}, 3.98278 X 10^{-2}, and 3.98230 X 10^{-2}, respectively. There is a considerable difference between the magnitudes for the cases of 4 and 4', explaining the preferential formation of 4. There is also a difference advantageous for 5 in the case of 5 and 5'. However, this difference seems to be too small to sufficiently explain the sole formation of 5.[10,11]

The preferential formation of the *exo*-isomer in the case of 4 is considered as follows. Because of the Mobius type π-system of 2, the secondary orbital interactions, which stabilizes the *endo*-transition state is considered to be too weak to determine the reaction mode. Thus, the sterically favored *exo* addition dominated the reaction.[13]

EXPERIMENTS

IR spectra were taken with a JASCO FT/IR 5300 spectrophotometer. MS spectra were measured with a Hitachi M–2000 spectrometer. NMR spectra were measured with Hitachi R–90 or Varian XL–200 spectrometer with tetramethylsilane as an internal standard. Wakogel C–200 and Wakogel B5F were used for column and thin–layer chromatography, respectively. Only a typical reaction is mentioned below.

Reaction of 2 with 1a. A mixture of 3 (1.48 g, 5.0 mmol) and 1a (4.70 g, 20 mmol) in anhydrous diglyme (15 mL) was heated at 126°C for 7 min. After filtration the filtrate was diluted with ether, washed with water, and dried over anhydrous sodium sulfate. Evaporaion of the solvent gave a black tarry material, which was chromatographed on silica gel to give a broun tarry material with an eluent of n–hexane–ethyl acetate (1:1). The tar was further separated with thin–layer chromatography on silica gel using n–hexane–ethyl acetate (3:2) as a developing solvent to give 4a (200 mg, 12 %, R_f=0.61)) and 5a (115 mg, 7 %, R_f=0.34)

4a: HRMS m/z: 345.0931. Calcd for $C_{22}H_{16}NOCl$ m/z: 345.0916. MS m/z (rel intensity): 345 (M^+, 100), 316 (41), 282 (23), 268 (15), 228 (22), 191 (35), 181 (38), 151 (20). IR (oil): 3019, 1696, 1495, 1092 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 2.61 (dd, H_a), 3.64 (ddd, H_g), 4.38 (d, H_j), 4.94 (dd, H_b), 5.98 (s, H_l), 6.00 (d, H_k), 6.08 (d, H_f), 6.13 (dd, H_c), 6.42 (dd, H_i), 6.57 (dd, H_h), 6.36–6.60 (m, 2H, H_d, H_e), 7.14–7.45 (m, 4H, aromatic protons). Coupling constants in Hz: J_{ab}=4.3, J_{ag}=5.2, J_{bc}=9.4, J_{cd}=4.8, J_{ef}=4.6, J_{gh}=7.1, J_{gk}=7.7, J_{hi}=8.3, J_{ij}=6.8. ^{13}C NMR ($CDCl_3$) δ ppm: 37.2, 44.6, 47.2, 115.4, 115.6, 121.3, 126.4, 126.5, 128.8, 129.3, 129.4, 129.7, 129.8, 131.0, 132.7, 133.7, 136.8, 149.6, 149.7, 168.2.

5a: HRMS m/z: 345.0933. Calcd for $C_{22}H_{16}NOCl$ m/z: 345.0916. MS m/z (rel intensity): 345 (M^+, 20), 316 (5), 281 (2), 223 (4), 167 (20). IR (oil): 3019, 1690, 1495, 1094, 735 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 2.61 (d, H_a), 3.80 (dd, H_g), 4.83 (dd, H_b), 6.04 (d, H_f), 6.07 (dd, H_c), 6.15 (s, H_l), 6.25 (d, H_k), 6.34 (d, H_i), 6.39 (dd, H_e), 6.41 (dd, H_d), 6.48 (dd, H_h), 6.57 (dd, H_j), 7.26–7.38 (m, 4H, aromatic protons). Coupling constants in Hz: J_{ab}=4.8, J_{bc}=9.9, J_{cd}=5.6, J_{de}=10.8, J_{ef}=4.6, J_{gh}=7.0, J_{gj}=8.0, J_{hi}=8.3, J_{jk}=10.1. ^{13}C NMR ($CDCl_3$) δ ppm: 42.4, 44.9, 72.1, 119.5, 120.0, 120.9, 121.5, 126.6, 127.6, 129.4, 129.5, 130.5, 131.0, 132.5, 132.7, 134.3, 137.0, 140.1, 154.8, 171.3.

4b: HRMS m/z: 325.1449, Calcd for $C_{23}H_{19}NO$ m/z: 325.1465. MS m/z (rel intensity): 325 (M^+, 100), 296 (62), 282 (42), 234 (52), 191 (68), 178 (55), 165 (53). IR (oil): 3020, 2950, 1690, 1490, 740 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 2.38 (s, 3H, Me), 2.60 (m, H_a), 3.57 (m, H_g), 4.35 (d, H_j), 4.94 (dd, H_b), 5.96 (m, H_k), 5.98 (s, H_l), 6.08 (m, H_f), 6.16 (m, H_c), 6.46 (m, H_i), 6.58 (m, H_h), 6.35–6.60 (m, H_d, H_e), 7.08–7.33 (m, 4H, aromatic protons). Coupling constants in Hz: J_{ab}=4.1, J_{bc}=10.8, J_{cd}=5.1, J_{gh}=7.8, J_{hi}=8.4, J_{ij}=6.2. ^{13}C NMR ($CDCl_3$) δ ppm: 20.9, 37.2, 44.6, 47.3, 115.3, 115.5, 121.3, 126.4, 126.5, 128.7, 129.3, 129.6, 129.7, 129.8, 130.8, 132.8, 137.1, 137.3, 149.4, 149.6, 168.3.

5b: mp 181–182°C. HRMS m/z: 325.1441. Calcd for $C_{23}H_{19}NO$ m/z: 325.1455. MS m/z (rel intensity): 325 (M^+, 91), 296 (65), 282 (55), 234 (64), 191 (100), 178 (80), 165 (66). IR (KBr): 3020, 1690, 1495, 745 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ ppm: 2.32 (s, 3H, Me), 2.60 (m, H_a), 3.75 (m, H_g), 4.90 (dd, H_b), 6.03 (d, H_f), 6.11 (dd, H_c), 6.16 (s, H_l), 6.25 (d, H_k), 6.36 (d, H_i), 6.59 (dd, H_j), 6.35–6.49 (m, 3H, H_d, H_e, H_h), 7.08–7.24 (m, 4H, aromatic protons). Coupling constants in Hz: J_{ab}=5.0, J_{bc}=10.0, J_{cd}=4.2, J_{ef}=5.0, J_{gh}=7.5, J_{gj}=7.5, J_{hi}=10.9, J_{jk}=10.0. ^{13}C NMR ($CDCl_3$) δ ppm: 20.9, 42.4, 44.9, 72.0, 119.8, 119.9, 121.0, 121.5, 126.3, 127.2, 129.3, 129.9, 130.3, 131,0, 132.0, 132.7, 137.2, 137.4, 139.7, 154.5, 171.5. Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 85.15; H, 5.93; N, 4.08.

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9. The PM3 MO calculations on 1 and 2 were carried out using an NEC PC-9801 RA 32-bit personal computer with "PASOCON MOPAC/386" program, which is based on the MOPAC (Ver. 5.0, QCPA No. 455) by Toray System Center.

10. The quotient of square of summation of products of orbital coefficients of the reaction points divided by the energy difference between the HOMO and the LUMO ($(\Sigma \phi_r \phi_s)^2/\Delta E$) is known to be usefull to explain the regioselectivity of reactions.[8,11] The results of the calculations concerning the present reactions were summerized in the following Table.

	Combinations of Frontier Orbitals	
	HOMO of 1 and LUMO of 2	LUMO of 1 and HOMO of 2
4	1.764×10^{-3}	1.475×10^{-4}
4'	1.530×10^{-3}	1.481×10^{-4}
5	2.253×10^{-3}	5.197×10^{-3}
5'	1.988×10^{-3}	5.197×10^{-3}

The preferential formation of 4 can be explained by the largest value (1.764×10^{-3}) calculated with the HOMO of 1 and the LUMO of 2. However, both 5 and 5' have the same value (5.197×10^{-3}) calculated with the LUMO of 1 and the HOMO of 2.

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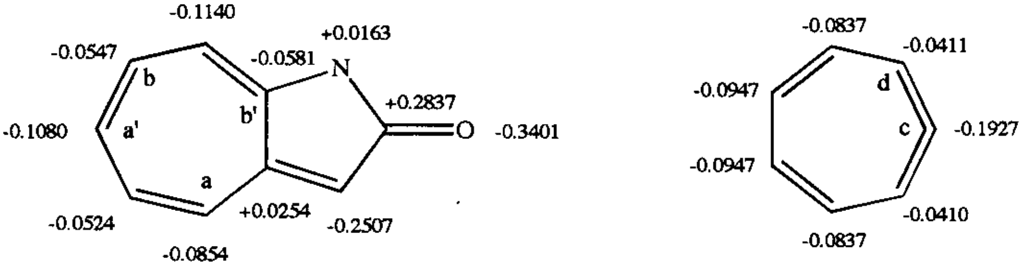
12. Net atomic charges of aza-azulanone and cycloheptatetraene were calculated as shown in the following Figure.[9] In the allenic bond, the sp-carbon assigned "c" is more negative than the sp^2 carbon "d". In the two sets of the 4π electrons components, "a" and "a'" are more negative than "b" and "b'", respectively. Thus, in order to form the products (4) and (5), the more negative carbon "c" must attack the more negative carbons "a" and "a'", respectively. This is unreasonable. Thus net atomic charges can not explain the reaction rationally.



Net Atomic Charges on Atoms Except Hydrogen Atoms

13. A carbene addition process, where 2b attacked 1 to form suitable three-membered ring intermediates which then rearranged to 4 and 5, can be proposed to be a possible mechanism. However, considering the nucleophilic character of the carbene (2b),[5,6] the negative net atomic charges on the carbon atoms of the seven-membered ring moieties of 1 seem to reject this possibility.

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