[Chem. Pharm. Bull. 30(6)1980—1985(1982)]

Molecular Orbital Calculations for Azaquinonoid-Ketene and Analysis of the Intramolecular Cycloaddition with the *N*,*N*-Dimethylanilino Group

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(Received October 26, 1981)

Intramolecular cycloaddition of azaquinonoid-ketene (**4**) generated from benzotriazinone derivative to *N*,*N*-dimethylanilino group afforded "unrearranged" acridone in sharp contrast to a carbon analog series (**1**).

Molecular orbital calculations and conformational studies using a model compound did not show much difference between azaquinonoid-ketene (**11**) and quinonoid-ketene (**12**), indicating similar propensity toward the $[{}_{\pi}4_{a}+{}_{\pi}2_{a}]$ pathway of **4** in terms of FMO theory.

These results led us to suggest the involvement of a concealed process in the transformation of **4** to "unrearranged" acridone (**9**), *i.e.*, a $[{}_{\pi}4_{a}+{}_{\pi}2_{a}]$ cycloaddition at the initial stage, by analogy with the carbon analog (**1**).

Keywords——$[{}_{\pi}4_{a}+{}_{\pi}2_{a}]$ cycloaddition; 6π electrocyclization; antarafacial role of aromatic ring; concealed process of cycloaddition; molecular orbital of azaquinonoid-ketene; conformational analysis; CNDO/2 calculation

As an extension of the recent finding that the quinonoid-ketene (**1**) underwent a facile regiospecific $[{}_{\pi}4_{a}+{}_{\pi}2_{a}]$ intramolecular cycloaddition with the *N*,*N*-dimethylanilino group to result in a novel formation of norcaradiene (**2**) followed by ring-opening to an azulenone derivative (**3**),[1] one might formally expect that an azaazulenone derivative (**6**) could be formed by intramolecular cycloaddition from azaquinonoid-ketenes (*N*-aryl iminoketenes) (**4**), several members of which have already been shown to yield acridone derivatives.[2] None of the compounds so far studied, however, contains an aromatic ring bearing powerful electron-donating substituents.

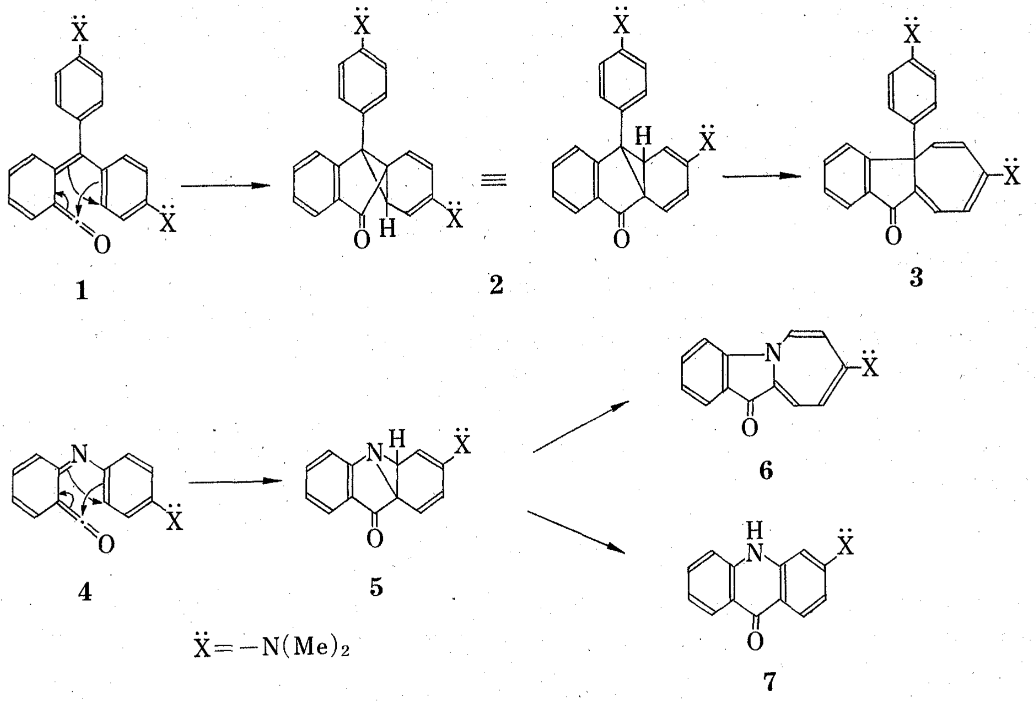


Chart 1

The lack of information concerning the effect of a powerful electron-donating substituent such as a dimethylamino group prompted us to examine the intramolecular cycloaddition of azaquinonoid-ketene (**4**) to the *N*,*N*-dimethylanilino group, and we found no evidence for the formation of the azaazulenone (**6**) or "rearranged" acridone derivative (**7**), in contrast to the results for the quinonoid-ketene series.

In view of the medicinal importance and usefulness of the acridone derivatives, it appeared worthwhile to investigate the reason for this regiochemical ineffectiveness of an electron-donating substituent to provide a basis for future experimental designs.

Our approach to the problem was to evaluate the effect of replacement of a carbon atom by a nitrogen atom upon the regiochemistry by means of molecular orbital calculation.

In the present paper, we compare the molecular orbitals of azaquinonoid-ketene and quinonoid-ketene and discuss the mechanism of cycloaddition of azaquinonoid-ketene to the dimethylanilino group; though the latter is apparently a 6π electrocyclization, the reaction may in fact occur initially through a process analogous to quinonoid-ketene; $[{}_{\pi}4_{a}+{}_{\pi}2_{a}]$ cycloaddition.

Results

It has been well documented that irradiation of benzotriazinone derivatives eliminates molecular nitrogen to form a benzoazetinone or the valence isomeric azaquinonoid-ketene, followed by a ring closure to acridone derivatives.[2] Thus, a nitrogen-purged methylene chloride solution of 3-(*p*-dimethylaminophenyl)-4(3*H*)-benzotriazinone (**8**) was irradiated through a Pyrex filter with a 400W high pressure mercury lamp. On chromatographic separation of the resulting solution, 2-dimethylamino acridone (**9**), but not the 3-isomer (**7**) was obtained as a major product (75% yield). The structure of **9** follows from the spectral properties and an independent synthesis from *o*-[*N*-(*p*-dimethylaminophenyl)-amino]-benzoic acid (**10**).[3] Thus, the replacement of bridgehead carbon in **1** by nitrogen as in **4** had a marked influence upon the regiochemistry (Chart 2).

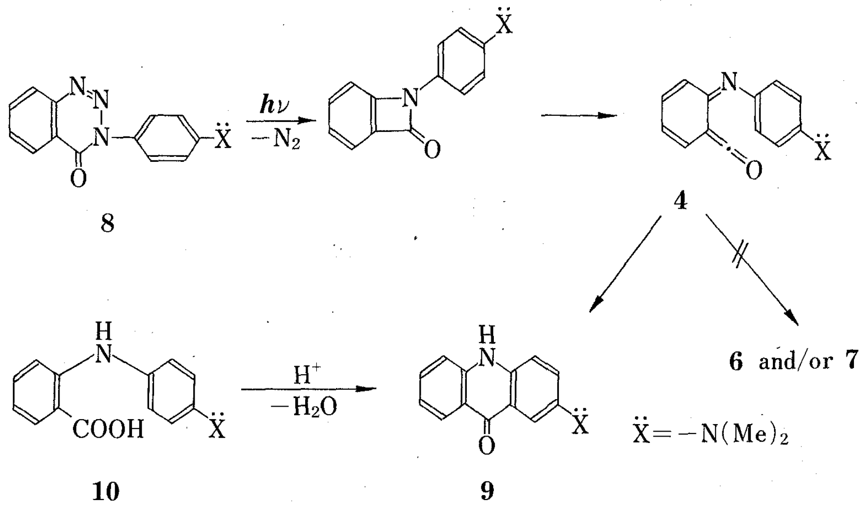


Chart 2

The method used for analysis of this intramolecular cycloaddition is the same as for the carbon analog, *i.e.*, separation of the molecule into two components, the azaquinonoid-ketene as a 4π system and dimethylaniline as a 2π system.[4] Thus, we carried out molecular orbital calculation of azaquinonoid-ketene (**11**), using the CNDO/2 approximation with Pople's original standard parameterization.[5] The frontier molecular orbital energies and coefficients of aza-

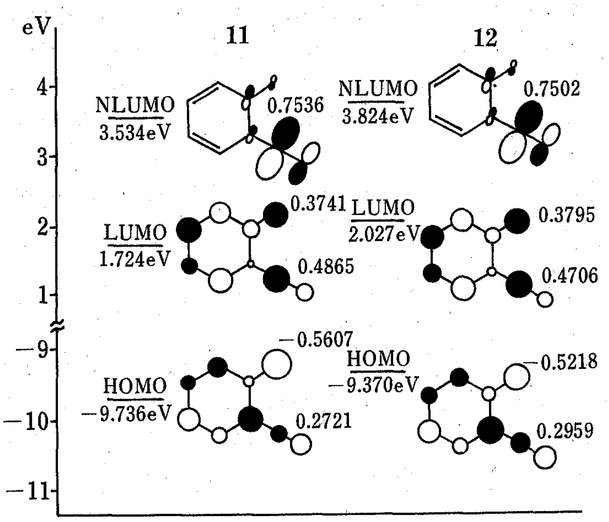
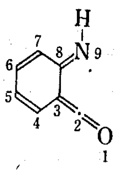


Fig. 1. Frontier Molecular Orbital Coefficients and Energies of **11** and **12** by CNDO/2 Approximation



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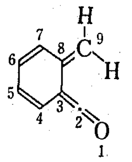

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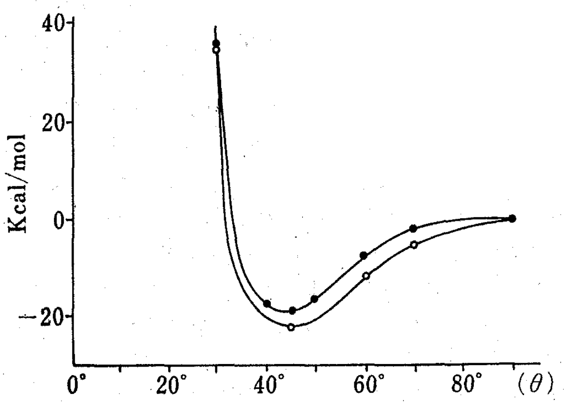


Fig. 2. Relative Total Energies of **13** and **14** during Rotation about the N_5–C_6 Bond and C_5–C_6 Bond

"Zero" energy corresponds to the 90° conformer.
13: —○—, **14**: —●—.

13 and **14**

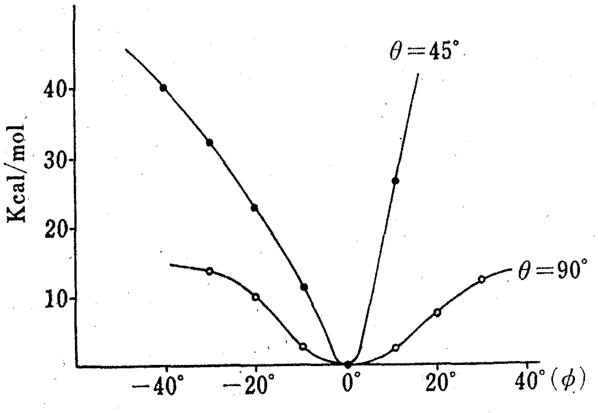
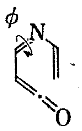


Fig. 3. Relative Total Energy of **13** during Twisting about the C_4–N_5 Bond

"Zero" energy corresponds to 45° (θ) and 90° (θ) rotational conformers.



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quinonoid-ketene (**11**) are shown in Figure 1, together with those of quinonoid-ketene (**12**) for comparison.

It is immediately seen that the distributions of frontier molecular orbital coefficients are similar.

To assess the conformational interaction between 4π-component and 2π-component, the total energies of *cis-cis*-vinyl imino-ketene (**13**) as a model molecule were also evaluated by the CNDO/2 method as a function of C_5–C_6 bond rotation without reoptimization of the rest of the molecule, *i.e.* "rigid rotation."

A plot of the relative total energy is shown in Figure 2, together with that of *cis-cis*-diene ketene (**14**) for comparison. Such conformational analysis yielded an energy minimum for 45° conformation in both cases.

Furthermore, twisting of the C=N bond from the ketene plane in the 45° and 90° conformers (**13**), investigated in order to evaluate the steric contribution, resulted in a sharp energy increase as shown in Figure 3.

It has been already shown in various cases that the usefulness of the CNDO/2 method in predicting molecular conformation by "rigid rotation" is limited to aliphatic molecules or polyatomic systems with well localized bonds, and calculations on conjugated systems by the CNDO/2 method fail to predict the molecular conformation, giving a perpendicular conformer as a stable geometry[6] due to underestimation of both the bond length of the carbon-carbon single bond and the conjugation effect.[7] Therefore, it is clear that the geometry with out-of-plane deformation of **13** and **14** by 45° stems from a charge-transfer stabilization by three-center bonding of the central carbon atom of the ketene moiety with π-electrons of the 2π-component,[8] whereas the very high electron- and core-repulsive contributions, *i.e.* steric effects, are responsible for the steep energy increase upon rotation of the C_5–C_6 bond toward the plane conformer.

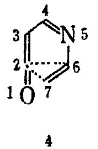
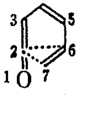
Discussion

It is now well established on the basis of theoretical analyses and experimental evidence that the propensity of ketene to undergo a thermally allowed antarafacial reaction is the result of the electrophilicity of the central carbon of the ketene induced by the in-plane π^*-orbital (LUMO for ketene).[10] We have shown previously[4] that the in-plane π^*-orbital is the NLUMO in **12**, in contrast to LUMO for the ketene and vinyl-ketene; however, the antarafacial pathway operated. It has also been shown,[4] that the LUMO of the quinonoid-ketene (**12**) and the HOMO of dimethylaniline have the smallest separation in energy, and therefore should yield the dominant stabilization in the transition state for the intramolecular cycloaddition of **1**, and the HOMO of dimethylaniline has the largest coefficient at the *para* position. A similar relationship for the molecular orbital energies was also obtained in the case of azaquinonoid-ketene (**11**).[11]

It is known that the aniline ring of benzylideneaniline is twisted out of the C–N=C-plane by 40—55° due to n–π conjugation, while stilbene is almost planar.[9] The azaquinonoid-ketene (**4**) also possesses a similar structural moiety and should have a preference for an antarafacial pathway in terms of an orthogonal approach of the relevant orbital between two components.

A comparison of the magnitude of atomic bond population between C_2–C_6 bond and C_2–C_7 bond calculated for the 45° conformers of (**13**) and (**14**) indicated that **13** might show a preference for an antarafacial pathway,[4,8] as shown in Table I.

TABLE I. Atomic Bond Population (M_{XY}) of Each 45° Rotational Conformer of **13** and **14**

	M_{26}	M_{27}	M_{27}/M_{26}
	0.0618	0.3427	5.5453
	0.0489	0.2950	6.0327

$$\Sigma_{XY}=\sum_{r}^{\text{on}X}\sum_{s}^{\text{on}Y}N_{r,s},\quad N_{r,s}=4\sum_{j}^{\text{occ}}C_r^jC_s^jS_{r,s}$$

Based on all the data thus obtained, there is no indication that azaquinonoid-ketene shows a preference for 6π electrocyclization. We, therefore, conclude that azaquinonoid-ketene (**4**) probably underwent a concealed process of cyclization with the *N*,*N*-dimethyl-

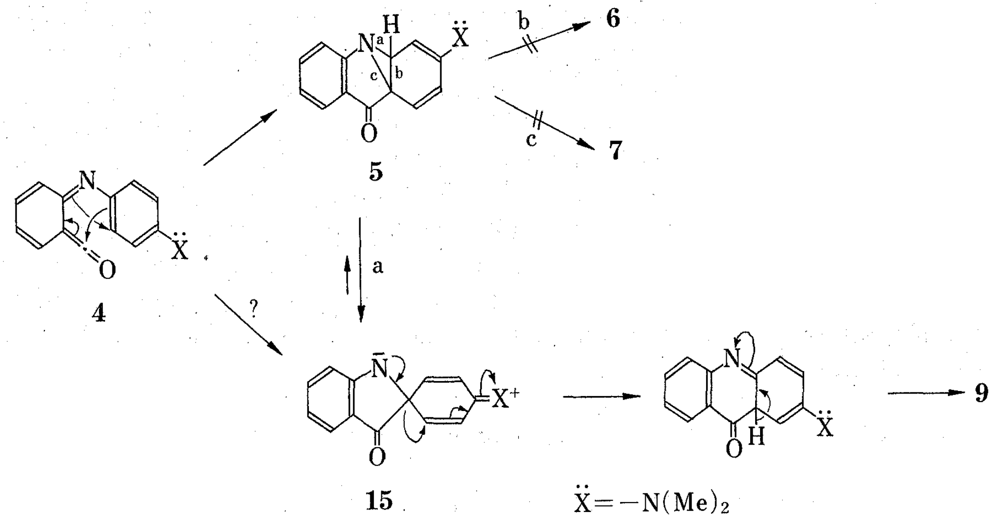


Chart 3

anilino group in an antarafacial fashion, *i.e.* a $[_{\pi}4_a+_{\pi}2_a]$ pathway to form azanorcaradiene (**5**), at an initial stage of the intramolecular cycloaddition. Thus, we propose the following sequence to yield "unrearranged" acridone (**9**) involving azanorcaradiene (**5**).

As shown in Chart 3, our rationalization involves an azanorcaradiene (**5**). In the initially formed azanorcaradiene (**5**), the bond *a* breaks readily than bond *b* or bond *c* due to the combined effects of an electron-donating substituent and replacement of a carbon atom by a nitrogen atom, and a spiro-intermediate (**15**) results, from which the "unrearranged" acridone (**9**) is formed as a sole product through 1,2-acyl shift followed by 1,3-hydrogen shift. Although the azanorcaradiene (**5**) may not be a discrete intermediate and the spiro-intermediate (**15**) may be formed directly, such regiochemistry is consistent with the molecular orbital consideration.

A spiro-intermediate such as **15** has been postulated in nitrene-induced rearrangements and cycloadditions starting from various precursors,12) and seems to be firmly established on the basis of the sufficient experimental data. It has also been shown that the spiro-intermediate in the cycloaddition of nitrogen-containing compounds undergoes 1,2-acyl shift exclusively.12)

Since interpretation and prediction of chemical reactions are often complicated by the blend of electronic, steric and other effects, the conclusion reached from the molecular orbital studies reported herein may be oversimplified. Nevertheless, it contributes to our understanding of the regiochemistry in two systems; azaquinonoid-ketene and quinonoid-ketene. It can be concluded that neither azaazulenone derivatives nor "rearranged" acridone derivatives may be obtainable through intramolecular cycloaddition of azaquinonoid-ketene derivatives.

Experimental

NMR spectra were obtained on a Hitachi R-20 spectrometer (60 MHz) with tetramethylsilane (TMS) as an internal standard. IR spectra were taken as KBr discs with a JASCO IRA-T spectrophotometer and were calibrated against polystyrene. UV spectra were measured in 100% ethanol with a Hitachi 323 spectrophotometer. Mass spectra were obtained at 70 eV with a JEOL JMS-D 300 spectrometer.

Calculations——All calculations were carried out on a FACOM M-200 computer at the Computation Center of Nagoya University. The CNDO/2 calculations were carried out with Pople's original standard parameterization.5) The plane geometries were assumed for the molecules (**11**) and (**12**), with all bond angles fixed at 120° except for 118° for $C_4C_3C_8$ ($=C_3C_8C_7$). The geometrical parameters were taken from the literature.13) When data were not available, standard bond lengths and bond angles were used; $r_{C-H}=1.08$, $r_{C-C}=1.46$, $r_{C-C}=1.33$, $r_{C_8=C_9}=1.31$, $r_{C=O}=1.16$, $r_{C-N}=1.31$ and $r_{N-N}=0.99$ Å.

3-(*p*-Dimethylaminophenyl)-4(3*H*)-benzotriazinone (8)——Aqueous sodium nitrite solution (20 ml) (1.95 g) was added dropwise to a cold solution of dilute hydrochloric acid (30 ml) containing anthranil-*p*-dimethylaminoanilide[14] (7.2 g), and the whole was stirred for 30 min at room temperature. The resulting solution was neutralized with aqueous ammonium hydroxide solution. The precipitated solid was collected and washed with water, then recrystallized from benzene to give **8** (4.4 g, 58.7%) as yellow needles, mp 146—147°C. *Anal.* Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.67; H, 5.16; N, 21.04. UV λ_{max} nm (ε): 256 (14900), 284 (8400), 311 (5400). IR cm^{-1}: $\nu_{C=O}$ 1680. MS *m/e*: 266 (M^+), 238 ($M^+ - N_2$, base). NMR ($CDCl_3$) δ: 3.02 (6H, s, *N*-methyl), 6.83 (2H, d, $J=9.0$ Hz, *N*-aromatic), 7.50 (2H, d, $J=9.0$ Hz, *N*-aromatic), 7.75—8.58 (4H m, aromatic).

Irradiation of 8——A solution containing **8** (500 mg) in dry methylene chloride (300 ml) was irradiated through a Pyrex filter with a 400 W high pressure mercury lamp under a nitrogen stream for 6 h. The resulting solution was concentrated under reduced pressure to give a brown solid, which was purified by column chromatography (neutral alumina) with methylene chloride at the eluent to give **9** (170 mg, 75.0%) mp 286—288°C as a major product. Compound (**9**) thus obtained was futher purified by recrystallization from ethanol to afford bright yellow needles, which were identical with an authentic sample (**9**),[15] prepared from *o*-[*N*-(*p*-dimethylaminophenyl)-amino]-benzoic acid (**10**).

References and Notes

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