CYCLOADDITIONS OF 1-SUBSTITUTED CIS- AND TRANS-2,3-DIPHENYLAZIRIDINES VIA AZOMETHINE YLIDES

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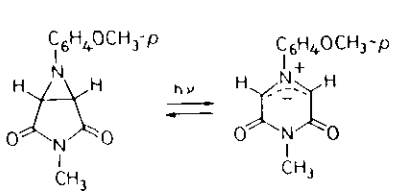
Dedicated to Tetsuji Kametani on the Occasion of His Retirement

Abstract - 1-Benzyl-cis- and -trans-2,3-diphenylaziridines combine at 110°C with olefinic dipolarophiles to produce pyrrolidine derivatives in high yields. Stereospecific conrotation for the ring opening of the aziridines to azomethine ylides was deduced from the structure of the cycloadducts. The rate constants of adduct formation with diethyl fumarate do not depend on the concentration of the dipolarophile. In contrast, ethyl cis- and trans-2,3-diphenylaziridine-1-carboxylate produce with dimethyl fumarate at 145° C the *same mixture of diastereomeric pyrrolidines both of which are derived from the exo,endo*-diphenyl substituted azomethine ylide.

The conrotatory thermal ring opening equilibrium of the aziridines cis-5 and trans-5 provided the first verification [1] of the Woodward-Hoffmann prediction for the electrocyclic process cyclopropyl anion ⇌ allyl anion.[2] An ensemble of kinetic methods established the free energy profiles of ring opening, cis,trans isomerization and ring closure for the aziridines 5 and 6.[3-6]



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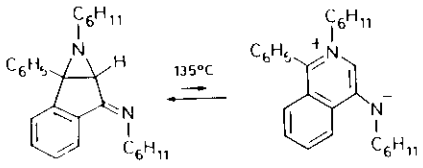
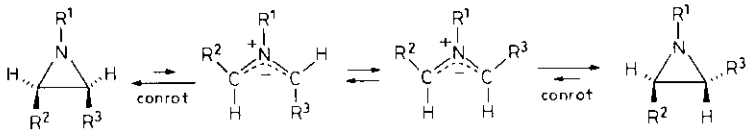


3 4

The sterically constrained bicyclic aziridine 1 is unreactive when heated to 180°C in the presence of dipolarophiles.[7] However, the orbital symmetry-forbidden disrotatory equilibrium 3 ⇌ 4 is established at 135°C, possibly due to the aromaticity of 4.[8] Violations of the Woodward-Hoffmann rules have likewise been observed for the conversions of bicyclic oxiranes [9] and even the monocyclic 2-cyano-cis-2,3-diphenyloxirane.[10] The interplay of orbital control with other factors determining stereochemistry and rate of electrocyclic reactions constitutes an intriguing problem. We report here on two further models.



cis 5-9 | *trans* 10-14 | *cis* 10-14 | *trans* 5-9

	R^1	R^2	R^3	
5	$C_6H_4OCH_3$-*p*	CO_2CH_3	CO_2CH_3	10
6	C_6H_5	C_6H_5	C_6H_5	11
7	$C_6H_5CH_2$	C_6H_5	C_6H_5	12
8	$C_6H_5CH_2$	$C_6H_4OCH_3$-*p*	$C_6H_4NO_2$-*p*	13
9	$CO_2C_2H_5$	C_6H_5	C_6H_5	14

A. Preparation and Equilibria of N-Benzylaziridines

N-Benzyldesylamine (73 %, mp 74-76°C),[11] prepared from benzoin and desylamine, was reduced by $LiAlH_4$ to erythro-2-benzylamino-1,2-diphenylethanol (91 %, mp 137-138°C). Reaction with thionyl chloride and ring closure with potassium t-butoxide produced cis-7, 56 %, mp 44-46°C; nmr ($CDCl_3$): δ 3.82 (s, 2 ring-H), 3.00 (s, CH_2). Treatment of the aminoalcohol with dibromotriphenylphosphorane and triethylamine[12] yielded trans-7, 57 %, mp 68-70°C, nmr ($CDCl_3$): δ 3.33 and 3.60 (AB, J = 13.8 Hz, CH_2), the ring protons give rise at 85°C to a sharp singlet at 3.25 which broadens at 35°C and is converted to an AB spectrum at -40°C with δ 3.18 and 3.45, $J_{2,3}$ = 3.3 Hz, due to the diminished N-inversion rate.

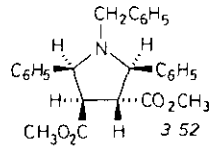
The aziridine cis-7 is stable at 140°C, but slowly decomposes at 160°C without trans-7 becoming observable by nmr; trans-7 is converted to 49 % cis-7 in 5 h at 160°C, concurrent with decomposition. The cis isomer of 7 is thermodynamically favored as it was noticed for 1,2,3-triphenylaziridine (cis : trans = 78:22 at 150°C).[13]

4-Methoxy-4'-nitro-trans-stilbene oxide and benzylamine afforded erythro-2-benzylamino-1-p-methoxyphenyl-2-p-nitrophenylethanol (80 %, mp 176-177°C).[14] The steric course of the cyclization by the dibromotriphenylphosphorane procedure[12] appears to depend on the amount of bromine used to prepare the condensing reagent: 0.95 equiv. furnished mainly trans-8, mp 94-96°C, whereas 1.0 equiv. gave predominantly cis-8 which is a colorless oil and the more stable isomer. Nmr of cis-8 ($CDCl_3$): δ 3.87 (s, CH_2), 3.15 and 3.08 (AB, $J_{2,3}$ = 6.5 Hz, 2-H and 3-H); trans-8 at -40°C: δ 3.33 and 3.60 (AB, J_{gem} = 13.8 Hz, CH_2), 3.18 and 3.45 (AB, $J_{2,3}$ = 3.3 Hz, 2-H and 3-H).

B. Cycloadditions with N-Benzylaziridines

Cis- and trans-7 smoothly combine with dimethyl fumarate in refluxing toluene, i.e., at 110°C, where no cis, trans isomerization of the aziridines takes place. Thus, the rotational barrier between the azomethine ylides, trans- and cis-12, must be much higher than their activation energies for recyclization, trans-12 → cis-7 and cis-12 → trans-7. The reaction of trans-7 with dimethyl fumarate provided 96 % of 15, mp 76-78°C. The chiral structure shows an ABCD spectrum of the ring protons. One of the ester methyl groups (δ 3.07) is shielded by a cis-vic-phenyl. The nmr spectrum of the crude product did not reveal signals of the diastereomers 16 and 17; 3 % 16 and

1 % 17 were recognized in artificial mixtures with 15.



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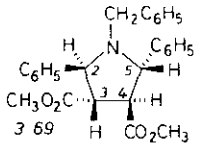

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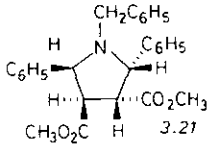

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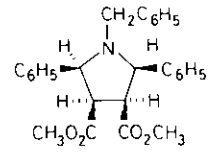
Cis-7 and dimethyl fumarate quantitatively afforded a 56:44 mixture of 16 and 17 which was separated by tlc on silica gel. Pyrrolidines 16, mp 132-133°C, and 17, mp 114-115°C, revealed in their nmr spectra the two-fold axis of symmetry. The shielding effect of the cis-phenyls on the ester methyl singlets of 17 allowed the assignment. The ring protons of 17 are of the AA'BB' type and those of 16 of the AA'XX' type due to the shielding of 3-H and 4-H by cis-located phenyls.



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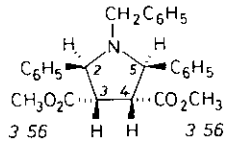

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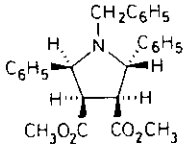

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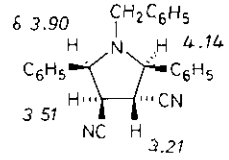
In the reaction with dimethyl maleate it was cis-7 which produced a single adduct (20, 92 %, mp 117-118°C), whereas trans-7 furnished a 55:45 mixture of 18 and 19. After separation by tlc, 18 showed mp 43-45°C and 19 95-96°C. The benzylic CH_2 protons occurred as singlets in 18 and 19, but as AB spectra in 15-17 and 20 due to the lack of a symmetry plane.



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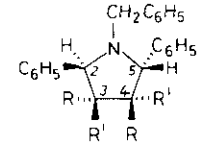
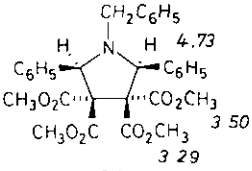


22 R = CN, R' = H
23 R = H, R' = CN



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From trans-7 and fumaronitrile at 110°C the adduct 21, mp 126-127°C, resulted in 90 % yield. 100 MHz spectra with double resonance technique [15] provided the τ and J values of the ABCD pattern of the ring protons. The two pyrrolidines which originate quantitatively from cis-7 were separated by tlc: 22, mp 157-158°C, and 23, mp 162-162.5°C; the nmr signals supplied a ratio of 72:28, while the dual-wavelength tlc scanner [16] gave 67:33. The AA'BB' spectra of the ring protons are consistent with the C_2 axis in 22 and 23.

Even tetramethyl ethylenetetracarboxylate as a much less active dipolarophile produced with trans-7 at 110°C 24 in 98 % yield, mp 132-135°C. The nmr reveals pairwise identical ester methyls and isochronous ring protons. The CH_2 singlet (δ 3.85) indicates the plane of symmetry.

Comparison of the cycloadduct structures with those of the aziridines cis-7 and trans-7 establishes stereospecific ring opening to the azomethine ylides trans-12 and cis-12, respectively, i.e., conrotation.

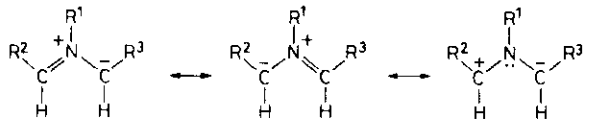
C. Rate Measurements of Cycloadditions

Although a one-step mechanism for the cycloaddition to dimethyl fumarate with inversion of aziridine configuration is hardly conceivable, kinetic results corroborate the two-step scheme. Dilatometric rate measurements [3] were carried out in the presence of excess diethyl fumarate. The pseudo-first-order constants did not depend on the dipolarophile concentration (Table), thus disclosing that the electrocyclic ring opening of cis-7 and trans-7 is becoming irreversible, i.e., the cycloaddition of the azomethine ylides trans-12 and cis-12 to fumaric ester is much faster than electrocyclic ring closure back to the aziridines. As in the case of aziridine 5,[3] but in contrast to 6,[5] the measured constant is identical with that of the ring opening step.

Table. Dilatometric rate constants in o-dichlorobenzene at 100°C

Aziridine (mM)	Diethyl fumarate (mM)	$10^5 k_1$ (sec^{-1})
cis-7 80, 80	681, 1162	1.22, 1.26
trans-7 40, 40	360, 853	22.8, 22.4
cis-8 37, 42	469, 969	17.5, 16.5
trans-8 31, 30	517, 1008	210, 207

Why is the conrotatory ring opening of trans-7 18 times faster than that of cis-7 ? The equilibrium shows that trans-7 is at a higher energy level than cis-7. Furthermore, the azomethine ylide cis-12 suffers less from van der Waals repulsion and phenyl twisting than the exo,endo-diphenyl substituted trans-12.



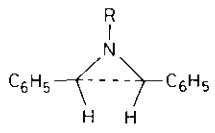
a b c

The allyl anion description of the azomethine ylide by resonance structures a and b suggests that substituents R^2 and R^3 which can take over negative charge will stabilize the 1,3-dipole. Does structure c noticeably contribute to the ground state ? In the aziridine 8 the p-methoxyphenyl group can stabilize a positive charge and the p-nitrophenyl a negative one. Indeed, cis-8 undergoes ring opening 13 times faster than cis-7, whereas the k_1 value of trans-8 exceeds that of trans-7 9-fold (Table).

D. Cycloadditions of 2,3-Diphenylaziridine-1-carboxylic Ester

According to Anastassiou and Hammer, [17] the ethyl 2,3-diphenylaziridine-1-carboxylates 9 establish a photosta-

tionary equilibrium of 90 % cis-9 and 10 % trans-9 (radiation of 2537 Å). The "hypothetical 4π 2-heterotrimethylene species" 25 was invoked as an intermediate.[17] We observed also a thermal cis,trans isomerization of 9; after 5 h refluxing in xylene, cis-9 had undergone 10 %, trans-9 19 % isomerization. Probably, the cis-aziridine is favored here as in the case of 6 - 8. We see no reason to doubt the intermediacy of the azomethine ylides trans-14 and cis-14 as normal 1,3-dipoles of the allyl type.[18] Azomethine ylides are hardly hypothetical; a stable crystalline representative[6,19] still undergoes 1,3-cycloadditions.[20]



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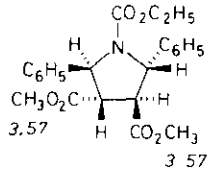

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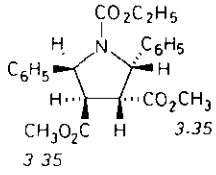

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The azomethine ylide intermediate 14 can be intercepted by cycloaddition to dimethyl fumarate. Whereas no cycloadduct was noticeable after 25 h in toluene at 120°C, heating of cis-9 in an excess of dipolarophile for 48 h at 145°C gave a high yield of 26 and 27 in a 55:45 ratio; 34 % of 26, mp 170-171°C, was isolated by direct crystallization, while tlc on silica gel provided 30 % of 27, mp 75-76°C. Isochronous ester methyl singlets in each of the two adducts combined with the known retention of dipolarophile configuration in 1,3-dipolar cycloadditions[18] require C_2 symmetry for 26 and 27.

In contrast to the behavior of aziridine 7, trans-9 afforded virtually the same mixture of 26 and 27 when heated with dimethyl fumarate under the above conditions. It is clearly the azomethine ylide trans-14 which is incorporated in the cycloadducts 26 and 27. We cannot exclude a forbidden disrotatory ring opening trans-9 → trans-14. For the time being we prefer another explanation: Cycloaddition can only be achieved in the temperature region of cis,trans isomerization of 9 (145°C). If one assumed that the rotation of the azomethine ylides, trans-14 ⇌ cis-14, is faster than their cycloaddition, then one could ascribe a higher rate constant of cycloaddition to trans-14 compared with cis-14. An analogous rate preference of trans-10 over cis-10 in their cycloadditions to less active dipolarophiles has indeed been observed.[21]

Aziridines are weak bases, i.e., the carbamate resonance in 9 is nearly unharmed. The iminium character of the nitrogen in the azomethine ylide 14 suppresses the carbamate resonance, a factor which will make the electrocyclic ring opening of 9 slow compared with 6 - 8.

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