REGIOSELECTIVITY IN THE DIELS-ALDER REACTIONS OF 2-VINYLINDOLES AND PYRANO[3,4-b]INDOL-3-ONES WITH CC-DIENOPHILES

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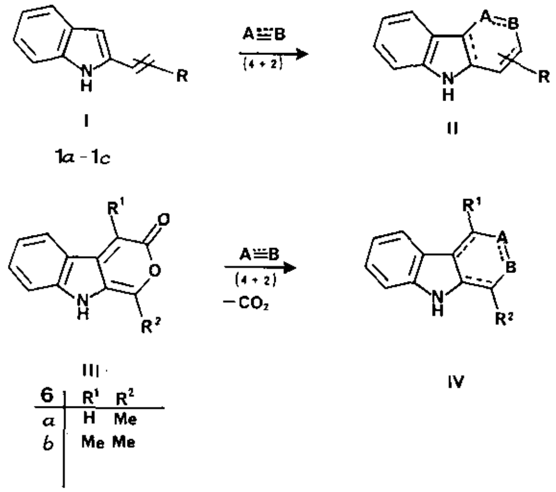
Abstract —— Diels-Alder reactions of 2-vinylindoles **1** and methylated pyrano[3,4-b]indol-3-ones **6** with acceptor-substituted CC-dienophiles (e.g. propynoates, ethyl phenylpropynoate, acrylonitrile, α-chloroacrylonitrile, methyl acrylate, 1-penten-3-one) proceed with poor to high regioselectivities to furnish functionalized carbazole derivatives. MNDO calculations have been carried out for the 2-vinylindole and pyrano[3,4-b]indol-3-one parent compounds and, in most cases, qualitative FMO analyses correctly predict the major products. The regiochemistries of the products from the reactions of the pyrano[3,4-b]indol-3-ones **6** with ethyl phenylpropynoate can be predicted by the simple charge controlled orientation in the transition states.

2-Vinylindoles I[1] and pyrano[3,4-b]indol-3-ones III[2], the latter being synthetic equivalents of indolo-2,3-quinodimethanes, represent synthetically attractive building blocks for the regiocontrolled [b]annellation of indoles in which the [4 + 2]cycloaddition is the predominant concept (Scheme 1). Whereas today extensive preparative data including application of the FMO concept for predicting the result of the reactions[3,5] are available for the 3-vinylindole series, there is still a lack of far-reaching studies on the Diels-Alder reactions of I as well as of the π-electronically related compounds III with acceptor-substituted dienophiles. Thus, we now report in this communication on some new synthetic results from the cycloaddition reactions of 2-vinylindoles I and methylated pyrano[3,4-b]indol-3-ones III with selected CC-dienophiles which should give rise to regioselectivity problems. On the basis of MNDO calculations on the parent compounds of the series I and III, predictions on the results of the reactions were made using qualitative FMO analyses[5,6,7].

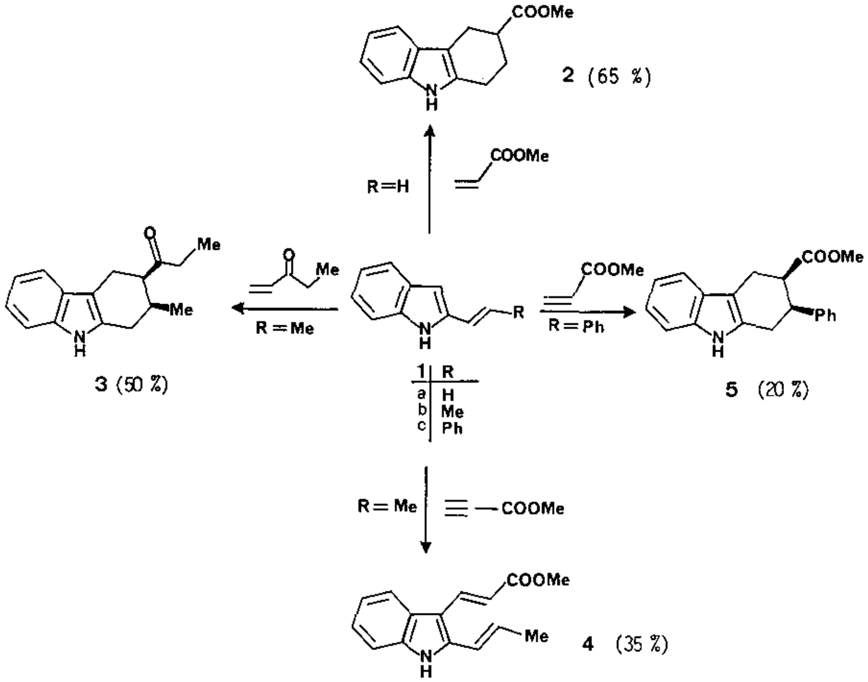


6	R^1	R^2
a	H	Me
b	Me	Me

Scheme 1

Reactions with 2-Vinylindoles

The first Diels-Alder reactions with 2-vinylindoles and prochiral CC-dienophiles to give functionalized carbazoles[4] have already shown that the regiochemistry with these 4π-reaction components is always controlled by the enamine structure of the indole nucleus. We have now investigated further Diels-Alder reactions of the parent compound 2-vinylindole **1a**[1], first synthesized by us, and its substituted derivatives **1b** and **1c** with methyl acrylate, 1-penten-3-one, and methyl propynoate. The results of these uniformly highly regioselective cycloaddition reactions (no further isomers detected by hplc and ^{1}H-nmr analyses of the crude product mixtures) are summarized in Scheme 2. Only those reactions which gave analytically and preparatively perceivable products out of the total number of reactant combinations possibly obtainable from the three dienophiles and compounds **1** are included. Low yields are accounted for by the formation of polymers. Compound **1a** reacts regioselectively with methyl acrylate under mild conditions to form methyl 1,2,3,4-tetrahydrocarbazole-3-carboxylate (**2**). Whereas 1-penten-3-one undergoes cycloaddition regio- and stereoselectively with **1b** to furnish the tetrahydrocarbazole **3**, the reaction of **1b** with methyl propynoate only takes place regioselectively to give the Michael adduct **4**. Finally, **1c** reacts regio- and stereoselectively with methyl acrylate to yield the carbazole derivative **5**. The Diels-Alder reactions giving rise to **3** and **5** should proceed by way of endo-[$_{\pi}4s + {}_{\pi}2s$]-transition states.



Scheme 2

Procedure for the Reactions of 2-Vinylindoles with CC-Dienophiles: 1 Mmol of the 2-vinylindole **1** and 1.1 mmol of the CC-dienophile were dissolved in 10 ml of dry toluene under an argon atmosphere and treated with 2 g of dried 4 Å molecular sieve. For the preparation of **2**, the mixture was heated under reflux for 5 d and, for the preparation of **5**, stirred at room temperature for 24 h.

For the preparations of **3** and **4**, 1 mmol of **1b** was dissolved in 1.5 mmol of the dienophile, a twentyfold amount by weight of silica gel 60 for column chromatography was added, and the mixture was allowed to stand at 20 °C for 3 d. All new compounds **2-5** were isolated by flash chromatography [Merck silica gel 60, grain size 0.040-0.063 mm, petroleum ether (bp 40-60 °C)/ethyl acetate (3/1, v/v]. The high resolution (400 MHz) nmr spectra, EI-mass spectra, and elemental analyses are in accordance with the given constitutions and relative configurations.

Reactions with Methylpyrano[3,4-b]indol-3-ones

In the Diels-Alder reactions of the pyrano[3,4-b]indol-3-ones **6** with the CC-dienophiles tested here (Table 1), a relatively poorly pronounced regioselectivity was found in the case of **6a** as compared with a strongly pronounced regioselecti-

Table 1: Diels-Alder Reactions of Pyrano[3,4-b]indol-3-ones **6a,b** with Electron-Poor Alkenes and Alkynes.

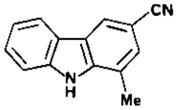
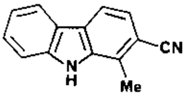
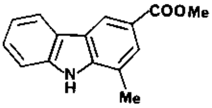
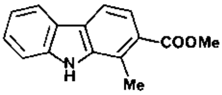
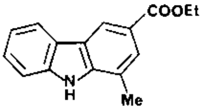
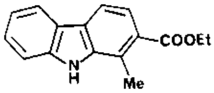
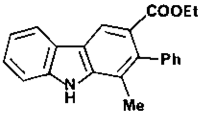
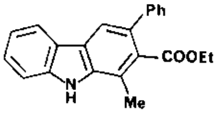
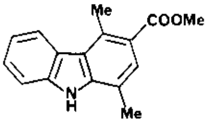
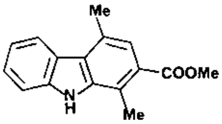
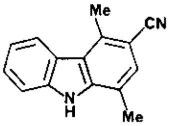
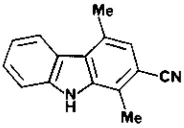
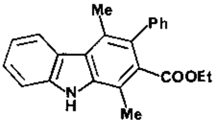
Entry	Diene	Dienophile	Reaction Conditions a)	Product b)	Yield [%]	Mp [°C]	Ratio [%] c) of 3-acceptor/2-acceptor substituted carbazole
1	**6a**	$H_2C=CHCN$	0.25 mM/50 mM, THF, 10 h, 66 °C	 **7**	8	183[8]	1 : 0.8
				 **8**	5	153	
2	**6a**	$H_2C=CClCN$	1 mM/2 mM, THF, 6 h, 66 °C	**7** **8**	9 6		1 : 0.7
3	**6a**	$H_2C=CHCO_2Me$	0.5 mM/1 mM, PhBr, 3 h, 156 °C	 **9**	50	187	1 : 0.5
				 **10**	25	132	
4	**6a**	$HC\equiv C\text{-}CO_2Et$	2 mM/3 mM, PhBr, 15 h, 136 °C	 **11**	33	151	1.5 : 1
				 **12**	22	123	
5	**6a**	$Ph\text{-}C\equiv C\text{-}CO_2Et$	1.5 mM/2 mM, PhBr, 16 h, 156 °C	 **13**	10	203	1 : 3
				 **14**	28	127	

Table 1: (Continued).

Entry	Diene	Dienophile	Reaction Conditions a)	Product b)	Yield [%]	Mp [°C]	Ratio [%] c) of 3-acceptor/2-acceptor substituted carbazole
6	**6b**	$H_2C{=}CHCO_2Me$	0.5 mM/2.5 mM, CH_3CN, 3.5 h, 82 °C	 **15**	63	153	1 : 0.03
				 **16**	2	– d)	
7	**6b**	$H_2C{=}CClCN$	0.7 mM/2.5 mM, CH_3CN, 1 h, 82 °C	 **17**	78	251-252	1 : 0.02
				 **18**	2	– d)	
8	**6b**	$HC{\equiv}C{-}CO_2Me$	0.5 mM/2.7 mM, CH_3CN, 7 h, 82 °C	**15**	85		1 : 0.02
				16	3		
9	**6b**	$Ph{-}C{\equiv}C{-}CO_2Et$	0.7 mM/2.2 mM, CH_3CN, 60 h, 82 °C	 **19**	11	204	only **19** detected

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a) Work-up: flash chromatography [Merck silica gel 60, grain size 0.040-0.063 mm, petroleum ether (bp 40-60 °C)/ethyl acetate].

b) The EI-mass spectra, nmr spectra, and elemental analyses are in good agreement with the given constitutions. The regiochemistries of the carbazoles were elucidated principally by ^1H-nOe measurements (400 MHz) and the J-modulated ^{13}C-nmr spin echo technique.

c) 400 MHz ^1H-nmr spectroscopic analysis of the crude mixture.

d) This regioisomer could not be separated completely from the main product.

vity for **6b**. In this series, the 1,4-dimethyl derivative **6b** exhibits an increased enophile reactivity in comparison with **6a**. In all of the cycloaddition reactions mentioned here, a bicyclic lactone is formed initially which spontaneously eliminates CO_2 and, in the case of reactions with C=C-dienophiles, then undergoes stabilization to the 14π-carbazoles by selective elimination. Reactions with alkynes lead directly to the carbazoles after extrusion of CO_2.

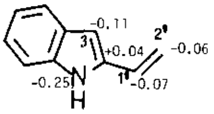
Prediction of the Regiochemistry with the FMO Concept

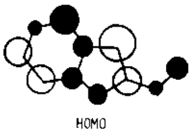
The qualitative FMO theory has been demonstrated to be a valuable model for the prediction of the regiochemistry of Diels-Alder reactions[7,10]. The weaknesses of the frontier orbital model have also been recognized and an alternative model for predicting the regiochemistry introduced[10]. For simple α-pyrones, the results on the regiochemistry of Diels-Alder reactions have also been discussed in terms of the net atomic charges of the reaction partners, secondary orbital interactions[11], and the possibility of steric effects[12]. However, the FMO theory[7,10] has been remarkably successful in providing a qualitative picture for the regiochemistry that can be based on generalized FMO's[13]. According to the FMO theory, regioselectivity is governed by the relative size of the atomic coefficients of the FMO's which, in turn, reflect the contribution of the overlap integral to the stabilizing interaction energy arising from the interaction of the HOMO of one reactant with the LUMO of the other reactant. This interaction energy is greater when the HOMO-LUMO frontier orbital pair is close in energy and the pair with the smaller energy gap is generally considered.

Compounds **I** and **III** can be considered as 2-aminobutadiene-related partners in Diels-Alder reactions. For estimation of the regiochemistry, eigen vectors, eigen values, and charge densities under optimization of the bond separations and bond angles have been calculated according to the MNDO method[14] (Tables 2 and 3) for the parent compounds I and III (R = H). FMO data are listed in Table 4 for the example of methyl acrylate as an acceptor-substituted CC-dienophile. Frontier orbitals for the other dienophiles used experimentally in this work have been described in Refs.[6,7,10,16,17]. According to the HOMO-LUMO energy separation of the reactants and on assumption of a concerted mechanism[15] with early transitions states (dominant HOMO/LUMO interaction according to the 3rd term of the perturbation equation)[7], all the Diels-Alder reactions of **1** and **6** mentioned here are

$HOMO_{diene}$-$LUMO_{dienophile}$ controlled processes. On the basis of the FMO data of the 2-vinylindole parent compound **1a**, the regioselectivities found experimentally in the reactions of **1a-c** with CC-dienophiles can be predicted unequivocally by the energetically preferred large-large/small-small interaction of the coefficients of the $HOMO_{diene}$ and $LUMO_{dienophile}$. The difference in the HOMO terminal coefficients of the 2-vinylindole is significant (> 0.01)[10]. The endo-transition state in the formation of the carbazole derivatives 3 and 5 should be energetically favored by a secondary frontier orbital interaction[5,7].

Table 2: Frontier molecular orbitals of the 2-vinylindole parent compound **1a** with details of the net atomic charges according to MNDO calculations[a),14].





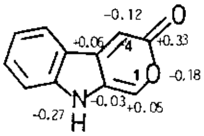
Atom	HOMO-1	HOMO	LUMO
1	+0.362	-0.256	-0.201
2	+0.219	+0.405	+0.376
3	-0.097	+0.502	-0.331
1'	-0.130	-0.157	+0.296
2'	-0.188	-0.284	+0.424

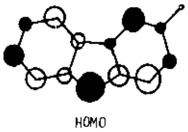
Energies (eV): HOMO-1, -8.66; HOMO, -8.28; LUMO: -0.03.

ΔH_f^0 = -71.1 kcal mol^{-1}; μ = 1.90 Debye.

[a] Fully optimized geometries.

Table 3: Frontier molecular orbitals of the parent pyrano[3,4-b]indol-3-one with details of the net atomic charges according to MNDO calculations[a),14].





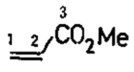
Atom	HOMO-1	HOMO	LUMO
1	-0.264	+0.409	+0.356
4	+0.345	-0.336	+0.467
4a	+0.204	-0.0464	-0.432
9	-0.118	-0.473	-0.068
9a	+0.009	+0.264	-0.104

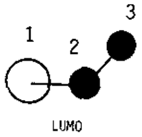
Energies (eV): HOMO-1, -9.69; HOMO, -8.47; LUMO: -1.00.

ΔH_f^0 = 4.47 kcal mol^{-1}; μ = 5.65 Debye. According to Ref.[5], the methyl derivatives examined here should exhibit only slight deviations in the frontier orbital coefficients[7].

[a] Fully optimized geometries.

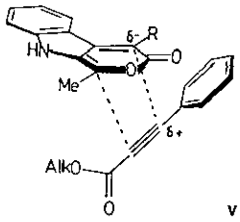
Table 4: Frontier molecular orbitals of methyl acrylate according to MNDO calculations[14] as a representative of the acceptor-substituted prochiral CC-dienophiles[16].





Atom	HOMO	LUMO
1	+0.495	+0.674
2	+0.456	-0.489
3	-0.240	-0.475

Energies (eV): HOMO, -11.02; LUMO, -0.15.



V

When the prediction of the regiochemistry is based on the calculated HOMO topology of the parent compound of **6**, the preferred direction of addition of the dienophiles should, in these cases, give rise to the 3-acceptor substituted carbazole derivatives as a consequence of the larger coefficients at C1 in comparison to those at C4 (difference > 0.010, see Table 3)[10]. This is in fact the case for the reactions of the methyl derivatives **6a,b** with the exception of the cycloadditions with ethyl propynoate (entries 5 and 9). However, the still relatively poor regioselectivities in the Diels-Alder reactions of **6a** (entries 1, 2, 3, and 4) are significantly increased by the introduction of a further methyl group as a result of the increase in the HOMO energy[6,7] (entries 6, 7, and 8). In the cycloaddition reactions of **6a,b** with ethyl phenylpropynoate the preferred direction of addition in this series is reversed (entries 5 and 9). These two Diels-Alder reactions apparently proceed in the first step preferentially under charge control[7] by way of the asymmetric transition state **V**; this is in accordance with the net atomic charges of the parent compound of **6** (Table 3) and of the phenylpropynoic ester[17]. As a result of the very low polarization of the LUMO coefficients of ethyl phenylpropynoate[17] in comparison with those of propynoates and, in this case, the higher $HOMO_{diene}$-$LUMO_{dienophile}$ energy separation (ΔE_{LUMO} propynoate/phenyl propynoate = 1.36 eV)[18], the FMO interaction is overcompensated by the coulombic attraction so that the regiochemistry is reversed. This reaction result can also be predicted by the simple resonance theory and is consistent with the calculated net atomic charge densities.

In conclusion, the simple qualitative FMO theory provides, in most cases of the described new reactions, a powerful empirical approach for the prediction of the regiochemistry in Diels-Alder reactions of 2-vinylindoles **1** and pyrano[3,4-b]indol-3-ones **6**. For the reaction of **6** with ethyl phenylpropynoate, the electrostatic model correctly predicts the experimental results. The synthetic outcome of the described Diels-Alder reactions is of great interest for further synthetic planning leading to alkaloids and pharmacologically active lead substances.

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