Monatshefte für Chemie 120, 27—34 (1989)

Monatshefte für Chemie
Chemical Monthly

New Structural Aspects of 3-Vinyl-1*H*-indoles for Predicting the Outcome of Diels-Alder Reactions

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Summary. Some selected 3-vinyl-1*H*-indoles have been synthesised and the first ^{13}C-NMR studies performed; in addition He(Iα) photoelectron spectra and the results of perturbation MO calculations of some examples of this class of compounds are presented. The molecular characteristics obtained thereby can be used to predict the results of $[_{\pi}4s + _{\pi}2s]$-cycloaddition reactions with 3-vinylindoles.

Keywords. 3-Vinylindoles; ^{13}C-NMR; Photoelectron spectra; Frontier orbitals.

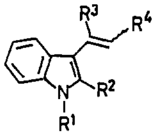
Neue strukturelle Aspekte von 3-Vinylindolen zur Vorhersage der Reaktionsergebnisse bei Diels-Alder-Reaktionen

Zusammenfassung. An selektiv synthetisierten 3-Vinyl-1*H*-indolen werden erstmals ^{13}C-NMR-spektroskopische Studien durchgeführt und exemplarisch an einigen Vertretern dieser Strukturklasse He(Iα)-Photoelektronenspektren sowie Ergebnisse von Störungs-MO-Rechnungen vorgestellt. Die daraus gewonnenen Moleküleigenschaften können zur Vorhersage des Reaktionsausganges von $[_{\pi}4s + _{\pi}2s]$-Cycloadditionen mit 3-Vinylindolen verwendet werden.

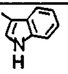
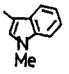
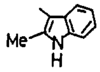
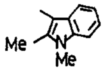
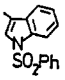
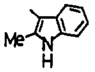
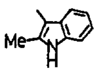
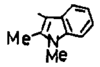
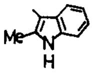
Introduction

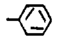
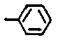
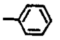
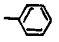
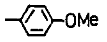
As a consequence of their 4π-electron structures incorporated in a heterocyclic framework, 3-vinyl-1*H*-indoles are synthetically attractive building blocks for the regio- and stereocontrolled [b]annellation of the indole skeleton [1–5]. Although the synthetic applications of these compounds in Diels-Alder reactions for the preparation of carbazole derivatives, heterocyclic analogues, and pharmacologically interesting lead structures have not been sufficiently well demonstrated [1–5], specific investigations on the molecular characteristics [1, 6, 7] that are responsible for the results observed from [4 + 2]cycloaddition reactions are still lacking. Indole can formally be described as an electronic combination of a benzene and an enamine moiety; in analogy, the 3-vinylindole system can be broken down into a benzene and a 1-aminobutadiene subunit. The latter is responsible for the general reaction behaviour of 3-vinylindoles.

Thus, in the present study, ^{13}C-NMR spectroscopic investigations on selected 3-vinylindoles **I** are described for the first time. In addition, He(Iα) photoelectron spectra as well as the results of perturbation MO calculations for the energetic and topological characterisation of the frontier orbitals which are of importance for cycloadditions are reported for some representatives of this class of compounds.



I

	R^1	R^2	R^3	R^4
1	H	H		H
2	Me	Me		H
3	H	Me		H
4	Me	Me		H
5	SO_2Ph	H		H
6	H	H		H
7	Me	H		H
8	Me	Me		H
9	SO_2Ph	H		H

	R^1	R^2	R^3	R^4
10	SO_2Ph	H		H
11	Me	H		H
12	SO_2Ph	Me		H
13	Me	Me		H
14	SO_2Ph	Me		H
15	SO_2Ph	H	H	H
16	SO_2Ph	Me	Me	H
17	SO_2Ph	H	Me	H
E-18	SO_2Ph	H	H	CO_2Et
E-19	Me	H	H	CO_2Et
E-20	Me	Me	H	CO_2Et
E-21	SO_2Ph	H	H	OMe
E-22	SO_2Ph	H	H	OMe
E-23	SO_2Ph	Me	H	OMe
E-24	SO_2Ph	H	H	$n\text{-}C_3H_7$
E-25	SO_2Ph	H	H	$n\text{-}C_3H_7$

Results and Discussion

^{13}C-*NMR Spectra*

On the basis of considerations on the ground state, the results observed from Diels-Alder reactions of **I** are assumed to be controlled, among other factors, by the conformation as well as the charge density distribution of the 1-aminobutadiene unit incorporated in the 10π-heterocyclic system [1, 6, 8]. The ^{1}H- and ^{13}C-NMR spectra should thus be suitable probes for the description of these structural characteristics. We have therefore synthesised the selected compounds **1**–**25** and recorded their ^{1}H- and ^{13}C-NMR spectra*. For some of the compounds, we have also investigated the temperature dependence (− 95 to + 80 °C) of the ^{1}H-NMR spectra; however, these

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* The parent compound of the series, 3-vinyl-1*H*-indole is thermally labile, air-sensitive, and readily undergoes polymerisation [9]; hence it cannot be investigated spectroscopically without decomposition taking place during the measurements.

results made no contribution to the understanding of the dynamic phenomena (e.g. analysis of the *s-cis-/s-trans* isomerisation or the position of the equilibrium). The 400 MHz ^{1}H-NMR spectra of **1**–**25** reflected only a "static" molecular structure in which characteristic shift effects on the 1-aminobutadiene structure could only be attributed to anisotropy effects. For a discussion of structural factors of **1**–**25** we have, therefore, examined the ^{13}C-NMR spectra (*J*-modulated spin-echo experiments, gated spectra, selective ^{1}H-decoupling) in more detail in order to obtain initial qualitative information on the charge density distribution of the diene subunit from the chemical shift data.

A partial, charge-induced polarisation in the 4π-electron structure of 3-vinylindoles is reflected in the shifts of the ^{13}C-NMR resonances which are principally influenced to varying degrees by electronic and/or steric effects of the substituents [10, 11]. A shift correlation of the carbon atoms in the 1-aminobutadiene structures of **1**–**25** is represented in Fig. 1. For compounds **1**–**12** and **15**–**19**, the expected charge alternation is clearly apparent from the ^{13}C-NMR shifts. The typical electronic structures of push-pull olefins are present in compounds **18**, **19**, and **20**. The enol ethers **21**–**23** formally represent "bis-donor butadienes" in

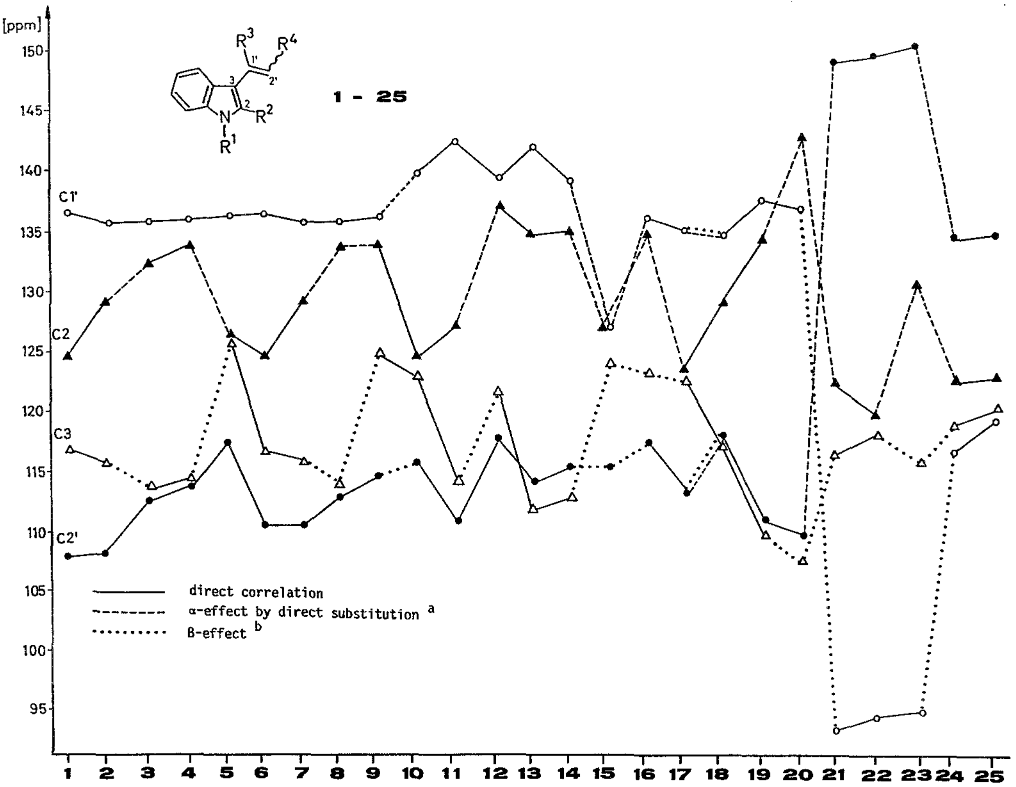
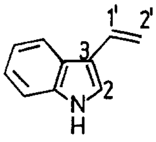


Fig. 1. ^{13}C-NMR chemical shift correlation diagramme for the carbon atoms in the aminobutadiene subunits of compounds **1**–**25** (*DMSO-d*$_6$)

[a] At about 10 ppm to lower field in the presence of and at about 10 ppm to higher field in the absence of additional substitution by a methyl group

[b] At about 7 ppm to higher field in the presence and at about 7 ppm to lower field in the absence of additional substitution by a methyl group

Table 1. Charge density distribution (net atomic charges and orbital populations) in the 1-aminobutadiene subunit of the parent compound 3-vinyl-1*H*-indole. Calculated according to the MNDO method [14][a]

	Atom	Net atomic charge q_x	σ and π electron density	Total π-electron density ε
	1	− 0.24033	5.2403	1.4549
	2	0.04267	3.9573	1.2060
	3	− 0.12504	4.1250	1.1721
	1'	− 0.02452	4.0245	1.2027
	2'	− 0.09327	4.0933	1.2378

[a] $\Delta H_f = 72.9\,\mathrm{kcal\,mol^{-1}}$; $\mu = 2.16$ Debye

which the conjugative interaction is markedly weakened as a result of the presence of substituents with related electronic requirements [12]. In the 2-methyl-substituted derivatives, steric pressure of the additional 2-methyl group on the indole ring induces a twisting of the two double bonds with respect to each other. The resultant shift effect can be observed particularly clearly on going from **1** to **3**, **17** to **16**, and **19** to **20**. The relatively irregular courses of the curves for C2 and C3 in Fig. 1 are indicative of the pronounced alpha- or beta-shift effects caused by the 2-methyl substitution. The positions of the curves with respect to each other gives some relative information on the charge density distributions of the diene systems in **1**–**25**. For example, in the lefthand part of the figure, C2' of the corresponding 3-vinylindoles shows the largest π-charge density [10, 11]. Without exception, a positive polarisation is observed for C2 and C1' of compounds **1**–**20** whereas, in contrast, this trend is not followed so strictly by C3 (△-line) and C2 (▲-line). It is interesting to note that the polarisation is reversed in the 2'-donor- or alkyl-substituted 3-vinylindoles **21**–**25**. With the exception of the latter compounds, the polarisations deduced from the present ^{13}C-NMR data agree relatively well with the charge densities calculated for the parent compound, 3-vinyl-1*H*-indole (Table 1) and with those in dienamines [13] (see also the ^{13}C-NMR data for the N-protected parent 3-vinylindole **15** in Fig. 1).

According to the electrostatic model for the control of the regiochemistry in Diels-Alder reactions with monoacceptor-substituted dienes (e.g. methyl acrylate), the indole nitrogen atom should represent the most important donor-structural element which induces the charge density distribution. With the exception of the reactions of the 2'-donor-substituted 3-vinylindoles **21**–**25**, this is in good agreement with the experimental results [1, 4].

He(Iα) *Photoelectron Spectra and Frontier Orbital Topologies of Selected 3-Vinylindoles*

The FMO concept represents a recognised model for the analysis of reactivity, regiochemistry, and stereochemistry (*endo*-/*exo*-selectivity) in Diels-Alder reactions

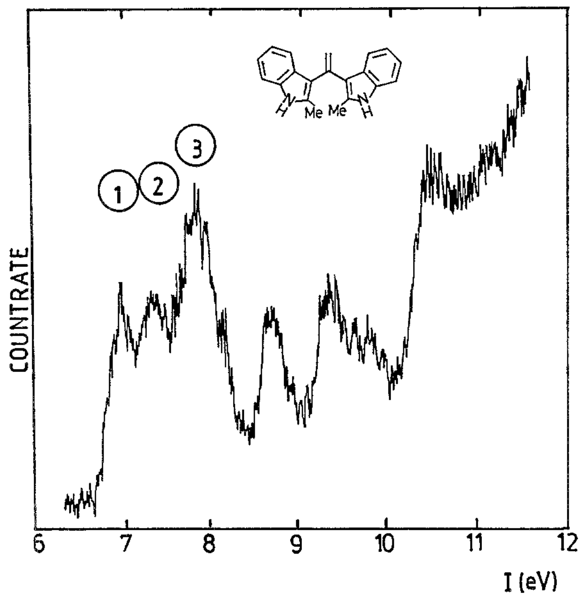


Fig. 2. He(Iα) photoelectron spectrum of compound **3**

[6, 15]. Thus, He(Iα) photoelectron spectra of some 3-vinylindoles having sufficient physical stability were measured for the first time for the experimental determination of the HOMO energies (Fig. 2 and Table 2); in addition, MO calculations (SCF-PPP, MNDO methods) were performed for the parent 3-vinylindole [9] and for the bisindolylethene **1** for a representation of the frontier orbital topologies.

The PE spectra had to be recorded at 150–210 °C with the result that practically no fine structure could be seen (Fig. 2). All of the compounds investigated, **1**, **3**, **4**, **6**, and **11**, exhibit 3 separate bands in the region ca. 7–8.5 eV (bands 1, 2, and 3 in Table 2) which are assigned to three π-MO's [17]. According to Koopmans' theorem [16], the bands 1 can be equated with the negative values of the HOMO energies determined by the SCF-MO method [19].

Table 2. Measured ionisation energies I_{vj} of compounds **1**, **3**, **4**, **6**, and **11** and literature values for indole and 2-methylindole

Compound	I_{vj} [eV] for bands[a]		
	1	2	3
1	7.1	7.5	8.0
3	7.0	7.4	7.9
4	6.9	7.3	7.8
6	7.1	7.5	8.0
11	7.5	8.0	8.5
Indole [17][b]	7.76	8.38	9.78
2-Methylindole [17]	7.63	8.17	9.46

[a] The first three bands are assigned to π-MO's

[b] $E_{\mathrm{HOMO}} = -7.86\,\mathrm{eV}$ (MINDO/3 [17])

The PE data for indole and 2-methylindole additionally listed in Table 2 show, in relation to the measured 3-vinylindoles, a higher first vertical ionisation potential [17]. When the HOMO energy of 1-aminobutadiene [18] ($E_{\mathrm{HOMO}} = -8.50\,\mathrm{eV}$ according to the MNDO method [14]) is also taken into the comparison, it is seen that all of the vinylindoles measured here possess a relatively high HOMO energy. The first vertical ionisation potentials of the bisindolylethenes **1**, **3**, **4**, and **6** show only slight differences to each other as a consequence of their common cross-conjugated trienes structure (Table 2). This is also in accord with the slight differences in the first vertical ionisation potentials of indole and methylindole [17].

On the basis of the high positions of the HOMO energies of the exemplarily measured 3-vinylindoles, it can be assumed that, in accordance with the FMO concept [6, 15], the $[_{\pi}4s + {}_{\pi}2s]$cycloadditions with 2π-acceptors proceed under $\mathrm{HOMO_{diene}}$-$\mathrm{LUMO_{dienophile}}$ control and those with 4π-acceptors under $\mathrm{HOMO_{dienophile}}$-$\mathrm{LUMO_{diene}}$ control. Both predictions of "normal" and "inverse" Diels-Alder reactions [6] are in good agreement with experimental results obtained using 3-vinylindoles [1].

SCF-MO calculations (PPP method [20–22]) on the parent compound, 3-vinyl-1*H*-indole, and on **1** additionally demonstrate the successful application of the FMO concept for the prediction of the regio- and *endo*-selectivity (via secondary frontier orbital interaction) of the $[_{\pi}4s + {}_{\pi}2s]$-cycloaddition [6, 15] (Fig. 3).

Furthermore, Fig. 4 illustrates the regioselectivity, which can be estimated by the MNDO method [14], of the "normal" Diels-Alder reaction of the parent compound, 3-vinyl-1*H*-indole, with acceptor-substituted dienophiles. The frontier orbital topologies shown in both figures for analysis of the results of Diels-Alder reactions with 3-vinylindoles have been fully confirmed experimentally by the observed regio- and stereospecificities of the cyclisations [1].

Conclusions

The structural data collected here for the vinylindole series show for the first time how the interplay between spectroscopic results and calculated MO topologies

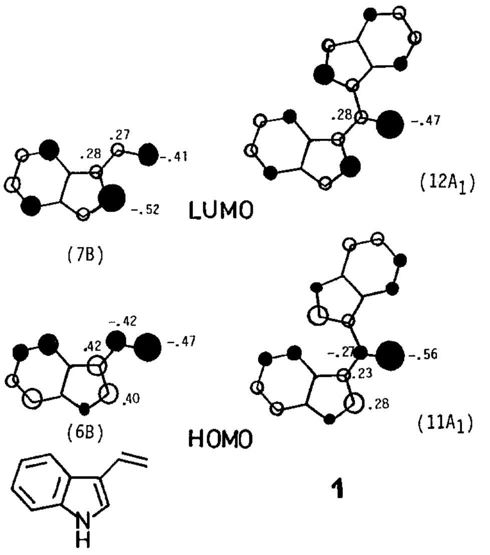


Fig. 3. Frontier orbitals of the parent compound, 3-vinyl-1*H*-indole, and the bisindolylethene **1** (SCF method, PPP calculation [20–22]). Coplanarity was assumed in the calculations. The low ionisation energies are unequivocally indicative of the π-character of the HOMO which is localised mainly in the aminobutadiene subunit. In bracket: symmetry symbols of orbitals

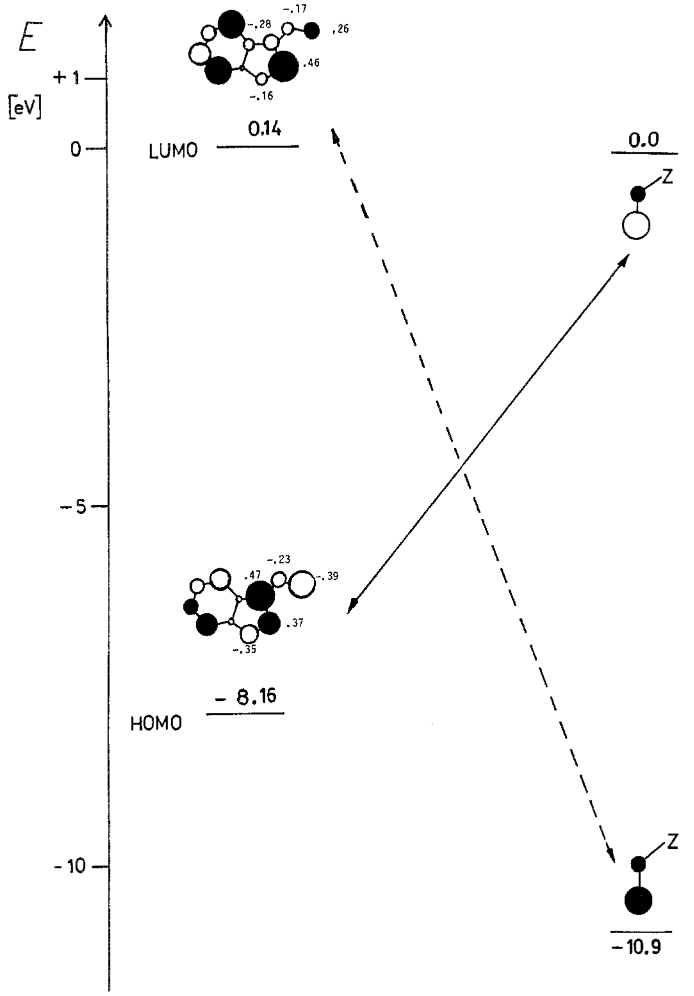


Fig. 4. Frontier orbitals of the parent compound, 3-vinyl-1*H*-indole, calculated by the MNDO method and estimation of the regioselectivity in the reaction with a monoacceptor-substituted dienophile. The $\mathrm{HOMO_{diene}}$-$\mathrm{LUMO_{dienophile}}$ energy separation determines the result of the $[_{\pi}4s + {}_{\pi}2s]$-cycloaddition

facilitates a good prediction of the stereochemical course (reactivity, regio- and stereochemistry) of Diels-Alder reactions according to the principles of normal and inverse electron demand.

Acknowledgements

We thank Prof. R. Gleiter (University of Heidelberg) for recording the PE spectra and for performing the SCF-MO calculations according to the PPP method (Fig. 3). We are also grateful to the Deutsche Forschungsgemeinschaft (Bonn) for financial support of this work.

Experimental

The preparations of some of the vinylindoles are described in Refs. [1, 23, 24]. Additional synthetic methods will be published later. ^{13}C-NMR spectra: Bruker WM 400 spectrometer (δ scale, *TMS* as internal standard); He(Iα) photoelectron spectra: Perkin-Elmer PS-18 spectrometer. The spectra have been calibrated with argon and xenon. Each spectrum was recorded several times to ensure reproducibility of the results. For the MO calculations, a planar geometry was assumed. The structural parameters for the indole skeleton were taken from Ref. [25] and the MNDO calculations were performed according to Ref. [14].

Note Added in Proof

Meanwhile own MNDO-calculations of the 2-vinylindole parent compound also predict reactivity and regioselectivity of this 4π component in Diels-Alder reactions very well ($E_{\text{HOMO}} = -8.25$ eV, HOMO coefficients at C3 = +0.50, at C2′ = −0.28; higher π electron density at C3 in relation to C2′).

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Received January 14, 1988. Accepted February 26, 1988