Quantum Chemical Analysis and Experimental Study of the Cycloaddition Reaction between Aminoacetylenes and 6-Nitroindolizines. NMR and ab Initio Evidence for the [4+2] Adduct Formation

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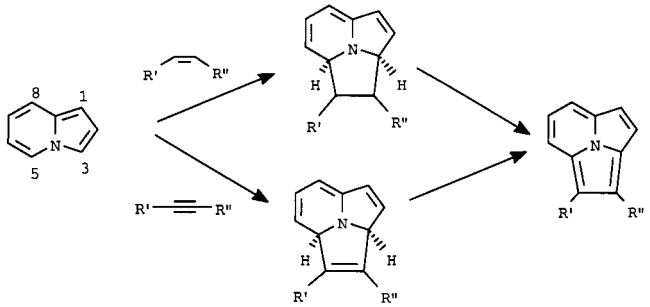
7-Methyl-6-nitro-2-phenylindolizine (**Ia**) reacts with 1-(diethylamino)-2-methylacetylene (**IIa**) giving 1:1 cycloadduct **IIIa** and not the expected product of dipolar [8+2] cycloaddition cyclazine **IVa**. According to NMR data the structure of **IIIa** consists of 1,2-oxazine fragment corresponding to the [4+2] cycloaddition of the acetylene to the sequence C(5)−C(6)−N−O of nitroindolizine. The mechanism of model reactions between nitroindolizine **Ib** and aminoacetylenes **IIb**,**c** is studied by an ab initio and AM1 method. Results of calculations indicate that the initially formed zwitterionic intermediates may undergo further ring closure either to cycl[3.2.2]azines **IVb**,**c** or 1,2-oxazine cycloadducts **IIIb**,**c**. Although the structures **IV** are lower in energy than **III**, the activation barrier for the formation of **III** is smaller than the barrier leading to **IV**.

Introduction

Cycloaddition of various dienophiles (alkenes and acetylenes) to indolizines leading to derivatives of the cycl[3.2.2]azine (Scheme 1) is well-reviewed.[1−3] The mechanism of these reactions is frequently regarded as a rare example of [8+2] cycloaddition, where the tetraene carbon framework of the indolizine bicycle plays the role of an 8 π-electron fragment. In general, this process may be either concerted or involve zwitterionic (and even biradical) intermediates, and there is yet no experimental evidence for the nature of the process. Also, no theoretical quantum chemical justification has been provided to clarify this problem.

Indolizine is usually regarded as the π-excessive heterocycle with the highest electron population of the carbon atom C_3,[4] and the major part of the chemistry of indolizines[5] is simple electrophilic addition and substitution at position 3. Some electron deficient alkenes form with indolizines the Michael adducts at position 3.[2a,6]

Scheme 1. Schematic Representation of the [8+2] Cycloaddition between Indolizines and Dienophiles[a]



[a] Intermediate structures can be easily oxidized to aromatic cyclazines.

Therefore, the possibility of dipolar stepwise mechanism of an [8+2] cycloaddition (electrophilic addition at C_3 and nucleophilic ring closure at C_5) cannot be excluded.

Nucleophilic addition and substitution reactions are not typical for indolizines. The unique family of substituted indolizines that may undergo such reactions with nucleophiles is represented by 6- and 8-nitroindolizines.[7,8] In the structure of these indolizines the carbon atom C_5 has a local electron deficiency, and many N- and O-nucleophiles readily form stable anionic σ-complexes at this position of 6(8)-nitroindolizines. Furthermore, the electron excessive nature of the carbon atom C_3 does not

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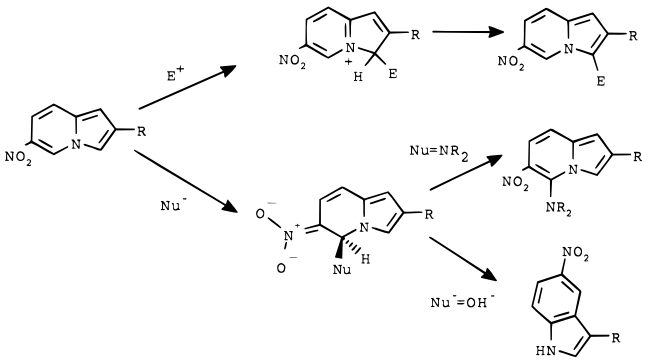
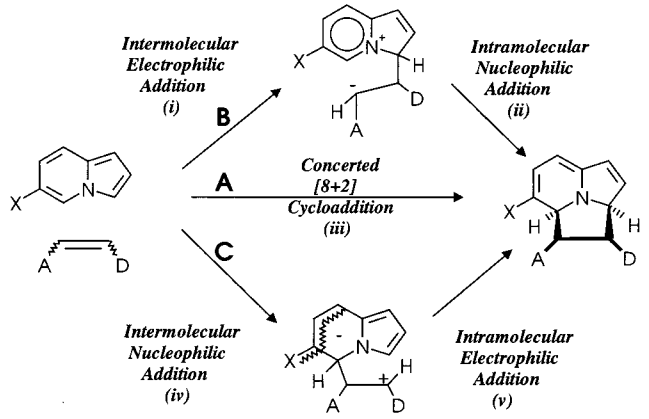
Scheme 2. Electrophilic and Nucleophilic Addition and Substitution Reactions of 6(8)-Nitroindolizines (Shown for 6-Nitro Isomer)



Scheme 3. Possible Mechanisms of [8+2] Cycloaddition

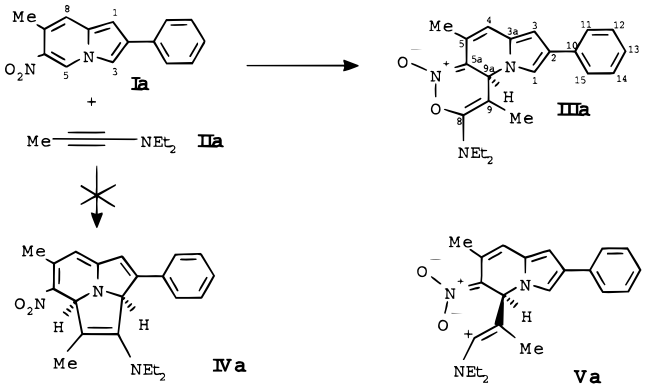


disappear in 6(8)-nitroindolizines, and many electrophilic reactions are reported for this family. The unique "amphoteric" nature[9] of 6(8)-nitroindolizines (Scheme 2) allows one to expect the possibility of unusual dipolar cycloaddition with the appropriate dienophiles. The first step of such reaction would be the nucleophilic addition at the position 5 followed by electrophilic intramolecular cyclization at the position 3.

In our recent communication[10] we have investigated theoretically the mechanism of [8+2] cycloaddition varying the polar nature of substituents in alkenes and comparing indolizine and 6-nitroindolizine. An ab initio and semiempirical (AM1 and SINDO1) calculations clearly confirm the possibility of three different mechanisms (Scheme 3). The concerted mechanism (A) is preferable, if there are no polar groups in a dienophile and indolizine. Another type (B) of stepwise cycloaddition (electrophilic addition−nucleophilic ring closure) should be realized for the case of nitroethylene. The last type (C) of dipolar cycloaddition (nucleophilic addition−electrophilic ring closure) would be expected for the reaction of 6-nitroindolizine with *N*,*N*-dimethylaminoethylene.

The last mechanism C is the most intriguing one, and its possibility (in contrast to cases A and B) has even never been discussed in the literature. No reaction of 6-nitroindolizines with the electron excessive alkenes have ever been reported. Our attempt to confirm experimentally the possibility of (cyclo)addition of 6-nitro-

Scheme 4. Reaction of Indolizine Ia and Aminoacetylene IIa



indolizines with simple aminoethylenes failed: no reaction occurs when 2-phenyl-6-nitroindolizine was refluxed with various enamines.[11] Meanwhile, as we found recently, 6-nitroindolizines may be involved in the [8+2] cycloaddition if the dimethyl acetylenedicarboxylate is chosen as the dienophile.[12] One would expect that acetylenes with donor substituents (e.g., highly reactive aminoacetylenes)[13] may be also involved in the [8+2] cycloaddition to 6-nitroindolizines, and the mechanism of the process may be related to the dipolar mechanism C.

In this article we study experimentally the reaction between 6-nitroindolizine and aminoacetylene and provide a theoretical quantum chemical analysis of the mechanism of the discovered process.

Results and Discussion

We found that the reaction of 2-phenyl-7-methyl-6-nitroindolizine **Ia** with 1-diethylamino-2-methylacetylene **IIa** led to the adduct **IIIa**.

According to the mass spectra, integral intensities in ^{1}H NMR spectra, and number of peaks in ^{13}C NMR spectra, the structure of the adduct was 1:1 (Scheme 4).

Careful NMR study of the obtained adduct was performed to elucidate its structure. The assignment of signals of protons and (nonquaternary) carbon atoms was carried out using ^{1}H and ^{13}C (proton decoupled and monoresonance) NMR spectra and multipulse 2D (COSY, HETCOR) and 1D (NOE) experiments (Table 1).

In the ^{1}H NMR spectra of the adduct the signals of the NEt_2 and CH_3 groups of the added acetylene together with a CH_3 group of the indolizine ring are observed in the aliphatic region. Assignment of protons H_1, H_3, and H_4 in the structure **IIIa** (former protons H_3, H_1, and H_8 of the indolizine **Ia**) as well as the protons of the 2-Ph group and Me group (attached to the pyridine fragment) was performed using NOE data and interproton coupling constants. According to these data the following sequence of closely spaced atoms can be traced:

$$\text{Me-}C_5 \leftrightarrow H_4 \leftrightarrow H_3 \leftrightarrow$$
$$o\text{-protons } H_{11}, H_{15} \text{ of 2-Ph} \leftrightarrow H_1$$

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Table 1. NMR Spectral Parameters of Ia and IIIa: ^{1}H and ^{13}C Chemical Shifts, Coupling Constants J_{HH} and J_{CH}, and Results of NOE Experiments

numbering of matching nuclei in **Ia**[a]	numbering of nuclei in **IIIa**[a]	$\delta(^1H)$, ppm (J_{HH}, Hz)		$\delta(^{13}C)$, ppm (^1JCH, Hz)		$^nJ_{CH}$ (Hz) obtained from SELJRES experiments for **IIIa**:[e] selective excitation of proton						results of NOE experiments for **IIIa**	
		Ia[a]	**IIIa**	**Ia**[b]	**IIIa**	H_1	H_3	H_4	H_{9a}	H_{16}	H_{17}	irradiated nucleus	% NOE (obsd proton)[h]
3	1	7.66	7.602 (1.6)	110.96 (189.5)	121.97 (188.1)		6.1		*g*			H_1	6.0 (H_{9a}); 5.7 (H_{11}); 3.8 (H_{17})
2	2[c]			*d*	135.00[f]	1.9	2.1						
1	3	6.72	6.480 (1.6; 0.3)	98.43 (173.7)	106.86 (170.6)	6.6		2.3				H_3	6.9 (H_4); 11.4 (H_{11})
9	3a[c]			*d*	131.03	6.4	7.6	6.0	*g*				
8	4	7.16	6.589 (0.3; 1.0)	119.26 (164.7)	125.16 (≈156)	2.2	2.3		1.4	5.9		H_4	5.5 (H_3); 6.7 (H_{16})
7	5[c]			*d*	118.00			1.9	*g*	7.1			
6	5a[c]			*d*	157.11			9.7	6.7	4.3			
	8[c]				169.24				4.4		4.2		
	9[c]				94.24				4.1		4.6		
5	9a	9.10	5.679	127.25 (185.1)	68.44 (147.4)	2.1					3.6	H_{9a}	4.7 (H_1); 1.8 (H_{17})
10	10[c]			*d*	126.45[f]	6.9	3.4						
11, 15	11, 15	7.65	7.523	126.44 (159.9)	125.22 (≈160)							H_{11}	3.1 (H_1); 5.9 (H_3); 12.1 (H_{12})
12, 14	12, 14	7.45	7.312	128.96 (159.4)	128.57 (≈161)							H_{12}	9.8 (H_{11}); 5.4 (H_{13})
13	13	7.31	7.164	127.66 (161.3)	125.88 (161.1)								
16	16	2.60	2.128 (1.0)	20.91 (129.9)	16.11 (128.5)			5.6				H_{16}	4.2 (H_4)
	17		1.474		17.18 (129.5)				5.3			H_{17}	3.0 (H_1); 1.1 (H_{9a}); 1.8 (H_{18a})
	18		3.895 (H_{18a})		42.65 (≈138)							H_{18a}	5.6 (H_{17}); 22.7 (H_{18b}); 9.0 (H_{19b})
			3.475 (H_{18b})		(≈138)								4.4 (H_{20}); 1.7 (H_{21})
	19		3.530 (H_{19a})		41.29 (138.5)							H_{19a}	18.2 (H_{19b}); 1.7 (H_{20}); 3.3 (H_{21})
			3.395 (H_{19b})		(138.5)							H_{19b}	5.3 (H_{18a}); 11.0 (H_{19a}); 2.5 (H_{20}); 7.0 (H_{21})
	20		1.315		14.57 (127.0)								
	21		1.222		12.58 (127.1)								

[a] See numbering of atoms in Scheme 4. [b] Assignment of signals in **Ia** was performed with COSY and HETCOR. [c] Quartenary carbon atoms. [d] Signals of quartenary carbons atoms in **Ia** at 122.08, 133.30, 133.88, 134.08, and 137.65 were not assigned. [e] SELJRES[15] is the nonrouting 2D-techniques which allows one to measure ^nJ(CH) for $n > 1$ by selective excitation of protons. [f] $^3J(C_2-C-C-H_{11}) \approx 7.6$ and $^3J(C_{10}-C-C-H_{12}) \approx 7$ Hz were estimated from the monoresonance ^{13}C spectra. [g] ^3J constants ($H_{9a}C_1$), ($H_{9a}C_{3a}$), and ($H_{9a}C_5$) were not observed in the SELJRES experiment. [h] % NOE was calculated by assuming 100% for the irradiated signal.[16]

Hence, this sequence in the adduct corresponds to the unchanged fragment C_7(Me)−C_8H−C_9−C_1H−C_2(Ph)−C_3H of the initial indolizine **Ia**. All signals of protons of the indolizine framework underwent an upfield shift, except that of H_3 which remained almost unchanged at 7.6 ppm. At the same time the most downfield signal H_5 of initial indolizine **Ia** (9.10 ppm) is not observed in the spectrum of the adduct, whereas the new one (H_{9a} in **IIIa**) at 5.68 ppm connected by the direct coupling constant $^1J_{CH} = 147.4$ Hz with carbon nuclei at 68.44 ppm appears.

The disappearance of the signal H_5 and retention of the signal H_3 of the initial indolozine **Ia** in the structure of adduct **IIIa** allow us to exclude the structure of cyclazine **IVa** from the possible reaction product: the acetylene moiety is clearly attached to the atom C_5 of the pyridine ring but not to the atom C_3 of the pyrrole fragment of molecule **Ia**.

The crucial point during the elucidation of the adduct **IIIa** structure was to assign the tertiary carbon atom with the chemical shift 68.44 ppm and determine its environment. We considered two alternatives: (a) Addition of acetylene may be accompanied by migration of the proton H_5 of initial indolizine and transformation of the carbon atom C_5 into the quarternary one with retention of its sp^2 hybridization. Then, the tertiary carbon atom at 68.44 ppm would belong to the added acetylene. (b) After acetylene addition, the hybridization of the C_5 atom in **Ia** becomes sp^3; then the tertiary carbon atom at 68.44 ppm would belong to the six-membered fragment of indolizine.

To clarify this dilemma we have carried out full assignment of the signals of carbon atoms including the seven quarternary ones. For this purpose we used the values of indirect coupling constants $^nJ_{CH}$ ($n > 1$) obtained in the course of the series of 2D experiments SELJRES (see Table 1). The superposition of obtained $^nJ_{CH}$ for each carbon atom fitted well with the multiplicity of their signals in the monoresonance ^{13}C spectrum.

On this base we detected the quarternary carbon atoms nearest to the phenyl substituent, namely C_{10}, C_2, and C_{3a} (126.45, 135.00, and 131.03 ppm, respectively), as well as the atoms neighboring to the methyl group of the indolizine fragment (δ for Me-C_5, NO_2−C_{5a}, and C_{3a} are 118.00, 157.11, and 131.03 ppm, respectively). Using the values of $^nJ_{CH}$ we placed the remaining quarternary carbon atoms at 169.24 (C_8) and 94.24 ppm (C_9) closer to the protons H_{17} of the methyl group of the added acetylene.

Finally, the signal of proton H_{9a} (attached to the tertiary carbon atom at 68.44 ppm) has a long-range coupling constant $^4J = 1.4$ Hz with the tertiary atom C_4 and, therefore, the peak at 68.44 ppm should be assigned to the sp^3 atom C_{9a} of the six-membered ring. (Alternative assignment of this carbon atom to acetylene fragment would require existence of the improbable constant $^6J = 1.4$ Hz.)

On the basis of the spectral data (Table 1) as well as results of Terrier,[14] we suppose the structure of the obtained adduct to be most likely isoxazine **IIIa** which can be considered as an unusual product of the [4+2] cycloaddition, where the sequence C_5−C_6−N−O of nitroindolizine plays the role of a diene-like moiety.

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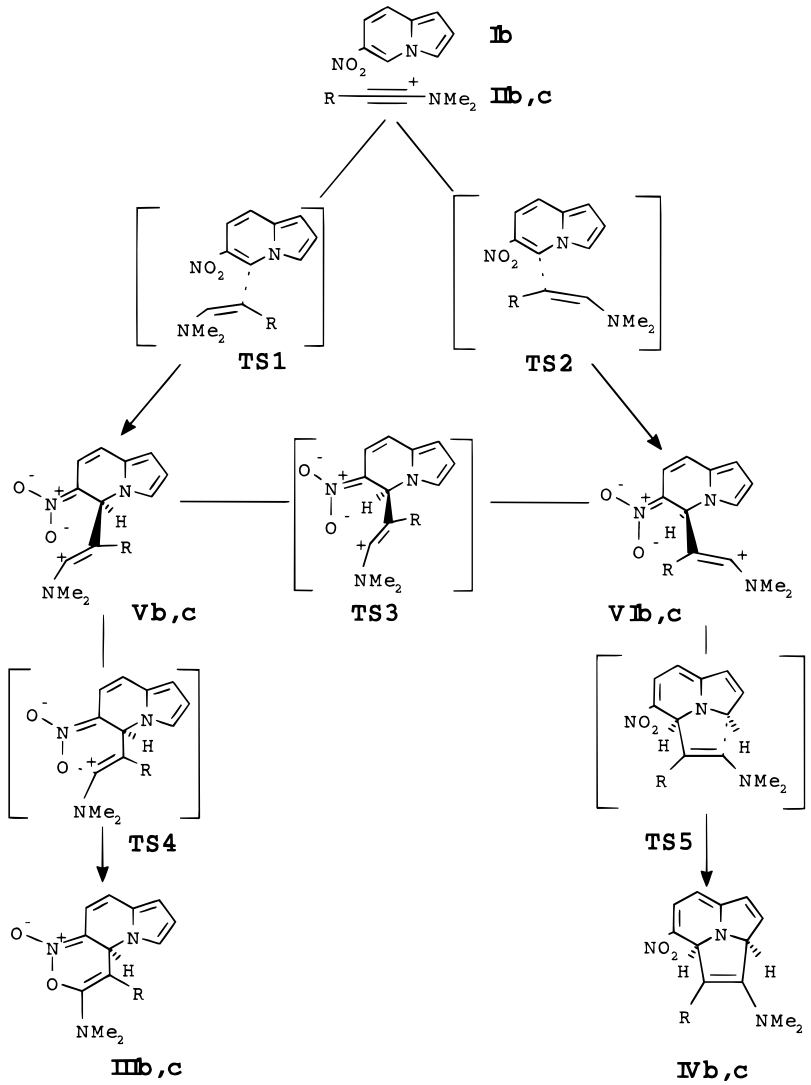
Scheme 5. Intermediates and Transition States of the Cycloaddition (b, R = H, and c, R = Me, for All Structures Except Ib)



The orientation of the aminoacetylene moiety in the adduct **IIIa** molecule was determined using the NOE technique. Thus, irradiation of the proton H_1 of the pyrrole ring causes response at protons H_{9a} (5.68 ppm) and the CH_3 group but not at the protons of the NEt_2 group. In turn, irradiation of protons H_{17} causes NOE at the nuclei H_1, H_{9a} and one of protons of the NEt_2 group. Hence, the methyl group of the aminopropyne fragment is located closer to atoms H_1 and H_{9a} than is the diethylamino group. The absense of response at the NEt_2 group upon irradiation of H_{9a} excludes migration of this proton to the aminoacetylene carbon atoms. Additional confirmation of the isoxazine structure of the adduct **IIIa** is the value of the chemical shift of the quaternary carbon atom at 169.24 ppm, typical for C−O bonds.

This quite unexpected experimental observation was theoretically examined and explained by the accurate ab initio study of the model reaction of 6-nitroindolizine with dimethylaminoacetylene.

Theoretical Study

For theoretical study of the discussed process we used the model reactions between 6-nitroindolizine **Ib** and simple *N*,*N*-dimethylaminoacetylenes **IIb**,**c**. For both reactions **Ib** + **IIb** and **Ib** + **IIc** the mechanisms have been investigated by the AM1 method, and the reaction **Ib** + **IIb** was additionally studied by ab initio RHF 6-31G*. (Both methods were used as implemented in Gaussian-94.)

The analysis of the potential energy surfaces (PES) for both reactions (**Ib** + **IIb** and **Ib** + **IIc**) was performed and the stationary points were located. All structures were fully optimized. No concerted pathway leading to **IIIb** was found. Structures **I**−**V** are minima on the PES without negative roots in the Hessian. Transtion states **TS1**−**TS5** are first-order saddle points on the PES with one negative root in the Hessian. The preliminary assumption on the regioselectivity of the reaction was that the carbon atom at the β-position of the aminoacetylenes binds to the six-membered ring of indolizine (as in

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Table 2. Energies (kcal/mol) of Reactants (I, II), Products (III, IV), Intermediates (V, VI), and Transition States (TS1, TS2, TS3, TS4, TS5) in Scheme 5

structure	**IIb**, $HC{\equiv}CN(CH_3)_2$ ab initio	**IIb**, $HC{\equiv}CN(CH_3)_2$ AM1	**IIc**, $CH_3C{\equiv}CN(CH_3)_2$ AM1
I + II	0	0	0
V	15.82	14.93	19.40
VI	15.58	14.28	21.11
III	−17.94	−9.45	−2.75
IV	−23.30	−24.31	−18.08
TS1	36.05	21.64	25.56
TS2	36.08	22.07	25.63
TS3	23.48	19.30	21.60
TS4	24.92	15.88	21.22
TS5	42.78	21.48	27.73

Scheme 5). An attempt to inverse the regioselectivity immediately resulted in a dramatic energy increase.

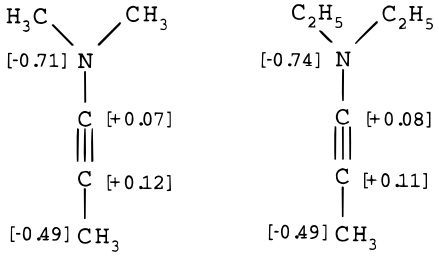
According to our calculations the mechanism of formation of the oxazines **IIIb**,**c** and cyclazines **IVb**,**c** can be generally represented by Scheme 5. Corresponding energies of the intermediates and transitions states are given in Table 2.

For both reactions the intermediates **V** and **VI** (Scheme 5) were discovered on the PES by ab initio and AM1 methods. The activation barriers leading to these intermediates are practically identical (cf. values **TS1** and **TS2** in Table 2). The structures of **V** and **VI** formally correspond to the nucleophilic attack of the β-carbon atom of the aminoacetylene to position 5 of the six-membered ring. The high dipole moment of about 17 D in the intermediates **V** and **VI** and charge distribution clearly indicate their zwitterionic character. The excess of electron density is located on the oxygen atoms of nitro group, whereas the positive charge is concentrated on the α-carbon atom of the aminoacetylene fragment.

The only difference between the structures **V** and **VI** is in the torsion angle between the aminoacetylene fragment and the plane of the indolizine bicycle. Therefore, the structures **V** and **VI** should be regarded as two rotational isomers (Scheme 6). The difference in their energies is negligible (see Table 2), and the rotation barrier is about 8 kcal/mol.

Evidently, the zwitterionic intermediates **Vb**,**c** are the precursors of the oxazines **IIIb**,**c**, whereas the zwitterions **VIb**,**c** are the intermediates of formation of the cyclazines **IVb**,**c**. The cyclazines **IV** are found more stable than the isomeric oxazines **III** (see Table 2). However, the activation barrier of the cyclization **VI** to **IV** is higher than for the barrier of conversion **V** to **III** (see Table 2). Therefore, just the difference in the activation energies at the step of cyclization (kinetic control) and not the final energy of the products (thermodynamic control) seems to be responsible for the experimentally observed direction of cycloaddition **I + II = III**. This effect is more pronounced in the ab initio calculation than in AM1. But except for the reduced barriers of the transition structures the AM1 results are very similar to the ab initio results and convey the same qualitative mechanism. It is worth mentioning that the charge distribution in the zwitterions **V** and **VI** is more favorable for the cyclization to oxazine **III** since the charge at the nitro group significantly exceeds the charge at position 3 of indolizine fragment.

Chart 1. Charge Distribution in Homologous Acetylenes IIb and IIa Computed by the ab Initio Method

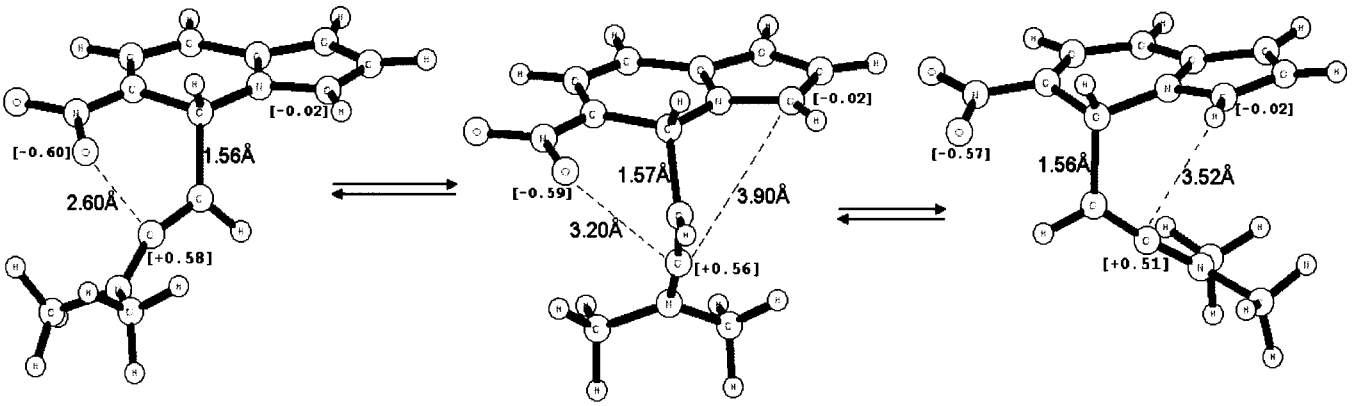


It is doubtful that the change from **IIb** to **IIa** (shift from NMe_2 to NEt_2 group) would seriously change the validity of the above theoretical conclusion. As it is shown in Chart 1, the charge distributions in **IIb** and **IIa** are almost the same.

Conclusion

It was discovered experimentally that in the case of reaction of 6-nitroindolizine with aminoacetylene the initial attack of dienophile indeed occurs at the six-membered fragment. Therefore, the theoretical prediction of the possibility of stepwise mechanism (step iv in Scheme 3) was confirmed by experiment. The initially formed zwitterion, however, is further stabilized by the intramolecular electrophilic attack to the oxygen atom of nitrogroup and not to the pyrrole fragment. Explanation of this fact on the background of ab initio calculations

Scheme 6. Important Geometrical Parameters (Å) and Atomic Charges (in Brackets) for Zwitterionic Intermediates Vb, VIb, and Transition State TS3



Vb **TS3** **VIb**

was suggested in terms of kinetic and thermodynamic control via the cycloaddition.

Experimental Section

NMR spectra were registered on a Fourier spectrometer (AM-360 "Bruker") (working frequency 360.13 and 90.56 MHz for ^{1}H and ^{13}C, respectively). The calculations were performed on SGI−Power Challenge M-Series RS8000 using Gaussian-94.[17]

2-Phenyl-7-methyl-6-nitroindolizine (**Ia**) was obtained according to the earlier described method;[17] samples of 1-(diethylamino)-2-methylacetylene and 1-ethoxy-2-methylacetylene were kindly offered by Prof. M. A. Kazankova. No reaction was observed when indolizine **Ia** was kept at 20 °C (or refluxed in benzene) for 48 h with 1-ethoxy-2-methylacetylene.

Reaction between Ia and IIa. To suspension of nitroindolizine (**Ia**) (0.12 g, 0.48 mmol) in benzene (20 mL) was added an excess of acetylene **IIa** (0.8 g, 7.21 mmol). After 24 h of keeping the mixture at 20 °C, homogeneous brown solution formed. The solvent was removed in vacuo at 30−40 °C. The residual oil was dissolved in chloroform (20 mL) and passed through a silica gel column (3 cm). The solution was collected and evaporated, and the resulting brown oil was purified by gradient column chromatography (SiO_2, hexane, and then 1:1 benzene/ethyl acetate). The fluorescent fraction was collected giving 0.065 g (37%) of 5,9-dimethyl-8-(diethylamino)-2-phenyl-6-oxo-9a(*H*)-indolizino[6,5-*c*][1,2]isoxazine (**IIIb**) as a brown oil. Mass spectrum [*m*/*z* (%)]: 363 (7.8, M^+), 264 (19), 263 (100), 235 (2.1), 221 (5.3), 194 (4.3), 100 (3.2), 72 (5.3).

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