JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 11, 201–208 (1998)

Mechanism of cycloaddition to indolizines

Vahan V. Simonyan, Alexander I. Zinin, Eugene V. Babaev and Karl Jug*

[1]Chemistry Department, Moscow State University, Moscow 119899, Russia.
[2]Theoretische Chemie, Universität Hannover, Am Kleinen Felde 30, Hannover D 30167, Germany

Received 3 February 1997; revised 16 June 1997; accepted 31 July 1997

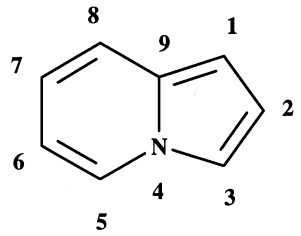
ABSTRACT: The peculiarities of [8 + 2] cycloaddition reactions of indolizines with dienophiles are reviewed. Quantum chemical SINDO1, AM1 and *ab initio* calculations of transition states were performed for [8 + 2] cycloaddition reactions of indolizine and 6-nitroindolizine with a series of alkenes with donor and acceptor groups. The calculations predict a dipolar cycloaddition mechanism (electrophilic addition and ring closure) for reactions of indolizine and 6-nitroindolizine with nitroethylene. For the reaction of 6-nitroindolizine with *N,N*-dimethylaminoethylene, the predicted mechanism corresponds to a previously unknown 'inverse' dipolar cycloaddition (nucleophilic addition and ring closure). © 1998 John Wiley & Sons, Ltd.

KEYWORDS: indolizines; cycloaddition; reaction mechanism

INTRODUCTION

Heterocycles form one of the most important and well investigated classes of organic molecules owing to their occurrence in living organisms and a wide range of biological activity. The key role in heterocyclic chemistry belongs to heteroaromatic structures, in particular to five- and six-membered rings and their fused-ring derivatives. It is well known that the difference in chemical behavior between five- and six-membered rings is accounted for by the different aromaticities and different π-excessive or π-deficient characters of their electronic structures, e.g. pyrrole and pyridine.[1,2]

Indolizine (**1**) is the simplest heteroaromatic molecule containing both a π-excessive pyrrole and a π-deficient pyridine ring with only one bridgehead nitrogen, the whole system being isomeric with indole.



The analogy with indole gave rise to an intensive development of indolizine chemistry to obtain biologically active structures that mimic indole derivatives (for reviews see, e.g., Refs 3 and 4).

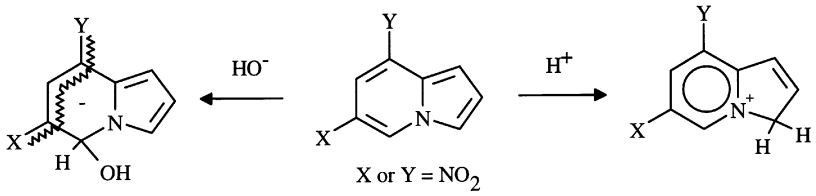
Being a 10 π-electron planar molecule, indolizine shows a behavior typical of aromatic systems. A number of estimates of its relative aromaticity and reactivity indices have been made.[5–9] As predicted, electrophilic substitution in indolizines takes place exclusively in the pyrrole ring, namely at positions 3 and 1. Nucleophilic reactions characteristic of pyridine are not known for indolizine, the only chemical evidence for the π-deficient character of its six-membered ring being increased C—H acidity of methyl groups in 5-methylindolizines employed in their reactions with carbonyl compounds.[10,11] Hence indolizine has been long considered as a typical π-excessive heterocycle like pyrrole or indole.

This viewpoint, however, was recently challenged. It has been shown that the introduction of a nitro group at position 6 or 8 of the indolizine bicycle imparts local π-deficient properties to its pyridine ring. Thus, 6- and 8-nitroindolizines readily undergo addition of a nucleophile at C-5, forming in an alkaline medium stable Meisenheimer-type anionic σ-complexes. At the same time, the π-excessive properties of their pyrrole ring are not lost, as is evident by protonation at C-3 in strong acids. This presents an unparalleled example of 'π-amphoteric' behavior of a heterocycle[12,13] (see Scheme 1).

Although indolizine is certainly aromatic, significant alternations of the bond lengths around the ring system were detected by x-ray,[14] NMR and UV spectroscopy[15] and even mass spectrometry[16] in various substituted indolizines. This prompts some tetraene-like character of the compound, in particular its ability to enter into cycloaddition reactions, which were indeed observed.[17–24] Various reactivity types can be found among the reactions of indolizines with unsaturated compounds. The following regularities can be revealed in these reactions.

**Correspondence to* K. Jug, Theoretische Chemie, Universität Hannover, Am Kleinen Felde 30, Hannover D 30167, Germany.
Contract/grant sponsor Volkswagen-Stiftung.

 CCC 0894–3230/98/030201–08 $17.50

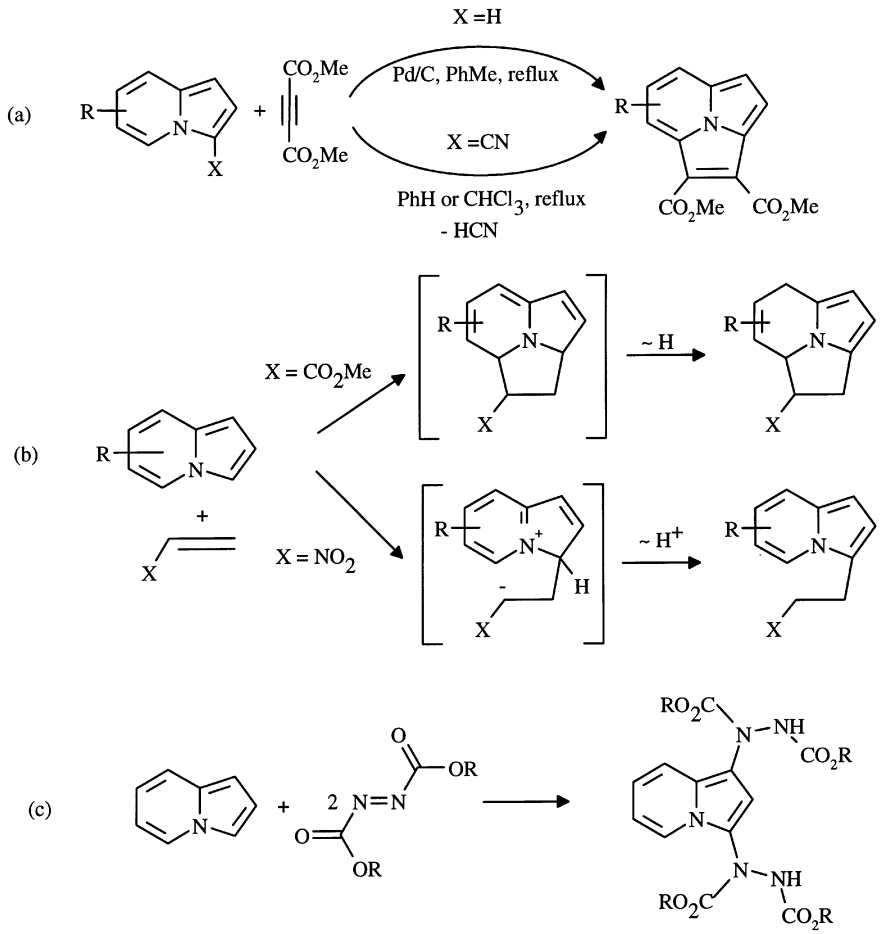


Scheme 1. Illustration of 'amphoteric' reactivity of 6(8)-nitroindolizines

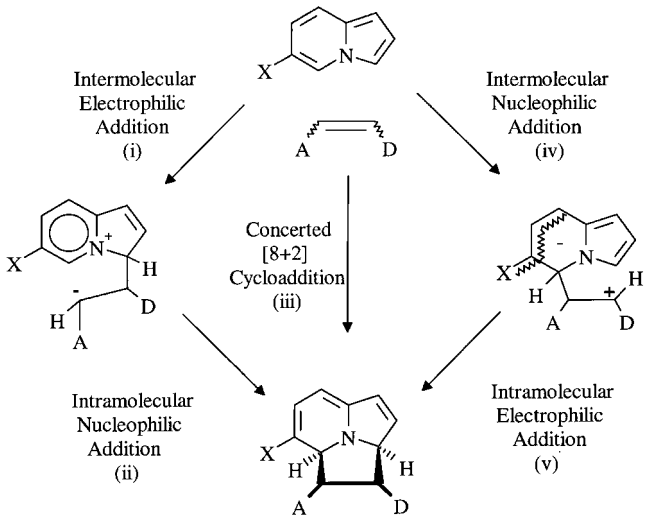
1. Formation of cycl[3.2.2]azines. Esters of maleic, acrylic,[17] acetylenedicarboxylic[18–24] and phenylpropiolic[18] acids and some 1,2-dicarbonitriles[23] enter into cycloaddition reactions [see reaction (a) in Scheme 2]. However, it is important to note that the formation of 'direct' Diels–Alder adducts has never been reported for these alkenes and alkynes. Instead, if the reaction of an alkyne with indolizine is carried out in the presence of a dehydrogenating catalyst, cycl[3.2.2]azines are formed that are the products of aromatization of the initial cycloadducts. If a leaving group is present at position 3 of indolizine, reactions with alkynes also lead to cycl[3.2.2]azines as a result of elimination of HCN.

2. Formation of either hydrocycl[3.2.2]azines or Michael adducts. Alkenes with stronger acceptor substituents, e.g. nitroethylene,[25] maleic anhydride and *N*-methylmaleimide,[17] mainly result in the products of 3-substitution. The product of reaction between indolizine and methyl acrylate has been treated as the result of cycloaddition followed by a 1,5-shift of hydrogen, [see reactions (b) in Scheme 2].

3. Formation of only the Michael adducts. Strong electrophiles such as tetracyanoethylene[26] and azodicarboxylates[24,27] attack positions 1 and/or 3 of the indolizine ring, forming exlusively Michael adducts [see reaction (c) in Scheme 2]. It should be also mentioned that simple



Scheme 2. Examples of cycloaddition and addition reactions of indolizines with dienophiles



Scheme 3. Possible mechanisms of the cycloaddition expected for 6(8)-nitroindolizines (example shown for 6-nitroindolizine, X = NO_2)

alkenes and alkynes (e.g. cyclohexadiene and diphenylacetylene) without electron-withdrawing groups do not react with indolizines.[18]

To explain this reactivity pattern and also the regioselectivity of the reactions of indolizines with acrylates, a mechanism was proposed.[17] The mechanism, generally represented in Scheme 3 by reactions (i) and (ii), includes electrophilic attack (i) of an alkene on C-3 of the indolizine ring with subsequent cyclization (ii) with formation of tetrahydrocyclazines or proton migration (forming a Michael adduct). The cyclic product can then undergo a sigmatropic hydrogen shift. In turn, an open-chain product (Michael adduct) can be further attacked by a second molecule of an electrophile at C-1.

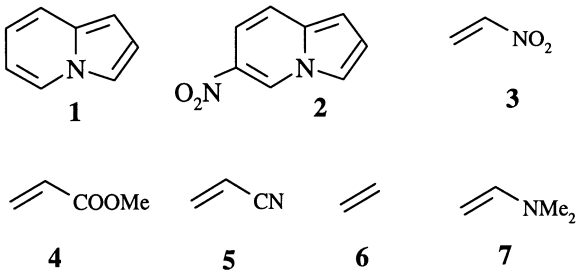
One may conclude that the possibility of [8 + 2] cycloaddition (iii), either concerted or *via* a biradicaloid intermediate, cannot be excluded on the basis of the present experimental data. Furthermore, if the polar mechanisms can indeed take place, one might expect one more possible mechanism of cycloaddition [see reactions (iv) and (v) in Scheme 3]. Indeed, if an alkene with a donor substituent would react with an indolizine having an electron-withdrawing group in the pyridine ring, then the first step of the cycloaddition may be intermolecular nucleophilic addition (iv), followed by intramolecular electrophilic ring closure (v). The appropriate indolizines may be 6(8)-nitroindolizines as described above, which are structures with comparable affinities to both electrophiles and nucleophiles. Therefore, for the reactions of 6(8)-nitroindolizines with substituted alkenes a variety of cycloaddition mechanisms may be expected, e.g. those presented in the Scheme 3.

Evidently, a predominance of one or another mechanism should strictly depend on the nature of the polar substituents in the alkene. To our knowledge, neither the reactions of nitroindolizines with unsaturated compounds nor the interaction of indolizines with nucleophilic (donor-substituted) alkenes have been yet investigated.

It was the aim of this study to clarify the details of the mechanism of cycloadditions to indolizines and to elucidate the factors determining the possibility, direction and regioselectivity of these reactions.

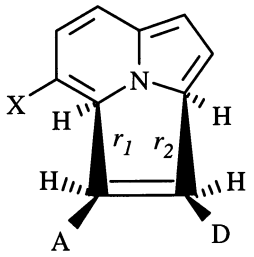
RESULTS AND DISCUSSION

Two indolizines (**1** and **2**) and the series of alkenes **3**–**7** with varying donor/acceptor property of the substituents were chosen.



Two semiempirical methods were applied for a theoretical study of the mechanisms of these reactions: SINDO1[28] and AM1.[29] The former was used with a new parametrization[28c] (version 3.4). The latter was used as implemented in MOPAC (version 6.0) and Gaussian-94. These methods are established and have been repeatedly used for this purpose in the past. The calculations were carried out at the SCF level. The analysis of the potential energy surfaces (PES) for the reactions of alkenes **3**–**7** with indolizine (**1**) and 6-nitroindolizine (**2**) was performed and the stationary points were located. For comparison, additional *ab initio* calculations were used for the cases of reactions of **1** + **3** and **2** + **7**. Initial assumptions on the structure of transition states (TSs) were based on the linear interpolation of the structures of the initial molecules (ensemble of an indolizine and alkene) and final products (*cis*-tetrahydrocyclazines) and scanning of internal coordinates with the highest contribution to the reaction coordinate. From a geometry near the saddle point the structures were optimized by the appropriate algorithm [implemented in SINDO1 (version 3.4), MOPAC (version 6.0), and Gaussian-94], thus giving the TS for the reaction of indolizine with ethylene.

The preliminary assumption on the regioselectivity of the reaction was the following: the donor-substituted end of the double bond of an alkene is electrophilic and hence binds to the five-membered ring of indolizine; analogously, the acceptor-substituted end of an alkene is nucleophilic and binds to the six-membered ring as in Scheme 3. The validity of this polarity control rule was proved by calculations: an attempts to inverse the regioselectivity immediately resulted in a dramatic energy increase. It was also proved that the most stable



Scheme 4. Structure of the TS for reactions of indolizines **1** and **2** with alkenes **3**–**7**

arrangement of reactants should have a *threo* configuration, and just these diastereomers were chosen for further calculations.

The most obvious way to describe changes in geometries via reaction is to present the lengths of the bonds to be formed, i.e. the distances between the ends of ethylene moiety and the corresponding C-5 and C-3 positions of the indolizine ring (denoted r_1 and r_2 in Scheme 4).

One can consider as the reference point for the influence of substituents on the mechanism of cycloaddition the reaction between unsubstituted indolizine (**1**) and ethylene (**6**). One makes the crude assumption that shortening of the r_1 distance in a transition state can be treated as evidence for the shift of the mechanism to an electrophilic addition process. On the other hand, shortening of the r_2 distance may be associated with the predominance of an as yet unknown nucleophilic addition mechanism. The results of calculations are presented in Table 1, where the corresponding activation energies are given together with the r_1 and r_2 values.

Analysis of the data in Table 1 gives rise to three possible mechanisms for the [8 + 2] cycloaddition reaction, as follows.

Concerted cycloaddition

In seven cases (namely **1** + **4**, **1** + **5**, **1** + **6**, **1** + **7**, **2** + **4**, **2** + **5** and **2** + **6**), the only TS found by both methods corresponds to a concerted cycloaddition of an alkene to indolizine; no zwitterionic intermediates have been located on PES. Both the SINDO1 and AM1 methods agree in predicting high activation energies for these reactions.

For reaction of the indolizine (**1**) with alkenes **4**–**6** the activation barrier decreases when the acceptor groups is inserted into the ethylene moiety, and the lowest activation energy (predicted by both methods) for this series is for the reaction **1** + **4**. This reaction (indolizine + methyl acrylate) is reported to occur as a formal cycloaddition. [see reaction (b) in Scheme 2]. An important feature of the influence of the CN and COOMe groups is the shortening of the distance r_1 and increase in the distance r_2 in the TSs, observed with both semiempirical methods. This may indicate that the mechanism of the reaction

Table 1. Results of SINDO1 and AM1 calculations of TSs and intermediates for reactions of indolizines **1** and **2** with alkenes **3**–**7**[a]

Reactants (function in alkene)	Mechanism	SINDO1						AM1					
		TS1		Zwitterion		TS2		TS1		Zwitterion		TS2	
		ΔE		ΔE		ΔE		ΔE		ΔE		ΔE	
		r_1	r_2	r_1	r_2	r_1	r_2	r_1	r_2	r_1	r_2	r_1	r_2
1 + **3**	(i) + (ii)	30.4		22.5		29.5		20.0		12.7		14.7	
(NO_2)		3.29	1.89	3.16	1.58	2.44	1.58	3.02	1.86	2.98	1.55	2.60	1.57
1 + **4**	(iii)	38.6		Not found		Not found		26.4		Not found		Not found	
(COOMe)		3.24	1.78					2.88	1.79				
1 + **5**	(iii)	42.1		Not found		Not found		29.8		Not found		Not found	
(CN)		>3.5	1.78					2.83	1.76				
1 + **6**	(iii)	61.3		Not found		Not found		35.3		Not found		Not found	
(H)		2.29	1.89					2.15	2.04				
1 + **7**	(iii)	53.9		Not found		Not found		37.8		Not found		Not found	
(NMe_2)		1.87	3.01					1.88	2.38				
2 + **3**	(i) + (ii)	34.4		30.8		36.3		26.7		22.4		23.6	
(NO_2)		3.29	1.78	3.18	1.61	2.49	1.58	2.01	1.81	2.96	1.56	2.66	1.57
2 + **4**	(iii)	43.8		Not found		Not found		32.5		Not found		Not found	
(COOMe)		3.29	1.78					2.90	1.73				
2 + **6**	(iii)	59.6		Not found		Not found		34.5		Not found		Not found	
(H)		2.15	2.01					2.08	2.11				
2 + **7**	(iv) + (v)	32.4		25.8		45.5		21.9		19.2		21.1	
(NMe_2)		1.89	3.54	1.60	3.76	1.64	2.45	1.84	3.16	1.60	3.07	1.58	2.49

[a] For every TS and zwitterionic intermediate energy ΔE (kcal/mol) is shown; r_1 and r_2 (Å) are the distances between an alkene and indolizine moieties in TS as indicated in Scheme 4.

Table 2. Results of *ab initio* calculations of TSs for reactions of **1** + **3** and **2** + **7** where the shift in reaction mechanism is predicted.[a]

Reactants (function in alkene)	**1** + **3** (NO_2)			**2** + **7** (NMe_2)		
	TS1	Zwitterion	TS2	TS1	Zwitterion	TS2
	ΔE	ΔE	ΔE	ΔE	ΔE	ΔE
Method	r_1 r_2	r_1 r_2	r_1 r_2	r_1 r_2	r_1 r_2	r_1 r_2
6–31G	25.4	11.7	21.2	20.9	19.5	21.3
	3.0 1.95	3.0 1.56	2.76 1.59	1.98 3.37	1.60 3.16	1.60 2.93
6–31G**[b]	26.8	16.4	26.3	28.4	27.5	28.6

[a] For every TS and zwitterionic intermediate energy ΔE (kcal/mol) is shown; r_1 and r_2 (Å) are the distances between an alkene and indolizine moieties in TS as indicated in Scheme 4.
[b] Geometries optimized by RHF 6–31G.

1 + **4** is much more likely to be explained in terms of a continuous shift from one discrete mechanism [concerted reaction (iii)] to another polar one [electrophilic addition (i) – ring closure (ii)] (Scheme 3).

The insertion of the donor NMe_2 group (cf. reactions **1** + **6** and **1** + **7**) shows the opposite (to the influence of acceptor groups) effect on the changes of distances r_1 and r_2. In spite of the concerted mechanism predicted for this reaction by both the SINDO1 and AM1 methods, the asymmetry of the TSs again indicates the trend of a change in mechanism to the opposite direction [nucleophilic addition (iv) – ring closure (v)] (see Scheme 3).

One can deduce from these data that the concerted cycloaddition of indolizine (**1**) with alkenes **6** and **7** may be impossible owing to the high activation barrier of the process. As was mentioned above, no such reactions have ever been performed, and the reaction of indolizine with simple cyclic alkenes gave no cycloaddition products.

'Direct' polar cycloaddition

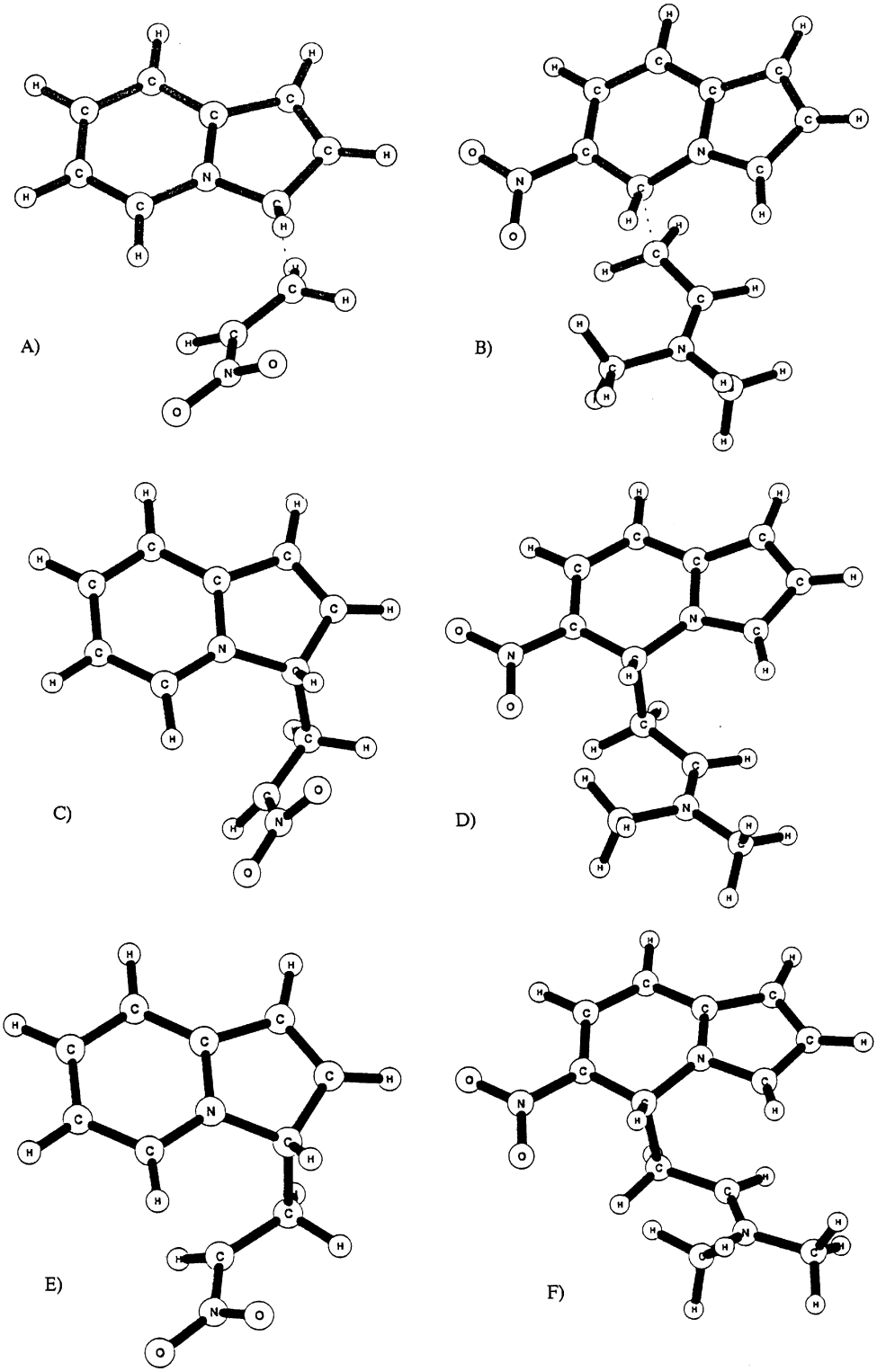
In the case of nitroethylene (reactions **1** + **3** and **2** + **3**) a pronounced change in reaction mechanism is observed. The zwitterionic intermediates can be located on the PES by both semiempirical methods (Table 1), and their appearance is also proved by *ab initio* calculations (Table 2). The activation barrier of their formation is the lowest in comparison with the analogous acceptor ethylenes **4** and **5**. The structure of the zwitterion (illustrated for reaction **1** + **3** by structure C in Scheme 5) corresponds to electrophilic addition of the nitroethylene to the five-membered fragment of the indolizine bicycle. The positive charge is localized in the indolizine ring, and the negatively charged fragment is the nitroethylene moiety. The second TSs (see, e.g., structure E in Scheme 5) leading from these zwitterions to the final cyclazines have been located for both reactions **1** + **3** and **2** + **3**. Therefore, the predicted mechanism for these reactions should be assigned to intermolecular electrophilic addition on the pyrrole moiety followed by intermolecular nucleophilic addition on the pyridine fragment.

As mentioned, the experimentally observed reaction of nitroalkenes with indolizines appeared to be exclusively Michael addition, thus corresponding only to the first step (i) in Scheme 3 followed by a proton shift. This means that the 'pure' dipolar mechanism of cycloaddition [including steps (i) + (ii)] is not realized in practice even for such a strongly π-deficient alkene as nitroethylene. The reason why no cycloaddition is observed may be due to the stability of the zwitterion C, the high acidity of the proton at position 3 and the high basicity of the carbanion center adjacent to the nitro group. As a result, the conjugated by-process of proton migration in the stable zwitterion may preserve the possibility of ring closure to the cycloadduct.

'Inverse' polar cycloaddition

The most intriguing situation occurs in the case of the reaction **2** + **7** (6-nitroindolizine with dimethylaminoethene). For this reaction, another type of zwitterion is discovered on the PES by the SINDO1 and AM1 methods. The structure of this zwitterion (structure D in Scheme 3) corresponds to nucleophilic attack of the carbon atom of the enamine on position 5 of the six-membered ring. The activation barrier for zwitterion formation (structure B in Scheme 5) is lower than in any of the investigated concerted reactions. The second TS (structure F) for ring closure of this zwitterion to a cyclazine structure may also be located on the PES by both semiempirical methods. Therefore, the general picture for the entire cycloaddition process corresponds to the mechanism (iv) + (v) in Scheme 3, i.e. to the nucleophilic attack of the π-excessive alkene on the pyridine ring of indolizine followed by intramolecular electrophilic cyclization according to both semiempirical methods. The same peculiarity of mechanism (appearance of zwitterion *D* and two TSs, *B* and *F*) was proved at the *ab initio* level (Table 2).

The charge distribution in zwitterion *D* is opposite to that zwitterion *C* in the 'direct' mechanism. Negative charge in structure *D* is located in the indolizine ring



Scheme 5. The geometry of TSs and zwitterions calculated by an *ab initio* method (RHF 6–31G). The structures correspond to the reactions **1** + **3** (A, C, D) and **2** + **7** (B, D, F). Structures A and B are the TSs leading to the zwitterions C and D, respectively and structures E and F are TSs for the formation of the cyclazine skeleton

(mainly at the 6-nitro group), whereas the positive charge is on the enamine fragment. Comparison of results for reactions of enamine **5** with indolizine (concerted mechanism) and 6-nitroindolizine ('inverse' polar cycloaddition) clearly illustrates that the 6-nitro group in the indolizine not only decreases the activation barrier, but also completely changes the reaction mechanism itself to type (iv) + (v).

Table 3. Illustration of predicted mechanisms

Substituent	Indolizine (**1**)	6-Nitroindolizine (**2**)
Nitroethylene (**3**)	(i) + (ii)	(i) + (ii)
Methyl acrylate (**4**)	(iii)	(iii)
Acrylonitrile (**5**)	(iii)	(iii)
Ethylene (**6**)	(iii)	(iii)
N,*N*-Dimethylaminoethylene (**7**)	(iii)	(iv) + (v)

CONCLUSION

Both the SINDO1 and AM1 semiempirical methods give consistent assignment of [8 + 2] cycloaddition reactions to one or another type of mechanism. A qualitative picture of the mechanisms predicted by the two methods is given in Table 3.

The reference reaction (**1** + **6**) is closest to a synchronous concerted mechanism. An increase in the acceptor properties of the substituent in ethylene leads to decrease in the activation barrier, higher asymmetry in geometry and charge distribution in TSs. The boundary case is nitroethylene, where the reaction occurs via a zwitterion, and the initial step is the electrophilic addition reaction. Insertion of the donor group in ethylene leads to the opposite trend in the geometry and charge distribution in the TS (reaction **1** + **7**); the mechanism, however, remains concerted. The appearance of a 6-nitro group in the indolizine ring slightly hinders the mechanism from occurring via 'direct' polar cycloaddition with alkenes **3**–**6** and promotes the opposite mechanism of 'reverse' cycloaddition in the case **2** + **7**.

Qualitative predictions of semiempirical methods on the shift in mechanism from concerted to dipolar for cases **1** + **3** and **2** + **7** are supported by *ab initio* calculations. Comparison of quantitative data (energy values and geometries for TS structures and zwitterions) obtained by *ab initio* methods (Table 2) with those obtained by the SINDO1 and AM1 methods demonstrate that the SINDO1 results are closer to the *ab initio* data than the AM1 results. Therefore, the SINDO1 method is better for use in further investigations of cycloaddition reactions in the indolizine series.

As mentioned above, no cycloaddition reaction is experimentally observed in the case of nitroethylene, probably owing to the possibility of proton shifts in the zwitterion leading to a Michael-type adduct. One may expect that the 'direct' polar cycloaddition mechanism would be the most probable for those indolizines where such a hydrogen shift is impossible e.g. in the series of 3-substituted indolizines (e.g. 3-methylindolizine and nitroethylene).

The predictions obtained for the reaction **2** + **7** may indicate the unknown ability of 6-nitroindolizines to react with donor-substituted alkenes (e.g. enamines or enol ethers) by a previously unknown mechanism, (iv) + (v) (see Scheme 3), with the initial step being a nucleophilic addition to C-5 of the pyridine fragment, followed by electrophilic ring closure to atom C-3 of the pyrrole fragment. The experimental confirmation of this hypothesis is under investigation.

Acknowledgments

The authors thank the Volkswagen-Stiftung for generous support of this work. V. V. Simonyan and A. I. Zinin thanks the members of theoretical chemistry group in Hannover for help with the calculations. The calculations were performed on a VPP300 at RRZN Hannover and on an SGI-Power Challenge M-Series RS8000.

REFERENCES

1. A. R. Katritzky and C. W. Rees (Eds). *Comprehensive Heterocyclic Chemistry*, Vols 1–8. Pergamon Press, Oxford (1984).
2. A. R. Katritzky, V. Feygelman, G. Musumarra, A. Barczynsky and M. Szafran. *J. Prakt. Chem.* **332**, 853–869 (1990).
3. F. J. Swinborne, J. H. Hunt and G. Klinkert. *Adv. Heterocycl. Chem.* **23**, 103–170 (1978).
4. W. Flitsch. in *Comprehensive Heterocyclic Chemistry*, edited by A. R. Katritzky and C. W. Rees, Vol. 4, p. 443. Pergamon Press, Oxford (1984).
5. H. C. Longuet-Higgins and C. A. Coulson. *Trans. Faraday Soc.* 87–94 (1947).
6. K. Fukui, T. Yonesawa, C. Nagata, H. Singu. *J. Chem. Phys.* **22**, 1433–1442 (1954).
7. E. M. Evleth. *Theor. Chim. Acta* **16**, 22–32 (1970).
8. P. Crews, R. R. Kinter and H. C. Padget. *J. Org. Chem.* **38**, 4391–4395 (1973).
9. B. A. Hess and L. S. Schaad. *Tetrahedron Lett.* **6**, 535–538 (1977).
10. J. W. Dick, W. K. Gibson, D. Leaver and J. E. Roff. *J. Chem. Soc, Perkin Trans. 1* 3150–3157 (1981).
11. R. J. Windgassen Jr, W. H. Saunders and V. Boekelheide. *J. Am. Chem. Soc.* **81**, 1459–1465 (1959).
12. E. V. Babaev. *Bull. Soc. Chim. Belg.* **101**, 823–824 (1992).
13. V. I. Terenin, E. V. Babaev, M. A. Yurovskaya and Yu. G. Bundel. *Khim. Geterotsikl. Soedin. (Engl. Transl)* **6**, 658–670 (1992).
14. E. Oeser. *Chem. Ber.*, **105**, 2351 (1972).
15. S. I. Bobrovskii, E. V. Babaev and Yu. G. Bundel. *Khim. Geterotsikl. Soedin. (Engl. Transl.)* **2**, 169–174 (1987).
16. S. I. Bobrovskii, E. V. Babaev and Yu. G. Bundel. *Moscow University Chem. Bull. (Engl. Transl.), Ser. Chem.* **40**, 112–113 (1985).
17. S. Ikeda, S. Kajigaeshi and S. Kanemasa. *Chem. Lett.* 367–372 (1976).
18. A. Galbraith, T. Small, R. A. Barnes and V. Boekelheide. *J. Am. Chem. Soc.* **83**, 453–458 (1961).
19. W. Flitsch and U. Kraemer. *Adv. Heterocycl. Chem.* **22**, 321–365 (1978).
20. J. Aihara. *Bull. Chem. Soc. Jpn.* **51**, 1788–1792 (1978).
21. E. K. Pohjala. *J. Heterocycl. Chem.* **15**, 955–960 (1978).

22. T. Uchida and K. Matsumoto. *Chem. Lett.* 149–150 (1980).
23. V. Batroff and W. Flitsch. *Liebigs Ann. Chem.* 621–628 (1987).
24. W. Flitsch and J. Heinrich. *Tetrahedron Lett.* **21**, 3673–3676 (1980).
25. I. Antonini, F. Claudi, U. Gulini, L. Micossi and F. Venturi. *J. Pharm. Sci.* **68**, 321–324 (1979).
26. O. Ceder and B. Hall. *J. Heterocycl. Chem.* **15**, 1471–1473 (1978).
27. M. Masumura and Y. Yamashita. *Heterocycles* **12**, 787–790 (1979).
28. D. N. Nanda and K. Jug. *Theor. Chim. Acta* **57**, 95–106 (1980); K. Jug and D. N. Nanda. *Theor. Chim. Acta.* **57**, 107–130, 131–144 (1980); B. Ahlswede and K. Jug. to be published.
29. M. J. S. Dewar, E. G. Zoebisch, E. F. Healey and J. J. P. Stewart. *J. Am. Chem. Soc.* **107**, 3902–3909 (1985).

