NUCLEOPHILIC RING OPENING AND THE FORMATION OF SATURATED HETEROCYCLES.

11. QUANTUM-CHEMICAL INVESTIGATION OF THE REACTIVITIES OF AZIRIDINE AND 2-METHYLAZIRIDINE IN AMINOLYSIS REACTIONS

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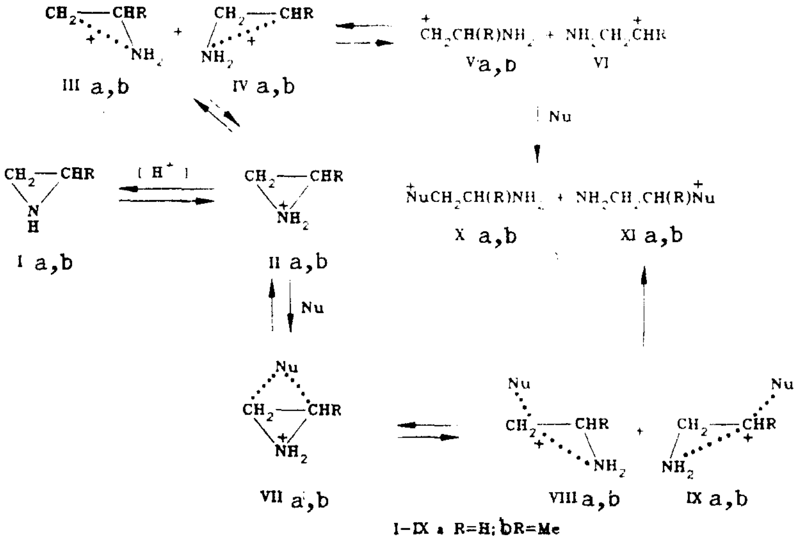
The aminolysis of aziridine and 2-methylaziridine in the gas phase was investigated by the MNDO method. Using the Germer solvatone model, modified for the MNDO computational scheme, we studied the effect of a polar medium on the ammonolysis of aziridine and 2-methylaziridine. We showed that the most probable mechanism for the investigated reactions is an A_c2 mechanism; however, in polar media the realization of the A_a2 mechanism is possible in the case of sterically hindered amines. We found that the determining factor for the nucleophilic opening of aziridine rings is the three-dimensional structure of the nucleophile rather than its basicity.

The study of processes involving the opening and formation of nitrogen-containing heterocycle that are intermediates in many organic reactions [2] is of great theoretical and practical interest. In the literature A1 and A2 mechanisms are used to describe such reactions; in the case of the A2 mechanism the question may revolve around not only the classical variant with the synchronous cleavage and formation of bond but also an asynchronous process. This is the so-called borderline [3] or loose [4] A2 mechanism. In the case of oxirane [3, 4] it has been shown that in the asynchronous process the rate of cleavage of the C—O bond is higher than the rate of formation of a new C—Nu bond. An extreme case of this sort of reaction pathway is the A1 mechanism in which the total cleavage of the C—heteroatom bond takes place even before the start of the formation of the C—Nu bond. Since in the Soviet literature the nomenclature of the types of mechanisms and transition states for reactions involving nucleophilic ring opening has not been firmly established, we will use the following terminology and designations: A_c2 will be used to designate the synchronous A2 mechanism, and A_a2 will be used to designate the asynchronous A2 mechanism.



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*See [1] for communication 10.

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TABLE 1. Geometrical and Energy Characteristics of the Steady-State Points on the Potential-Energy Surface of Reactions Involving the Amination of Aziridine and 2-Methylaziridine

Reaction	Mechanism	Steady-state point	Heats of formation, kJ/mole		ℓ, pm*				Angles, deg*		
			Gas phase	Solution	$N_{(1)}-C_{(2)}$	$N_{(1)}-C_{(3)}$	$C_{(2)}-C_{(3)}$	$C_{(3)}-Nu$ ($C_{(2)}-N_{(4)}$)	$N_{(1)}C_{(2)}C_{(3)}$ ($N_{(1)}C_{(3)}C_{(2)}$)	$C_{(2)}C_{(3)}Nu$ ($C_{(3)}C_{(2)}N_{(4)}$)	$N_{(1)}C_{(2)}C_{(3)}Nu$ ($N_{(1)}C_{(3)}C_{(2)}Nu$)
(1)		I b	70,9		148,4	147,5	152,3		(59,3)		
(1)		II b	761,5	622,5	152,7	151,3	152,4		(60,4)		
(1)		IV b	862,3	695,8	230,3	146,3	151,7		(101,2)		
(1)	A_a2	IX b	802,1	631,5	230,7	146,4	151,7	(306,1)	(101,4)	(97,6)	(174,1)
(1)	A_c2	IX b	809,3	650,4	201,6	146,5	151,6	(235,1)	(85,1)	(97,6)	(166,9)
(1)		III b	918,3	738,5	146,9	231,9	150,0		102,7		
(1)	A_a2	VIII b	855,7	671,4	147,0	228,7	150,5	313,5	100,5	109,0	−155,0
(1)	A_c2	VIII b	802,1	652,1	148,2	176,6	152,1	201,3	72,0	104,9	177,3
(2)—(11)		I a	105,3		147,9	147,9	151,5		59,2		
(2)—(11)		II a	801,5	656,4	151,8	151,9	151,7		60,0		
(2)—(11)		IIIa, IVa	942,7	758,4	146,3	233,1	149,9		103,8		
(2)	A_a2	VIIIa, IXa	877,6	685,2	146,5	230,8	150,2	306,6	102,1	101,0	179,7
(2)	A_c2	VIIIa, IXa	830,2	676,1	147,5	177,2	151,1	205,1	72,8	103,8	−159,6
(3)	A_a2	VIIIa, IXa	874,0		146,5	230,5	150,2	300,9	101,9	102,0	180,0
(3)	A_c2	VIIIa, IXa	836,7		147,4	179,0	151,2	207,9	73,6	103,3	−155,8
(4)	A_a2	VIIIa, IXa	849,1		146,5	230,9	150,2	304,8	102,1	101,3	179,9
(4)	A_c2	VIIIa, IXa	811,0		147,4	178,9	151,3	207,6	73,6	103,1	−153,3
(5)	A_a2	VIIIa, IXa	885,9		146,5	230,3	150,3	298,9	101,8	102,0	179,8
(5)	A_c2	VIIIa, IXa	849,5		147,4	179,1	151,2	208,5	73,7	103,3	−158,4
(6)	A_a2	VIIIa, IXa	882,7		146,6	230,4	150,2	305,2	101,9	106,0	178,8
(6)	A_c2	VIIIa, IXa	858,5		147,1	184,1	151,0	213,1	76,3	106,5	−159,1
(7)	A_a2	VIIIa, IXa	841,1		146,5	227,0	150,2	333,8	99,8	107,4	178,5
(7)	A_c2	VIIIa, IXa	826,7		147,0	187,7	151,0	215,3	78,1	107,9	−158,8
(8)	A_a2	VIIIa, IXa	1006,0		146,5	231,1	150,1	308,9	102,3	103,0	178,7
(8)	A_c2	VIIIa, IXa	964,6		147,0	178,0	151,2	205,7	73,1	102,7	−155,1
(9)	A_a2	VIIIa, IXa	829,3		146,5	230,5	150,2	311,9	101,9	101,2	179,6
(9)	A_c2	VIIIa, IXa	803,0		147,1	180,5	151,1	213,3	76,7	103,4	−155,6
(10)	A_a2	VIIIa, IXa	895,9		146,6	230,6	150,2	303,3	102,0	101,7	180,0
(10)	A_c2	VIIIa, IXa	871,9		147,1	185,4	151,0	213,1	76,9	104,0	−158,4
(11)	A_a2	VIIIa, IXa	726,1		146,5	226,8	150,1	333,3	99,7	100,1	179,5
(11)	A_c2	VIIIa, IXa	702,2		147,0	184,3	151,0	213,1	76,4	104,2	−157,9

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*For the reactions of 2-methylaziridine: bond lengths $C_{(2)}—C_{(5)}$ 151.5 (Ib), 151.9 (IIb), 147.3 (IVb), 147.5 (IXb, A_a2), 149.9 (IXb, A_c2), 155.9 (IIIb), 155.5 (VIIIb, A_a2), 153.0 pm (VIIIb, A_c2). Angle $C_{(3)}C_{(2)}C_{5)}$ 125.0° (Ib), 123.2° (IIb), 126.3° (IVb), 125.6° (IXb, A_a2), 124.6° (IXb, A_c2), 116.6° (IIIb), 116.4° (VIIIb, A_a2), 118.80° (VIIIb, A_c2). Angle $N_{(1)}C_{(3)}C_{(2)}C_{(5)}$: −104.7° (Ib), −106.9° (IIb), −79.7° (IXb, A_a2); −86.7° (IXb, A_c2), −122.7° (IIb), −122.7° (VIIIb, A_a2), −119.0° (VIIIb, A_c2).

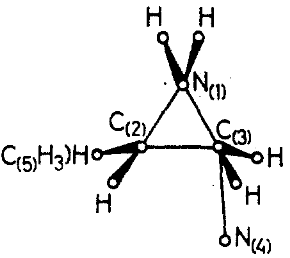
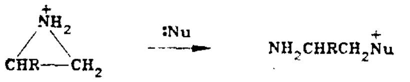


Fig. 1. Numbering and orientation of the atoms adopted in the calculations of the surface potentials of the energies of the amination of 2-methylaziridine and aziridine [$N_{(4)}$ is the nitrogen atom of the nucleophile].

We will represent the realization of these mechanisms for the reactions that we studied by means of the scheme shown above.

In order to make a detailed study of the mechanism of the nucleophilic opening of small nitrogen-containing heterocycles we carried out the quantum-chemical investigation of the surface potential energy of a series of ammonolysis reactions of the 2-methylaziridinium cation and the ammonolysis of the aziridinium cation by a number of nitrogen-containing nucleophiles.



(1) - (11)

(1) R=Me; (2)—(11) R=H; (1, 2) Nu=NH_3; (3) Nu=$MeNH_2$; (4) Nu=$EtNH_2$; (5) Nu=$H_2N(CH_2)_2NH_2$; (6) Nu=Me_2NH; (7) Nu=Et_2NH; (8) Nu$(CH_2)_2NH$; (9) Nu= =$(CH_2)_5NH$; (10) Nu=$HN(CH_2CH_2)_2NH$; (11) Nu=$O(CH_2CH_2)_2NH$

These processes in the gas phase were investigated by the semiempirical MNDO method [5], which was previously used successfully to study small saturated heterocycles [6] and their reactions [3, 4]. To evaluate the energy of nonspecific solvation in the ammonolyis reactions of aziridine and 2-methylaziridine we used the German solvatone model [7] realized within the framework of the MNDO scheme (see the method used to carry out the calculations); we examined the energically more favorable "rear" attack of the substrate [8-11] (Fig. 1), which leads to the formation of a reaction product in the trans conformation.

The geometrical characteristics of the transition states and their enthalpies obtained as a result of the calculations are presented in Table 1. The activation and thermodynamic parameters of reactions (1)-(11) in the gas phase are indicated in Table 2. The expansion of the designations used in them is given in the scheme and in Fig. 1. The activation and thermodynamic parameters of the ammonolysis reactions of aziridine and 2-methylaziridine in a polar medium are presented in Table 3. We reckoned the enthalpies of activation from the prereaction electrostatic ion-molecular complexes (VIIa, b), the energy characteristics of which correspond to the local minimum on the potential-energy surface of the reaction in the case of drawing together of the separate reactants. These complexes constitute a model of an intimate ion pair of reacting charged particles in solution. The intimate ion pairs (Xa, b; XIa, b) also complete the chain of transformations of the reactants. An examination of the ion-molecular complexes for related A2 processes in the aliphatic series demonstrated the expediency and correctness of this model for the gas phase and in solution [12].

It is known [1, 13] that opening of aziridines by aliphatic amines proceeds under specific acid catalysis. One can find an explanation for the increase in the reactivities of aziridines due to activation by acids by examining the Wiberg bond indexes for aziridines Ia, b and their protonated forms IIa, b [14] and the charge-density distribution. Loosening of the C—C bonds occurs in the protonation of small nitrogen-containing heterocycles. Protonation of aziridine leads to a decrease in the Wiberg indexes of the C—N bonds from 0.989 (Ia) to 0.869 (IIa); these values for 2-methylaziridine are, respectively, 0.979 and 0.847 (the CH_3CH—N bond) and 0.991 and 0.875 (the CH_2—N bond). Protonation of nitrogen-containing heterocycles is also accompanied by a simultaneous increase in the positive charges on the carbon atoms (for aziridine Ia and its protonated form IIa they are, respectively, 0.074 and 0.332 of the electron charge); asymmetry in the charge-density distribution is observed for 2-methylaziridine: in the unprotonated form the high charge is located on the primary carbon atom (0.088, as compared with 0.050 of the electron charge), while in the protonated form it is located on the secondary carbon atom (0.339 and 0.329 of the electron charge), although the difference in the latter case is very insignificant. The CH_3CH—N bond in 2-methylaziridine is longer than the CH_2—N bonds; this asymmetry is retained upon its protonation (see Table 1).

TABLE 2. Calculated Energy Characteristics of Reactions Involving the Amination of Aziridine and 2-Methylaziridine in the Gas Phase

Reaction	$\Delta H^{\neq}$, kJ/mole			ΔH, kJ/mole
	$A1$	A_a2	A_c2	
(1)*	100,8	88,4	95,5	−58,7
(1)**	156,8	142,1	88,6	−53,2
(2)	141,2	123,2	78,2	−82,1
(3)	141,2	123,1	85,8	−73,4
(4)	141,2	122,8	84,8	−78,0
(5)	141,2	123,7	87,3	−72,6
(6)	141,2	125,3	101,2	−49,5
(7)	141,2	129,4	115,0	−40,2
(8)	141,2	122,2	80,9	−88,6
(9)	141,2	124,2	97,9	−58,7
(10)	141,2	124,4	100,4	−54,4
(11)	141,2	127,8	103,9	−45,5

*Attack at the CH_3CH group.
**Attack at the CH_2 group.

TABLE 3. Energy Characteristics of the Reactions of 2-Methylaziridine and Aziridine with Ammonia in a Polar Solvent

Reaction	ΔH, kJ/mole			ΔH, kJ/mole
	$A1$	A_a2	A_c2	
(1)*	73,4	59,5	78,3	−68,0
(1)**	116,1	99,5	80,2	−63,3
(2)	101,9	81,0	71,9	−88,2

*Attack at the CH_3CH group.
**Attack at the CH_2 group.

In summarizing the information state above, one may note that in protonated 2-methylaziridine the $CH_3CH—N$ bond is weaker than the $CH_2—N$ bond, and, with respect to this criterion, nucleophilic attack at the sterically hindered carbon atom is more favorable. However, from the point of view of the steric requirements, nucleophilic attack at the primary carbon atom is more favorable.

It is apparent from Tables 1-3 that in the case of nucleophilic opening of 2-methylaziridine in the gas phase and in a polar medium cleavage of the $CH_3CH—N$ bond should proceed via the A_a2 mechanism, while cleavage of the $CH_2—N$ bond should proceed via the A_c2 mechanism. This result is in good agreement with the experimental data [1]. However, it follows from a comparison of the calculated enthalpies of activation that the two ring-opening pathways are equally probable and that for a polar medium attack at the CH_3CH group is even more favorable. These conclusions contradict the results reported in [1], in which it was demonstrated that opening of the 2-methylaziridine ring takes place primarily with cleavage of the C—N bond attached to the primary carbon atom. The discrepancy between the calculated values and the experimental results is evidently associated with the fact that reactions with attack at the secondary carbon atom have higher entropies of activation [1]. However, the solvatone model used does not make it possible to evaluate these quantities, since it satisfactorily describes only the effect of the polarity of the medium but does not deal with the issue of the solvate shell of the solvent surrounding the reacting particles as a whole. A pronounced change in the first solvate shell of the of the polarity of the solvent occurs when a hydrophobic methyl substituent is introduced into the aziridine ring; attack at the CH_2 group requires that it undergoes less deformation than in the case of attack at the $CHCH_3$ group.

In analyzing the effect of a methyl substituent on the characteristics of the transition state of the investigated reactions with attack at the CH_2 group it is apparent that the introduction of a methyl radical into the ring leads to an increase of ≈ 10.5 kJ/mole in the $\Delta H^{\neq}$ value for the gas phase (see Table 2); this difference decreases in a polar medium (see Table 3). This sort of change in the reactivity is evidently associated with an increase in the σ-aromatic character of the aziridine ring upon introduction of electron-donor substituents of the alkyl type, and the greater its σ-aromatic character, the higher the energy of activation of its nucleophilic opening.

An investigation of the effect of the structures of nitrogen-containing nucleophiles on the progress of reactions (2)-(11) shows that in all of the prereaction VIIa complexes, the bond lengths, Wiberg indexes, and charge distribution in the aziridine ring are virtually identical and differ only slightly from the drawn-together aziridinium cation and nucleophile. Only the distances from the nucleophiles to the ring carbon atoms vary; an increase in the bulk of the nucleophile is accompanied by an increase in the length of the C—Nu bond. Thus in the (2)—(7) series the C—Nu bond length changes as follows: 354.9, 364.3, 365.3, 366.5, 372.7, and 394.7 pm. On the other hand, for the approximately identical-in-size piperidine, piperazine, and morpholine molecules the increase in the length of the C—Nu bond in prereaction complex VIIa (378.3, 391.5, and 391.6 pm, respectively) occurs symbatically with the decrease in the basicities in the indicated series of amines.

The enthalpies of activation of reactions (2)-(11), which proceed via the A_c2 mechanism, reaching the highest values for sterically hindered diethylamine (115.0 kJ/mole), also increase with an increase in the bulk of the nucleophile; from the magnitudes of the enthalpies of activation one can single out three groups of nucleophiles: the first group includes ammonia, primary amines, and aziridine ($\Delta H^{\neq}$ = 78-88 kJ/mole), the second group includes secondary amines ($\Delta H^{\neq}$ = 98-104 kJ/mole), and the third group includes sterically hindered diethylamine. However, the pattern is completely different for the A_a2 mechanism: 3.1 kJ/mole, although here sterically hindered amines and amines with low basicities constitute exceptions. The closeness of the enthalpies of activation for the A_c2 and A_a2 mechanisms in the case of sterically hindered amines for the gas phase makes it possible to assume that transition from the A_c2 mechanism to the A_a2 mechanism, which leads to leveling of the sensitivity of the substrate with respect to the nature of the nucleophile.

If one examines the structures of the transition states of the A_c2 mechanism for reactions (2)-(11) (see Table 1), one may note that they become more product-similar, i.e., looser, with an increase in the bulk of the nucleophile.

In the series of secondary cyclic amines [reactions (9)-(11)] the structures of the transition states differ in virtually no way from one another (see Table 1). The enthalpy of activation changes by only 6 kJ/mole on passing from piperidine to morpholine, remaining appreciably smaller for the $\Delta H^{\neq}$ value for diethylamine (see Table 2). Thus the three-dimensional structure of the nucleophile is more important than its basicity for reactions involving the nucleophilic opening of aziridines by amines.

COMPUTATIONAL METHODS

The computations were carried out by the MNDO method [5] with complete optimization of all of the geometrical parameters. The condition for localization of the saddle point as the transition state for reactions (1)-(II) was inversion to the null norm of the gradient of the potential-energy function of the system and the existence of a single negative eigenvalue for the Hess matrix. The search for points that correspond to the local minimum on the potential-energy surface for reactions (1)-(11) was accomplished by the Davidon—Fletcher—Powers method [15, 16]. The condition for finding a point with a local minimum was inversion to the null of the norm of the gradient of the potential-energy function of the system and the existence of only positive eigenvalues for the Hess matrix.

To study the effect of the polarity of the medium we used the Germer solvatone model [7] in the self-consistent variation modified with allowance for the peculiarities of the MNDO computational procedure. The solvatone model presupposes that each atomic center induces, in the solvent medium, a point charge that is equal in magnitude and opposite in sign with respect to the Mulliken charge of the atom. Within the framework of this model one solves the self-consistent polyelectron problem (12), the electron Hamiltonian of which is the sum of the Hamiltonian of the molecule in the gas phase ($\hat{H}^0$) and the term that takes into account interaction with the medium ($\hat{H}^s$) (14):

$$\hat{H}'\psi = E\psi, \tag{12}$$

$$\hat{H}' = \hat{H}^0 + \hat{H}^s, \tag{13}$$

$$\hat{H}^s = \frac{\varepsilon - 1}{2\varepsilon}\left(\sum_k^K \sum_i^I \frac{q_k}{r_{ik}} \sum_k^K \sum_n^N \frac{q_k Z_n}{r_{kn}}\right), \tag{14}$$

where ε is the dielectric constant (it was assumed that ε = 78), K, N, and I are the total numbers of solvatones, atoms, and electrons in the system, k, n, and i are the numbers of solvatones, atoms and electrons, Z_n are the charges of the atomic cores, q_k are the solvation charges, and r_{ik} and r_{kn} are the solvatone—electron and solvatone—skeleton distances.

In the approximation used here we assumed that $r_{ik} = R_s(i \in K)$ and that $r_{kn} = R_s(K = N)$, where R_s (the distance from the solvatone to "its own" atomic skeleton or its electrons) is a variable parameter, a decrease or increase in which models, respectively, the increase or decrease in the polarity of the medium. For the interaction of the solvatones with "any" skeletons and electrons

$$r_{ik}=R_s+R_{IK}\,(i\in I\neq K),\quad r_{kn}=R_s+R_{KN}\,(K\neq N),$$

where R_{IK} and R_{KN} are the distances between the IK and KN atoms.

In the calculations we used $R_s = 300$ pm. In this case we achieved the best agreement between our calculated and experimental [1, 13] values of the activation and thermodynamic parameters of the reactions of aziridines with nitrogen-containing nucleophiles. The calculations were made with EC-1052 and EC-1060 computers.

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