NUCLEOPHILIC REACTIONS INVOLVING OPENING AND CLOSING OF SATURATED HETERORINGS (REVIEW)

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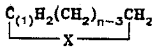
Experimental and calculated data on the mechanism and principal kinetic characteristics of processes involving the opening of saturated heterorings by nucleophiles, as well as reactions involving ring closing that proceed with departure of a nucleophilic particle, are correlated.

Reactions involving the opening and formation of saturated heterorings, with which the interests of theoretical and practical organic chemistry have been closely interwoven, have been the subject of intensive study for a long time. Many reactions – for example, electrophilic addition to multiple bonds [1, 2], a number of rearrangements, and a set of phenomena that are called assistance by a neighboring group [3] – involve the intermediate formation of saturated heterocyclic systems – both three-membered rings (3MR)* and multimembered rings (up to 17MR) [4]. The significance of the processes indicated above therefore goes far beyond the bounds of strictly nucleophilic reactions involving the formation and opening of the rings of these compounds. In addition, the basic principles of reactions of this type have not been discussed in the literature in nearly as much detail as the reactivities of aromatic heterocycles [5] or the reactions of saturated rings that proceed without their opening [6-8]. As in the past [9], chief attention has been paid to an examination of the relationship between the strain of the rings and their reactivities [10, 11]. It seems, however, that the numerous experimental and theoretical investigations that have been recently conducted make it possible to discuss more extensively the factors that determine the occurrence of the indicated processes. In the present review we have attempted a discussion of this sort.

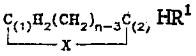
Primarily research from the nineteen seventies to nineteen eighties is examined here. In individual cases we have drawn upon the results of earlier research, as well as data from the reviews on the chemistry of rings that contain oxygen [12-14], nitrogen [6, 8], sulfur [15], and halogens [1, 16]. Reactions involving the opening and formation of saturated heterorings that proceed via nucleophilic elimination with respect to exocyclic or endocyclic bonds [10, 11] and intramolecular addition to multiple bonds [17] are not examined. Let us also point out that the bulk of the available data pertains to reactions of 3MR that contain one heteroatom (oxiranes, aziridines, and thiiranes), and many aspects of the reactivities will therefore be discussed only in the case of these systems.

1. General Concepts Regarding the Mechanism

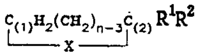
A mechanism involving bimolecular nucleophilic addition (A2) is generally accepted for reactions involving ring opening in the case of nucleophilic attack at the unsubstituted $C_{(1)}$ atom in structures I-III [6, 18-20].†


$\underbrace{C_{(1)}H_2(CH_2)_{n-3}CH_2}_{X}$

I


$\underbrace{C_{(1)}H_2(CH_2)_{n-3}C_{(2)}}_{X}HR^1$

II


$\underbrace{C_{(1)}H_2(CH_2)_{n-3}C_{(2)}}_{X}R^1R^2$

III

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*Here and subsequently, n-membered rings are denoted by nMR.

†Here and subsequently, the apical group of the rings is denoted by X, while the entering (in the case of ring opening) or leaving (in the case of ring closing) nucleophile is denoted by Nu.

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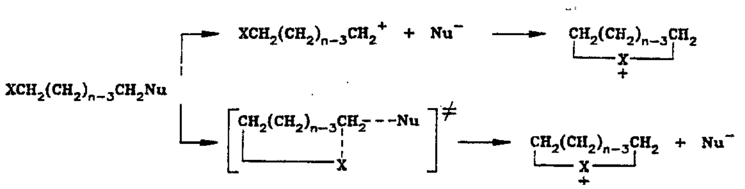
The addition of a nucleophile to a substituted carbon atom [$C_{(2)}$ in structures II and III] has been previously regarded as monomolecular ring opening in the rate-determining step of the process with subsequent fast addition of the nucleophile (A1) [6]. Data on the stereoselectivity and activation parameters of these reactions served as the basis for this. However, up until now, it has been shown in a number of studies that reactions involving the opening of heterorings, regardless of the site of attack, are bimolecular in most cases [18, 19, 21-23]. This mechanism has been confirmed experimentally only for a few systems, the opening of which via an A1 mechanism leads to stable carbonium ions of the allyl and benzyl type [24-26]. Quantum-chemical semiempirical calculations (in the case of protonated aziridines and oxiranes) also indicate the energic preferableness of the A2 mechanism over the A1 mechanism both in the gas phase [27, 28] and in polar solvents [29].

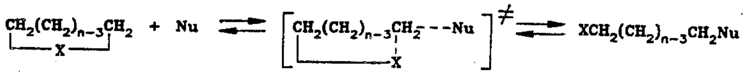
Mechanism (1) has been proposed in the past for nucleophilic processes involving the formation of rings (the extremely characteristic reaction with the uncharged starting reagent is presented in the scheme as an example) [30, 31], but pseudobimolecular mechanism (2) has also become generally accepted at the present time [32-49]. Scheme (1) is regarded as one of the possible reaction pathways only in some cases (for example, for the formation of sulfur-containing 3MR [50]).



(1)

(2)

Taking into account the material set forth above, we will subsequently direct our chief attention to reactions with the synchronous cleavage of an old bond and the formation of a new bond. The rate-determining steps of nucleophilic processes involving the opening and closing of saturated rings can then be represented as, respectively, the forward or reverse reaction (3).

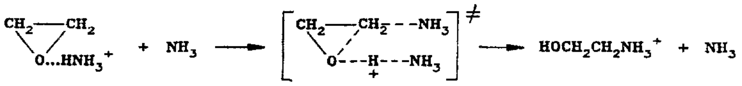


(3)

X=O, NH, S, F^+, Cl^+, OH^+, NH_2^+, SH^+ etc.; Nu=HF, H_2O, NH_3, F^-, Cl^-, CH_3O^- etc.

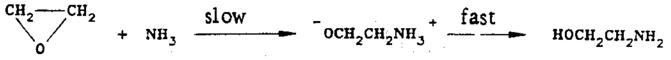
Let us immediately state that Scheme (3) is simplified and needs to be defined concretely. It is known that acidic and alkaline catalysis of the opening [6, 8, 13, 51-54] and alkaline catalysis of the closing [36, 38] of rings have a very great effect on the rates and regio- and stereoselectivity of reactions with rings. Nitrogen-containing heterorings are opened only under the conditions of catalysis, which also accelerates the opening of oxygen- and sulfur-containing rings extremely substantially [6, 12, 13, 15, 55-58].

Depending on the type of reagent and the conditions under which the process is carried out, protonated (at the apical group) rings (for example, in the amination of aziridine [59, 60]) or complexes formed by the ring with an electrophilic particle [15] may participate in acid-catalyzed liquid-phase ring-opening reactions. In the case of complexes formed by the ring with an electrophilic particle proton transfer to the apical group occurs in the rate-determining step of the process. The amination of oxirane (4) probably may serve as an example [61]:



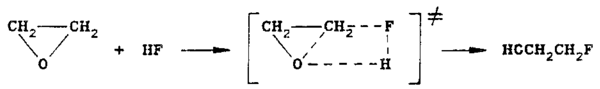
(4)

When ring opening is possible without catalysis, unstable highly polar products cannot be detected, since proton transfer and the formation of more stable forms occur very readily. Thus calculations [61] have shown that the second step (intramolecular proton transfer) in gas-phase reaction (5) proceeds virtually without a barrier.



(5)

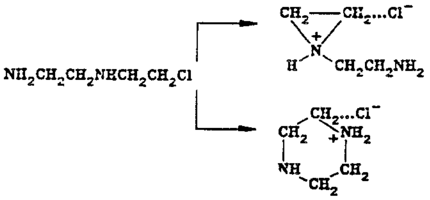
Computational methods have also been used to study noncatalytic proton transfer in the rate-determining step of reaction (6) [62] via a mechanism that has been frequently proposed in experimental studies for ring opening in aprotic low-polarity media [24, 63]. In this case four elementary acts of cleavage and formation of bonds, rather than the two indicated in reaction (3), occur simultaneously.



(6)

In ring-forming reactions the reaction with the catalyst occurs prior to the rate-determining step and reduces to detachment of a proton from the nucleophilic group of the open system [36].

For processes in which charged particles with opposite signs participate or are formed one must take into account the effects of ion pairing, which are extremely significant in these cases [64]. Intimate ion pairs are formed in the rate-determining step in reactions (7) and (8) [65]. It is completely possible that the different abilities of 3MR and 6MR to form ion pairs also affect the competition of the two pathways of the process here.

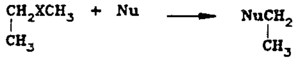


(7)

(8)

Taking into account the stipulations set forth above we can continue our discussion of Scheme (3), which will prove to be useful for the interpretation of many general problems of reactivity. The specific characteristics of reactions (3) can evidently be revealed by comparison of them with both nucleophilic addition to double bonds (A_{db}) (9) and S_N2 processes (10).

$$CH_2{=}X + Nu \longrightarrow NuCH_2X \tag{9}$$



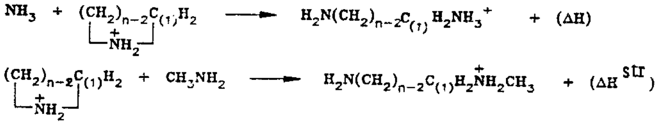
$$\underset{CH_3}{CH_2}XCH_3 + Nu \longrightarrow Nu\underset{CH_3}{CH_2} \tag{10}$$

The similarity between reactions (3) and S_N2 processes is quite evident. However, the comparison with A_{db} processes (i.e., with reactions of "two-membered rings") requires some refinements. Addition to double bonds frequently proceeds with synchronous proton transfer, i.e., via a mechanism similar to Scheme (6). However, in the case of rings the potential barrier of reaction (6) is very high [62], and this mechanism can hardly be realized frequently under actual conditions. Those A_{db} processes in which proton transfer does not occur (for example, reactions with anionic nucleophiles) are primarily included in the context of our examination.

For the subsequent discussion it will be useful, where possible, to distinguish between the thermodynamic and kinetic parameters of the processes.

2. Thermodynamic Examination

The heat effect (ΔH) of the forward or reverse reaction (3) can be represented (in the case of processes involving the amination of protonated nitrogen-containing rings) as the sum of the heats of reactions (11) and (12) [66].



(11)

TABLE 1. Strain Energies of Cycloalkanes (kJ)/mole)

n	3	4	5	6	7	8
Exptl. [67]	115.6	109.7	27.2	0.0	26.4	40.2
ΔH^{str}*	115.1	109.7	26.0	0.8	25.1	39.4

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*Calculated from Eq. (11) using the data in [68].

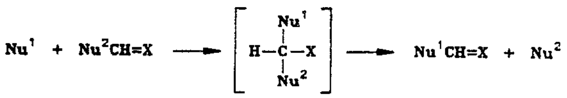
$$NH_3 + H_2N(CH_2)_{n-2}C_{(1)}H_2\overset{+}{N}H_2CH_3 \longrightarrow H_2N(CH_2)_{n-2}C_{(1)}H_2NH_3^+ + CH_3NH_2 + (\Delta H^{cl}) \tag{12}$$

$$\Delta H = \Delta H^{str} + \Delta H^{cl} \tag{13}$$

A similar expansion can be written for the heat effects of any reactions (3) with charged of neutral systems, as well as for A_{db} processes.

Reaction (12) is nucleophilic substitution at primary $C_{(1)}$ atom, i.e., an S_N2 reaction. The heat effect (ΔH^{str}) of homodesmic reaction (11) can be interpreted as the ring-strain energy. The ΔH^{str} value corresponds very well to the strain energies obtained from the heats of combustion [67] (Table 1). Let us note, however, that the ΔH^{str} values for heterorings may differ appreciably from the values that are normally used. This indicates only that a universal scale of strains does not exist, since their values in any procedure of determination depend on the choice of systems that are taken as standard ("unstrained") systems [69].

For reactions in the gas phase yet another term – the energy of the hydrogen bond between the terminal groups, which is extremely high in charged systems (~60 kJ/mole for protonated α,ω-amino alcohols $HO(CH_2)_{n-1}NH_3^+$ [70]) – is added to Eq. (13). The effect of intramolecular hydrogen bonding levels out in protic solvents, and the thermodynamics of reactions (3), as well as A_{db} processes, depend on two parameters – ΔH^{cl} and ΔH^{str}. Their ratio determines the direction of the process. If $\Delta H^{cl} > 0$ and $|\Delta H^{cl}| > |\Delta H^{str}|$, the equilibrium is shifted to favor the formation of cyclic systems, and nucleophilic ring-closing reactions are observed. Let us note that the exchange of nucleophiles that is extremely characteristic in series of unsaturated systems (see, for example, the kinetic investigation of a number of gas-phase exchange processes [71]), i.e., the rapid "opening" and "closing" of a double bond that proceeds through a tetrahedral transition state or, more frequently, through an intermediate, is not typical for rings:



$$Nu^1 + Nu^2CH{=}X \longrightarrow \left[H{-}\underset{Nu^2}{\overset{Nu^1}{C}}{-}X \right] \longrightarrow Nu^1CH{=}X + Nu^2$$

This is explained by the fact that the ΔH^{str} value, which is close to zero for many double bonds with heteroatoms, is, as a rule, significant in cyclic systems, and, all other things being equal, ring closing proceeds with much greater difficulty than ring opening.

Thermodynamic examination makes it possible to graphically interpret the effects of acidic and alkaline catalysis.

It has been shown by semiempirical calculations [28] that the heat effects of gas-phase reactions (14) and (15) are close and amount to –100.5 and –80.9 kJ/mole, respectively. However, the first (rate-determining) step of noncatalytic reaction (14) is sharply endothermic: Its heat is +175.9 kJ/mole. Protonation of the ring (a model of acidic catalysis) changes the thermodynamics of the rate-determining step of the process.

(14)

(15)

An analysis of the (11)-(13) expansion presented above shows that protonation of the ring chiefly changes the ΔH^{cl} value.

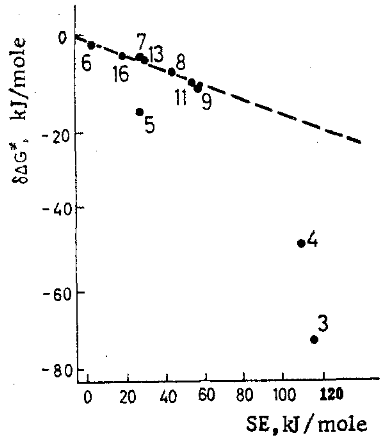
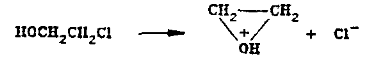
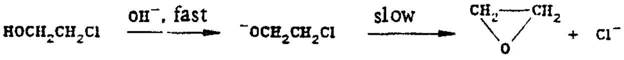


Fig. 1. Dependence of the $\delta\Delta G^{\neq}$ value on the ring-strain energy for reactions (18); $\delta\Delta G^{\neq} = \Delta G^{\neq}(n) - \Delta G^{\neq}\ (n = 6)$. The numbers next to the points denote ring size n.

Basic catalysis of cyclization can be examined in the case of reactions (16) and (17) with 2-chloroethanol [36, 38]. In this case the use of a catalyst in solutions also affects primarily the heat of the closing reaction ΔH^{cl}.


(16)


(17)

Taking into account the relationship between the heat effects of S_N2 reactions and the nucleophilicity and nucleofugitivity of the reagents it can be stated that acidic catalysis of ring-opening reactions ensures intensification of the nucleofugitivity of the "leaving" group, while alkaline catalysis of ring-opening and ring-closing processes increases the nucleophilicity of the group that acts as the "entering" group here.

The effect of a polar solent on the thermodynamics of reactions (3) is quite clear. Polar media should stabilize the zwitter-ionic intermediates and the charged products in noncatalytic reactions of the (14) and, particularly, (16) type, thereby facilitating their occurrence significantly [72, 73]. The heats (and rates) of catalytic reactions of the (15) and (17) type depend on the polarity of the medium considerably less appreciably [59].

Let us note that the schemes presented here are in their own way extreme cases of maximal catalysis of the reaction or its complete absence. Diverse intermediate forms of interaction of the reacting complex with the solvent and catalyst are possible under actual conditions (see section 1) [15, 29, 74].

It is apparent that thermodynamic analysis still does not settle the problem of the description of the reactivity in the indicated processes. Thus for reaction series in which only the ring size (the n value) is varied the ΔH^{cl} values are almost constant, and the differences in the heat effects are associated chiefly with the magnitudes of the strains. However, as we will subsequently show, the relationship between the ring strains and the reactivities is ambiguous, which makes a detailed examination of the kinetic characteristics of these reactions necessary.

3. Kinetic Peculiarities of the Processes

The dependence of the free energy of activation ($\Delta G^{\neq}$) on the strain for reactions involving opening of nitrogen rings by the methoxide anion in methanol (18) has been studied over an extremely wide range (Fig. 1) [56, 57, 75].


(18)

A linear dependence of $\delta\Delta G^{\neq}$ on the ring-strain energy (SE) with a slope of ~0.2 was satisfactorily observed for n > 5. At the same time the 3-5MR showed anomalously high activities – the deviations from the straight line were 54.4, 29.3, and 12.6 kJ/mole, respectively. The indicated anomalies are associated chiefly with the enthalpies of activation, since the entropy contributions in this series are close to one another [56].

TABLE 2. Free Energies ($\Delta G^{\neq}$), Enthalpies ($\Delta H^{\neq}$), and Entropies ($\Delta S^{\neq}$) of Activation of Ring-Closing Reactions (19) of Bis(sulfonyl) Carbanions [46]*

n	$\Delta G^{\neq}$, kJ/mole	$\Delta H^{\neq}$, kJ/mole	$\Delta S^{\neq}$, J/mole-deg K
3	73	86	+42
4	103	91	−39
5	83	68	−51

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*With alkali–ethanol as the medium at 298 K.

The differences in the enthalpies of activation $\delta\Delta H^{\neq} = \Delta H^{\neq}(n) - \Delta H^{\neq}$ ($n = 6$) can be determined for reactions involving the cyclization of diethyl malonate anions ($n = 4...21$) [47]. They are 12.6 ($n = 4$), −10.9 ($n = 5$), 0 ($n = 6$), 5.9 ($n = 7$), 10.5 ($n = 8$), 16.3 ($n = 10$), 0.8 ($n = 13$), and −3.3 kJ/mole ($n = 21$). A linear correlation of the enthalpies of activation and the ring strain with a slope of the straight line of ~0.5 is observed here when $n \geq 6$ [47].

Thus the closing of small rings ($n < 6$) also proceeds anomalously rapidly. This peculiarity is traced well in the case of reaction (19) [46].

$$(C_6H_5SO_2)_2\bar{C}(CH_2)_{n-1}Cl \longrightarrow (C_6H_5SO_2)_2\underbrace{C(CH_2)_{n-1}} + Cl^- \qquad (19)$$

It is apparent from Table 2 that 3MR are the most active in the series. This can be ascribed to a significant extent to the entropy of activation. The sharp change in this value on passing from 4MR to 3MR is associated with the absence in the latter case of the necessity for orientation of the chain that links the nucleophile with the electrophile [46]. Nevertheless, it is apparent from the data in [46, 47] that the enthalpies of activation of reactions involving the closing of small rings are also far from symbatic with respect to the strains. The $\Delta H^{\neq}$ values in the formation of highly strained 3MR and 4MR are not much higher than for unstrained 6MR, and are even lower in the case of 5MR.

The anomalies in the behavior of small rings are far from being exhausted by the indicated facts. Thus retention of the configuration of the reaction center has been noted for a number of reactions involving opening and closing of 3MR [24, 63, 76, 77]. In processes involving opening of unsymmetrically substituted 3MR nucleophilic attack is often directed to the sterically more hindered center [6, 22, 24, 78].

The material set forth above can be interpreted in the following way. In medium-sized and large rings ($n > 5$) the geometrical structure of the reaction center virtually does not differ from the structure of the saturated sp^3-hybridized carbon center in acyclic systems [69]. Hence it may be assumed that the S_N2 mechanism is a good model for reactions involving the opening and closing of medium-sized and large rings. The principal peculiarities of nucleophilic substitution processes (the orders of nucleophilic activity, the effect of substituents attached to the reaction center, the structures of the transition states) [79] are then also characteristic for reactions with rings [65, 80], although the strain energies of these systems, which are sometimes rather significant (52.8 kJ/mole for cyclononane [67]), substantially facilitate their opening and hinder their formation. The linear dependence of this energies of activation on the strain that was noted above for this range makes it possible, in principle, to calculate the activation parameters of reactions (3) from the characteristics of the corresponding S_N2 processes by introducing corrections for the ring strains. In those cases in which $\Delta H^{str} \approx 0$ ($n = 6$, $n > 20$) one should expect closeness or coincidence of the kinetic and thermodynamic parameters of reactions (3) and S_N2 processes. Kinetic investigations of a series of forward and reverse reactions (3) ($n = 6, 7$) showed that their activation parameters are, as a rule, close to the parameters of S_N2 processes of the (12) type [37, 49, 56].

This simple picture is clearly unsuitable for reactions with small rings. The structures of the reaction centers here occupy an intermediate position between sp^2- and sp^3-hybridized centers in A_{db} and S_N2 processes [81].

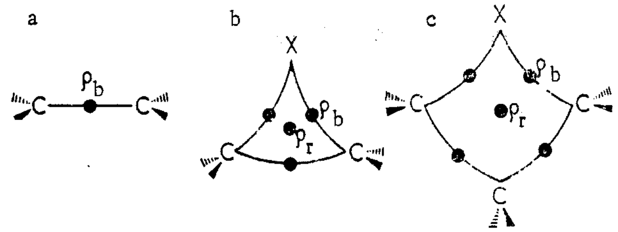

Fig. 2. Pathways of maximum electron density (MED): a) ethylene; b) three-membered ring; c) four-membered ring. The critical points of the bonds and densities of the rings are denoted by dark circles; ρ_b and ρ_r are the electron densities at these points.

4. Peculiarities of Reactions with Small Rings

4.1. Structural Characteristics of Small Rings. For the interpretation of the anomalies noted above it is necessary to briefly discuss the modern concepts regarding the structure of small rings. The information communicated here does not pretend to be complete and is restricted only to those parameters of rings that determine their activities in reactions with nucleophiles.

The traditional chemical description of nucleophilic substitution reactions assumes the existence of a reaction center at which localized bonds with leaving and entering groups are cleaved and formed. In the case of small (particularly three-membered) rings some doubt arises regarding the possibility of isolating this sort of local center. One must evidently take into account interaction of the nucleophile with the cyclic system as a whole. The appearance in the past of the Coulson–Moffitt [82] and Walsh [83] models was explained by an understanding of the unsuitability of concepts regarding σ bonds of the ordinary type in 3MR. In principle, there is no difference between these two models, since they are provided by two sets of basis orbitals that are related by a unitary transformation. As applied to the processes being described here, the concepts regarding the σ-aromatic character of 3MR [84] and the similarity between these systems and π complexes [22] recently developed by Dewar are probably more useful.

Within the framework of the σ-conjugation model [84] cyclopropane is isoconjugated with benzene and cyclobutane is isoconjugated with cyclooctatetraene; therefore, 3MR has σ aromatic systems, while 4MR are σ antiaromatic. Concepts regarding the delocalization of σ electrons have also been developed on the basis of other models [85, 86]. It is assumed that this effect, which is rather weak when $n = 4$, is very great for 3MR. The closeness of the strains for 3MR and 4MR can be explained thereby. The real strain (RS) when $n = 3$ is considerably greater than when $n = 4$ and corresponds to much greater distortion of the bond angles, but it is compensated to a significant extent by σ-aromatic stabilization (AS). The observed strain energies of 3MR are the difference between these two values. It has been assumed [84] that in ring opening aromatic stabilization is lost more slowly initially than the rate at which the real strain decreases; this ensures the ease of deformation of 3MR in the case of small degrees of opening.

The interaction of the boundary orbitals in the formation of 3MR from an olefin (the basal group) and an apical X group has also been examined [22, 87]. It was shown that the similarity between 3MR and π complexes increases with an increase in the electronegativity of the apical group. It follows from semiempirical calculations [22] that the similarity between the geometrical structure of the basal group and the ethylene structure increases in the following order of apical groups: $CH_2 < NH < O \approx NH_2^+ < OH^+ < F^+$. The reaction of nucleophiles with 3MR (particularly for $X = O$, NH_2^+, OH^+, F^+) therefore resembles A_{db} processes in many respects.

The orbital concepts set forth above receive graphic illumination within the framework of a model of small rings based on an analysis of the distribution of one-electron density ρ, which is invariant with respect to unitary transformations of the molecular orbitals [87, 88]. This model defines the chemical bond between the pair of interacting atoms as the pathway of maximum electron density (MED) between them. The structure of any molecule is described by the number and form of the critical (stationary) points at which $\nabla\rho = 0$. A molecular graph, i.e., a set of critical points and a corresponding network of pathways

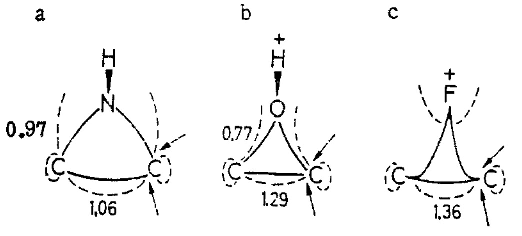

Fig. 3. Molecular graphs and $\nabla^2\rho$ concentration fragments: a) aziridine; b) protonated oxirane; c) the fluoroethylene cation. The concentration gaps at the basal carbon atoms are indicated by arrows. The bond orders are denoted by the numbers.

of MED that link together the nuclei in the molecule, corresponds to each system. Topological analysis of the charge distributions makes it possible to compare small rings with saturated and unsaturated compounds. It was shown that in the ethylene molecule the densities of the π orbitals are not spatially separated from the densities of the σ orbitals. Distribution ρ in this molecule has a single critical point (Fig. 2a), i.e., there are not two separated bonds in "cycloethane." In 3MR there are three separate MED that link together atoms in pairs (Fig. 2b); this draws them close to rings with large dimensions.

However, the separation of the bonds in 3MR is expressed rather weakly. Electron density η is very high over the entire ring (for an extensive series of 3MR η = 82-86% [87]),* since surface (aromatic) delocalization of the σ electrons in the plane of the ring occurs in these systems. For 4MR (Fig. 2c) the η value decreases sharply (33% for cyclobutane), indicating considerably greater localization of the electrons near the MED. Three-membered (but not four-membered!) rings should therefore display a definite similarity to unsaturated compounds — particularly in reactions with nucleophiles. The electronic strucutres in 4MR and 5MR resemble the structures of saturated systems to a much greater extent.

An investigation of the electron-density distribution and Laplacian operator $\nabla^2\rho$ of a number of 3MR has shown that an increase in the strength of the CC bond and weakening of the CX bonds occur with an increase in the electronegativity of the apical X group (Figs. 3a-3c). The ring is convex for X = CH_2 and NH and concave when X = NH_2^+, OH^+, and F^+; for X = F^+ it is very close to a T structure (a π complex). The carbon atoms in 3MR have concentration gaps on the sides of the CC and CX bonds (Fig. 3); this makes two pathways of nucleophilic attack (from the rear and frontal), which lead, respectively, to inversion and retention of the configuration of the reaction center, possible. The more electronegative the X group, the wider the concentration gaps and the weaker the CX bond; nucleophilic attack is therefore easier for concave 3MR.

4.2. Stereo- and Regiochemistry of Reactions with Small Rings.

Complete or partial retention of the configuration of the reaction center has been noted in some reactions involving opening [24-26, 63] and closing [6, 12, 89] of 3MR. This has been previously explained within the framework of a monomolecular reaction mechanism (see section 1). Concepts regarding the participation of nonclassical carbonium ions in the process [76, 77] and regarding the effects of the microstructure of the solvents [26, 90] have also been invoked.

The state of the problem does not yet make it possible to dwell on any one explanation. However, it may be noted that an interpretation of the noted facts is also possible on the basis of a bimolecular mechanism. The realization of not only nucleophilic attack from the rear and frontal nucleophilic attack has been examined in both experimental [24, 63] and computational [28, 91] studies. Both of these pathways are possible (see subsection 4.1 and Fig. 3), but, as demonstrated by the calculations in [28], attack from the rear is appreciably more preferable (the difference in the energy barriers was more than 60 kJ/mole) as a consequence of the mutual repulsion of the entering nucleophile and the apical group in the case of frontal attack. However, one cannot completely exclude frontal addition [splitting out (for ring-closing reactions)] of the nucleophile. In some cases it can be realized, for example, with the specific assistance of solvent molecules.

Thus the reactions of 3MR also occupy an intermediate position between A_{db} and S_N2 processes here. The two pathways of attack are identical in reactions involving double bonds, whereas in S_N2 reactions in which frontal attack is also, in principle, possible, the energy barrier for it is higher by 200-220 kJ/mole than for attack from the rear [79].

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*$\eta = (\rho_r/\bar{\rho}_b)\cdot 100\%$, where $\bar{\rho}_b$ is averaged over all of the bonds.

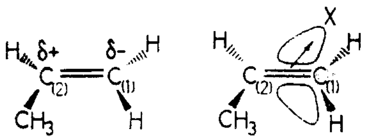


Fig. 4. Polarization of the bonds in propene and in the π complex.

If, therefore, the possibility of the realization of frontal addition is sufficiently problematic for 3MR, it can be disregarded completely in the case of rings with larger dimensions.

Different explanations have also been given in the literature for the above-noted facts of Markovnikoff (with respect to the sterically less accessible carbon center) addition of nucleophiles to 3MR. Dependence of the regiospecificity on the conditions under which the processes are carried out, the solvents and catalysts used, the temperature, etc. has been noted. The participation of ion pairs in the reactions has been proposed [90, 92]. The existence of a step involving one-electron transfer (an SETmechanism) [20, 93] or the occurrence of reactions of α,α-disubstituted heterorings via an $A2^+$ mechanism [94], which includes the formation of a tertiary carbonium ion, which reacts with the nucleophile in the rate-determining step, has been postulated.

Among the factors that determine the regioselectivity of reactions involving the opening of 3MR, competition between the electronic and steric effects can probably be singled out as the principal factor [12, 18]. Electronic factors, which favor Markovnikoff addition, have been discussed in the case of methyl-substituted rings [22], which were compared here with π complexes (see subsection 4.1). The π orbital of propene is polarized, as indicated in Fig. 4. The addition of an X group does not change the picture qualitatively, so that the resulting π complex is also asymmetric. The X group is situated closer to the unsubstituted $C_{(1)}$ atom, and the substituted $C_{(2)}$ center is therefore more electropositive and the $C_{(2)}X$ bond is longer and weaker than the $C_{(1)}X$ bond. The more electronegative the apical X group, the more strongly pronounced the properties of the π complex and the more appreciable the Markovnikoff pathway of attack. At the same time, the bulkier the substituent, the more readily the normal, i.e., anti-Markovnikoff, addition takes place. According to the calculations in [22], for methyl-substituted 3MR the probability of attack at the substituted atom increases in the following order of apical groups: $O < S \approx NH_2^+ \approx OH^+ < SH^+ < Cl^+$. In fact, opening of halonium ions proceeds with the preponderant formation of the Markovnikoff isomer [1, 16]; this is also characteristic for processes involving the opening of oxides under conditions of catalysis by acids [12, 13, 25].

4.3. Structural and Energy Characteristics of the Transition States. The available data have been obtained chiefly by methods of quantum chemistry [28, 29, 61, 62, 66, 95-97] and, to a lesser extent, from kinetic experiments [46, 49, 75, 81, 98, 99]. The quantum-chemical calculations were made in most cases by semiempirical methods that do not pretend to have quantitative reliability; however, the necessary qualitative agreement between the results is observed. Perhaps only the structures of the transition states (TS) for the reactions involving the closing of bromoalkylamines presented in [95] give rise to serious doubt. As already noted in [97], the method of molecular mechanics used here is unsuitable for the study of the saddle points of the potential energy surface.

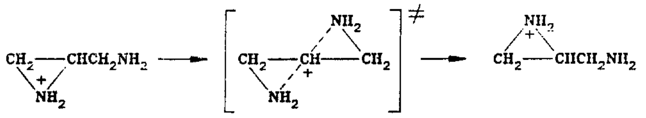
The degree of deformation of 3MR in the TS of processes involving nucleophilic opening is low. This follows from calculations [28, 61, 96] and experiments [98]. For reactions involving the formation of 3MR calculations [97] and experiments [46] indicate a somewhat more open TS with significant separation of the leaving group. The degree of opening of the ring in the TS increases with an increase in n [66, 97].

A rapid decrease in the strain in the case of low degrees of opening of the ring has been proposed to explain the high activity in reactions with 3MR [98, 99]. This has something in common with Dewar's hypothesis regarding a nonsynchronous change in the aromatic stabilization and real strain in the course of deformation of 3MR (see subsection 4.1).

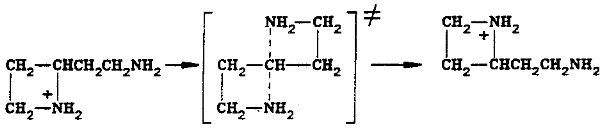
A model of "σ assistance" of reactions involving the formation of 3MR and 5MR was proposed in [97]. However, this model does not contradict the concepts in [84] and is actually one method for setting forth the concept of the σ-aromatic character of small rings.

Much higher sensitivity of the rate of the process to the character of the substituent when n = 3 than for n = 4-13 has been shown by investigations of the kinetics of reactions involving the formation of N-substituted azacycloalkanes [49, 81]. This can be explained by the fact that conjugation of the substituents with the σ-aromatic system of 3MR changes the strain and has a substantial effect on the reactivity [46, 81].

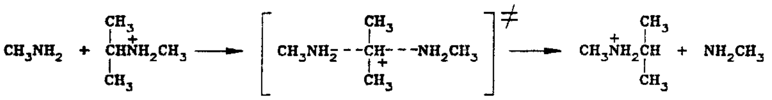
It must be noted that the model of σ-aromatic character cannot fully explain the anomalies of small rings. It is apparent from section 3 that not only "aromatic" 3MR and 5MR but also "antiaromatic" 4MR display increased activity in ring-opening and ring-closing reactions. There are also evidently other kinetic (independent of the thermodynamics of the processes) factors that favor reactions with small rings. Their effect is illustrated graphically by calculations by the MINDO/3 method of the following three thermally neutral reactions [66]: rearrangements of 3MR (20) and 4MR (21) (related to rearrangements of the Payne type [100, 101]) and S_N2 process (22).



(20)



(21)



$$CH_3NH_2 + CH_3\overset{+}{N}H_2CH(CH_3)_2 \longrightarrow \left[CH_3NH_2\cdots\overset{+}{C}H(CH_3)_2\cdots NH_2CH_3\right]^{\neq} \longrightarrow CH_3\overset{+}{N}H_2CH(CH_3)_2 + NH_2CH_3$$

(22)

For reactions (20)-(22) the calculated enthalpies of activation are, respectively, 75.4, 134.4, and 237.0 kJ/mole. Although the computational procedure overstates the difference in the energy barriers, it is apparent that the rearrangements proceed more readily than the S_N2 reaction not only for n = 3 but also for n = 4. This phenomenon does not yet have a generally accepted explanation, but it has been proposed that the observed anomaly is associated with stereochemical effects of the reaction center — for example, with a decrease in steric hindrance upon approach of the nucleophile [75]. In this connection let us point out that breaking down of the potential barriers in A_{db} and S_N2 reactions into components [102, 103] has shown that the difference between their values is associated chiefly with the increased ease of deformation of the substrate in the first case. It might be assumed that reactions with small rings occupy an intermediate position between A_{db} and S_N2 processes here also. The indicated factor then ensures the incrased activity of all small rings (n < 6) as compared with saturated systems.

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PHOTOCHEMICAL REACTIONS OF 7-AMINOCOUMARINS

1. [2 + 2]-CYCLOADDUCTS WITH VINYL BUTYL ETHER AND ACRYLONITRILE

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L. K. Denisov, and I. I. Grandberg

UDC 547.587.51:541.14'634:543.51'422.25

Adducts of [2 + 2]-cycloaddition to the 3–4 bond were isolated in the photochemical cycloaddition of vinyl butyl ether and acrylonitrile to 4-methyl-7-diethylaminocoumarin. The stereochemical structures of the compounds obtained as isomers of the "head-to-tail" type with an endo or exo orientation of the substituents were established by means of PMR spectroscopy. As a result of an evaluation of the effect of sensitizers and one-electron oxidizing and reducing agents it was found that the investigated reactions proceed through the singlet excited states of 7-aminocoumarins. It is assumed that the regiospecificity of the [2 + 2]-cycloaddition is determined by the $C_{(3)}$ reaction center of the coumarin fragment.

The interest in 7-aminocoumarins is due primarily to their intensive luminescence [1, 2]. However, despite the large number of studies involving the photophysical investigation of aminocoumarin dyes, insignificant study has been devoted to their photochemical reactions. The aim of the present research consisted is an investigation of the photochemical reaction of 4-methyl-7-diethylaminocoumarin (I) and 4-methyl-7-aminocoumarin (II) with olefins.

It is known that 7-aminocoumarins, in contrast to other coumarins, are not inclined to form [2 + 2]-photodimers in solution [3]. Successive N-dealkylation occurs in the irradiation of 7-dialkylaminocoumarins [4], whereas photooxidation of the alkyl substituents attached to the nitrogen atom occurs under the influence of oxygen [5]. The unique character of the structures of 7-aminocoumarins consists in their capacity for pronounced charge separation upon photoexcitation [6]. The available quantum-chemical calculations of the structures of various coumarins [7, p. 18; 8] confirm high localization of the charge on the 3–4 bond, as well as of the spin density on the $C_{(3)}$ atom in the singlet and triplet excited states. This fact makes it possible to assume that the photoexcitation of coumarins I and II in the presence of olefins should lead to regioselective reactions with the participation of the 3–4 bond. The experiments carried out confirmed this assumption.

We studied the possibility of the synthesis of cycloadducts of 7-aminocoumarins I and II with olefins that contain substituents with different electronic properties – vinyl butyl ether and acrylonitrile. Cyclobutane derivatives III and IV were obtained as a result of the reaction of coumarin I with vinyl butyl ether. Only V and VI were obtained as the principal products in the reactions of coumarins I and II with acrylonitrile.*

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*According to the results of TLC and mass spectroscopy, other isomeric adducts are present in small amounts (<5%) in the reaction mixtures in this case.

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