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Origin of the Reactivity Differences of Substituted Aziridines: CN vs CC Bond Breakages

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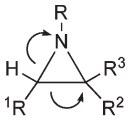

CN vs. CC

Aziridines are broadly used as starting materials for various chemical syntheses, and the underlying reactions (CN vs CC bond breaking accompanied by an attack of a nucleophile or a dipolarophile) are strongly influenced by the substitution pattern. The present study investigates reaction courses of possible ring-opening reactions accompanied by the attack of a nucleophile for different substitution patterns of the aziridine. Information is obtained through the computation of the underlying potential energy surfaces and reaction paths. The results provide insight into the mechanisms of different ring-opening reactions and explain how the kinetics and thermodynamics of the reaction are influenced by substituents. This allows predicting substitution patterns that steer the reaction course to either CN or CC bond cleavage.

Introduction

Due to their versatile reactivity, aziridines are broadly used as starting materials for various chemical syntheses.[1,2] The corresponding reactions (Figure 1) include nucleophilic ring opening under cleavage of the CN bond[3−7] as well as thermal or photochemical CC bond breaking leading to azomethine ylides. The latter can undergo 1,3-dipolar cycloadditions[8−11] or less frequently investigated and observed[12,13] addition of nucleophiles. The actual reaction paths are strongly determined by the substitution pattern of the aziridine and the reaction conditions. *N*-Unsubstituted (R = H, Figure 1),[14,15] *N*-formylated (R = CHO),[16] and *N*-halogenated (R = Hal, CF_2CO_2R)[17] aziridine-2,3-dicarboxylates have been observed to react with sulfur nucleophiles via CN

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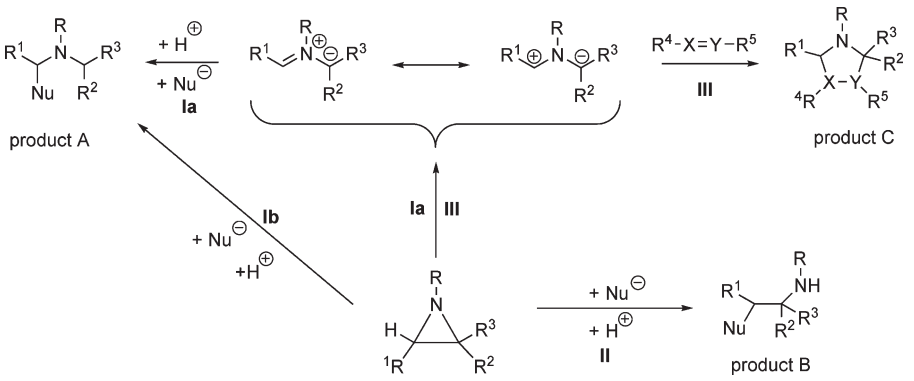

FIGURE 1. Possible reactions of aziridines.

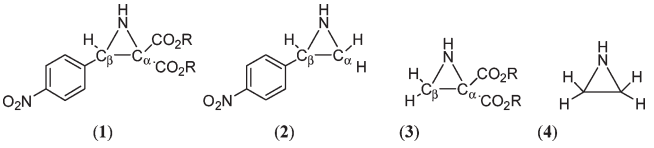

FIGURE 2. Investigated aziridines with varying substitution patterns, R = methyl.

bond breaking (path II, Figure 1). For aziridinium, the reaction ran over sequential transition states.[18] In contrast to these substitution patterns, *p*-nitrophenylaziridine-2,2-dicarboxylate (**1**) (Figure 2) was shown to undergo CC bond cleavage in the reaction with sulfur, nitrogen, and oxygen nucleophiles (path Ia, Figure 1).[12,13]

Kinetics and thermodynamics of the CN bond-breaking processes in *N*-unsubstituted or *N*-alkylated aziridine-2-carboxylates and aziridine-2,3-dicarboxylates are strongly dependent on the pH value of the reaction medium.[14−16] This was also found in enzymatic environments where aziridines react under CN ring-opening reactions with the nucleophilic active site of cysteine proteases. In the inhibition process, the thiolate moiety of the active site attacks one of the electrophilic carbon centers of the heterocycle and induces a ring-opening C−N bond cleavage. Due to the strong exothermicity of the ring-opening reaction, the enzyme becomes irreversibly blocked. CC bond-breaking reactions were never observed in this connection. The ring opening is accompanied by a protonation of the emerging negatively charged moiety. Computations show that the protonation influences only the thermodynamic of the epoxide ring opening. For the corresponding aziridine reaction, activation and reaction energies are strongly lower; i.e., both thermodynamic and kinetics are influenced. Since the nearby protonated His199-residue (cathepsin B enumeration) forms a strong salt bridge to carboxylate substituents, at least for such systems the necessary proton seems to stem from the solvent. These theoretical findings excellently explain why aziridine-based inhibitors are only active at low pH values while epoxide-based inhibitors are also active at much higher pH values.[19−22]

In the case of unsymmetrically substituted aziridines, nucleophilic ring opening can occur by attack at either C_α or C_β (for numbering of the carbon atoms see Figure 2).[23,24] The regioselectivity of the nucleophilic attack has been investigated in quite some detail.[15,25] In solvents, generally only partial regioselectivity is observed. It is determined by an interplay between the electrophilicities of the carbon centers,[15,25] i.e., by the substituents at these carbon atoms, and by steric effects.[26] In protein environments, the nucleophilic attack can occur regiospecifically on the less electrophilic carbon atom due to noncovalent interactions between protein and ligand which direct the less electrophilic ring carbon onto the nucleophilic center of the protein.[23] Regiospecific addition at C_β was found for the reaction of *p*-nitrophenylaziridine-2,2-dicarboxylate (**1**, Figure 2) with nucleophiles.[12,13] Experimental electron density determinations of aziridine (**1**)[13,27] by means of ultrahigh-resolution X-ray diffraction experiments showed that indeed C_β is the more positively polarized carbon atom. However, this explanation neglects other effects, such as steric hindrance or rapid change of the electronic character along the reaction path, which may also influence the reaction kinetics and thermodynamics. Furthermore, it is also not yet understood how different substituents at the aziridine moiety influence a preference for the CN or the CC bond-breaking reaction.

The aim of the present investigation is to provide insight into the reactivity of aziridine compounds that is sketched in Figure 1. For that purpose, the reaction paths of the possible ring-opening processes (CN vs CC ring opening, C_α vs C_β attack of a nucleophile) are determined with quantum chemical computations. Several substitution patterns of the

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aziridine ring are investigated with and without the presence of proton donors. This reveals the mechanisms of the investigated reaction paths and shows how the reaction course is influenced by substituents.

Model System and Computational Details

In order to investigate the influence of the substitution pattern on the reactivity of aziridine derivatives, the reaction paths I and II (Figure 1) have been computed for the aziridine compounds depicted in Figure 2. In all cases, methyl thiolate has been used as model nucleophile. Ring-opening reactions of aziridines are strongly influenced by the pH value of the environment. Unfortunately, the pH-dependency cannot be appropriately represented by continuum solvation models that are straightforwardly applicable to calculations of such reaction profiles. It can, however, nicely be described by model systems which incorporate appropriate proton sources and accounts for the overall polarizability of the solvent by the continuum solvation model (COSMO)[28] ($\varepsilon = 78.39$).[14,15] Due to the high basicity of the emerging amide group, proton sources are even necessary to simulate aziridine experiments performed at quite high pH values. As shown previously the activation barrier of aziridines along reaction II for example correlates nicely with the proton donor ability of the included proton source (e.g., water vs ammonium) since the protonation takes place before the transition state is reached.[14−17] Using ammonium as proton source, a barrier of about 60 kJ mol^{-1} is computed for the reaction path II of compound **4**. It increases to 118 kJ mol^{-1} if water is used and to 126 kJ mol^{-1} if no source is included. These computations also showed that a second discrete solvent molecule should be positioned near the negatively charged sulfur since it weakens the nucleophilicity of the attacking methyl thiolate and hence increases the computed activation barriers.[14] This approach reliably predicted the influence of substitution pattern and environment on the inhibition potency of epoxides and aziridines. Hence, we adopted it for the present questions. Since the corresponding experiments were performed at moderate pH values, two ammonium groups have to be used as proton donors. As an example, Figure 3 shows the composition of the model system used to study the reactivity of *p*-nitrophenylaziridine-2,2-dicarboxylate (compound **1**).

For all computations except the gas phase, the COSMO approach was used to mimic a polar solvent ($\varepsilon = 78.39$). Compounds **1** and **4** are defined in Figure 2. The left solvent molecule (column 1) is positioned at the nitrogen center of the aziridine ring while the right one is positioned at the thiolate moiety.

To describe reactions Ia and Ib (Figure 1), two-dimensional potential energy surfaces (PESs have been computed for compound **1** by varying the bond distances between C_α and C_β, $R(C_\alpha-C_\beta)$, and either C_α or C_β and the sulfur center of the attacking thiolate ($R(C_\alpha-S)$ and $R(C_\beta-S)$, respectively) independently (see Figure 2 for the numbering of the carbon atoms). The PESs of reaction II were represented with the $C_\alpha-N$ and the $C_\alpha-S$ ($C_\beta-N$; $C_\beta-S$) bond distances for the nucleophilic attack at C_α (C_β). For each grid point of the two-dimensional PESs (grid size 0.1 Å), these

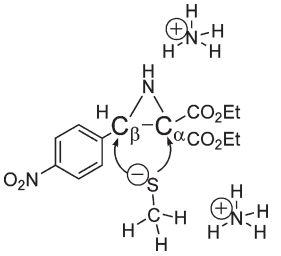

FIGURE 3. Sketch of the model system employed for the computations of the reaction coordinates. The two ammonium molecules represent the protic solvent, whereas the polarizability of the remaining solvent is taken into account by the COSMO model.

reaction coordinates were fixed while all other internal degrees of freedom were optimized. The geometries obtained in this process were used to determine barriers and reaction energies. All geometry optimizations were performed using density functional theory (DFT) at the RIDFT[29]/B-LYP[30]/TZVP[31] level. Since the B-LYP functional often underestimates reaction barriers, energies were computed for the B-LYP structures at the DFT/B3[32]-LYP/TZVP level. For compounds **2**−**4**, only the reaction paths Ia and II have been computed. DFT is well-known to describe many properties with an excellent cost−benefit value.[33−35] Nevertheless, this is often based on an error compensation which does not work in all cases,[36−39] and indeed, often multireference approaches are necessary to obtain reliable reaction paths or properties.[40−44] For the reaction of thiolate with aziridine, the B3-LYP/TZVP//BLYP/TZVP approach closely resembles the results obtained with MP2/aug-cc-pVTZ or CCSD(T)/aug-cc-pVTZ.[14] For the activation energies DFT, MP2 and CCSD(T) differ around 2 kJ mol^{-1}, while the reaction energies vary by about 10 kJ mol^{-1}. Since the differences between the various systems are considerably larger, the B3-LYP/TZVP//BLYP/TZVP approach seems to be sufficiently accurate for our purpose. All calculations were performed with the TURBOMOLE[45] program package.

The computations of the reaction paths turned out to be quite delicate, since many internal degrees of freedom change

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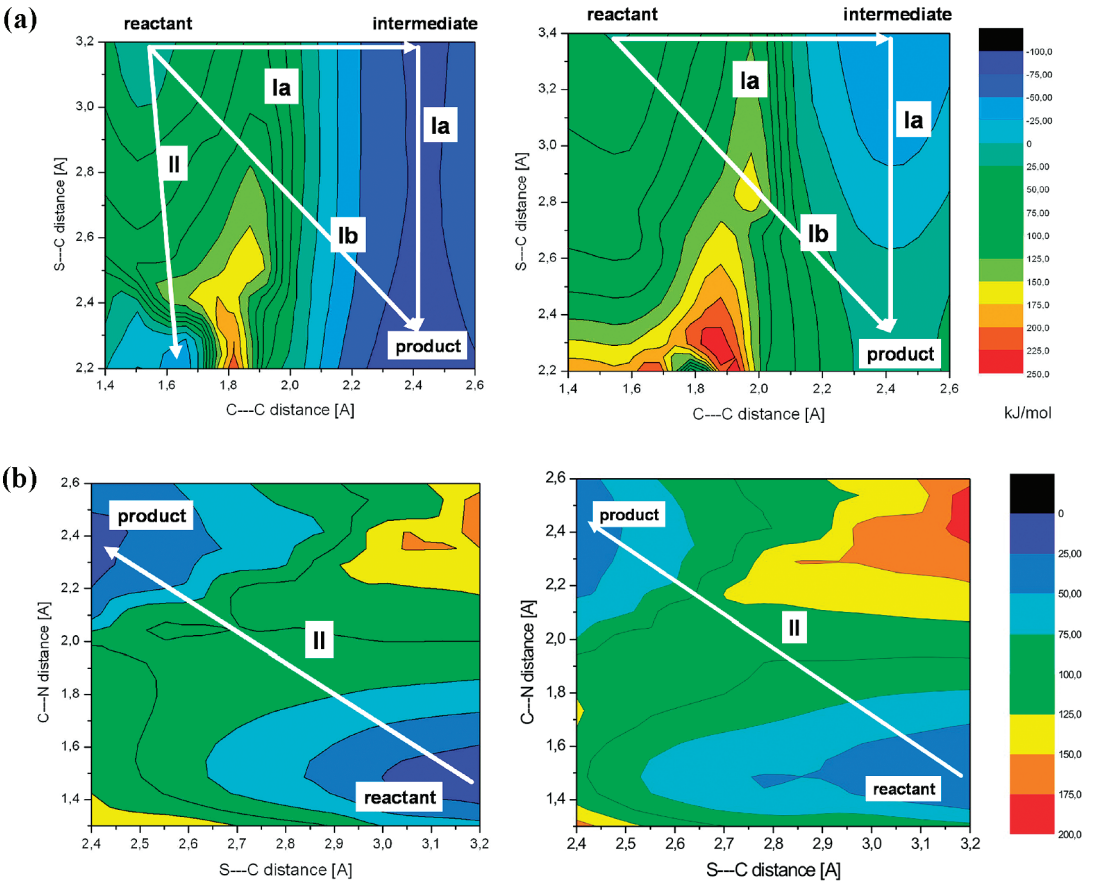

FIGURE 4. (a) Computed potential energy surfaces for compound **1**. The corresponding reaction paths are indicated. The left-hand side gives the computations of the β- and the right-hand side of the α-attack of the methylthiolate. Mechanisms can be taken from Figure 1. (b) Computed potential energy surfaces for reaction II of compound **1**. The reaction path is indicated. The left-hand side represents the computations of the β- and the right-hand side of the α-attack of the methylthiolate. Mechanisms can be taken from Figure 1.

significantly along the reaction path. Numerous test computations turned out to be necessary to ensure a proper treatment of the protonation processes. The ammonium ions are connected to the reacting species by hydrogen bonds. Such hydrogen bonded systems typically possess several local minima which are separated by small barriers and differ only slightly in energy. At room temperature such small barriers are easily surmounted; i.e., the ammonium ions will adopt the energetically lowest orientation. However, simple energy minimizations frequently fail to find the lowest minima as they are normally trapped in the local minimum near the starting structure. Hence, different orientations were manually tested to ensure a proper orientation of the ammonium ions at the investigated points of the surfaces.

Another difficulty results from proton transfer processes to emerging proton acceptor sites. Previous computations showed that a correct description of reaction II is only possible if the protonation of the emerging amide is correctly taken into account.[14−17] For reaction mechanism I, such a protonation may occur at C_α which is formally negatively charged in the azomethine ylide intermediate. The correct description of this protonation is quite difficult since for compounds **1** and **3** C_α is connected to two ester groups. They hinder the protonation due to geometrical and electronical reasons. The carbanionic center of the azomethine ylide is electronically stabilized due to delocalization of the negative charge over the ester groups. This delocalization is amplified by the hydrogen bonds between the ammonium ions and the ester groups; i.e., the ammonium ions form stronger bonds to the ester groups when the CC bond is broken. This electronic effect is fully taken into account in the present calculations. However, due to these hydrogen bonds and due to the geometrical extensions of the ester groups, the proton transfer from the ammonium to the negatively charged carbon atom proceeds only via narrow reaction channels and is additionally hindered by energy barriers. Nevertheless, in reality a protonation will take place if it is thermodynamically favored since proton transfer reactions are very fast. In the computations, however, the corresponding reaction paths are difficult to find. Hence, various computations with differently oriented ammonium ions (e.g., positioned near the carbonyl oxygen of the ester or near the arising carbanionic center) were performed. Furthermore, to ensure that the lowest reaction path is indeed obtained, all reactions were also calculated backward starting from protonated C_α centers.

Results and Discussion

The computed surfaces for compound **1** are depicted in Figure 4. The geometrical arrangements at important points on the reaction courses are presented in Figure 5. Table 1

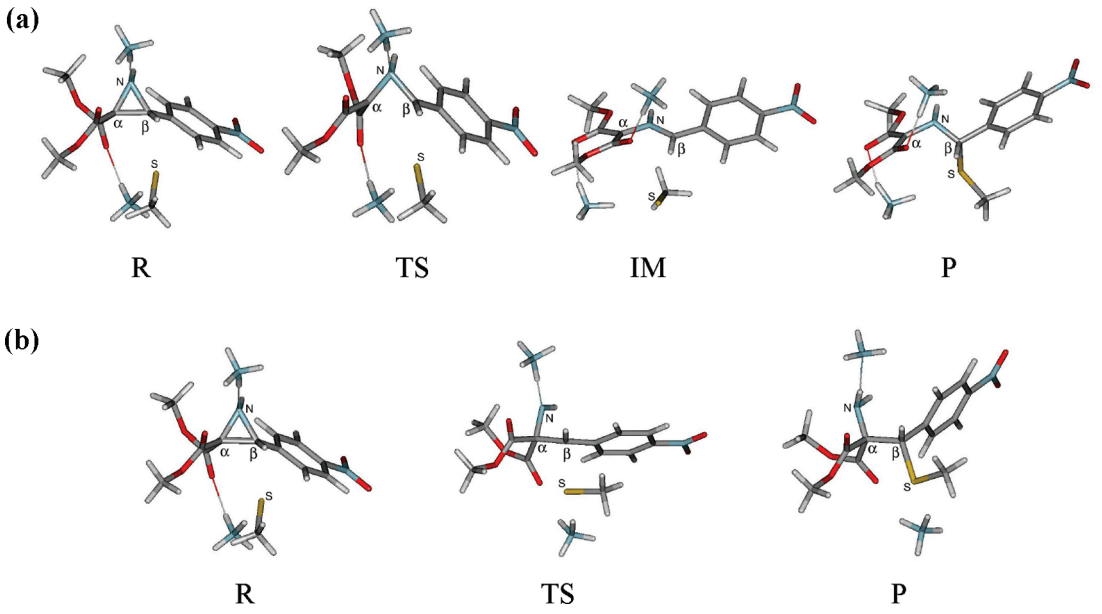

FIGURE 5. (a) Geometrical arrangements of reactants (R), transition state (TS) of the CC-bond breaking, ring-opened intermediate (IM), and product (P) for the stepwise reaction Ia (β-attack) for compound **1**. The geometrical arrangements are given for the β-attack. (b) Geometrical arrangements of reactants (R), transition state (TS), and product (P) for the reaction II (β-attack) for compound **1**.

TABLE 1. Influence of the Substitution Pattern on the Reaction Profiles of the CC or CN Ring-Opening Reactions (in Each Computation Two Ammonium Ions as Possible Proton Donors Were Included; All Values in kJ mol^{-1})

	reaction path Ia			reaction path II	
compd	TS	intermediate	product	TS	product
1, β-attack	88	$-84/-89^{a}/-21^{a,b}$	$-103/-94^{b}$	100	-70
1, α-attack	88	$-84/-89^{a}/-21^{a,b}$	[c]	113	-49
2, β-attack	140	[c]/$38^{a,d}/-12^{a,b}$	[c]/-60^{b}	n.d.[e]	-87
3, β-attack	126	[c]/$-54^{a}/19^{a,b}$	$-101^{a}/-100^{b}$	n.d.[e]	-89
4	229^{a}	[c]/ $84^{a}/3^{a,b}$	[c]/-74^{b}	60^{e}	-99^{e}

[a]Computed without nucleophile. [b]Protonated at C_α. [c]No appropriate stationary point found. [d]Possesses one remaining imaginary frequency (see the Supporting Information). [e]Not determined. [e]Taken from ref 14.

collects the relative energies of these points with respect to the reactants. It also summarizes the data computed for compounds **2**−**4**.

Figure 4a shows that for compound **1** reaction I proceeds according to the stepwise reaction path Ia. The barrier of the CC bond breaking leading to the azo methinylide intermediate (IM) is about 90 kJ mol^{-1}. For the subsequent attack of the nucleophile at C_β (see Figure 2 for the numbering of the carbon atoms) the reaction surface does not show a further barrier. Hence, the azomethine ylide depicted in Figure 5a is not an intermediate in the strict sense but could still be located as a shallow minimum. The missing barrier explains why the azomethinylide intermediate reacts very rapidly with nucleophiles leading to product A (Figure 1). The corresponding barriers of the 1,3-dipolar cycloaddition[8,9,46,47] are also quite small so that product C will be formed if dipolarophiles are present. Please note the low basicity of the emerging C_α carbon which is formally negatively charged (Figures 1 and 6). In case of the azomethine ylide, its protonation is endothermic and even after the addition of the nucleophile the deprotonated form is more stable than the protonated one. A protonation could occur via a proton transfer from one of the ammonium ions; however, the resulting structures are higher in energy. This behavior is explainable since the product obtained from **1** via reaction Ia resembles the situation found for the Claisen condensation.[48] All steps of the Claisen condensation are reversible except for the last one in which the formed β-keto ester is deprotonated. The Claisen condensation reaction is driven to complete due to the thermodynamic stability of the resulting carbanionic product. A similar stability is also expected for our product. The corresponding attack of the nucleophile at C_α possesses a repulsive reaction path (Figure 4a, right side) which could be expected since C_α is formally negatively charged.

Figure 4b indicates that for reaction II of compound **1** ring-opening and approach of the nucleophile proceed in a concerted manner. The β-attack is kinetically and thermodynamically preferred; however, the computed barriers indicate that the CC bond breaking (reaction Ia) proceeds about 2000 times faster than the CN bond breaking. This explains why only product A is found in the corresponding experiments.[12,13]

To study the importance of the different substituents for reaction I, the profiles of reaction Ia were also computed for compounds **2**−**4** (Table 1). For compound **2** which possesses no ester groups, the barrier of the CC bond cleavage is computed to be about 140 kJ mol^{-1}; i.e., it is considerably larger than that found for compound **1**. This shows the importance of the ester groups for the stabilization of the intermediate azomethine ylide. The importance is also underlined by the fact that the protonation of C_α is exothermic for **2** while it was endothermic for **1**.

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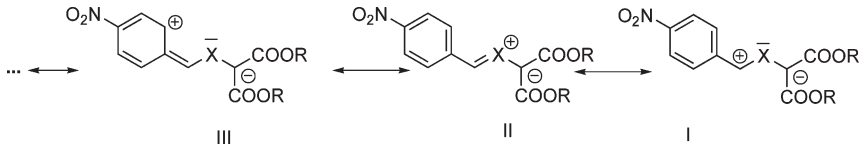

FIGURE 6. Intermediates of the CC ring-opening reaction. X = NH, O. The dots indicate additional resonance structures.

The nitrobenzene group is also promoting reaction course Ia, but it is slightly less important than the ester groups. If it is replaced by hydrogen (compound **3**), the barrier is about 130 kJ mol^{-1}. If only the nitro group is replaced by hydrogen the situation does not change much. This shows that the phenyl group is especially important while the nitro group does not favor the CC bond breaking additionally. Please note that for **2** and **3** the azomethinylide intermediate directly reacts with a present nucleophile. The reaction would be still stepwise but the intermediate can only be characterized if no nucleophile is present. Finally, for the nonsubstituted aziridine **4** the barrier for the CC ring-opening reaction I is much higher than that of the corresponding CN ring-opening reaction.

In summary, the computations indicate that the CC bond-breaking reaction will only take place if both carbon atoms are bound to stabilizing substituents. Less substituted compounds are expected to react via the CN bond-breaking pathway since the corresponding reaction barriers are considerably lower (Table 1). These results explain why the chemistry of aziridines is dominated by CN ring-opening reactions while CC bond-breaking reactions are only observed for properly substituted aziridines.

CC bond-breaking reactions of epoxides are rarely observed (e.g., with tetracyanoethylene oxide);[49] i.e., for epoxides even stronger stabilizing substituents are necessary to steer the chemistry from CO to CC bond-breaking paths. This can be rationalized by the electronic structure of the intermediate of the CC ring-opening reaction (Figure 6). For X = O, resonance structure II and also the push−pull effects (resonance structures III and related ones) stabilize the cationic center of the respective oxirane compound less effectively. Thus, C−C bond breaking in oxiranes requires even more and stronger stabilizing substituents (e.g., four nitrile groups).

(49) (a) Friedrich, K.; Rieser, J. *Liebigs Ann. Chem.* **1976**, 641–647. (b) Flemming, J.; Dolphin, D. *Tetrahedron Lett.* **2002**, *43*, 7281–7283.

Summary

In the present study, we characterize mechanisms as well as kinetic and thermodynamic parameters of the fundamental reactions of aziridines as a function of the substitution pattern. While reaction II (CN bond cleavage and nucleophilic attack) represents a concerted process, reaction I (CC bond cleavage and nucleophilic attack) is a stepwise reaction. The CC bond cleavage, which represents the first step, is the rate determining. After the formation of the azomethine ylide the attack of the nucleophile is nearly barrier-free. In principle, the substitution pattern does not influence the reaction course but affects the reaction barriers considerably. While the reaction barrier of the CC bond cleavage decreases if hydrogen is replaced by electron-withdrawing substituents such as carboxylate or nitro-phenyl the barrier of the CN bond-breaking reaction path increases with cumulative substitution. The computed data predict that a steering from the CN to the CC ring opening requires stabilizing substituents at both carbon centers. For *p*-nitrophenylaziridine-2,2-dicarboxylate the carboxylate substituents are found to be more important but also the *p*-nitrophenylgroup considerably contributes to the lowering of the reaction barrier of the CC bond cleavage.

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Supporting Information Available: Cartesian coordinates, total energies, zero point frequencies, and the number of imaginary frequencies of stationary points. This material is available free of charge via the Internet at http://pubs.acs.org