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Theoretical Studies about the Influence of Different Ring Substituents on the Nucleophilic Ring Opening of Three-Membered Heterocycles and Possible Implications for the Mechanisms of Cysteine Protease Inhibitors

Holger Helten,[†] Tanja Schirmeister,[‡] and Bernd Engels*,[†]

Institut für Organische Chemie and Institut für Pharmazie und Lebensmittelchemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany

engels@chemie.uni-wuerzburg.de

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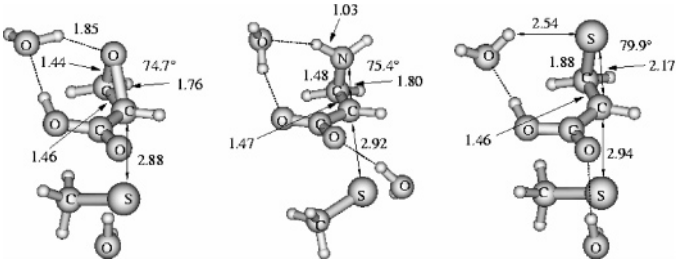

Epoxides, aziridines, and thiiranes are electrophilic building blocks that are widely used in synthetic organic chemistry. As a result of their reactivity against nucleophiles they are also used as electrophilic "warheads" for irreversible peptidic or peptidomimetic cysteine protease inhibitors. A general feature of these inhibitors is the remarkable higher inhibition potency of derivatives containing a free carboxylic acid in comparison to corresponding esters. In contrast, experimental investigations about the reaction of methyl thiolate with substituted epoxides revealed a contrary reactivity pattern. These studies also gave information about the regioselectivity of such reactions; however, mechanistic studies were not performed. By analyzing the computed energy profiles of the corresponding reactions we investigate the substituent effects (H vs ester vs carboxylic acid) on the kinetics and thermodynamics of the ring opening by the nucleophile methyl thiolate. Our model computations nicely explain experimental results concerning variations in the reactivities and the regioselectivities and indicate different reasons for the increased inhibition potency of three-membered heterocycles containing an acidic substituent. For aziridines an intramolecular water-mediated acid catalysis seems to be the main reason for the high activity of these inhibitors in acidic media. For epoxides and thiiranes this catalysis is not found, confirming the hypothesis that an ionic interaction between negatively charged carboxylate and the histidinium ion of the active site of the proteases mainly causes the high inhibitory activity of the acids compared to the esters.

Introduction

Ring-opening reactions of three-membered heterocycles play important roles in synthetic organic chemistry,[1] in biocatalytic reactions,[2a,b] and in a variety of biologically relevant processes.[2c−g] An important example of the latter are epoxide-, aziridine-, and thiirane-based peptides and peptidomimetics that are used as irreversible inhibitors of cysteine proteases.[3−7] Their inhibition potency is

* To whom correspondence should be addressed. Fax: +49 (0)931/888 5331.
[†] Institut für Organische Chemie.
[‡] Institut für Pharmazie und Lebensmittelchemie.

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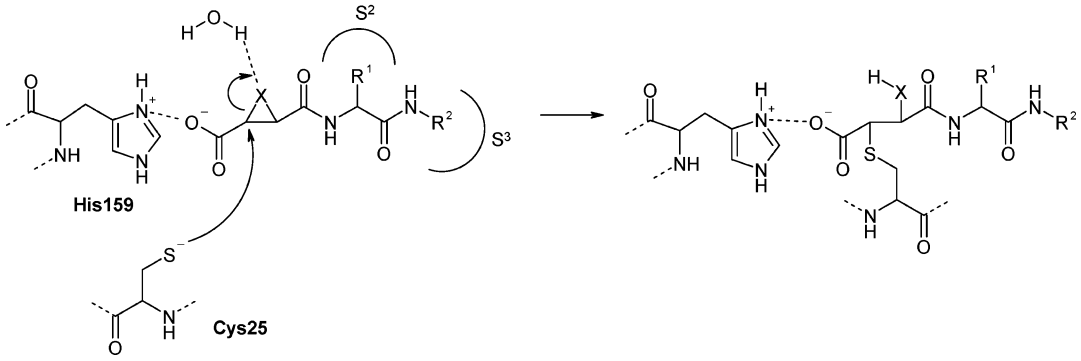

FIGURE 1. Proposed inhibition mechanism of cysteine protease inhibitors containing three-membered heterocycles (His159, Cys25: active site diad, papain numbering).

usually characterized by two inhibition constants (eq 1, minimal two-step mechanism for irreversible enzyme inhibition where E = enzyme, I = inhibitor, EI = noncovalent enzyme−inhibitor complex, E-I = inactivated enzyme): the dissociation constant K_i, characterizing the preliminary reversible complexation step, and the first-order rate constant of inhibition k_i, describing the rate of irreversible enzyme alkylation (Figure 1).

$$\mathrm{E} + \mathrm{I} \overset{K_i}{\rightleftharpoons} \mathrm{EI} \xrightarrow{k_i} \mathrm{E\text{-}I}$$

A general feature of these inhibitors is the remarkable difference in inhibition potencies between derivatives containing a free carboxylic acid and those with an ester moiety attached to the ring. Whereas the free acids are highly potent, the esters are weaker by orders of magnitude.[8−10] For epoxides this has been studied in detail.[8c,e] The following sequence of inhibition activity was found: $\underline{CO_2H}$ > $CONH_2$ > $COCH_3$ > $\underline{CO_2Et \approx CO_2Me}$ > $CH_2OH \approx H$.

This is in contrast to the reactivity of α,β-epoxycarbonyl compounds in their ring-opening reaction with methyl thiolate, which represents a model reaction for the alkylation step of the inhibition. For these reactions Bihovsky[11a] found that the rate constant for epoxides with R = CO_2CH_3 (k = 0.44) is much higher than the corresponding value for epoxides with R = CO_2^- (k = 0.01). In summary, the trend $COCH_3$ > $\underline{CO_2CH_3}$ > $CONH_2$ > $\underline{CO_2^-}$ was determined. These investigations also revealed differences in the regioselectivity of the reactions. For esters the rate constants for α- and β-attack are very similar (k_α = 0.25 vs k_β = 0.19), whereas for CO_2^- they differ by a factor of 2 (k_α = 0.0036 vs k_β = 0.0064). On the basis of explanations for S_N2 reactions of α-halo-carbonyl compounds[11b,c] it was assumed that the carbonyl moiety activates the α-carbon, while sterical hindrances have an opposite effect. However, no theoretical investigations were performed to elucidate the importance of the various effects (electronic, steric, environment).

The results found for these reactions can be expected to be mainly influenced by the kinetics of the ring-opening reaction, whereas for the inhibition of proteases by epoxides the stability of the noncovalent enzyme inhibitor complex (EI) also has to be taken into account. Assuming that the alkylation step of the inhibition reaction (k_i) is determined by the same factors as the above-mentioned model ring-opening reaction, the discrepancies in the trends of both reactions must be connected to the preliminary inhibition step (K_i). Indeed, the overall trends in the inactivation of cysteine proteases by oxirane-carboxylic acids are generally explained by a favorable ionic interaction between the carboxylate and the positively charged imidazolium ion of His159 of the active site (Figure 1).[12] A support of this explanation is provided by an experimental differentiation between the influence of the ring substituents on the reversible and the irreversible step of the inhibition.[8c] These experiments showed that the replacement of the R = CO_2H substituent of the epoxide ring by R = CONHOH, $CONH_2$ or $COCH_3$ changed the first-order rate of inhibition k_i only slightly. Similar investigations for aziridines and thiiranes are missing.

Results and discussions

To understand the effects determining the kinetics of the ring-opening reactions of three-membered rings with different substituent patterns and to understand the differences between their inhibition potencies against cysteine proteases, we computed the reaction barriers and energies for ring-opening reactions of oxirane (Figure 2, $R^1 = R^2 = H$), oxirane-2-carboxylic acid ($R^1 = CO_2H$, $R^2 = H$), methyl oxirane-2-carboxylate ($R^1 = CO_2CH_3$, $R^2 = H$), and oxirane-2,3-dicarboxylic acid ($R^1 = R^2 = CO_2H$) with methyl thiolate. The reactions of the analogous

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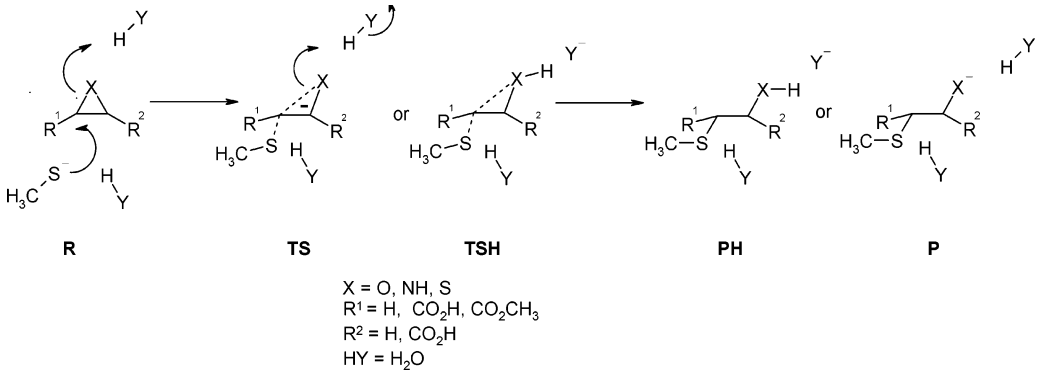

FIGURE 2. Model reaction for the alkylation of methyl thiolate by three-membered heterocycles: R denotes reactants, TS transition state, TSH protonated transition state, P unprotonated product, and PH protonated product.

TABLE 1. Influence of Substituents on the Reaction Profiles of the Ring Opening Reactions[a]

		epoxide			aziridine			thiirane		
	ring substituent	TS	P	PH	TS	TSH	PH	TS	P	PH
entry 1	$R^1 = R^2 = H$	+14.4	−17.2	−25.6[b]	+28.3		−6.1	+10.0	−17.6	
entry 2	$R^1 = CO_2CH_3$, $R^2 = H$	+14.4	−15.1	*c*	+28.0		−0.6	+9.2	−14.7	
entry 3	$R^1 = CO_2H$, $R^2 = H$	+17.2		−38.3		+12.4	−28.9	+9.8	−15.7	−27.3
entry 4	$R^1 = H$, $R^2 = CO_2H$	+14.3		−36.3		+13.9	−26.2	+10.4	−19.7	−22.2
entry 5	$R^1 = CO_2H$, $R^2 = CO_2H$	+15.0		−39.1		+15.0	−29.8	+8.4	−21.2	−23.3

[a] TS and P denote the transition states and the products, respectively. A water-mediated proton transfer from the carboxylic acid during the ring opening is indicated by the abbreviation PH for protonated products or TSH for protonated transition states. Values are in kcal mol^{-1}. [b] Computed with the standard GAUSSIAN settings for the COSMO approach, geometries not fully optimized; [c] Computation did not converge.[16]

aziridine and thiirane derivatives were calculated as well. To compute the reaction profiles, density functional theory was employed.[14] In our model system (Figure 2) two water molecules were employed to mimic molecular effects of environments with weak proton donor ability. Water molecules placed in the vicinity of the heteroatom of the three-membered ring were found to be necessary to include effects that arise if a proton moves from the solvent to the solute.[15] As will become clear later on, these water molecules are also important to describe the influence of acidic substituents. Bulk effects of the environment were also accounted for by employing the COSMO approach with the standard parameter settings used in the TURBOMOLE.[16] All calculations were performed with the TURBOMOLE or the GAUSSIAN program package.[17] The accuracy of the chosen approaches was proven in previous studies.[15] The computational results are summarized in Table 1, which gives the relative energies with respect to the reactants (kcal mol^{-1}).[18] The geometrical arrangements for the transition states can be taken from Figure 3. Because the reactions in which the substituted α-carbon center is attacked by the methyl mercaptan show the same trends as the ones in which the methyl mercaptan addition takes place at the unsubstituted β-carbon center, Figure 3 only contains the former.

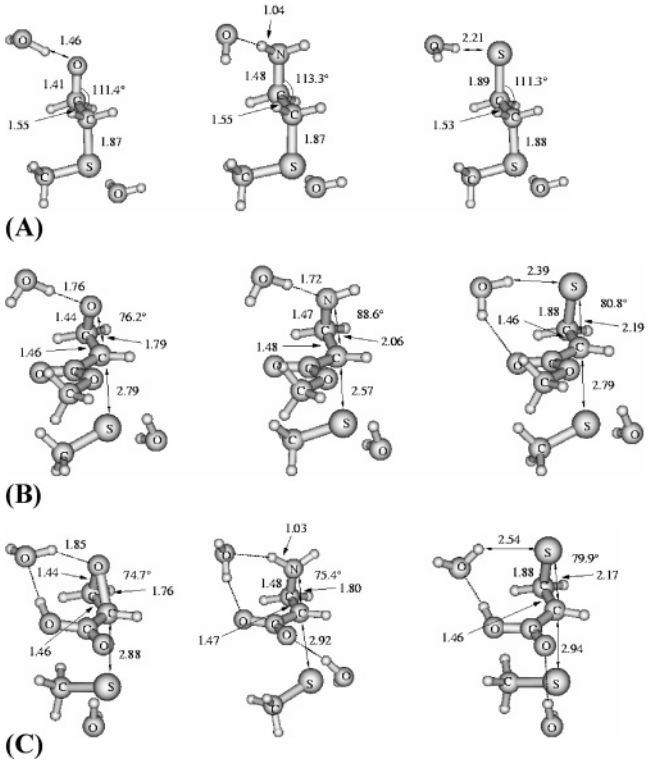

FIGURE 3. Geometrical arrangements of the transition states for (A) entry 1 of Table 1 ($R^1 = R^2 = H$), (B) entry 2 of Table 1 ($R^1 = CO_2CH_3$; $R^2 = H$), and (C) entry 3 of Table 1 ($R^1 = CO_2H$; $R^2 = H$). The oxirane is given at the left-hand side, followed by aziridine (middle) and thiirane (right-hand side).

(13) The corresponding pK_a values for ethyl aziridine-2,3-dicarboxylate have experimentally been determined in the authors' groups to be 3.8 and 4.8.

(14) The geometrical parameters of the relevant stationary points of the potential energy surface were computed with the BLYP functional[19] in combination with a TZV+P basis set.[20] All stationary points were checked by frequency calculations. All energies were obtained from B3LYP single point calculations in combination with a TZV+P basis. These values showed an excellent agreement with CCSD(T) results, whereas the BLYP underestimated the barrier heights considerably. All calculations were performed with the TURBOMOLE program package.

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Our calculations for $R^1 = R^2 = H$ (Figure 2) indicate that kinetically and thermodynamically the aziridine ring opening is unfavored compared to the ring opening of the epoxide and thiirane.[15] If a hydrogen ($R^1 = H$) is replaced by an ester group ($R^1 = CO_2CH_3$), nearly no changes are found for the reaction barriers and all reactions become only slightly less exothermic.[16] Dramatic changes are found, however, if the hydrogen is replaced by a free carboxylic acid ($R^1 = CO_2H$, Figure 3C). For aziridine the reaction barrier decreases by about 16 kcal mol^{-1} and the reaction becomes considerably more exothermic (−6 to −28.9 kcal mol^{-1}). For the epoxide the reaction barrier increases slightly (+14.3 vs +17.2 kcal mol^{-1}) but the absolute value of the reaction energy increases from 17 to about 38 kcal mol^{-1}. In the case of the thiirane the introduction of a carboxylic acid group only leads to small changes in the reaction barrier (+10 vs +9.8 kcal mol^{-1}) and energy (−17.6 vs −27.3 kcal mol^{-1}).

The computed results obtained for epoxides with $R = CO_2CH_3$ and CO_2H systems are in good agreement with the experimentally observed rate constants ($k_{(ester)} = 0.44$ min^{-1}, $k_{(carboxylate)} = 0.01$ min^{-1}), which also showed a faster rate for the ester.[11a] The somewhat higher difference between ester and carboxylate found by the experiments[11a] compared to the computed results can easily be explained by the repulsion of the two negatively charged reactants (carboxylate and thiolate), which lowers the rate constant for the carboxylate to a larger extent than for the free acid. The geometrical structures of the transition states (see Supporting Information) show that the steric hindrances are quite similar for $R = CO_2H$ and CO_2CH_3. This indicates that electronic effects seem to be responsible for the lower reactivity of the former systems and underlines their importance in comparison to steric effects.

For $R = CO_2H$ the attack at the β-position (Table 1, entry 4) of the epoxide is predicted to possess a lower barrier compared to that of the α-attack (Table 1, entry 3). This is again in good agreement with the experimentally obtained trend (α-attack = 0.0036 min^{-1} vs β-attack = 0.0064 min^{-1}).[11a] Since those data have also been obtained with the carboxylate and not with the free acid,[11a] the somewhat more preferred β-attack of the carboxylate compared to the acid may also be due to the repulsion of carboxylate and thiolate. For the ester the experiment only found a very small regioselectivity. This is also in agreement with our computations that found nearly identical barriers for the α-attack at the epoxide with $R = CO_2CH_3$ and the reaction of the unsubstituted epoxide.

Our model computations predict that acidic substituents increase the reaction barrier of the alkylation step of the overall inhibition mechanism. This finding supports experimental results that indicate that the improved inhibiton potency of epoxides with acidic substituents do not result from influences on the alkylation step but from a favorable ionic interaction between carboxylate and imidazolium ion stabilizing the noncovalent enzyme inhibitor complex and thus improving K_i.

While for epoxides only small to moderate changes in the reaction barriers are computed, for aziridine a tremendous effect is predicted. The reasons for the dramatic changes found for the acid-substituted aziridine become obvious from Figure 3, which gives the geometrical arrangements of the transition states of the different systems. Mediated by a water molecule already at the transition state of the aziridine ring opening the proton of the acid moiety is transferred to the emerging NHR^- unit. In comparison to $R^1 = H$ (Figure 3A) and $R^1 = CO_2CH_3$ (Figure 3B), this leads to a sharp decrease of the reaction barrier and to an increase in exothermicity. For the epoxide system only a strong increase in the exothermicity arises because solely the product is protonated. The reaction barrier is only slightly influenced because at the transition state the basicity of the emerging alcoholate is not yet high enough to induce a proton transfer. For the thiirane system we find the same behavior. For all systems the proton transfer from the carboxylic acid group to the hetero centers influences the reaction in a similar manner as found for an acid environment.[15] Considering the regioselectivity of the ring-opening reactions for aziridine and thiirane the computations predict almost no differences between α- and β-attack. Our explanation depends on the availability of water molecules that can act as a proton relay. Because of the nature of the active site such water molecules should be available.[12]

The results for the aziridine model reaction clearly show that the high inhibition potency of aziridines with free carboxylic acid groups compared to the esters not only is due to a favorable ionic interaction with the histidinium ion of the active site but also is caused by a direct participation of the carboxylic acid in the ring-opening process. Naturally, this intramolecular catalysis will only be possible with the protonated free acid and not with the carboxylate. Thus, decreasing pH values leading to a protonation of the carboxylate will, in

(16) Although continuum approaches can simulate the bulk effects of the solvation of neutral systems quite well, sometimes problems arise if charged species are involved.[21,22] In the present study such problems only appeared in combination with the hydroxyl anion that arises if a proton transfer from a water molecule occurs. For such situations the standard parameters used in the Gaussian program show a better agreement with experimental findings than those used in the TURBOMOLE, but only in a few cases the computations converged. Furthermore, also this ansatz showed varying results as a function of the number of explicitly considered water molecules. Overall, employing the Gaussian parameters, reactions in which a hydroxyl group appeared became more exothermic. For all other systems the differences between both approaches are small. A detailed discussion of the problems can be taken from our previous study.[15]

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(18) Computations showed that in our model system entropy effects mainly influence the energy difference between reactant and transition state. This indicates that these effects are more connected with the association process (K_i) than with the reaction itself (k_i). Therefore in the present study electronic energies instead of free energies are used.

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contrast to the epoxides, result in increased inhibition potency. This is in nice agreement with the different inhibitory behavior of aziridine- and oxirane-carboxylic acids at low pH values.[8c,9c,d] Our calculations also indicate that the pK_a value of 3.6−3.8[9c,13] determined from the pH dependency of the inhibition of aziridine carboxylic acids and which has been attributed to the protonated aziridinium ion should rather be attributed to the carboxylic acid.

The calculations especially indicate that for an understanding of the reactivity of the aziridines the strong basicity of the emerging leaving group NHR^- is more important than the electrophilicity of the attacked carbon center. For epoxides the basicity of the alcoholate group only influences the thermodynamics and is less important for the kinetics of the ring opening. For the thiirane only small influences are found.

Concerning the results obtained with the 2-carboxylic acids compared to those of the 2,3-dicarboxylic acids (Table 1, entry 5), a remarkable difference between the computational predictions and the inhibition potencies can be found. Although the oxirane-2,3-dicarboxylic acid is an only very weak protease inhibitor (about 300 times weaker than its half ester),[8a] almost no differences are found in the computations. This means that other effects that probably affect K_i rather than k_i are the main reasons for the inhibitory behavior of the dicarboxylic acid.

Summary

Our calculations nicely explain the experimental results obtained for reaction constants and regioselectivity of ring-opening reactions of substituted epoxides. The analysis of the various effects underlines the importance of electronic effects in comparison to steric effects. Comparing the computed reactions of the α- and β-attack our investigations also contribute to the understanding of the regioselectivity of synthetically useful ring-opening reactions. By predicting that the reaction barrier of the ring-opening reactions of epoxides with a free carboxylic acid function is actually higher than the one for epoxide itself, our calculations also resolve the discrepancy between the experimentally obtained rate constants of the reaction of α,β-epoxy carbonyl compounds with methyl thiolate and the trends in the corresponding inhibition potencies.

By characterizing the corresponding reactions of aziridines and thiiranes our investigation broadens the knowledge about similarities and differences in the reactivity of three-membered heterocycles. For aziridines the computations indicate that, similar to an acidic environment, a free acid as substituent enhances the ring opening to a much greater extent than for epoxides or thiiranes. This gives new hints to explain the experimental results obtained with aziridine carboxylic acids at low pH values. It also indicates that a carboxylic acid moiety at the three-membered ring differently influences the inhibition potency of the three compared ring systems. For epoxides the ionic interaction between negatively charged carboxylate and histidinium ion is predominant for the higher inhibition potencies of the carboxylates at pH 6−7. The same seems to be true for thiiranes. For aziridines an intramolecular acid catalysis mediated by a water molecule seems to be the main cause for the higher inhibition potencies of the protonated free acids at pH 4. For the final clarification of these hypotheses the proteinic environment (by QM/MM computations) has to be taken into account.

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Supporting Information Available: Graphical representation of the geometrical arrangement of transition states and products together with the reaction profiles, and Cartesian coordinates of all stationary points together with the total energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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