Is nucleophilic cleavage chemistry practical for 4-membered heterocycles?†

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A computational study at the MP2(Full)/6-311++G(d,p)//MP2(Full)/6-31+G(d) level of the ammonolysis of halogen substituted azetidines, oxetanes and thietanes was performed in the gas phase and in the commonly used solvent, acetonitrile. Using the free energy of activation of a benchmark reaction for evaluation of synthetic viability, several haloazetidines and oxetanes that possessed the required reactivity were identified; however, no substituted thietane investigated herein was determined to be synthetically useful under the mild conditions selected for this study. In the case of the azetidines, the side reaction of displacement of halide ion was determined to be the preferred reaction course in acetonitrile; however, the amino product of the reactions of the 2-haloazetidines cleaved at an acceptable rate under mild conditions. For the oxetane derivatives investigated, 2-fluorooxetane proved to be a direct source of ring cleavage product. Nucleophilic cleavage of halogen-substituted azetidines and oxetanes is predicted to be a viable source of functionalized three-carbon moieties under mild conditions in organic synthesis.

1. Introduction

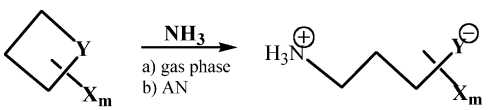
Three-membered heterocycles,[1] especially oxiranes and thiiranes are useful reagents in the repertoire of the synthetic chemist due in large part to their facile cleavage and transformation into 2-substituted alcohols and thiols, respectively, in nucleophilic substitution chemistry. Their nitrogen analogs, the aziridines,[2] are typically converted to amides or sulfonamides in order to elevate their reactivity to useful levels. We have recently found on the basis of high order *ab initio* calculations that the sluggish reactivity of aziridine can be overcome by adding halogen substituents at one or both of the carbon positions.[3]

The synthetic potential of four-membered heterocycles[4] in nucleophilic substitution reactions as a strategy for appending 3-functionalized propyl moieties has yet to be fully realized. Since many methods exist for cleavage by means of Brønsted or Lewis acids,[5] an approach to exploit this chemistry under mild, nonacidic conditions to possibly fragile molecules late in a synthesis was sought.

The challenge presented by successfully cleaving these heterocycles under the stipulated conditions would appear to be formidable. Wainwright and co-workers[6] cleaved the azetidine ring with 1,4,8,11-tetraazacyclotetradecane, but as its tosylate, and using rather vigorous conditions (150–154 °C) Ghosez[7] found that a 2-azetidinylideneammonium salt chose to cleave its exocyclic carbon-nitrogen bond upon hydrolysis, forming a β-lactam. Oxetane has been cleaved with sodium thiophenoxide but elevated temperatures are required.[8] Thietane is inert upon prolonged heating with diethyl- or dibutylamine.[9]

The parent 4-membered rings are typically less reactive than their 3-membered analogs. Superficially, this is surprising since the ring strain energies of these 3- and 4-membered rings are comparable. The calculated strain energies (kcal/mol) of the three- and four-membered rings for each heteroatom are, respectively: N, 27.3[1b] and 25.2[10]; O, 26.1[10] and 26.3[10]; S, 19.3[10] and 23.1.[10] We have proposed that the disjoined effect makes an important contribution to enhanced reactivity in these Menshutkin-type reactions of 3- but not 4-membered rings.[10]

In an effort to discover methods of activating the ring cleavage reaction to useful synthetic levels, an *ab initio* computational study of the effect of halogen substitution on the nucleophilic cleavage of azetidine (Y = NH, m = 0), oxetane (Y = O, m = 0), and thietane (Y = S, m = 0) (Scheme 1) was undertaken. Syntheses of a number of halo derivatives of 4-membered rings have been reported.[11] A benchmark reaction, cleavage by ammonia of the synthetically useful reagent, oxirane, at 298 K in acetonitrile (AN) was chosen as the benchmark reaction to assess synthetic utility under mild conditions ($\Delta G^{\ddagger} = 28.3$ kcal/mol). The importance of the potentially competing reaction, nucleophilic displacement of halide, was assessed.



Y = NH, O, S
X = F, Cl, Br; m = 1 - 2

Scheme 1 Nucleophilic cleavage of 4-membered heterocycles by ammonia.

The relative reactivities of the typical nucleophile ammonia with azetidine, oxetane and thietane and their fluoro, chloro and bromo derivatives were determined in the gas-phase and in the common solvent, acetonitrile (AN), ε = 35.9.[12] It was not practical to study all possible ring regio- and stereoisomers of

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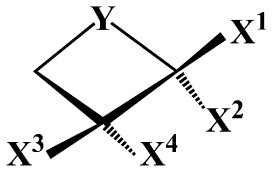
Table 1 Four-membered heterocycles studied computationally in nucleophilic substitution reaction with ammonia



1 Y = NH, **2** Y = O, **3** Y = S

	X^1	X^2	X^3	X^4
a	H	H	H	H
b	F	H	H	H
c	H	H	F	H
d	F	F	H	H
e	H	H	F	F
f	F	H	H	F
g	F	H	F	H
h	Cl	H	H	H
i	H	H	Cl	H
j	Cl	Cl	H	H
k	Cl	H	H	Cl
l	Cl	H	Cl	H
m	Br	H	H	H
n	Br	Br	H	H

these four-membered heterocycles. Based on our previous results,[3] the compounds chosen for the present investigation are provided in Table 1.

2. Computational methods[3a]

Ab initio calculations were performed at the MP2(Full)/6-311++G(d,p)//MP2(Full)/6-31+G(d) level using the Gaussian 03 suite of programs.[13] A scaling factor of 0.9646 was used for the thermal correction to the computed energies at 298.1 K.[14]

The solvation model for acetonitrile was SCI-PCM.[15,16] Criteria for establishing the transition and ground states were calculation of one and zero imaginary frequencies, respectively. GaussView 3.09[17] was used for animation of the sole imaginary frequency of a transition state, and IRC calculations were used to verify location of the transition states. Rate differences between azetidine invertomers were determined to be insignificant. Ring strain energies (SE) were estimated using the method of Dudev and Lim.[17]

3. Results and discussion

Given the anticipated decreased rates of cleavage reactions for four- as opposed to three-membered heterocycles, it appeared prudent, especially in view of our previous finding that haloaziridines can undergo halide loss followed by rearrangement in the presence of NH_3,[3a,3c] to study a reasonable potential side reaction for these haloheterocycles, nucleophilic displacement of halide:

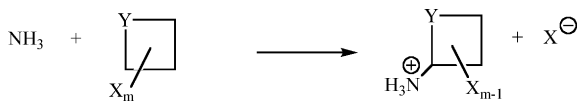


Table 2 Free energies of activation for halide displacement in the gas phase and in acetonitrile (AN) solution

	$\Delta G^{\ddagger}$ (kcal/mol)	
	Gas Phase	AN
2-Fluorocyclobutane	62.5	38.8
2-Chlorocyclobutane	54.1	24.6
1b	53.2	21.5
1h	38.2	–2.6
1i	49.6	–11.0
1j	22.9	–4.4
1m	30.6	15.2
2b	60.4	22.3
2h	44.6	4.7
2m	—	0.02

The rates of this halide ion displacement reaction were calculated for representative heterocycles, and carbocycles, fluoro- and chlorocyclobutane using *ab initio* methodology (Table 2).

The 2-haloheterocycles have substantially lower $\Delta G^{\ddagger}$ values than the corresponding cyclobutanes, with the better leaving chloride and bromide ions proceeding in essentially barrierless processes. A ring nitrogen is apparently particularly effective in stabilizing the transition state. Heterocycles **1h** and **2h**, for example, undergo bond length contractions of the bonds between the reaction center and heteroatom to distances of 1.313 and 1.296 Å, respectively in AN; the average imine and carbonyl bond lengths are 1.28 and 1.21 Å,[18] respectively.

Halide displacement in AN for every heterocycle of Table 2 has a lower free energy of activation than 28.3 kcal mol^{-1} calculated for the benchmark reaction. Accordingly, an extensive study to obtain mechanistic insights concerning the effects of substituents on the rate of the cleavage reaction was undertaken to profoundly increase its relative rate (Table 3.)

The regioselectivity of attack by ammonia was initially investigated with fluoroazetidines, **1b** and **2d**, and dichlorooxetanes **2k** and **2l**. Overwhelming regioselectivity was calculated for C_4 (Table 3.) This is reasonable since attack at C_4 permits the electron-withdrawing substituent(s) to facilitate departure of the leaving group by dispersal of negative charge. To further explore the question of regioselectivity, computations were conducted. For *cis*- and *trans*-2,4-difluoroazetidine attack must occur at a position bearing a fluorine substituent, In the gas phase, these compounds were determined to have free energies of activation of 75.3 and 64.1 kcal/mol, respectively. When corrected for ring strain energies (28.4 and 27.2 kcal/mol, respectively) the reaction rates relative to azetidine were 3.81×10^{-2} and 4.61×10^{7}. The result for the *trans* compound suggests that the predominant factor encumbering nucleophilic cleavage at C_2 of **1b** is the absence of a good leaving group. Although the *trans* diastereomer reacts about 200 times slower than **1b**, it is clear that the presence of a fluorine at the reaction center is not the major rate-retarding effect that virtually eliminates C_2 attack of ammonia on **1b**. The lower reactivity of the *cis* stereoisomer can be rationalized by the unfavorable electrostatic energy resulting from the rather small distance (2.983 Å) between the two fluorines in its transition state as opposed to 4.330 Å for *trans*.

The calculated ring strain energies compiled in Table 3 contribute to acceleration of the cleavage reactions relative to acyclic analogs. This effect is smaller for the thietanes due to diminished

Table 3 Gas phase substituent effects on the relative rates of the ring cleavage reaction of 4-membered heterocycles with NH_3, with and without strain energy corrections[a]

						Salient distances[d,e]		
	$\Delta H^{\ddagger}$[b]	$\Delta G^{\ddagger}$[b]	k_{rel}	SE[b]	k'_{rel}[c]	Y–C_2	X–C_2(C_3)[f]	H_2N-H···X
1a	71.3	76.5	1.00	25.2	1.00E+00	1.449[3a]	—	—
1b	59.5	62.3	2.69E+10	25.9	8.27E+09	1.350	1.613	—
1b @ C_2	81.5	85.0	6.25E-07	25.9	1.92E-07	2.317	1.376	—
1c	63.5	66.5	2.22E+07	29.6	1.33E+04	1.452	(1.455)	(2.100)
1d	52.5	58.5	1.71E+13	26.0	4.43E+12	1.345	1.422 1.469	—
1d @ C_2	93.3	99.7	9.64E-18	26.0	2.50E-18	2.647	1.339 1.351	2.200 2.226
1e	62.4	65.6	9.96E+07	29.6	5.95E+04	1.453	(1.388) (1.447)	(2.157) (2.610) (2.681)
1f	55.4	58.3	2.04E+13	27.7	3.01E+11	1.385	1.470 (1.424)	(2.169) (2.888)
1g	53.5	56.5	4.83E+14	26.4	6.38E+13	1.361	1.529 (1.417)	(2.178) (2.717)
1h	62.0	59.3	3.97 E+10	26.4	5.24E+09	1.363	2.023	—
1i	60.7	63.4	4.31E+09	27.3	4.31E+09	1.479	(2.190)	2.374 2.938
1j	46.6	47.7	1.23E+21	21.7	4.52E+23	1.286	3.844 1.696	2.238
1k	49.1	50.9	5.58E+18	23.4	1.16E+20	1.286	3.800	2.274
1l	55.1	57.8	4.87E+13	27.7	7.17E+11	1.328	2.179	(2.634) (2.893)
1m	55.8	57.4	9.32E+13	25.5	5.62E+13	1.356	2.241	—
1n	40.6	40.8	1.36E+26	24.4	5.15E+26	1.285	3.517 1.851	2.554
2a	51.7	58.4	1.99E+13	25.6[g]	1.01E+13	1.386	—	—
2b	42.2	45.3	7.11E+22	26.1	1.56E+22	1.322	1.503	—
2c	45.6	49.8	3.62E+19	23.3	8.92E+20	1.400	1.465	2.701 2.124
2d	37.6	40.1	5.43E+26	23.9	4.86E+27	1.299	1.402 1.438	—
2f	38.5	43.2	2.69E+24	25.3	2.27E+24	1.321	1.495 (1.415)	(2.452)
2g	34.7	38.2	1.12E+28	24.1	7.14E+28	1.337	1.459 (1.424)	(2.200) (2.725)
2h	39.0	41.7	3.35E+25	26.0	8.70E+24	1.311	2.020	—
2i	46.3	49.6	5.37E+19	22.6	4.31E+21	1.394	(1.864)	(2.520) (2.934)
2j	34.3	36.7	1.44E+29	26.0	3.74E+28	1.301	1.813 1.922	—
2k @ C_2	53.7	57.0	1.98E+14	23.6	2.94E+15	1.395	1.769 (1.890)	(2.509) (2.822)
2l @ C_2	52.4	56.2	7.70E+14	23.2	2.25E+16	1.392	1.752 (1.847)	(2.490)
2k	36.8	39.2	2.02E+27	23.6	3.00E+28	1.311	1.990 (1.792)	2.803
2l	34.7	38.1	1.400E+28	23.2	4.09E+29	1.335	1.893 (1.805)	2.601 (2.928)
2m	35.5	38.4	7.72E+27	26.7	6.15E+26	1.301	2.256	—
2n	30.7	32.8	1.13E+32	25.5	6.81E+31	1.295	2.121 1.980	—
3a	50.6	54.6	1.06E+16	23.1[g]	3.66E+17	1.821	—	—
3b	47.8	52.9	2.12E+17	19.0	7.40E+21	1.777	1.428	—
3d	42.7	45.8	3.26E+22	18.5	2.64E+27	1.752	1.415 1.390	—
3h	44.5	47.8	1.14E+21	19.0	3.99E+25	1.777	1.856	—
3j	42.0	45.2	8.43E+22	17.6	3.12E+28	1.761	1.802 1.848	—
3m	42.8	45.3	7.07E+22	19.0	2.46E+27	1.757	2.065	—
3n	39.1	41.8	2.66E+25	18.9	1.10E+30	1.738	2.045	—

[a] Unless otherwise indicated, attack occurs at C_4. [b] In kcal/mol. The experimental values are given in brackets. [c] Relative rate with strain energy (SE) included. [d] Distances in Å; for H_2N-H···X, only distances < 3.0 Å are included. [e] Average distances[19] (Å): C–N, 1.47; C–O, 1.43; C–S, 1.82. C=N, 1.28; C=O, 1.21, C=S, 1.63; C–F, 1.40; C–Cl, 1.79; C–Br, 1.97. [f] Bond distance to C_3 is given in parentheses, if applicable. [g] Ref. 19.

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ring strain as the result of the longer C–S bond relative to C–N and C–O. The largest effect is found in the oxetane series for **2m** and **2i**, the former having a relative acceleration of about 10^3.

The superior leaving group abilities of alkoxide and thiolate are responsible for the profoundly high rate of cleavage of the chalcogen heterocycles relative to the azetidines.[20,21]

Since halogen substituents are more electronegative than hydrogen, it is not surprising that they provide transition state stabilization of the developing negative dipole. In addition, halogens can promote stabilization through partial double bond by means of their partial dissociation. The smallest contribution of this type is found with the thietanes since C=S bonds are considerably weaker then C=NH or C=O bonds. Inspection of transition state geometries reveals another potential stabilizing factor: the proximity of halogen to the incoming ammonia creating favorable electrostatic stabilization.

In the polar aprotic solvent, acetonitrile (AN), reactions are accelerated due to the dipolar nature of the transition state. Significant elongation of the C_2–X distances with respect to the gas phase were observed: for the azetidine series, the largest lengthening of 2.6 Å was found for **2m**. As noted above, minimal changes occured in the thietane series due to the weakness of the C=S bond.

The halide displacement side reaction overwhelms the desired cleavage reaction in AN for all cases with the exception of **2b**. This finding led to an examination of the cleavage reactivity of the product of this reaction, the 2-aminoheterocycle, with ammonia. It was discovered that this compound reacted with $\Delta G^{\ddagger} = 24.7$ kcal/mol, exceeding that of the benchmark reaction of 28.3 kcal/mol. Calculations for the oxetane and thietane products of this displacement reaction resulted in rates too slow for synthetic application.

In the cases of the lowered acceleration that typifies the azetidines, unlike their oxetane and thietane analogs, the leaving group ability of the halogen is exploited to form a partial C_2–N double bond; this halogen virtually dissociates, moving close to the incoming ammonia permitting the transition state to enjoy stabilization due to electrostatic attraction. The smallest change, 8.27×10^4 is that calculated for 2,2-dichlorooxetane **2j**. The results found in Table 3 demonstrate that one of the chloro groups of **1j** is essentially dissociated. The strength of the partial carbonyl bonds of **2j** and **2n** are apparently sufficient to lead to superior overall relative reactivity in the absence of long C_2–X bonds. Similar results are found in comparison to the thietanes that rely exclusively on the excellent leaving group ability of thiolate ion as evidenced by small departures of the C_2–S bond lengths from the average. A feasible explanation for the reduced rate factor of **2c** is that for **1c** the C_3–Cl bond has been elongated by 22%, while that of the oxetane by only 4%, **1c** has a larger electrostatic contribution.

Stereoisomerism effects were explored. The *cis*-2,3-difluoroheterocycles **1g** and **2g** are more reactive than their *trans* isomers by factors of 212 and 3.14×10^4, respectively, while *trans*-2,3-dichloroazetidine **1k** is 1.62×10^8 more reactive than **1l**, but *cis*-2,3-dichlorooxetane **2l** is more reactive than *trans* **2k** by a factor of 13.6. A reasonable rationalization of the difluorooxetanes results is that the vector sum of the bond moments of the C_2–F and C_3–F bonds of **2g** is oriented such that electron removal from the developing charge on oxygen is assisted. These bond moments for *trans* isomer **2f** tend to cancel each other (Fig. 1) Given the high electronegativity of oxygen and its ability to compete for electron density, this effect would be expected to only produce a large change in transition state stabilization in the case of substitution by fluorine, the most electronegative atom. Azetidines **1f** and **1g** should have attenuated effects since the less electronegative nitrogen provides less resistance than oxygen to formation of a heteroatom–C_2 double bond. The calculated faster reaction rate of 2,3-dichlorooxetane **2l** would be experimentally measurable, however, it constitutes a difference in activation energies of a mere 1.1 kcal/mol, too small to be confidently explained.

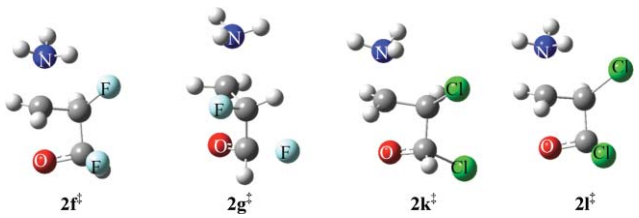

Fig. 1 Transition-state geometries of pairs of diastereomeric 2,3-dihalooxetanes.

The gas phase determinations were used to select substrates for the more expensive calculations in AN. In most cases, the Y–C_2 bond distances underwent only minor changes relative to the gas phase. On the other hand, lower than for the X–C_2(C_3) distances were calculated for azetidines **1b**, **1h**, **1j**, **1m** and **1n** in the gas phase. In the most extreme case, the excellent bromo leaving group of **1m** is found to be *ca*. 2.6 Å further from C_2 in AN. Since the transition states in these Menschutkin-type reactions generate a partial positive charge on the nucleophile and a partial negative charge on the leaving group, it is not unexpected that reactions in the polar, aprotic solvent, acetonitrile, would proceed faster than those in the gas phase (Table 4) For example, unsubstituted **1a**, $\Delta G^{\ddagger}$ decreases from 76.5 to 62.9 kcal mol^{-1} For the compounds selected, reactions in AN led to an average decrease in $\Delta G^{\ddagger}$ of *ca*. 15 kcal mol^{-1} with respect to the corresponding gas phase reaction. When compared with halide displacement (Table 2), only **2b** is cleaved at a faster rate. The transition state for the cleavage reaction requires an elongation of the C_2–F bond to 1.494 Å, while the corresponding value for the halide displacement reaction is 2.221 Å, demonstrating that fluoride is a poor leaving group (Fig. 2).

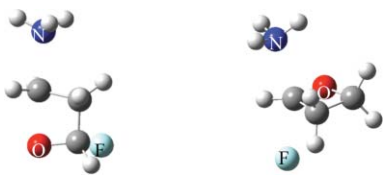

Fig. 2 Comparison of the transition states of **2b** in cleavage and halide displacement.

It is possible, however, to have a successful cleavage reaction even if halide displacement occurs preferentially. This would be the case if the 2-amino product of this reaction is cleaved at an acceptable rate. The $\Delta G^{\ddagger}$ for this compound was determined to be 24.7 kcal mol^{-1} lower than our benchmark reaction. Any

Table 4 Substituent effects on the relative rates of cleavage of 4-membered heterocycles with NH_3 in AN with and without strain energy corrections[a]

			Salient transition state distances			
	$\Delta G^{\ddagger b}$	k_{rel}[c]	k'_{rel}	$Y–C_2$	$X–C_2(C_3)$	$H_2N\text{-}H\cdots X$
1a	61.0	1.000	1.00E+00	1.470	—	—
1b	41.7	4.29E+15	4.05E+13	1.290	3.011	—
1c	61.0	8.37E+01	6.31E-04	1.473	1.445	2.371
						2.690
1d	47.2	6.84E+10	3.20E+09	1.353	1.450	—
					1.447	
1e	59.8	3.59E+03	4.42E-03	1.470	1.395	2.840, 2.704
						2.402
					1.410	
1h	23.1	3.47E+26	7.50E+26	1.287	4.404	2.393, 2.718
						2.934
1i	25.9	2.53E+02	1.53E+24	1.466	1.837	—
1j	8.20	1.52E+28	1.78E+41	1.282	4.777	2.417
					1.701	
1m	5.30	9.69E+29	3.86E+40	1.287	4.843	2.590
1n	2.44	2.12E+30	3.07E+13	1.282	4.727	2.618
					1.862	
2a	39.7	1.36E+14	2.12E+15	1.425	—	—
2b	20.8	6.38E+28	1.40E+28	1.348	1.494	—
2d	11.2	4.78E+29	2.76E+37	1.319	1.419	1.418
2h	26.2	1.770E+22	7.49E+24	1.332	1.993	—
2m	7.49	8.71E+27	1.28E+38	1.268	2.897	—
3a	29.6	7.23E+15	3.52E+24	1.832	—	—
3b	27.4	9.53E+17	1.56E+29	1.792	1.436	—
3d	26.3	1.35E+16		1.765	1.408	—
					1.398	
3h	27.0	1.77E+22	2.73E+29	1.802	1.810	—
3m	2	8.72E+27	2.39E+29	1.783	2.022	—

[a] Attack occurs at C_4. [b] In kcal/mol. k'_{rel} = relative rate with respect to azetidine with strain energy included. Azetidine reacts 2.25×10^{11} times faster in acetonitrile than in the gas phase.

2-substituted haloazetidine would be a suitable substrate for nucleophilic cleavage chemistry.

When a similar calculation is performed for 2-aminooxetane, the product of halide displacement for monosubstituted 2-halooxetanes, a synthetically unacceptable $\Delta G^{\ddagger} = 40.9$ kcal mol^{-1} was obtained; **2b** represents the most favorable oxetane discovered for cleavage chemistry.

No acceptable solution for cleavage chemistry has yet been found for the thietanes. While thietane itself is the most reactive parent four-membered heterocycle, we have found, in accord with the results of Molina *et al.*,[22,23] rather unremarkable substituent effects accompany cleavage.

4. Conclusions

The reactivity of the 4-membered heterocycles investigated computationally in Menschutkin-like cleavage chemistry by ammonia was increased markedly by means of halogen substitution in the gas phase and especially in AN solution. The nucleophilic substitution pathway was found to outpace cleavage chemistry in all cases studied with the exception of oxetane **2b**. For 2-haloazetidines, however, the product of the faster this reaction, 2-aminoazetidine, is cleaved under the mild conditions demanded by this investigation. Upon hydrolysis the cleavage products of 2-substituted and 2,2-disubstituted heterocycles are carbonyl and carboxylic acid equivalents, respectively.[24] Even with halogen substitution, thietanes could not be increased to exceed that of the chosen benchmark for useful reactivity.

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