Origins of Regio- and Stereoselectivity in Acid-Promoted Reactions of α-Lactams

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α-Lactams (aziridinones) have been shown to react with nucleophiles at both the acyl (C-2) and α (C-3) carbons. Products of C-2 attack are observed with strong nucleophiles, and products of C-3 attack are observed with weak nucleophiles in the presence of Brønsted and Lewis acids. C-3 attack proceeds with inversion of configuration at the C-3 carbon. A cationic intermediate activated toward C-3 attack has been implicated in this substitution process, but the structure of this intermediate is unknown. Density functional theory calculations (at the B3LYP/6-31G(d) level) were used to examine various candidate structures for this intermediate and to assess their reactivity. Initial protonation on oxygen or nitrogen leads to several cyclic cations with relative energies within several kcal/mol of each other. Direct nucleophilic attack at both C-2 and C-3 of these structures was examined, and the substitution transition state with the lowest relative energy corresponds to C-3 attack on the *O*-protonated species with inversion of configuration at C-3. This mechanism is consistent with the experimental results.

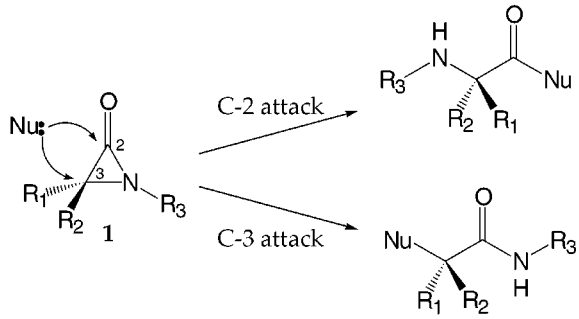
Introduction

A definitive review of the chemistry of α-lactams (aziridinones) was published in 1968 by Sheehan and Lengyel[1] that summarized both the thermal reactions of α-lactams and their reactions with nucleophiles. This review utilized publications from several laboratories to evaluate the structure and reactions of α-lactams and became the mechanistic cornerstone for subsequent studies of their chemistry.

The α-lactam structure **1** (Scheme 1) was proven by Baumgarten, who was the first to isolate an α-lactam.[1,2] He showed by a variety of methods that the structure was a fully covalent one with a carbon−oxygen double bond. A variety of α-lactams have since been isolated, and all are characterized by a bulky substituent on nitrogen (*N*-*tert*-butyl, *N*-adamantyl, or *N*-trityl), which is postulated to kinetically stabilize the α-lactam structure.[1,3,4] The X-ray structure of 1,3-diadamantylaziridinone was obtained in 1972,[4] further validating the work of Baumgarten.[1,2]

α-Lactams tend to react rapidly with nucleophiles at room temperature to give two distinct types of products (Scheme 1). In one type of product, the nucleophile becomes bound to the acyl carbon (C-2), resulting in a 2-amino acid derivative. In the other type of product, the nucleophile becomes attached to the α-carbon (C-3), resulting in a 2-substituted secondary amide. The type of product that is obtained depends on the α-lactam, the nucleophile, and the reaction conditions. Based on reactions of isolated α-lactams with nucleophiles, some trends in reactivity were observed.[1] As a general rule, good nucleophiles such as alkoxides, ammonia, and dimsyl anion react with α-lactams to give products derived from acyl (C-2) addition. In contrast, weaker nucleophiles such as water, alcohols, halides, and some amines react with α-lactams to give products derived from addition to the α (C-3) carbon. In virtually all cases where C-3 addition was predominant, the reaction mixture was protic.[1]

Scheme 1



A great deal of effort was expended in trying to understand the structural factors that govern the stability of α-lactams and how those structural features influence the regiochemical course of the reactions of α-lactams with nucleophiles.[1] Such insight is critical to the further development of α-lactams as synthetic intermediates, but unfortunately, no general understanding of the regioselectivity of nucleophile incorporation has emerged. Consequently, interest in and work on these

(1) Lengyel, I.; Sheehan, J. C. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 25−36.
(2) (a) Baumgarten, H. E. *J. Am. Chem. Soc.* **1962**, *84*, 4975−4976. (b) Baumgarten, H. E.; Fuerholzer, J. J.; Clark, R. D.; Thompson, R. D. *J. Am. Chem. Soc.* **1963**, *85*, 3303−3305.
(3) Sheehan, J. C.; Lengyel, I. *J. Am. Chem. Soc.* **1964**, *86*, 1356−1359. See also a discussion of data from Fuerholzer, J. J., Ph.D. Dissertation, University of Nebraska, 1965, found in ref 1.
(4) Wang, A. H.-J.; Paul, I. C. *J. Chem. Soc., Chem. Commun.* **1972**, 43−44.

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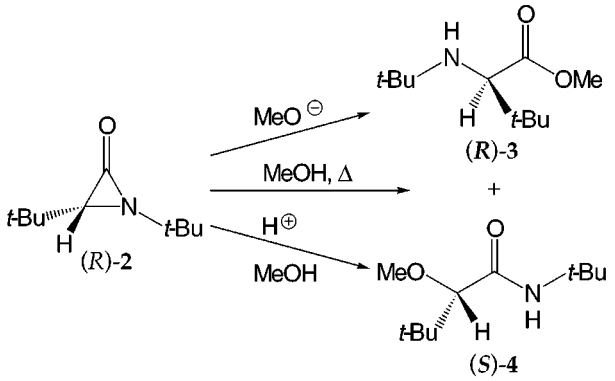
Scheme 2



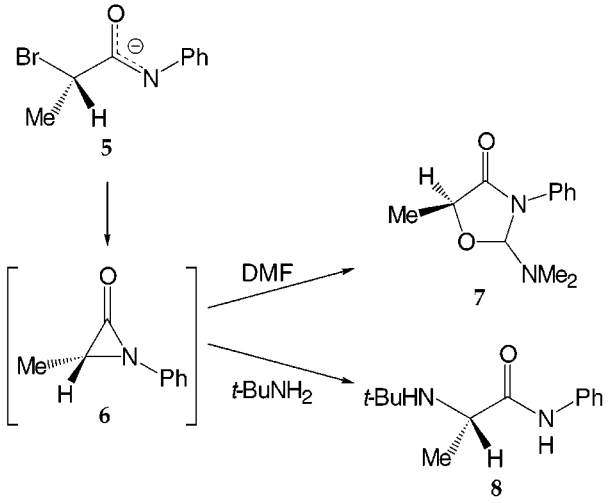
intriguing and potentially valuable intermediates waned until recently.[5]

While Sheehan did not specifically suggest it,[1] the origins of the C-2 and C-3 products often have been assumed to result from competitive attack by the nucleophile at C-2 or at C-3 of the α-lactam (Scheme 1). This mechanistic scenario was recently utilized by the groups of Quast,[6] Maran,[7] and D'Angeli[8] to explain the stereochemistry of nucleophile incorporation at C-3.

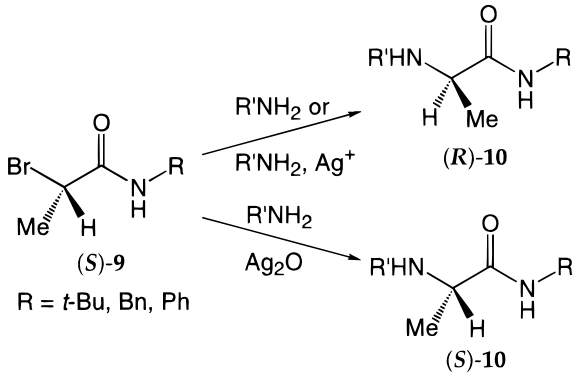
Quast prepared (*R*)-1,3-di(*tert*-butyl)aziridinone **2** and studied its methanolysis under various conditions (Scheme 2).[6] It was observed that methanolysis of (*R*)-**2**, in the absence of added base or acid, gave a 18:82 mixture of (*R*)-α-aminoester **3** (the product of C-2 addition with retention of configuration at C-3) and (*S*)-α-methoxyamide **4** (the product of C-3 addition with inversion of configuration at C-3). However, basic methanolysis of (*R*)-**2** gave only (*R*)-**3**, while acidic methanolysis of (*R*)-**2** gave only (*S*)-**4** (Scheme 2).[6b] On the basis of these experiments, it was concluded that the C-3−N bond of aziridinone (*R*)-**2** is "cleaved by nucleophiles with a high degree of stereospecificity and inversion of configuration".[6b] Reaction of (*R*)-**2** with magnesium halides (MgX_2) also gave C-3 products with inverted (*S*) configurations at the α-position. The changes in product partitioning as a function of the nucleophilicity or acidity (Brønsted or Lewis) of the reaction components were not addressed.

Maran studied the reactions of electrochemically generated scalemic α-bromoamide anion **5** (Scheme 3).[7] The α-lactam **6** was suggested as the key reactive intermediate formed from **5** upon loss of bromide. In the presence of DMF, bromide loss led to oxazolidinone **7**, while in the presence of *tert*-butylamine, α-aminoamide **8** was produced. The configuration of the α-carbon in both **7** and **8** was retained, consistent with a double inversion process involving nucleophilic addition of DMF or *tert*-butylamine to C-3 of **6**. However, while Quast found that reaction of α-lactam (*R*)-**2** with DMF to give an analogous oxazolidinone required heating at 100 °C for 4 days,[6b] formation of **7** took place under the conditions of the electrolysis (RT, hours). In addition, reaction of **6** with *tert*-butylamine gave only C-3 product **8**, yet recent results using several isolated α-lactams show that their reactions with benzylamine in THF give only C-2 products.[9] In view of these disparate results, confirmation of the intermediacy of α-lactam **6** in this process requires further experiment.

Scheme 3



Scheme 4



D'Angeli studied the reactions of scalemic α-bromo propanamides **9** with amines under several conditions (Scheme 4).[8d] Reaction of (*S*)-**9** with amines, with or without addition of soluble silver(I), gave substitution products (*R*)-**10** with inversion of configuration at the α-carbon. Conversely, reaction of (*S*)-**9** with amines in the presence of heterogeneous silver oxide (Ag_2O) gave products (*S*)-**10** with retention of configuration at the α-carbon. Formation of products with inverted configuration was attributed to direct displacement of bromide or silver-complexed bromide from **9** by the amine. The intermediacy of an α-lactam in the Ag_2O-promoted reactions was postulated in order to explain the formation of

(5) Work on α-lactams since the Sheehan review, ref 1, until 1990 includes: (a) Coutts, I. G. C.; Southcott, M. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 767−771. (b) Scrimin, P.; Cavicchioni, G.; D'Angeli, F.; Goldblum, A.; Maran, F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 43−47. (c) Baumgarten, H. E.; Chaing, N.-C. R.; Elia, V. J.; Beum, P. V. *J. Org. Chem.* **1985**, *50*, 5507−5512. (d) Bladon, C. M.; Kirby, G. M. *J. Chem. Soc., Chem. Commun.* **1982**, 1402−1404. (e) Cavicchioni, G.; Scrimin, P.; Veronese, A. C.; Balboni, G.; D'Angeli, F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2969−2972. (f) Zanotti, G.; Filira, F.; Del Pra, A.; Cavicchioni, G.; Veronese, A. C.; D'Angeli, F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2249−2253. (g) Baumgarten, H. E.; McMahan, D. G.; Elia, V. J.; Gold, B. I.; Day, V. W.; Day, R. O. *J. Org. Chem.* **1976**, *41*, 3798−3805. (h) Talaty, E. R.; Dypuy, A. E., Jr.; Utermoehlen, C. M.; Stekoll, L. H. *J. Chem. Soc., Chem. Commun.* **1973**, 48−49.

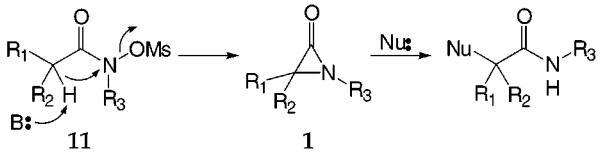
(6) (a) Quast, H.; Leybach, H.; Würthwein, E.-U. *Chem. Ber.* **1992**, *125*, 1249−1262. (b) Quast, H.; Leybach, H. *Chem. Ber.* **1991**, *124*, 2105−2112.

(7) Maran, F. *J. Am. Chem. Soc.* **1993**, *115*, 6557−6563.

(8) (a) Marchetti, P.; D'Angeli, F.; Bertolasi, V. *Tetrahedron Asymm.* **1997**, *8*, 3837−3842. (b) D'Angeli, F.; Marchetti, P.; Rondanin, R.; Bertolasi, V. *J. Org. Chem.* **1996**, *61*, 1252−1255. (c) D'Angeli, F.; Marchetti, P.; Bertolasi, V. *J. Org. Chem.* **1995**, *60*, 4013−4016. (d) D'Angeli, F.; Marchetti, P.; Cavicchioni, G.; Maran, F.; Bertolasi, V. *Tetrahedron: Asymmetry* **1991**, *2*, 1111−1121.

(9) Shimazu, M.; Endo, Y.; Shudo, K. *Heterocycles* **1997**, *45*, 735−744.

Scheme 5



products with retained configuration at the α-position (via a neighboring group-assisted double inversion mechanism), but it was noted that the details of activation by Ag_2O are not well understood. Similar stereochemical results have recently been reported for reactions of **9** with methanol and secondary amines,[8c] amide anions,[8b] and heterocycles,[8a] but the involvement of α-lactams was not implicated in these later studies.

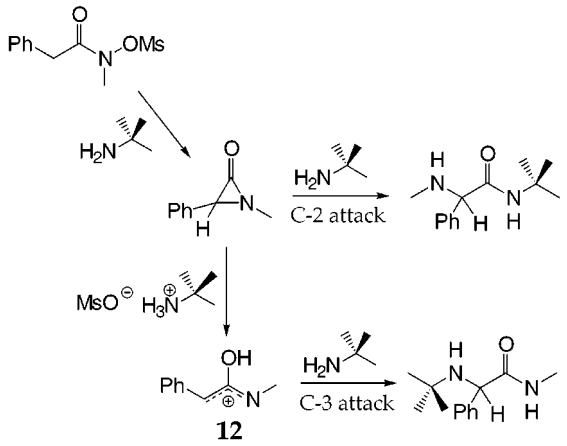
Simple nucleophilic attack at C-3 of an α-lactam intermediate with concomitant ring opening has been proposed in these studies[6−8] to explain the stereospecific incorporation of nucleophiles. While direct nucleophilic attack at C-3 of α-lactam intermediates cannot be eliminated as a mechanistic possibility, the data obtained with pure scalemic α-lactams as starting materials[6] show that the C-2/C-3 product distribution is influenced significantly by the acidity and/or nucleophilicity of the reaction medium. A more complex scheme is necessary to account for such observations.

Our interest in α-lactams arose from a study of the chemistry of *N*-sulfonyloxyamides **11** (Scheme 5), which were readily converted to 2-substituted amides in the presence of base and an added nucleophile.[10] The first step in this process is conversion of the *N*-sulfonyloxyamide to an α-lactam by a concerted, base-promoted 1,3-elimination (Scheme 5).[11]

Although the formation of 2-substituted amides from the α-lactam is consistent with the behavior of α-lactams described previously,[1] direct nucleophilic attack on the saturated C-3 carbon of the α-lactam could not adequately account for all of the experimental observations. First, we found that even very feeble nucleophiles such as chloride ion, water, and even mesylate ion were, on occasion, incorporated at the 2-position of the amide product;[10] normally, such weak nucleophiles do not attack saturated carbons effectively. Second, the strain of the three-membered ring is expected to render the carbonyl group of the α-lactam much more electrophilic than the C-3 carbon, favoring attack by the nucleophile at C-2. This is analogous to the heightened electrophilicity of the carbonyl group of cyclopropanones due to ring strain.[12] Finally, we found that, contrary to normal expectations, more sterically hindered amine nucleophiles attack the more sterically congested C-3 position preferentially.[10c]

Resolution of this mechanistic dilemma was achieved with experiments using *tert*-butylamine as the nucleophile, which gives products of *both* C-2 and C-3 attack (Scheme 6).[13] It was found that the ratio of C-2 to C-3 products is linearly dependent on the concentration of

Scheme 6



tert-butylamine. This finding effectively rules out the traditional mechanism involving direct C-2 vs C-3 attack, which predicts that the product ratio should be independent of nucleophile concentration, in favor of a stepwise mechanism involving the α-lactam as the first-formed intermediate and an additional ionic species, originally formulated as **12** (Scheme 6), as a second intermediate. If good nucleophiles are present in solution, they intercept the α-lactam intermediate in a second-order nucleophilic addition to the acyl carbon to give C-2 products. If only weak nucleophiles are present, and under protic conditions, the α-lactam is converted to a protonated ionic species such as **12**, which then reacts rapidly with nucleophiles at the α-carbon to give C-3 products. In this way, even poor nucleophiles can be incorporated effectively due to the heightened electrophilicity of the protonated species (a Lewis acid could activate the α-lactam toward C-3 addition in an analogous manner). This scenario nicely explains not only the current results but many of the earlier results as well.[1]

While it is clear that a second, ionic intermediate is involved in the formation of C-3 products, and while this intermediate was originally written as **12**,[11,13] the structure of this cation remains to be defined. Any reasonable structure must accommodate the requirements that chirality at C-3 is maintained throughout the course of the reaction and that configurational inversion at C-3 accompanies incorporation of the nucleophile at that position.[6−8] Computational studies were undertaken to elucidate the nature of the cationic intermediate and to assess its reactivity. The only computed pathway for C-3 addition that is consistent with the experimental observations involves nucleophilic attack on the α-carbon of an *O*-protonated α-lactam.

Methods

All calculations were performed with the GAUSSIAN 94 program.[14] All stationary point geometries were optimized and their energies calculated using density functional theory at

(10) (a) Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1995**, *60*, 7043−7046. (b) Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1995**, *60*, 5992−5994. (c) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1993**, *58*, 2355−2359. (d) Hoffman, R. V.; Nayyar, N. K.; Klinekole, B. W. *J. Am. Chem. Soc.* **1992**, *114*, 6262−6263. (e) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1992**, *57*, 5700−5707.

(11) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Am. Chem. Soc.* **1993**, *115*, 5031−5034.

(12) (a) Wasserman, H. H.; Clark, G. M.; Turley, P. C. *Top. Curr. Chem.* **1974**, *47*, 73−156. (b) Salaün, J. *Chem. Rev.* **1983**, *83*, 619−632.

(13) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1995**, *60*, 4121−4125.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Repogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzales, C.; Pople, J. A. *GAUSSIAN94*; Gaussian, Inc.: Pittsburgh, PA, 1995.

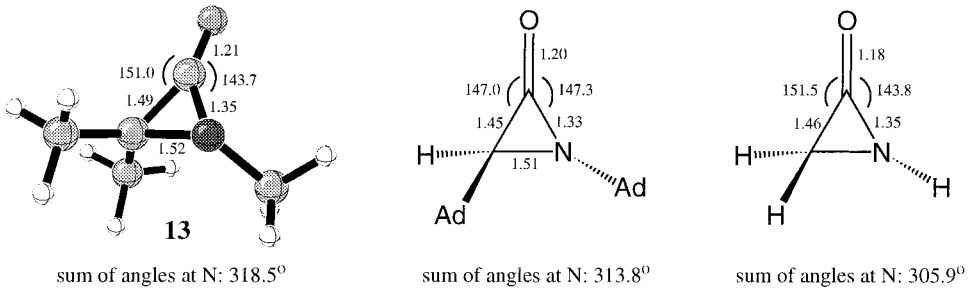
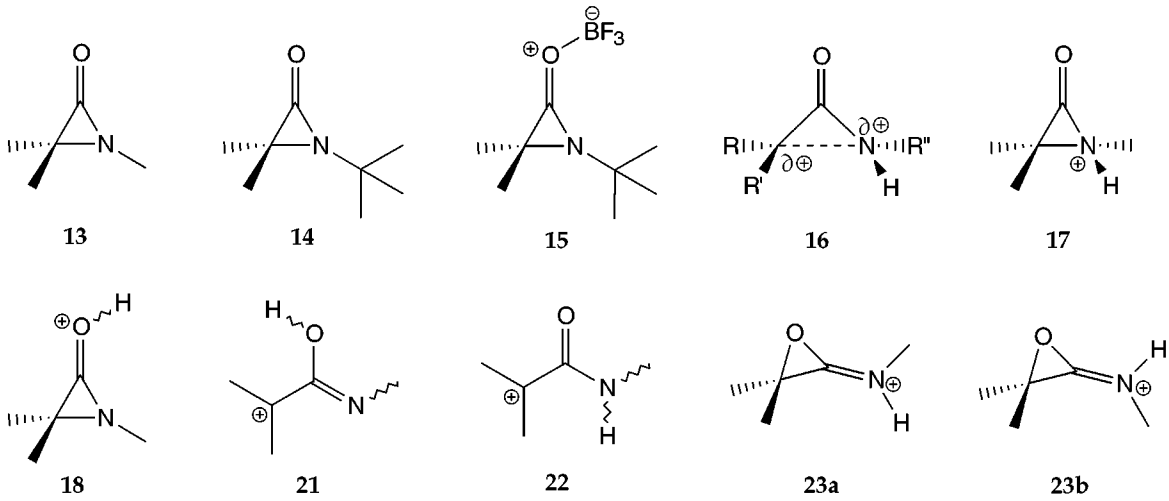


Figure 1. α-Lactam structures. Selected distances are in angstroms and angles are in degrees. The structure of **13** has been computed in this work, that of the diadamantyl derivative was elucidated by X-ray crystallography as reported in ref 4, and that of the parent aziridinone was computed as described in ref 17.

Chart 1



the B3LYP/6-31G(d) level.[15] All stationary points were characterized by frequency calculations at the B3LYP/6-31G(d) level, and zero-point energy corrections (scaled by 0.9806)[16] from these calculations are included in the reported energies. All transition states were further characterized by analysis of the vibrational modes corresponding to their imaginary frequencies or by intrinsic reaction coordinate (IRC) calculations as described in the text.

Results and Discussion

α-Lactam Structures. 1,3,3-Trimethylaziridinone **13** (Chart 1) was chosen as the model α-lactam for this study. Although the in situ generation of α-lactams by Hoffman requires a conjugating substituent at C-3,[10,11,13] the chemistry of **14**, and other isolable α-lactams with alkyl substituents at C-3, is well-known.[1,3] In both cases, reaction with weak nucleophiles leads to substitution at C-3.

The fully optimized structure of **13** (at the B3LYP/6-31G(d) level) is shown in Figure 1. The computed structure is in agreement with structural data reported previously on 1,3-diadamantylaziridinone (X-ray crystal structure)[4] and the parent aziridinone (HF/6-31G(d) calculations).[17] Both the crystallographically and computationally determined structures suggest that these α-lactams are characterized by carbon−oxygen double bonds and pyramidal ring nitrogens (Figure 1).

Protonation of the α-Lactam. Several structures for the cationic intermediate have been suggested. Ring-opened cation **12** has been the most common proposal;[10,13] however, this structure cannot account for stereospecific incorporation of nucleophiles at C-3. The reaction of **14** under Lewis acidic conditions led to the proposal of intermediate **15** (Chart 1); however, ring opening to an analogue of **12** was assumed to follow complexation.[1] Preliminary AM1 calculations suggested the possibility of partially ring-opened structures such as **16** as well. To assess the plausibility of various protonated structures, both *O*- and *N*-protonation were examined at the B3LYP/6-31G(d) level of theory.

The structures shown in Figure 2 are local minima at the B3LYP/6-31G(d) level of theory (except for **22**; see below). *N*-Protonated α-lactam **17** is 1.6 kcal/mol lower in energy than *O*-protonated **18a** and 3.1 kcal/mol lower in energy than *O*-protonated **18b** (Chart 1 and Figure 2). The gas-phase proton affinity (on nitrogen) for **13** is predicted to be approximately 2 kcal/mol larger than that for an acyclic model amide (*N*,*N*-dimethyl-2-methylpropanamide), in accord with the predictions of Greenberg for the parent aziridinone.[17] The *N*-protonated parent aziridinone was, in fact, found to be unstable toward ring opening and decarbonylation and could not be located as a minimum at this level of theory (in agreement with earlier results at the HF and MP2 levels),[17,18] suggesting that substitution is necessary for stabilization of the *N*-protonated form. Structural distortions on going from **13** to **17** are consistent with reduced amide resonance

(15) (a) Becke, A. D. *J. Chem. Phys.* **1996**, *104*, 1040−1046. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(16) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.
(17) Greenberg, A.; Hsing, H.-J.; Liebman, J. F. *J. Mol. Struct. (THEOCHEM)* **1995**, *338*, 83−100.
(18) Lien, M. H.; Hopkinson, A. C. *J. Am. Chem. Soc.* **1988**, *110*, 3788−3792.

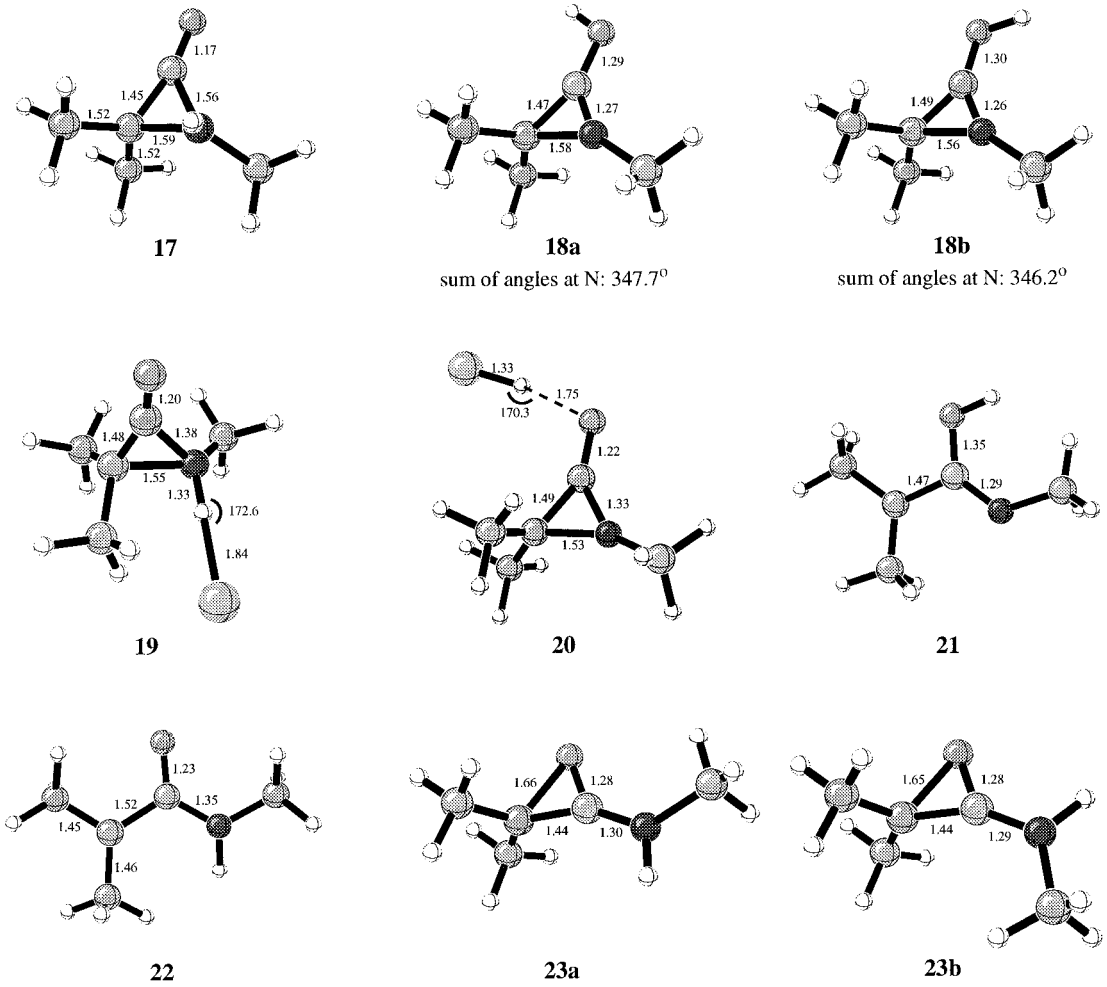


Figure 2. Protonated structures calculated at the B3LYP/6-31G(d) level. Selected distances are in angstroms and angles are in degrees.

(reduction in C=O and increase in C-2−N bond lengths), increased hyperconjugation between $\sigma_{C-3-C(Me)}$ and $\pi^*_{C=O}$ (decrease in C-2−C-3 bond length; the carbonyl antibonding orbital is a better acceptor when amide resonance is reduced), and increased hyperconjugation between $\sigma_{C-H(Me)}$ and σ^*_{C-3-N} (increase in C-3−N bond length; the C-3−N antibonding orbital is a better acceptor when the nitrogen is protonated).

O-Protonated structures **18a** and **18b** are also significantly distorted from α-lactam **13**. *O*-protonation favors increased amide resonance, which leads to a shortening of the C-2−N bond and planarization of the nitrogen (compare Figures 1 and 2). These changes introduce additional strain into the three-membered ring, which is partly accommodated by a lengthening of the C-3−N bond relative to that in **13**. This increase in the C-3−N bond length is consistent with activation of this bond toward cleavage under protic conditions.

In addition, several complexes of **13** with HCl were located at the B3LYP/6-31G(d) level (see Figure 2). Both the complex in which the HCl molecule hydrogen-bonds to the lactam nitrogen (**19**) and that in which it hydrogen-bonds to the carbonyl oxygen (**20**) show distortions in bond lengths of lesser magnitude but consistent with those observed for cations **17** and **18**.

Several ring-opened cations (**21** and **22**) were also examined (Chart 1 and Figure 2). In all *O*-protonated species **21**, C-3 was conjugated to the carbonyl (or nearly so; the lowest energy conformer is shown in Figure 2). All attempts to lengthen the C-3−N bond in *N*-protonated **17** led to keteniminium oxides **23a** and **23b** (Chart 1 and Figure 2), which are predicted to be 15 and 13 kcal/mol more stable than **17**, respectively (in accord with earlier calculations on protonated aziridinone itself),[17] making them the lowest energy protonated species found. No minima corresponding to cations **16** or **22** could be located. Constraining **22** to be planar led to a structure approximately 13 kcal/mol higher in energy than **23a** (Figure 2). The predicted stability of the keteniminium oxides **23a** and **23b** prompted a detailed study of their formation from *N*-protonated α-lactam **17**.[19]

Rearrangement of the *N*-Protonated α-Lactam. The *N*-protonated α-lactam **17** can rearrange to two possible keteniminium oxides, **23a** and **23b**, in an exothermic process (Figure 3) similar to that suggested as a pathway for the thermal decomposition of neutral α-lactams.[1,5,6] Transition structures (**24a** and **24b**) connecting **17** with **23a** and **23b** have been located at the B3LYP/6-31G(d) level (Figure 4). Rearrangement occurs via a concerted 1,3-alkyl shift (Scheme 7).

Transition structures **24a** and **24b** (Figure 4) are early and primarily reflect initial bond-breaking, which occurs

(19) Rearrangement of the *O*-protonated species **18** was not examined since an analogous rearrangement would lead to an *O*-protonated ketenimine oxide, which would likely open directly to species such as **21**.

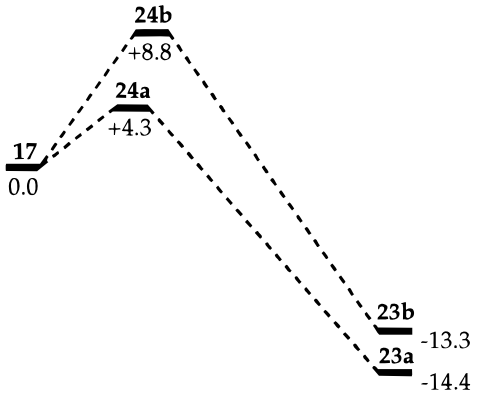


Figure 3. Energetics of the rearrangement process that converts **17** to **23a** and **23b**. Reported energies (kcal/mol) relative to that of **17** were calculated at the B3LYP/6-31G(d) level and include zero-point energy corrections scaled by 0.9806.

through a thermal two-electron disrotatory electrocyclic process. In these transition states, the filled breaking σ_{C-3-N} bonding orbitals can interact favorably with the unfilled $\pi^*_{C=O}$ antibonding orbitals as shown in Figure 5. In doing so, a three-center two-electron aromatic bonding array is formed. This interaction is absent in **17** since the σ_{C-3-N} bonding orbital and the $\pi^*_{C=O}$ antibonding orbitals are orthogonal. Consequently, the carbonyl bond is lengthened by 0.02−0.03 Å in the two transition structures relative to the *N*-protonated α-lactam intermediate **17** (compare Figures 2 and 4). Disrotation of the breaking bond in the transition state (Figure 5a) allows it to interact with the lobe of the π^* orbital which is orientated on the same face of the lactam ring as the breaking bond.[20] To increase orbital overlap, both the carbonyl and the breaking bond tilt toward each other (Figures 4 and 5b,c). The nitrogen-side of the breaking bond tilts toward the π^* orbital more than the C-3-side in both transition states, since the electron density in the breaking σ-bonding orbital can be better accommodated by the more electronegative nitrogen. This is consistent with the nitrogen acquiring a lone pair and C-3 acquiring cationic character. Hyperconjugation with the developing cationic center results in the C(Me)−C-3 bond lengths shortening in the transition states by 0.03−0.04 Å relative to those in **17** (compare Figures 2 and 4).

Since the nitrogen in the protonated α-lactam is not symmetrically substituted, two different disrotatory transition states (**24a** and **24b**) are possible. Transition structure **24b**, in which the two methyl groups rotate inward, is approximately 4.5 kcal/mol less stable than transition structure **24a**, in which the two methyl groups rotate outward (Figure 3). This difference in stability can be attributed to two main factors. First, the methyl−methyl steric interaction in **24b** is greater than in **24a** (Figure 5d). This is reflected in the differences in C-3−N and C(Me on C-3)−C(Me on N) distances (0.16 and 0.53 Å, respectively) and the C(Me)−C-3−N−C(Me) torsional angles (3.7° for **24b** and 10.9° for **24a**). Second, the nitrogen side of the breaking bond is tilted closer to the π^* orbital in **24a** than it is in **24b** (Figure 4), thus increasing the orbital overlap and the stabilization associated with this interaction.

An IRC calculation starting from transition state **24b** demonstrated that the rearrangement pathway is concerted. Motion prior to the transition state is dominated by the bond-breaking and rotation processes described above. After the transition state is reached, rotation about the C-2−N bond continues while rotation about the C-2−C-3 bond reverses direction and the carbonyl oxygen returns to the plane of C-2, C-3, and N. Overall, this rearrangement is formally a [1a,3s] Woodward−Hoffmann-allowed sigmatropic shift. However, the structural changes that occur along the rearrangement pathway are more characteristic of a pseudopericyclic reaction,[21] characterized by two concerted but asynchronous processes: a thermal two-electron disrotatory electrocyclic ring opening, followed by nucleophilic attack on C-3 by the carbonyl oxygen.

Nucleophile Incorporation. An explanation for the process of nucleophile incorporation must account for both the regiochemical and stereochemical issues described above. In the presence of proton donors, C-3 attack must be preferred over C-2 attack, and this process must proceed with net inversion at C-3. Several cationic structures have been described above, and which of these is involved in nucleophilic attack at C-3 is the subject of the remainder of this report.

The relative energies of *O*- and *N*-protonated cyclic cations **17** and **18** are close enough to each other to suggest that all of these structures are formed under protic conditions. Rearrangement to ring-opened cations such as **21** and **22** is unlikely, however, since such processes would lead to stereochemical scrambling at C-3, which is not observed experimentally.

O- and *N*-protonated cyclic structures such as **17** and **18** could be attacked directly by nucleophiles at either C-2 or C-3. For this scenario to be consistent with experimental results, the preferred pathway must involve attack at C-3. Four transition states were located for attack of chloride ion at both C-2 and C-3 of cyclic cations **17** and **18a** at the B3LYP/6-31G(d) level (Figure 6). Although attempts to locate complexes of **17** and **18a** with chloride ion led to HCl complexes **19** and **20** in the gas phase (Figure 2), the existence of protonated species such as **17** and **18** is likely in solution due to solvation of the chloride anion. The structures of transition states for chloride incorporation and their relative energies are shown in Figure 6. The lowest energy transition state is that for C-3 attack on the *O*-protonated cation. This process will relieve the increased ring strain caused by protonation. The activation barrier for this reaction (from HCl complex **20**) is computed to be approximately 15 kcal/mol in the gas phase, and this transition state does lead to inversion at C-3 upon nucleophile incorporation. This scenario (preferential C-3 attack on the *O*-protonated cation) is consistent with the experimental results.

While the barrier to chloride (or HCl) attack on cation **18a** is slightly greater than that for rearrangement of

(20) This interaction is reminiscent of the interaction between the breaking σ bond and the σ^* orbital of the leaving group which controls the relative rates of reactions of epimers in the concerted solvolysis/disrotatory ring openings of cyclopropyl derivatives to allyl cations. See, for example: Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 396−397. Schleyer, P. v. R.; Van Dine, G. W.; Schöllkopf, U.; Paust, J. *J. Am. Chem. Soc.* **1966**, *88*, 2868−2869.

(21) For leading references see: (a) Fabian, W. M. F.; Bakulev, V. A.; Kappe, C. O. *J. Org. Chem.* **1998**, *63*, 5801−5805. (b) Birney, D. M.; Ham, S.; Unruh, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 4509−4517.

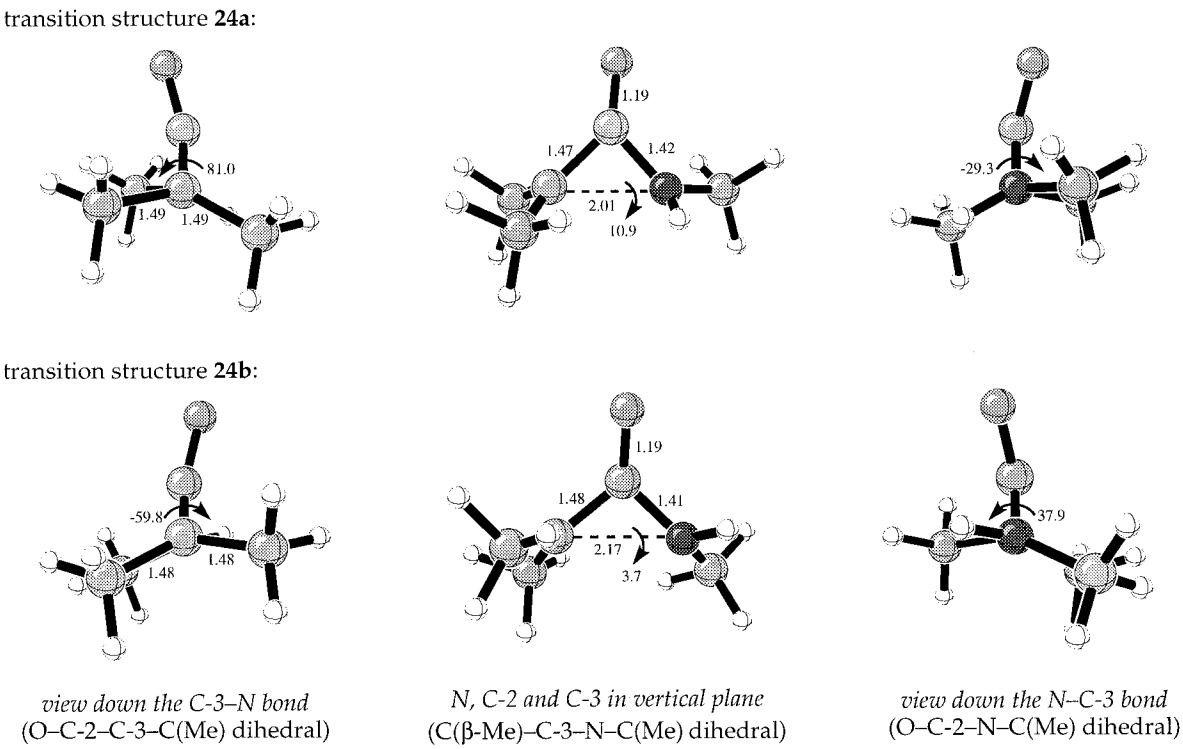
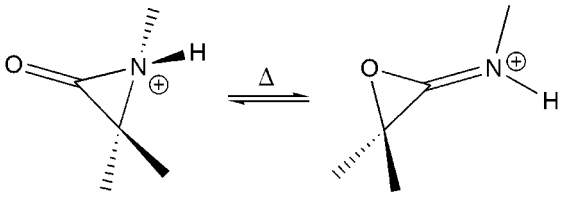


Figure 4. Rearrangement transition structures **24a** and **24b** calculated at the B3LYP/6-31G(d) level. Selected distances are in angstroms and angles are in degrees.

Scheme 7



17 **23a**

N-protonated cation **17** to form keteniminium oxides **23a** and **23b**, it is dangerous to compare these activation energies directly. While the nature of solvation effects on each process is unclear, specific solvation of the 1,3-shift by a hydrogen-bonded water molecule is calculated to lead to an increase in activation energy of approximately 3 kcal/mol. This increase is likely a result of the greater charge delocalization in transition states **24a** and **24b** than in cation **17**. In addition, rearrangement to the keteniminium oxides **23a** and **23b** followed by nucleophilic attack at C-3 would likely lead to net retention at that center (by a double inversion process). Computations[22] predict that attack of a water molecule on keteniminium oxide **23a** with inversion (backside attack) is favored by approximately 7−8 kcal/mol over attack with retention (frontside attack), as expected. Since net retention is *not* observed experimentally, it is likely that the rearrangement process is either disfavored or rapidly reversible in solution or that the keteniminium oxides **23a** and **23b** are not stable intermediates in polar solvent.

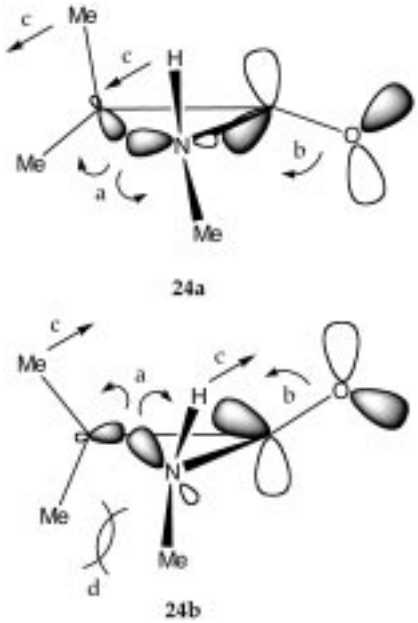


Figure 5. FMO considerations in the initial portion of the rearrangement reaction coordinate: (a) disrotation, (b) carbonyl tilt, (c) breaking-bond tilt, and (d) steric interaction which destabilizes **24b** with respect to **24a**.

Conclusions

Computational results support the proposal that a cationic intermediate is involved in the reactions of weak nucleophiles with α-lactams.[13] Although many cationic

(22) Optimizations at the B3LYP/6-31G(d) level led to a true transition state for frontside attack. The activation energy for backside attack was estimated from a series of constrained optimizations in which the forming O−C bond length was varied from 1.45 to 2.85 Å.

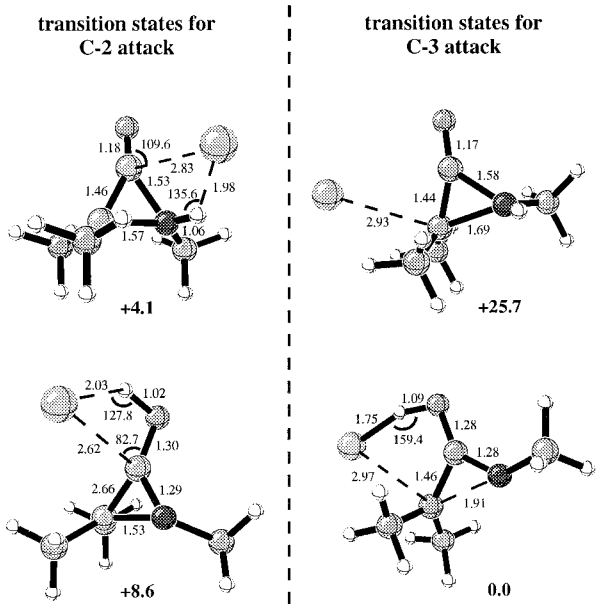


Figure 6. Transition structures for chloride (HCl) attack calculated at the B3LYP/6-31G(d) level. Selected distances are in angstroms and angles are in degrees. Reported energies (kcal/mol), relative to that of the transition state for attack on C-3 of the *O*-protonated cation, were calculated at the B3LYP/6-31G(d) level and include zero-point energy corrections scaled by 0.9806.

intermediates may be formed under the experimental reaction conditions, preferential attack of nucleophiles on the *O*-protonated intermediate **18** is predicted to be the most likely pathway for nucleophile incorporation at C-3. This process is more facile than nucleophilic attack on the same *O*-protonated cation at C-2 or the *N*-protonated cation **17** at C-2 or C-3. This scenario is consistent with the observed regio- and stereoselectivity of nucleophile incorporation.

Stated differently, the computational results suggest that *O*-protonation of the α-lactam activates C-3 toward addition of nucleophiles. It is likely that analogous activation of C-3 can also be achieved by species other than a proton. For example, *O*-complexation of α-lactams by Lewis acids (such as metal cations) might also be effective in promoting selective C-3 attack. Even general acid catalysis or strong H-bonding could potentially serve the same purpose. The experimental evaluation of these possibilities is in progress.

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