Electrospray Ionization (ESI) Fragmentations and Dimethyldioxirane Reactivities of Three Diverse Lactams Having Full, Half, and Zero Resonance Energies

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S *Supporting Information*
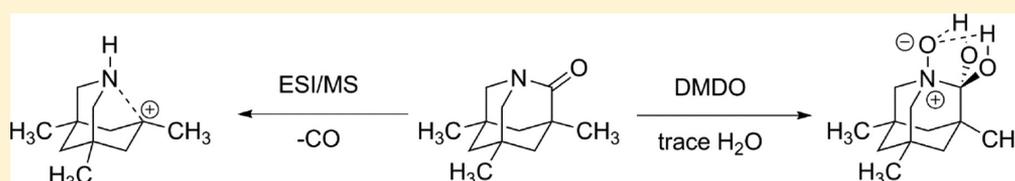
ABSTRACT: Three lactams having, respectively, ~20, ~10, and 0 kcal/mol of resonance energy have been subjected to electrospray ionization mass spectrometry (ESI/MS) as well as to attempted reaction with dimethyldioxirane (DMDO). The ESI/MS for all three lactams are consistent with fragmentation from the N-protonated, rather than the O-protonated tautomer. Each exhibits a unique fragmentation pathway. DFT calculations are employed to provide insights concerning these pathways. *N*-Ethyl-2-pyrrolidinone and 1-azabicyclo[3.3.1]nonan-2-one, the full- and half-resonance lactams, are unreactive with DMDO. The "Kirby lactam" (3,5,7-trimethyl-1-azaadamantan-2-one) has zero resonance energy and reacts rapidly with DMDO to generate a mixture of reaction products. The structure assigned to one of these is the 2,2-dihydroxy-*N*-oxide, thought to be stabilized by intramolecular hydrogen bonding and buttressing by the methyl substituents. A reasonable pathway to this derivative might involve formation of an extremely labile *N*-oxide, in a purely formal sense, an example of the hitherto-unknown amide *N*-oxides, followed by hydration with traces of moisture.

INTRODUCTION

Unstrained amides and lactams, such as *N*-ethyl-2-pyrrolidinone (**1**, R = C_2H_5), have 15–20 kcal/mol of stabilization (resonance) energy, and this is reflected in the high rotational barriers of the amides (Scheme 1).[1−6] Protonation on oxygen rather than on nitrogen is favored by 10−15 kcal/mol.[7−14] Despite this selectivity, protonation on nitrogen does play the key role in acid-catalyzed N−H proton exchange in unstrained primary and secondary amides, including peptides and proteins.[15] In contrast, the bridgehead bicyclic lactam **2** ("2-quinuclidone")[16−22] and its derivatives as well as 3,5,7-trimethyl-1-azaadamantan-2-one (**3**, "Kirby lactam")[23−26] have orthogonal amide linkages and zero resonance energy and as such behave more like amino ketones rather than lactams. Woodward and co-workers actually considered the 2-quinuclidone system and predicted ketone-like properties over seven decades ago.[27] Indeed, Woodward and co-workers performed a calorimetric study[28] on penicillin that strongly suggested the *β*-lactam structure later proven by Crowfoot and co-workers.[29] Protonation on nitrogen is favored by ca 20 kcal/mol in these species such as **2** and **3**.[10,11] Distortion of the amide linkage is quantified by three independent parameters:[30] twist angle about the OC−N bond (*τ*), pyramidalization at nitrogen (*χ*$_N$), and pyramidalization at the carbonyl carbon

(*χ*$_C$). Since this last parameter is usually quite small,[30] a three-dimensional plot of energy versus *τ* and *χ*$_N$ is quite useful.[5] There can be a delicate balance between protonation on oxygen or nitrogen depending on these parameters. For example, 1-azabicyclo[3.2.2]nonan-2-one favors methylation on nitrogen (**4**), whereas slightly less distorted 1-azabicyclo[3.3.2]decan-2-one favors methylation on oxygen (**5**).[12,31] 1-Azabicyclo[3.3.1]-nonan-2-one (**6**) has roughly half the resonance energy of an unstrained amide and is the only known example in which both N-protonated (**6-NH$^+$**) and O-protonated (**6-OH$^+$**) tautomers coexist in comparable concentrations.[32,33]

The gas-phase proton affinity of 1-azabicyclo[2.2.2]octan-2-one (**2**) is 964.2 kJ/mol (230.4 kcal/mol), some 15−20 kcal/mol higher (more basic) than typical amides and lactams,[22] and slightly lower than the published value for the corresponding amine, 1-azabicyclo[2.2.2]octane (975 kJ/mol or 233.1 kcal/mol).[34] Such increased localization of the nitrogen lone pair, resulting from N−CO twisting and/or pyramidalization at the amide nitrogen, should increase the propensity for other electron-pair sharing reactions beyond protonation. One intriguing possibility is the formation of hitherto unknown
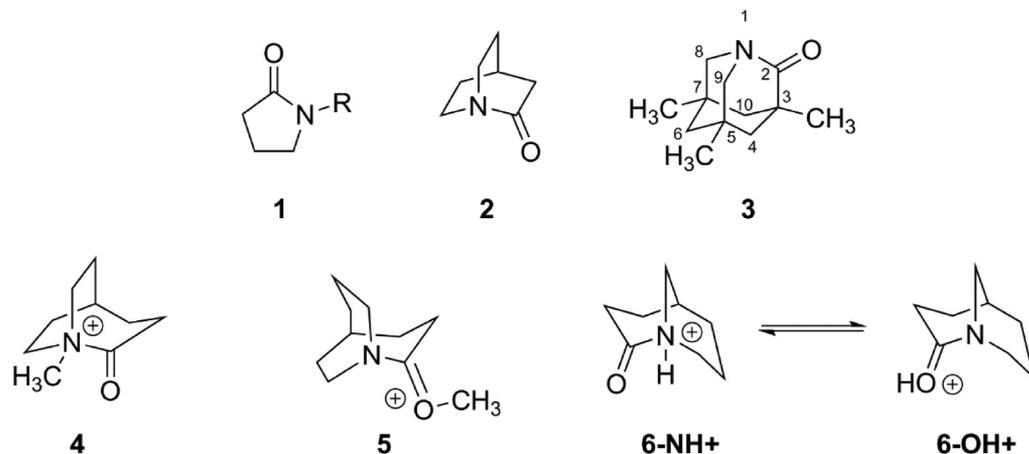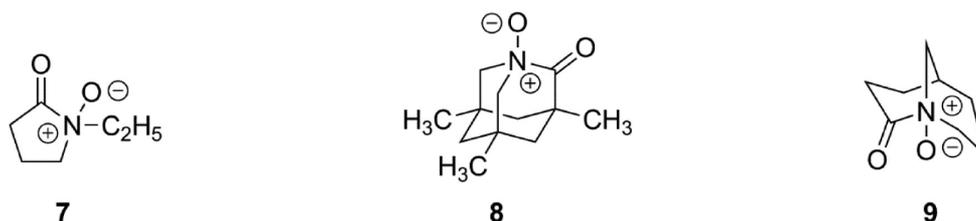
Scheme 1

Scheme 2

Scheme 3. Mechanism Proposed by Crotti et al.[39] for Formation of *m/z* 69 Ion in the ESI/MS Study of 2-Pyrrolidinone*[a]*
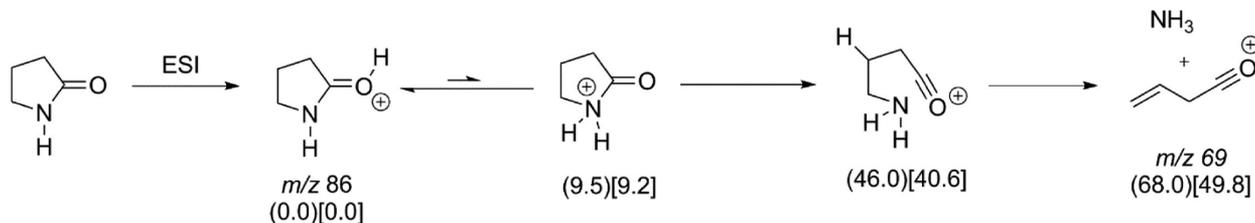
*[a]*The calculated (B3LYP/6-31G*) relative energies in kcal/mol in parentheses agree well with the published values[39] (calculated relative standard scaled free energies are in brackets).

amide *N*-oxides (e.g., **7**) (Scheme 2). Although no amide *N*-oxides have been isolated or observed spectroscopically, the intermediacy of a urea *N*-oxide has been postulated,[35] and so too has the intermediacy of a carbamate *N*-oxide.[36] Whereas formation of an *N*-oxide from an unstrained amide or lactam (e.g., **7**) would entail a large resonance-loss penalty, no such loss would be associated with formation of **8**. Of course, it can be cogently argued that **8** is actually an *alpha*-keto tertiary amine *N*-oxide rather than an amide *N*-oxide. Tertiary amine oxides are well-known stable compounds. While Cope eliminations of amine *N*-oxides to form alkenes and hydroxyl-amines are well-known reactions, **8** lacks *β*-hydrogens and even the as-yet-unknown unsubstituted compound would be unlikely to undergo this reaction for steric reasons. 1-Azabicyclo[3.3.1]-nonan-2-one (**6**) is, however, most certainly a lactam in its chemical and spectroscopic properties. Formation of the amide (lactam) *N*-oxide **9** might be feasible since roughly 10 kcal/mol, rather than 20 kcal/mol, of resonance energy would be lost. Indeed, similar logic (reduced rotational barrier associated with reduced energy) was invoked to rationalize the intermediacy of the carbamate *N*-oxide,[36] and this principle would seem to apply to ureas[35] as well. An earlier published series of HF ab

intio calculations (6-31G*) predicted that (gas-phase) reactions of planar lactams (e.g., **1**) with H_2O_2 are endothermic (ΔE = +4 to +6 kcal/mol) and mildly exothermic for the orthogonal bridgehead lactams **2** and **3** (ΔE = −8.7 and −8.8 kcal/mol).[37] These calculations predicted mild exothermicities for reactions of unstrained lactams with dimethyldioxirane (e.g., ΔE = −6.6 kcal/mol for **1**) and significant exothermicities for **2** and **3** (−19.2 and −19.3 kcal/mol).[37] Although energetically attractive, the predicted lengthening of the CO−N bonds (e.g., 0.11 Å upon conversion of **1** to **7** and 0.06 Å upon conversion of **3** to **8**),[37] suggest very enhanced lability.

Despite the fact that an MP2/6-31G** study found O-protonated formamide to be ca. 60 kJ/mol (ca. 14 kcal/mol) more stable than its N-protonated tautomer, gas-phase chemical ionization using CH_4 as reagent gas produced only NH_4^+, corresponding to CO loss, reflecting fragmentation of the N-protonated tautomer.[38] Only when much more exothermic proton transfers (e.g., H_2 as reagent gas) were explored were H_2O and NH_3 loss, both originating from the O-protonated tautomer, observed in addition to loss of CO from the N-protonated tautomer.[38] The origins of this nonstatistical behavior were attributed to (a) simultaneous dynamic

formation of both N- and O-protonated tautomers, (b) a much higher pair of barriers to decomposition of the O-protonated tautomer (284 and 289 kJ/mol {ca. 68 and 69 kcal/mol}, respectively), and (c) nonstatistical partitioning of the transition state connecting the O-protonated to the N-protonated tautomer, on the one hand, and formation of HCO$^+$ with loss of NH$_3$ on the other.[38] This experimental (ca. 3 × 10^{-7} Torr) and computational study quite naturally explored only unimolecular decomposition pathways for the two protonated formamide tautomers.[38]

An electrospray ionization tandem mass spectrometry study[39] of 2-pyrrolidinone reported elimination of NH$_3$ and formation of the unsaturated acylium ion depicted in Scheme 3 (the calculated relative energies in parentheses compare well with the published energies[39]). The proposed mechanism involved initial O-protonation, followed by isomerization to the N-protonated tautomer (calculated to be 9.5 kcal/mol higher in energy), cleavage of the weakened N—CO bond, followed by further fragmentation, and shifting of H from C to N.[39] A detailed comparison of calculated gas-phase proton affinities for 2-pyrrolidinone (O-protonated), using a range of DFT and ab initio methods, with the experimental value was published in a follow-up study.[40] The solution-phase result for 2-pyrrolidinone resembles the gas-phase result for the much simpler molecule formamide only insofar as the lower energy CI decomposition of formamide (CH$_4$ as reagent gas) also derives from the less stable, N-protonated tautomer. One might have imagined distinct fragmentation pathways for O-protonated versus N-protonated lactams or amides as a means for distinguishing the protonation site in "borderline" bridgehead bicyclic lactams, such as the [3.2.2] and [3.3.2] systems cited earlier. However, it appears that the pathways proceed via N-protonated tautomers even if these are present in vanishingly low concentrations. Before describing the present experimental study, it is worthwhile noting that electrospray ionization-induced fragmentations of benzamides[41] and fatty acid primary amides (RCONH$_2$)[42] appear to be well explained by their initially formed, more stable O-protonated tautomers. This is because alternative rearrangement and fragmentation pathways are very accessible via the initial O-protonated MH$^+$ ions derived from these molecules.

The present study compares ESI mass spectra for three tertiary lactams (**1**, **3**, and **6**) differing markedly in their structures and thermodynamic stabilization (resonance) energies. There are no published CI or electrospray studies of significantly twisted lactams or amides. However, Ly et al. observed the fragmentation of the N-protonated tetrafluoroborate salt of **2** using collision induced dissociation (CID) and observed loss of 44 mass units (vinyl alcohol).[22]

■ COMPUTATIONAL METHODOLOGY

Calculations were performed using Spartan 10 and Gaussian 09W with DFT (B3LYP/6-31G*, enthalpies and free energies were calculated using a scale factor of 0.9804, or B3LYP/6-31+G**, scale factor of 0.964).[50,51] Model ^{1}H and ^{13}C NMR spectra were calculated in Spartan 10 at the EDF2/6-31G* level of theory. The RMS error between experimental and calculated ^{13}C chemical shifts is 1.8 ppm for Spartan 10.[50] Images were created from Spartan and Gaussian files using CYLview.[52]

■ RESULTS AND DISCUSSION

Electrospray Mass Spectrometry. Figure 1A is the ESI mass spectrum of N-ethyl-2-pyrrolidinone. Prominent features
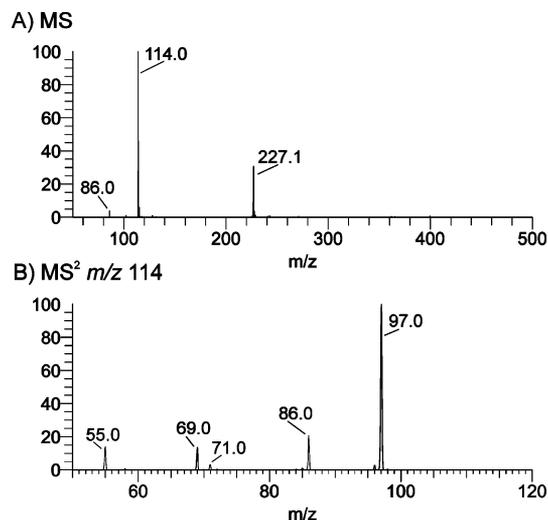
Figure 1. (A) ESI/MS of N-ethyl-2-pyrrolidinone. (B) MS/MS of m/z 114 ion.

include the M+1 (MH) ion (protonated N-ethyl-2-pyrrolidinone), the proton-bridged dimer (m/z 227), and a small m/z 86 peak corresponding to loss of C$_2$H$_4$. The MS/MS (MS^2) spectrum of the m/z 114 ion (Figure 1B) shows prominent m/z at 97, 86, 69, and 55. The m/z 86 ion is likely derived from the concerted rearrangement depicted in Scheme 4. Since m/z 86 corresponds to the M+1 observed for 2-pyrrolidinone itself, the fragmentation to m/z 69 (loss of NH$_3$) is consistent with the results of Crotti et al.[39] These authors do not explicitly report an m/z 55 ion, although one may envision loss of CH$_3$NH$_2$ from the m/z 86 ion. Interestingly, ESI of N-methyl-2-pyrrolidinone does not include an MH-17 (m/z 83) ion but does include m/z 69 and m/z 58 ions assigned by the authors to [MH−CH$_3$NH$_2$]$^+$ and [MH−CH$_3$NCH]$^+$ ions.[53] Although it might be tempting to postulate the m/z 97 to arise from loss of OH from the more stable O-protonated m/z 114 ion, this homolytic cleavage requires in excess of an estimated[34] 100 kcal/mol and is clearly prohibited. Instead, this appears to correspond to loss of NH$_3$ as observed for 2-pyrrolidinone itself.[39] Perhaps it is initiated by rearrangement of ethyl from N to O starting from the N-protonated m/z 114 ion. Scheme 5 depicts an alternative mechanism to that in Scheme 3 for loss of NH$_3$ from N-protonated 2-pyrrolidinone (relative energies in parentheses). The cyclopropyloxocarbenium ion postulated in Scheme 5 is stable in superacid at −80 °C.[54] However, the rearrangement step to generate this ion is calculated to have a very high barrier.

Although ESI/MS is regarded as a "soft technique", relative to electron impact (e.g., 70 eV), for example, it is worthwhile noting that the internal energies of ions using this technique may also be significant. While the specifics vary considerably with instrument conditions, internal energies in the range of 1.3−2.2 eV (30−50 kcal/mol) are not uncommon.[55] This allows for sizable activation energies and endothermicities in rearrangements and fragmentations.

The ESI/MS of 1-azabicyclo[3.3.1]nonan-2-one is shown in Figure 2A. It is a very simple spectrum showing primarily the M+1 ion and the hydrogen-bridged dimer (m/z 279). Figure 2B is the MS^2 spectrum for the M+1 ion (m/z 140). The very clean fragmentation to m/z 96 is attributed to loss of vinyl alcohol analogous to the loss of vinyl alcohol from N-protonated 1-azabicyclo[2.2.2]octan-2-one and attributed to

Scheme 4. Postulated Mechanism for Loss of C_2H_4 from *N*-Ethyl-2-pyrrolidinone in ESI/MS[a]

m/z 114
(0.0)[0.0]   (12.6)[10.7]   (51.3)[47.0]   *m/z* 86
(33.0)[20.1]
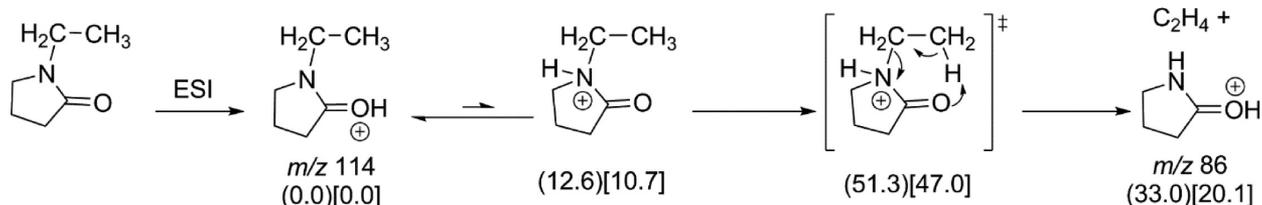
[a]Calculated (B3LYP/6-31G*) relative total energies are in parentheses, and relative standard scaled free energies are in brackets.

Scheme 5. Postulated Alternative Mechanism (See Scheme 3) for Loss of NH_3 from 2-Pyrrolidinone in ESI/MS[a]

(0.0)[0.0]   (9.5)[9.2]   (46.0)[40.6]

(76.9)[69.3]   (27.5)[25.2]   (37.5)[32.7]

NH_3 +

(63.9)[47.4]
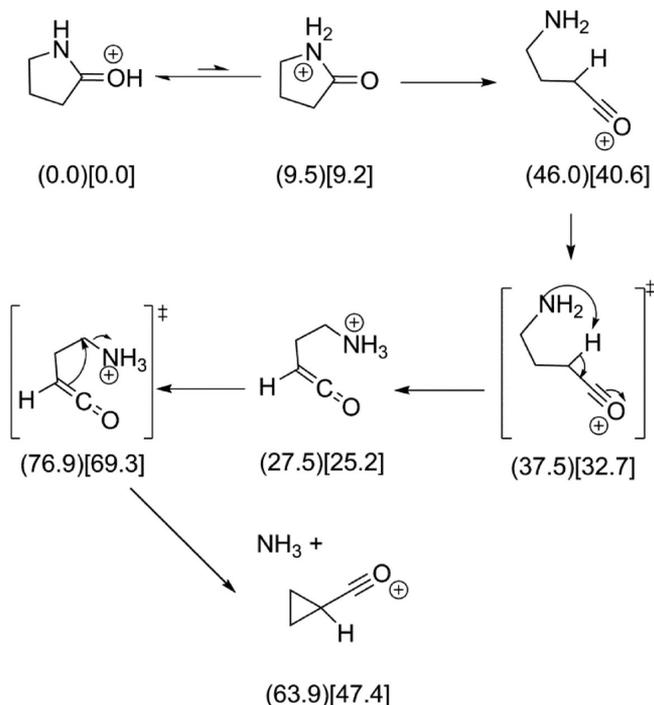
[a]Calculated (B3LYP/6-31G*) relative energies in kcal/mol shown in parentheses, and relative standard scaled free energies are in brackets.
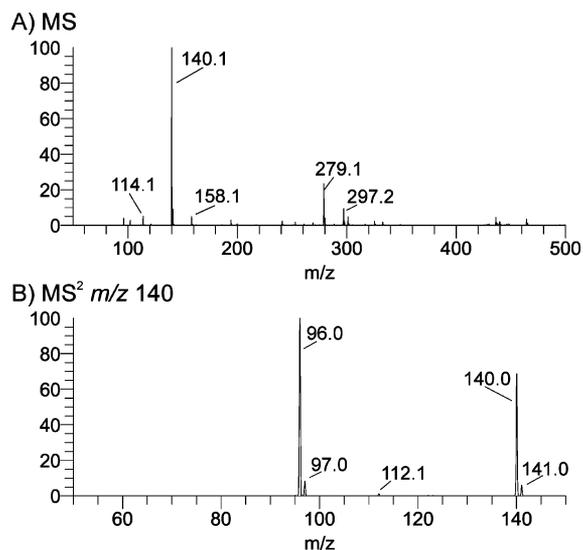
Figure 2. (A) ESI/MS of 1-azabicyclo[3.3.1]nonan-2-one. (B) MS[2] of the *m/z* 140 ion.

McLafferty rearrangement.[22] The corresponding postulated mechanism for 1-azabicyclo[3.3.1]nonan-2-one, also concluding with a McLafferty rearrangement, is depicted in Scheme 6. For this molecule, although N- and O-protonated tautomers are of comparable stability, fragmentation also originates entirely from the N-protonated tautomer. The calculations for the corresponding extrusion of vinyl alcohol from the [2.2.2] system are depicted in Scheme 7. The energies, including the activation parameters, for the two postulated McLafferty rearrangements are quite similar. A seeming oddity in Schemes 6 and 7 is the calculated result of slightly lower total energies for the McLafferty transition states than for the products. This is certainly, in part, an artifact of enhanced ion–dipole attraction in the transition state relative to the separated ion and molecule in the gas phase.[56a,b] In each case, the predicted free energies are significantly lower than those of the transition states due to dissociation into an ion and a molecule.

Figure 3A is the ESI/MS of the Kirby lactam. The MS[2] fragmentation of the M+1 ion (*m/z* 194) loses 28 mass units. This is fully consistent with the N-protonated M+1 ion losing CO as the initial step to yield *m/z* 166. From this ion are derived *m/z* 149 (loss of NH_3) and *m/z* 135 (loss of CH_3NH_2?). Once again, and unsurprisingly, it is the N-protonated lactam (this time, it is the O-protonated lactam that is present in vanishingly small concentrations) that determines the fragmentation pathway (Scheme 8).

Reaction with Dimethyldioxirane. Table 1 lists (gas-phase) standard free energies of reaction and free energies of activation for the three lactams investigated in this study for their reactions with dimethyldioxirane to yield the lactam N-oxide and acetone. This is, of course, a critical question concerning the chemical reactivities of three lactams; calculations were performed with and without diffuse functions (B3LYP/6-31G* and B3LYP/6-31+G**). The N-oxidation of *N*-methyl-2-pyrrolidinone is calculated to be only mildly exergonic with the highest activation. N-Oxidation of 1-azabicyclo[3.3.1]nonan-2-one is slightly more exergonic and faster. N-Oxidation of the Kirby lactam is calculated (B3LYP/6-31+G**) to be considerably more exergonic with an activation barrier 9 kcal/mol lower than that of *N*-methyl-2-pyrrolidinone.

Mixing *N*-methyl-2-pyrrolidinone with DMDO/CDCl₃ under ambient conditions did not lead to a reaction: NMR spectra were identical to those of the starting materials. The same observation was made for *N,N*-dimethylacetamide. 1-Azabicyclo[3.3.1]nonan-2-one also did not react with DMDO/CDCl₃. In contrast, 3,5,7-trimethyl-1-azaadamantan-2-one reacted rapidly with DMDO/CDCl₃. Figure 4 displays the ¹H NMR spectrum of the crude solid product obtained from mixing a roughly 2:1 ratio of this lactam to DMDO/CDCl₃. The lactam was used in excess to try to minimize overoxidation as well as to retain some unreacted starting material for spectroscopic comparison. The resonances (ppm, after 0.11

Scheme 6. Postulated ESI Fragmentation Pattern of 1-Azabicyclo[3.3.1]nonan-2-one with Loss of Vinyl Alcohol via McLafferty Rearrangement As Postulated for N-Protonated 1-Azabicyclo[2.2.2]octan-2-one[22a]
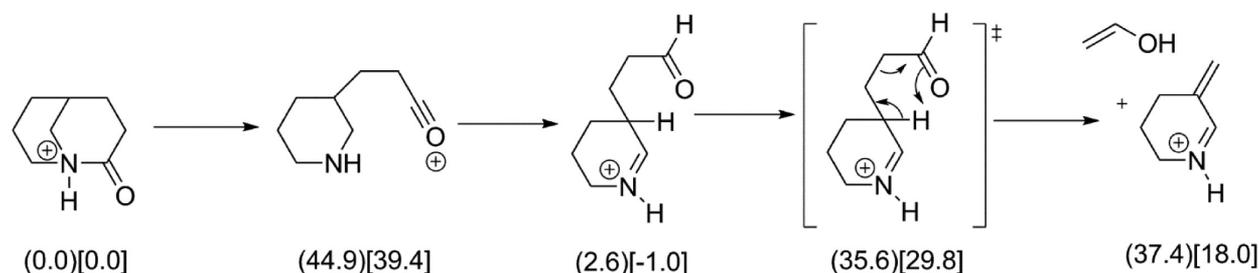
(0.0)[0.0]   (44.9)[39.4]   (2.6)[-1.0]   (35.6)[29.8]   (37.4)[18.0]

[a]Calculated (B3LYP/6-31G*) relative energies in kcal/mol are in parentheses, and relative standard scaled free energies are in brackets.

Scheme 7. Ly et al.[22] Postulated Pathway for Fragmentation of N-Protonated 1-Azabicyclo[2.2.2]octan-2-one in Their Collision-Induced Dissociation (CID) Study of the Tetrafluoroborate Salt[a]

(0.0)[0.0]   (39.5)[35.3]   (3.5)[0.3]   (38.7)[33.9]   (38.9)[20.5]
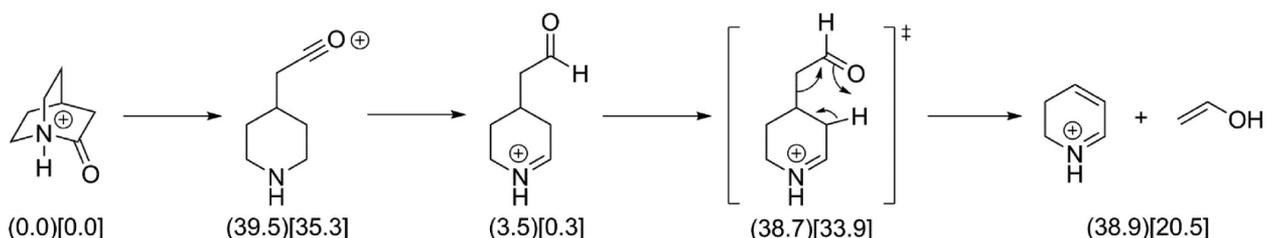
[a]The relative calculated (B3LYP/6-31G*) energies (kcal/mol) are in parentheses, and the calculated relative scaled free energies are in brackets.
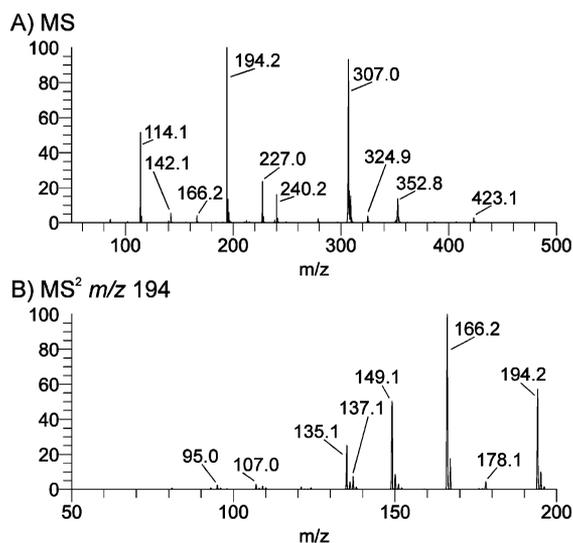
Figure 3. (A) The ESI/MS of Kirby lactam. (B) MS^2 of the m/z 194 ion.

ppm offset correction) at 3.00 (4H), 1.79 (2H), 1.65 (1H), 1.55 (3H), 1.07 (3H), and 0.86 (6H) correspond to unreacted Kirby lactam.[23−25] The upfield methyl singlets suggest at least two other related reaction products present in significant quantity. The resonances (0.10 ppm offset corrected) at ca. 3.6 and 3.8 ppm suggest methylene protons on carbons attached to a N−O functionality or to an O−H or an O−R functionality.

Thin-layer chromatography (silica gel) (95% ethanol) led to clean separation of two fractions: R_f 0.50 and R_f 0.75. The R_f 0.50 fraction consisted of essentially pure Kirby lactam (^{1}H and ^{13}C NMR spectra). Although arguably less polar than the oxidized compounds in the R_f 0.75 fraction, the Kirby lactam has basicity comparable to, if slightly weaker than, an amine. Figure 5a is the ^{13}C NMR spectrum (CDCl$_3$) of the R_f 0.75 fraction. Figure 5b shows the expansion of the 10−70 ppm section of this ^{13}C NMR spectrum. The downfield peaks at 187.7 and 108.8 ppm in Figure 5a are noteworthy. The downfield resonance is consistent with a carboxyl or a carboxylate carbon. The resonance at 108.8 ppm is consistent with a gem-diol carbon. The resonance at 52.2 ppm (Figure 5b) is consistent with the value reported for the N−CH$_2$ carbons of the amino acid derived from simple hydrolysis of the lactam

Scheme 8. Postulated Initial Steps in the Fragmentation Pathway for the ESI of Kirby Lactam[a]
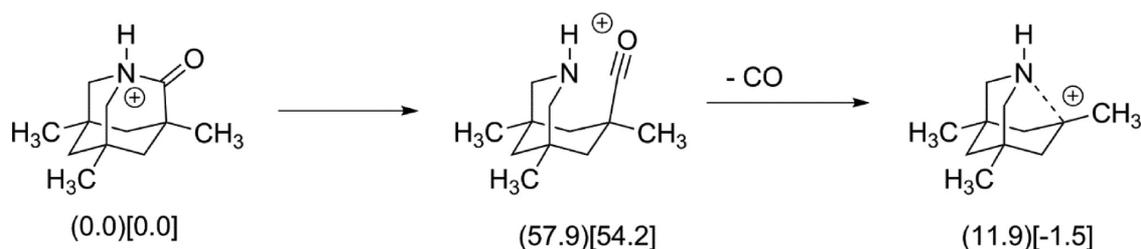
(0.0)[0.0]   (57.9)[54.2]   (11.9)[-1.5]

[a]Calculated relative energies in kcal/mol are in parentheses, and relative standard scaled free energies are in brackets.

Table 1. Calculated (B3LYP/6-31+G**) Standard Free Energies of Reaction (ΔG^{o}) and Scaled Activation ($\Delta G^{\ddagger}$) in kcal/mol for Oxidation of Lactams with Dimethyldioxirane To Produce Lactam N-Oxides and Acetone

lactam	B3LYP/6-31G*		B3LYP/6-31+G**	
	ΔG^{o}	$\Delta G^{\ddagger}$	ΔG^{o}	$\Delta G^{\ddagger}$
N-Methyl-2-pyrrolidinone (**1**, R = CH$_3$)	−4.0	35.8	−7.8	34.9
1-Azabicyclo[3.3.1]nonan-2-one (**6**)	−7.5	32.0	−13.0	29.8
3,5,7-Trimethyl-1-azaadamantan-2-one (**3**) ("Kirby lactam")	−17.2	27.5	−22.6	26.1
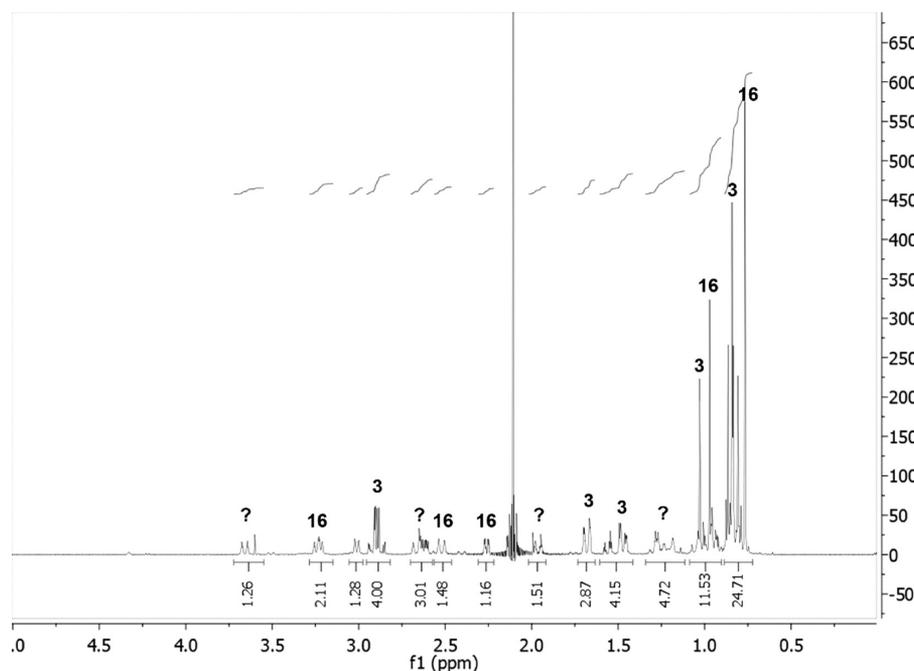
Figure 4. ^{1}H NMR (CDCl$_3$, offset upfield by 0.10 ppm) of the crude solid product derived from mixing roughly a 2:1 ratio of 3,5,7-trimethyl-1-azaadamantan-2-one, **3** (in CDCl$_3$), with DMDO/CDCl$_3$. Unreacted Kirby lactam is present along with at least two products (**16** is tentatively assigned).

(see **14** below; 52.5 ppm, D$_2$O−CD$_3$CN) and is consistent with the 187.7 ppm peak (190.0 ppm, D$_2$O−CD$_3$CN).[25] The two resonances at 66.4 and 67.4 ppm are consistent with some C−N−O as well as some C−O functionalities. (There are also two smaller resonances in this region.) Although the Kirby lactam itself has resonances at 65.97 and 52.2 ppm,[25] this starting material was cleanly separated from the reaction products by TLC. It is interesting to note the calculated (gas-phase) ^{13}C chemical shifts upon conversion of the Kirby lactam to its N-oxide (Scheme 9). The predicted change in downfield shift of the carbonyl carbon (C2) is only 2.3 ppm, whereas the predicted change for C8,9 is 16.3 ppm, apparently a much more sensitive probe.

How well do the calculations reproduce experiment? Table 2 lists experimental solution (and calculated gas-phase) ^{13}C chemical shift values for a series of compounds in this series. It appears that the chemical shifts are well reproduced with calculated C2 values typically 3−7 ppm downfield from the experimental value and C8,9 typically 0−5 ppm downfield from the experimental value.

The downfield ^{13}C chemical shift at 108.8 ppm (Figure 5a) suggests a *gem*-diol. At this point, reference is made to the ESI mass spectra in Figure 6A,B, of the R_f 0.75 fraction dissolved in ethanol. Figure 6A is the MS/MS (MS^2) derived from m/z 228. Figure 6B is the MS^3 derived from m/z 210. The major pathway suggests loss of water from the O-protonated species (**18**) derived from **16**, followed by loss of carbon monoxide

(Scheme 10). Table 3 compares calculated (vacuum) chemical shifts for the N-oxide-2,2-diol **16** with *possible* assignments from the experimental ^{13}C NMR and ^{1}H spectra. Scheme 10 depicts the structure calculated for **16**. It is important to note that **16** is calculated in the present study to be 15 kcal/mol higher in energy than **17** in vacuum, although this value is calculated to be only 5 kcal/mol in dichloromethane, acetone, or water. It should be noted that a series of proton transfers to form **17**, some of which are energetically demanding, may also explain why **16** is formed preferentially. While the 1.58 Å N−C2 bond calculated for **16** is quite long and a potential source of instability, intramolecular hydrogen bonding (Figure 7) as well as the aforementioned buttressing by the methyl groups[26] provides stability. Although it is tempting to invoke **17** as a product in the mixture, one might have expected an additional carboxyl carbon in the ^{13}C NMR spectrum. As noted earlier, the carboxylate carbon (187 ppm) is attributed to **14**. While an m/z 184 is observed in the ESI/MS of the R_f 0.75 fraction in ethanol, the MS^2 of m/z 228 (Figure 6A) shows no evidence of m/z 184 corresponding to expected loss of CO$_2$ from **17**. Such negative evidence is not, of course, very strong. While N-hydroxylamines are typically 5 orders of magnitude weaker bases than the corresponding amines,[57] simple N-hydroxyamino acids are zwitterionic.[58] The product (**16**) would appear to be kinetically determined (relative to **17**).

It is worthwhile recalling the behavior of the Kirby lactam under conditions of low, medium, and high pH as published by
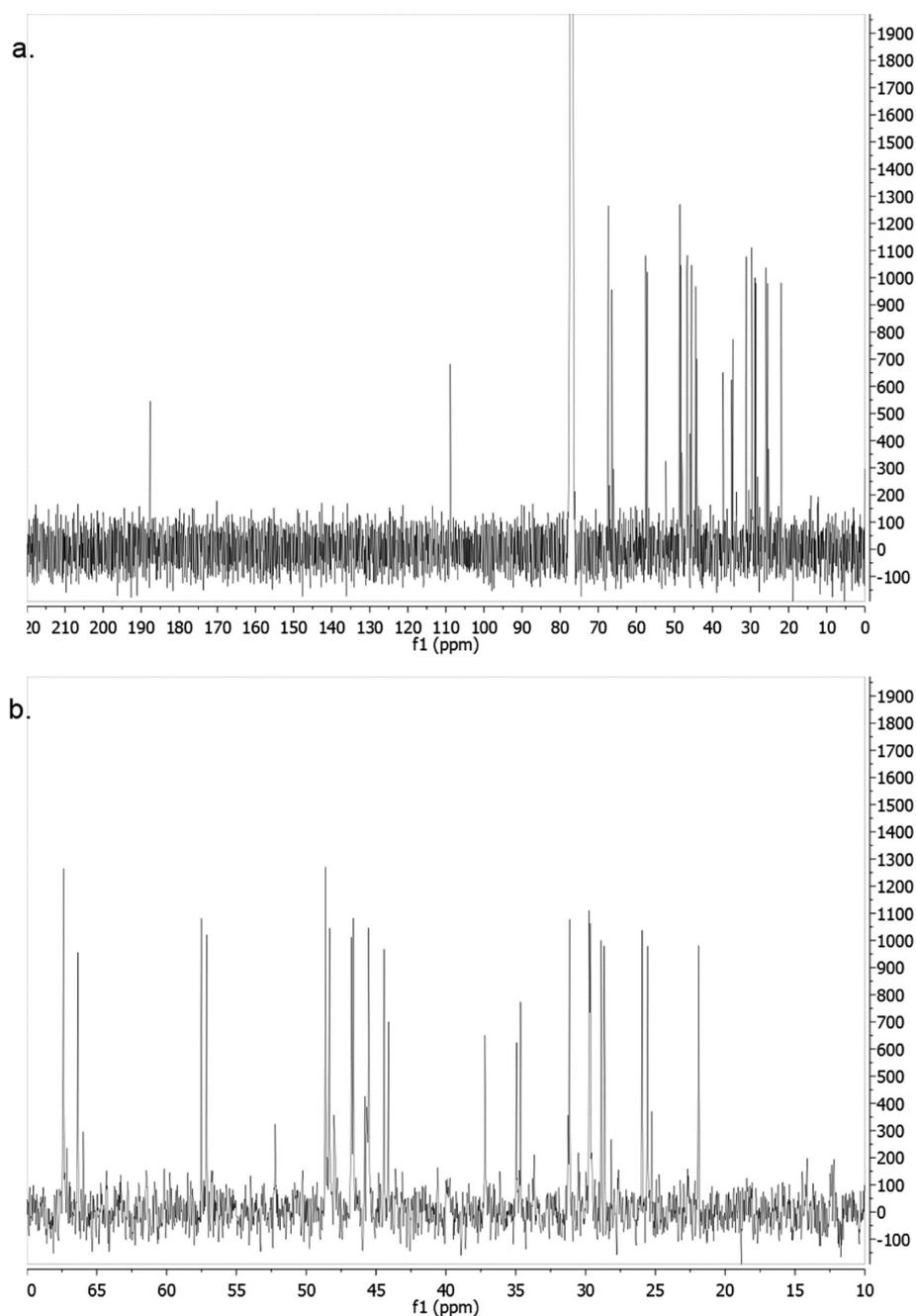
Figure 5. (a) ^{13}C NMR (CDCl$_3$) spectrum of the TLC fraction (R_f 0.75) of the reaction products of Kirby lactam with DMDO in CDCl$_3$. (b) Expanded scale of the NMR spectrum (a).

Scheme 9. Calculated (Vacuum) Chemical Shifts for Kirby Lactam and the Corresponding N-Oxide
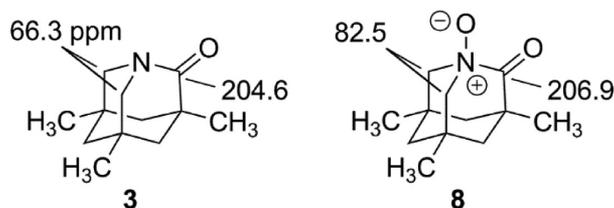
Kirby (Scheme 11).[25] At pH 3.30, only the N-protonated diol **13** is present. At pH 7.45, only the zwitterionic amino acid **14** is present. At pH 12.5, only the anionic **18** is observable. However, at pH 4.28, both **13** and **14** are observed separately at

room temperature. Warming the solution at this pH causes coalescence at 60−63 °C (rate = 280 s^{-1}). To exchange **13** and **14**, loss or gain of a proton is required.

The *N*-oxide-2,2-diol **16** is a neutral analogue of **13**, the N-protonated hydrate of the Kirby lactam observed at low pH (3.30). The neutral *N*-oxide is stabilized by intramolecular hydrogen bonding. Unlike most carbonyl hydrates, **13** has been isolated in pure form,[25] so it is not unreasonable that **16** can also be isolated.

There remain considerable uncertainties in other assignments in the TLC R_f 0.75 fraction. One may consider rearrangement of an initially formed *N*-oxide to the hydroxylamine lactone **15**. Concerted rearrangements of hypothetical acyclic amide *N*-oxides to such esters are calculated to be both

Table 2. Comparison of Selected Experimental (Solution) and Calculated (Gas-Phase) ^{13}C Chemical Shifts for C2 and C8,9 for Relevant Model Compounds[a]

Molecule	C2 (exp't)	C2 (calc'd)	C8,9 (exp't)	C8,9 (calc'd)
Kirby Lactam (CDCl₃) (3)	200.0	204.6	66.0	66.3
Kirby Lactam, N-Protonated (10) (CD₃CN)	179.1	182.4	62.3	66.5
Kirby Lactam, N-Methylated (11)	178.2	185.4	72.3	74.6
Kirby Lactam Acetal (12) (CDCl₃)	105.1	109.0	58.7	60.4
Kirby Lactam, N-Protonated Hydrate (13) (CDCl₃)	107.5	111.7	57.1	62.1, 61.4
1-Azabicyclo[3.3.1]nonan-2-one (6)	185.0	182.6	C8: 51.5; C9: 52.8	C8: 52.0 C9: 53.4
1-Azabicyclo[3.3.1]nonan-2-one, N-Protonated (6-NH⁺)	178.6	179.6	C8 or C9 ca 56.0 or 56.5	C8: 54.2 C9: 57.7
Amino Acid (Zwitterion) (14)	190.0		52.5	
Kirby Lactam N-Oxide (8)	-------	206.9	------	82.5
Kirby Lactam Hydroxylamine Lactone (15)	-------	184.2	------	63.7
Kirby Lactam N-Oxide-2,2-Diol (16)	------	110.7	------	72.3
Kirby Lactam N-Hydroxyamino Acid (17)	------		------	
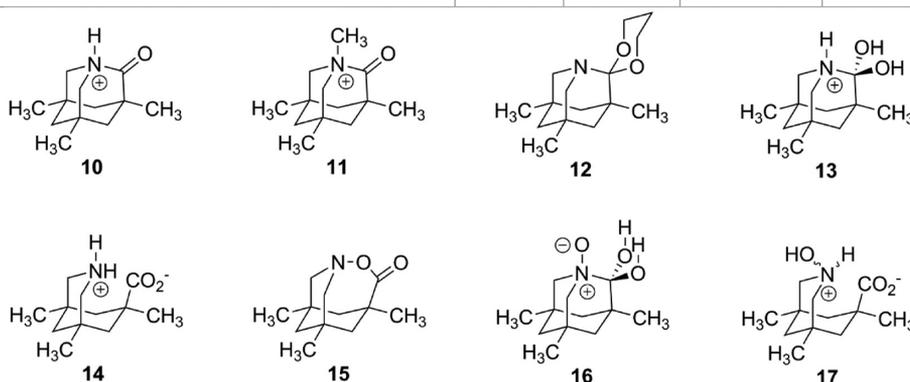
[a]Note that, for ease in comparison, the numbering scheme has been retained for the amino acid (14) and for the N-hydroxyamino acid (17).
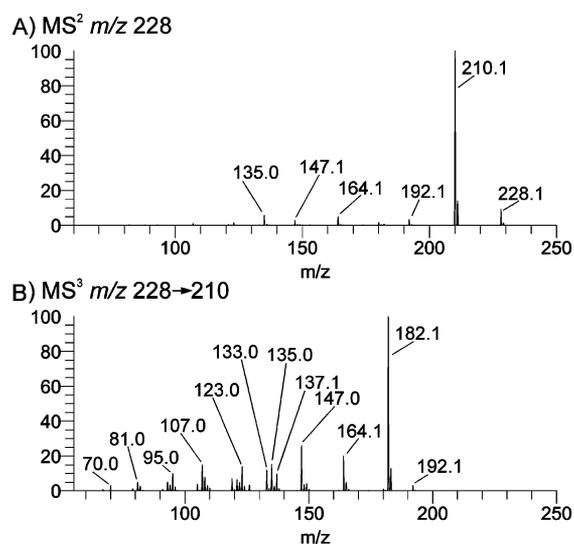
Figure 6. (A) The MS/MS (MS²) derived from m/z 228 of the R_f 0.75 fraction dissolved in ethanol. (B) The MS³ derived from m/z 210.

exothermic and extremely rapid.[37,59] However, the geometry for concerted rearrangement requires approach of the oxy anion via a trajectory essentially perpendicular to the plane of the carbonyl group. This is unlikely for **8**, which is calculated to have a very high (>35 kcal/mol) barrier to this rearrangement.[59] Alternatively, one might imagine N−C2 cleavage in **8**, followed by rapid formation of **15**. However, the IR spectrum of the R_f 0.75 TLC fraction (Supporting Information, S2b) shows no evidence of a carbonyl group when compared to the dry Kirby lactam (Supporting Information, S2a).The possibility of N−C2 cleavage, followed by immediate loss of CO (analogous to Scheme 7), suggests other possible products including **19** and **20** (Scheme 12). The IR spectrum is consistent with C−O stretching frequencies, and the m/z 166 (loss of CO from the m/z 194 ion) in the ESI/MS of the R_f 0.75 fraction could be consistent with N-protonated **19** (see also Table 2). The sharp band at 729 cm⁻¹ and broad bands between 1600 and 1700 cm⁻¹ (Supporting Information, S2b) might even suggest the possibility of nitrite[60] species such as **21** or **22**. One might imagine formation of the nitroso compound **23** by analogy to rearrangement of similarly substituted

Scheme 10. Proposed ESI Fragmentation Scheme of the Proposed *N*-Oxide-2,2-diol 16
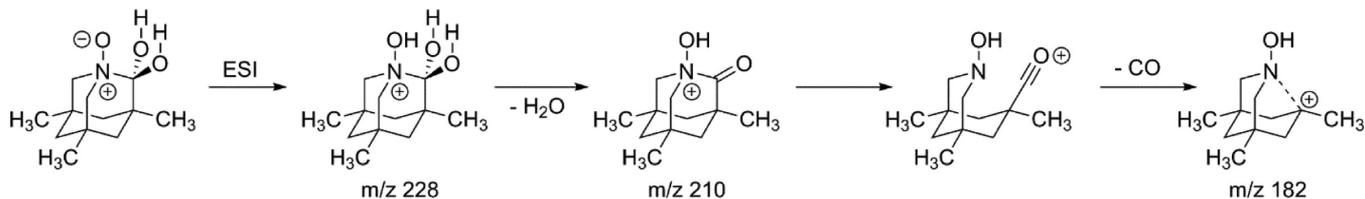
Table 3. Calculated ^{13}C and ^{1}H NMR Chemical Shifts (Vacuum) with Experimental Chemical Shifts (CDCl$_3$) in the TLC R_f Fraction 0.75 *Tentatively* Assigned to the *N*-Oxide 2,2-diol 16

	^{13}C chemical shift (calc'd)	^{13}C chemical shift (exp't)		^{1}H chemical shift (calc'd)	^{1}H chemical shift (exp't)
C2	110.7	108.8	8,9-H$_{eq}$	3.25	3.3
C8,9	72.3	67.4	8,9-H$_{ax}$	2.54	2.6
C6	48.0	48.6 or 48.3	4,10-H$_{eq}$	2.23	2.35
C4,10	45.2	45.5	6-H$_{eq}$	1.33	(1.3–1.4)
C3	36.3	37.2	6-H$_{ax}$	1.30	(1.3–1.4)
C5,7	31.1	31.2	4,10-H$_{ax}$	1.09	(1.1–1.15)
C5,7-Me	27.5	26.0, 28.7, or 28.9	3-CH$_3$	1.17	1.1
C3-Me	24.3	25.6 or 26.0	5,7-CH$_3$	0.90	0.9
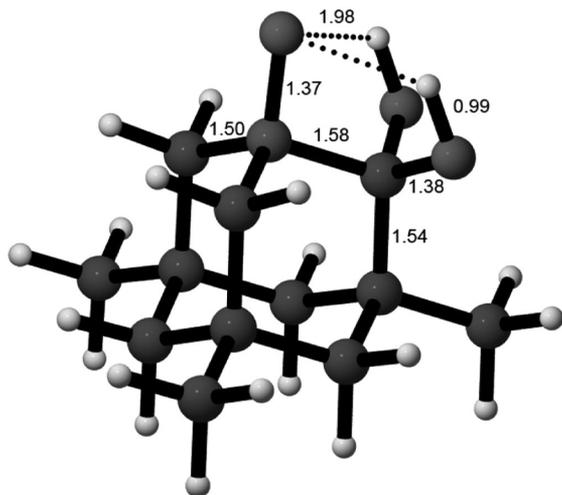
Figure 7. Selected calculated (B3LYP/6-31G*) bond lengths for the 2,2-dihydroxy-*N*-oxide of Kirby lactam (**16**), emphasizing the hydrogen bonds that stabilize the ion despite an elongated (1.58 Å) N—C2 bond.

Scheme 11. Structures of Species Derived from 1-Azaadamantan-2-one in Aqueous Media at Different pH Published by Kirby and Co-workers[25]

species[61,62] not as sterically constrained as **21**. However, the downfield chemical shifts calculated for a nitroso carbon (ca. 90–110 ppm) are absent and there is no evidence for an oxime rearrangement product in the ^{13}C NMR spectrum of the R_f 0.75 TLC fraction. To date, there is insufficient information for definitive assignments of all of the products of reaction between the Kirby lactam and DMDO. Low-temperature NMR analysis was performed; however, the results were not definitive. The results are included in the Supporting Information.

Assuming that a major product of the reaction between the Kirby lactam and DMDO, in the presence of a trace of water, is the 2,2-dihydroxy-*N*-oxide **16**, a key question is the pathway. Does it proceed via oxidation by DMDO to the sought-after *N*-oxide **8**, followed by hydration to **16**, or does hydration to **25** precede oxidation (see Scheme 13)? The calculated free energies suggest that initial oxidation to **8** is favored. This is intuitively reasonable because the Kirby lactam nitrogen is a strong nucleophile and DMDO is a strong electrophile. A desired comparison of activation barriers is limited at this level

of calculation. Combination of a single molecule of water with the Kirby lactam provides a complex in which the water molecule hydrogen bonds simultaneously with the lactam's nitrogen and oxygen atoms. The problem is one in which solvation and dynamics should furnish a more reasonable approach. It is interesting that the calculated energy of activation and scaled free energy of activation for attack of DMDO on hydrate **25** (0.5 and 13.7 kcal/mol) are much lower than the corresponding activation barriers for attack of DMDO on the Kirby lactam itself. This reflects the incipient hydrogen bonding present in the product **16**. It is well to remember that, in aqueous solution, the product of reaction of water with the Kirby lactam is the amino acid (**14**) rather than **25**. These are different solution conditions than a trace of water in CDCl$_3$ solution.

Scheme 12
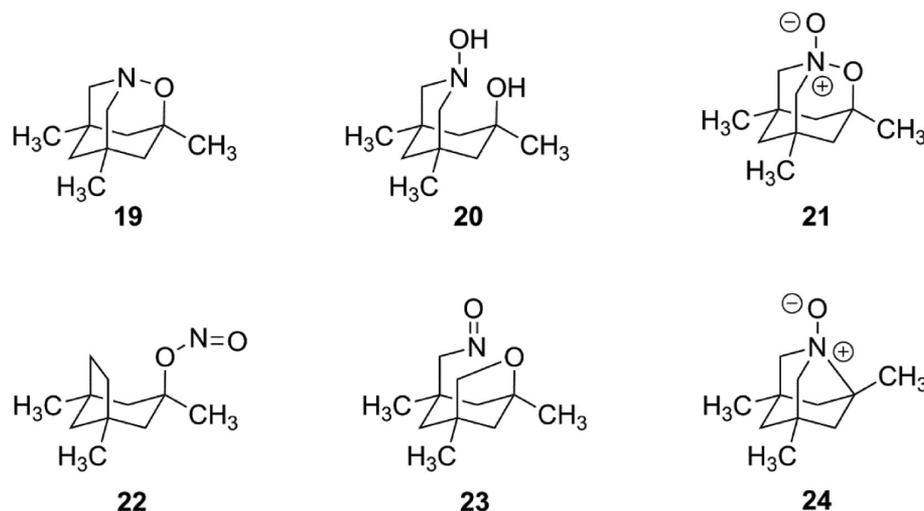
Scheme 13. Comparison of Two Alternative Pathways To Form the 2,2-Hydroxy-N-oxide of Kirby Lactam: Oxidation, Followed by Hydration, or Hydration, Followed by Oxidation[a]
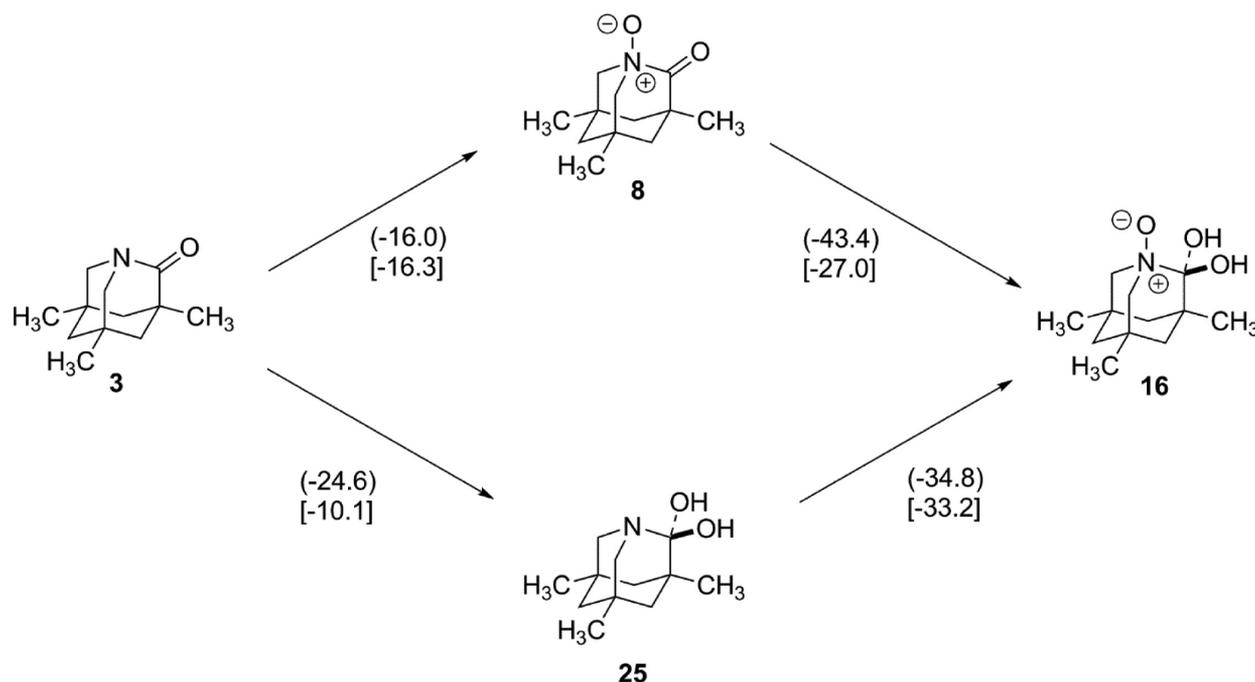
[a]Calculated relative total energies (kcal/mol) are in parentheses, and calculated relative free energies are in brackets.

CONCLUSIONS

The three lactams investigated in this study have ca. 20, ca. 10, and 0 kcal/mol of stabilization (resonance) energy, respectively. The first, N-ethyl-2-pyrrolidinone, protonates virtually exclusively on oxygen; the third, 3,5,7-trimethyl-1-azaadamantan-2-one (Kirby lactam), protonates virtually exclusively on nitrogen. The second, 1-azabicyclo[3.3.1]nonan-2-one, forms both N- and O-protonated species in equilibrium. Despite these major differences, the ESI/MS for all three indicate that fragmentation originates from the N-protonated tautomer.

N-Ethyl-2-pyrrolidinone, N,N-dimethylacetamide, and 1-azabicyclo[3.3.1]nonan-2-one do not react with dimethyldioxirane (DMDO) at ca. 20−25 °C. The Kirby lactam (3,5,7-trimethyl-1-azaadamantan-2-one) does react rapidly with dimethyldioxirane. In the presence of a trace of water, there is some hydrolysis of the lactam to its amino acid. The lactam also forms at least two products involving oxidation at the bridgehead nitrogen. On the basis of ^{13}C and ^{1}H NMR as well as ESI/MS, one product is identified as the N-oxide-2,2-diol (16), possibly formed by transient formation of the N-oxide, followed by addition of water to form the gem-diol. This interesting structure is an analogue to the structure of the N-protonated gem-diol of the Kirby lactam that is the exclusive species observed by Kirby in aqueous solution at pH 3.30. Although the N−C2 bond in this molecule is calculated to be quite long (1.58 Å), intramolecular hydrogen bonding and steric buttressing by the methyl substituents should stabilize this structure. Although other oxidation products are clearly

present, they are not separated and it is difficult to assign structures on the basis of limited spectroscopic data.

It is possible that the postulated unstable *N*-oxide of the Kirby lactam was observed by NMR at −50 °C, and this would be consistent with initial formation of **8**, followed by addition of water to form **16**. However, it is clear that, even in this most favored case (i.e., **8**), amide *N*-oxides are exceedingly unstable and readily hydrate in the presence of a trace of water and may also rapidly lose CO. While, constitutionally speaking, the *N*-oxide of the Kirby lactam (**8**) is formally an "amide *N*-oxide", it is, in reality, a tertiary *alpha*-ketoamine oxide. Future studies will include more strictly anhydrous conditions and the use of the more reactive methyltrifluoromethyldioxirane in place of DMDO in order to probe the potential reactivity of the 1-azabicyclo[3.3.1]nonan-2-one, calculated to have half the stabilization energy of an unstrained amide or lactam.

■ EXPERIMENTAL SECTION

N-Ethyl-2-pyrrolidone and *N,N*-dimethylacetamide were used as supplied. 1-Azabicyclo[3.3.1]nonan-2-one[43−47] was synthesized according to a published procedure,[43] and the spectroscopic properties of the neutral and protonated compounds matched those reported.[32] 3,5,7-Trimethyl-1-azaadamantan-2-one was synthesized according to a published procedure,[23−25] and its ^{1}H and ^{13}C NMR as well as its IR spectra were identical to those of the published compound. Dimethyldioxirane (DMDO) was prepared using the method of Murray and Singh[48] and was extracted into CDCl$_3$ using a published procedure.[49] Addition of DMDO in CDCl$_3$ to lactam in CDCl$_3$ was performed at ambient temperatures (20−25 °C). Prior to exposure to DMDO, the Kirby lactam/CDCl$_3$ solution was dried using anhydrous sodium sulfate. The studies were performed using a 0.5 molar ratio of the lactam to DMDO (regardless of solvent) and yielded a mixture. ^{1}H NMR (400 MHz, CDCl$_3$; see Figure 4; assignments are tentative) − δ: 3.69−3.63 (dm, 1H, *J* = 12.5 Hz, unassigned), 3.27−3.20 (m, 2H, **16**), 3.03−2.99 (dm, 1H, *J* = 9.2 Hz, unassigned), 2.94, 2.98 (AB(ABXY), 4H, *J*$_{AB}$ = 13.4 Hz, *J*$_{AY}$ = 2.18 Hz, *J*$_{BX}$ = 4.21 Hz, A does not couple to X and B does not couple to Y, **3**), 2.70−2.59 (m, 3H), 2.55−2.49 (dm, 1.5H, *J* = 13.6 Hz, **16**), 2.28−2.24 (dm, 1H, *J* = 8.63 Hz, **16**), 2.0−1.93 (dm, 1.5H, *J* = 13.0 Hz, unassigned), 1.77−1.72 (dm (X), *J* = 12.5 Hz, 2H, **3**), 1.62 (dt (Y), *J* = 12.5, 2.21 Hz, 1H, **3**), 1.51−1.57 (dm, *J* = 12.85 Hz, 3H, **3**), 1.34−1.10 (m, 5H, unassigned), 1.06−0.91 [m including: 1.03 (s, 3H, **3**), 0.97 (s, 3H, **16**)], 0.89−0.73 [m, including: 0.86 (s), 0.84 (s, 6H, **3**), 0.83 (s), 0.81 (s), 0.77 (s, 5H, **16**)]. ^{13}C NMR (101 MHz, CDCl$_3$) δ 207.26, 200.35, 187.88, 109.03, 98.39, 67.60, 66.57, 66.20, 57.73, 57.36, 52.43, 48.84, 48.56, 46.97, 46.86, 46.44, 45.75, 44.64, 44.32, 43.76, 37.42, 35.16, 34.88, 31.38, 31.17, 30.72, 29.96, 29.88, 29.10, 28.87, 26.18, 25.77, 25.47, 23.45, 22.12. Product after column performed: ^{13}C NMR (101 MHz, CDCl$_3$) δ 187.68, 108.81, 67.39, 66.36, 57.51, 57.14, 52.22, 48.62, 48.34, 48.02, 46.75, 46.63, 45.81, 45.53, 44.43, 44.11, 37.20, 34.95, 34.66, 31.15, 29.74, 29.66, 28.88, 28.65, 25.96, 25.56, 25.25, 21.90.

A low-temperature reaction was performed by adding a DMDO/CDCl$_3$ solution, stored overnight at −20 °C, and cooled in a dry ice/acetone bath just prior to use, to a precooled (dry ice/acetone) solution of the Kirby lactam in CDCl$_3$ in an NMR tube. The solution was immediately mixed and inserted into the NMR probe and precooled to −50 °C. ^{13}C NMR (126 MHz, CDCl$_3$): δ 181.41, 176.01, 106.89, 94.73, 87.41, 67.05, 66.31, 64.98, 64.52, 64.23, 59.75, 58.51, 56.32, 53.74, 52.19, 47.86, 47.42, 45.63, 45.24, 45.13, 44.99, 44.83, 43.22, 43.18, 42.71, 42.64, 37.88, 35.52, 34.72, 34.26, 33.53, 33.51, 32.95, 32.52, 31.97, 31.40, 31.38, 30.87, 30.49, 30.11, 29.80, 29.43, 28.66, 28.54, 28.32, 27.93, 27.87, 25.91, 22.96, 22.81, 18.36, 15.37, 14.38, 14.23.

Electrospray ionization mass spectrometry experiments (ESI-MS) were performed on a ThermoFisher (San Jose, CA) LTQ mass spectrometer equipped with a TriVersa Nanomate (Advion, Ithaca, NY) nanoelectrospray source. For electrospray ionization mass spectrometry experiments, samples were dissolved in ethanol/

isopropanol for direct infusion. All interrogated ions were proton adducts [M + H]$^+$. For all direct infusion experiments, the signal was averaged over multiple scans to achieve suitable spectrum quality. In general, spray voltages on the Nanomate were typically set to 1.4−1.8 kV with nitrogen gas pressure set to 0.3−0.4 psi; this was generally sufficient to generate a spray current between 10 and 200 nA. For the LTQ, the capillary temperature was set to 180 °C. Capillary voltage and tube lens voltage were set to 49 and 125 V, respectively, and were tuned to maximize intensity of the precursor ion while minimizing in-source fragmentation. For fragmentation experiments, activation Q was set to 0.250 and activation time was 30 ms, which are default values. Normalized collision energy was set to 35%. Isolation widths were typically set to 2 *m/z* to capture complete precursor isotopic envelopes.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Select NMR, IR, and MS spectra, images of McLafferty rearrangement calculated transition states, and Cartesian coordinates/calculated energies for all ground-state and transition-state molecules are located in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
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