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The mechanism of the reaction between an aziridine and carbon dioxide with no added catalyst

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Abstract

The mechanism of the reaction at room temperature between an unactivated 2-alkyl aziridine and carbon dioxide to generate the corresponding oxazolidinone in glass has been studied. Theoretical calculations suggest that this reaction should not proceed at room temperature in the absence of a catalyst. In cases where a reaction was observed, kinetic studies show that the reaction displays a zero-order dependence with respect to aziridine, indicating that free aziridine is not involved in the rate-determining step. An ammonium salt generated *in situ* acts as a catalyst. The amount of this catalyst is diminutive, which prevented spectroscopic identification, and it is not readily removed from the starting material using chromatography.

KEYWORDS

aziridine, calculations, carbon dioxide, catalysis, kinetics

1 | INTRODUCTION

According to recent reviews, in comparison to activated aziridines, few papers have been published on the chemistry of readily available unactivated *N*-alkyl aziridines.[1] One reaction of an *N*-alkyl aziridine is the insertion of carbon dioxide into a C–N bond to generate an oxazolidinone, which is an important class of compounds used as chiral auxiliaries, as metal ligands, and as pharmaceuticals (specifically as antibiotics).[2–4] Although carbon dioxide is abundant, renewable, nonflammable, and inexpensive, due to its stability,[5,6] using this resource as a synthetic feedstock typically requires difficult to synthesize catalysts, high pressures (typically over 100 atm), and/or high temperatures (typically over 100°C).[7–10] In addition, most of these reactions only work with mono-aryl substituted aziridines, such as **4**, and fail with alkyl-substituted compounds, such as **1**.

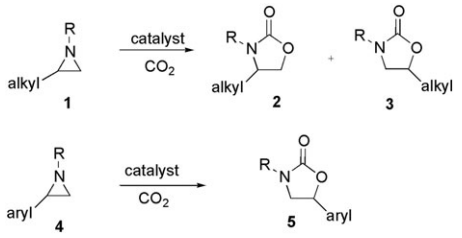
For the past several years, we have been investigating the reactions shown in Scheme 1 in which both alkyl- and aryl-substituted unactivated aziridines (**1** and **4**) are converted to the corresponding oxazolidinones at low pressure and temperature using a salt, such as LiI or NH_4I, as a catalyst in THF.[11–14]

When a control experiment using no catalyst in THF was allowed to go for an extended period (12 vs 4 h or less when a salt is used) at room temperature, the reaction of compound **1** (Scheme 1, R = $PhCH_2$ and alkyl = CH_3) with CO_2 (3 atm) gave oxazolidinones **2** + **3**, albeit in very low yield. Because the aziridine is an oil and CO_2 is a gas, the reaction was attempted with no solvent. When aziridine **1** was stirred, with no catalyst or solvent, under a CO_2 pressure of 3 atm for 12 hours, the yield of oxazolidinones **2** + **3** increased to 37% from the 7% in THF. Increasing the applied pressure of CO_2 to 4 atm did not have a significant impact on the observed yield, giving products **2** + **3** in approximately 40%. Under all conditions, compound **2** is the major isomer, typically being formed with a product ratio of about 13:1. At approximately the same time, it was reported in the literature that *N*-alkyl-2-aryl aziridines (**4**) will generate the corresponding oxazolidinone (**5**) with no catalyst at high temperature and pressure.[15] These results led to an effort to discover the mechanism of the conversion of an aziridine with CO_2 into an oxazolidinone using no catalyst.

2 | RESULTS AND DISCUSSION

2.1 | Possible mechanisms

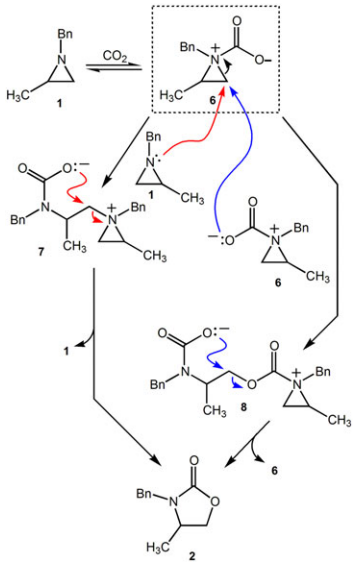
On the basis of literature precedent, we initially proposed two possible mechanisms for these transformations, both



SCHEME 1 Conversion of an unactivated aziridine to an oxazolidinone

involving an initial nucleophilic capture of CO_2 by the aziridine lone pair, giving acyl-intermediate **6**. The proposed mechanisms then differ because of a different nucleophile used for subsequent steps. One mechanism involves a variation of the mechanism proposed for the high-temperature–no-catalyst reaction,[15] in which a second acyl-aziridine **6** adds via nucleophilic attack of the carboxylate group (blue arrows). The other is a variation of the mechanism proposed in a recent study using an amino acid as the catalyst for the aziridine to oxazolidinone conversion,[10] in which addition of a second aziridine **1** occurs via the nitrogen lone pair (red arrows). These proposed mechanisms are shown in Scheme 2 for prototypical compound **1**.

We did not consider the unimolecular reaction mechanism in which the carboxylate in compound **6** attacks the 3-position to give compound **2** directly. For any unimolecular cyclization to occur, the orbitals of the nucleophile and of the electrophile must properly align. The molecular requirements for this type of alignment are illustrated by Baldwin's Rules for ring closure.[16,17] This reaction would be classified as 5-endo-tet, which is disfavored because of lack of proper orbital overlap.



SCHEME 2 Initially proposed mechanism for the conversion of **1** to **2**

2.2 | Attempted trapping of intermediates

The trapping of any reaction intermediate by a dipolarophile was next attempted. When dimethyl acetylenedicarboxylate (DMAD) was added to the reaction mixture, no intermediate was trapped. Instead, a dark intractable material was generated. This same material formed either when subjecting the reaction to carbon dioxide or not. None of the oxazolidinone was observed. Adding THF to dilute the solution and cooling the reaction under ice did not help avoid the formation of the intractable material. Another dipolarophile, ethyl cyanoformate, was tested, and it also did not react with any intermediate. The reaction proceeded as if no trapping reagent was added.

To determine if the reaction between **1** and CO_2 proceeds by a polar mechanism or by a radical mechanism, one equivalent of the radical trap 1,4-cyclohexadiene was added to aziridine **1**. The reaction gave the exact same mixture of **2** + **3.** Next 4 equivalents of 1,4-cyclohexadiene were added to the reaction of **1** and CO_2. Over 30% of aziridine **1** was converted to oxazolidiones **2** + **3** after 2 days. Thus, it is not likely the reaction of **1** and CO_2 follows a radical mechanism.

2.3 | Computational study

The lack of trapping could result from the absence of intermediates, ie, a concerted reaction, or intermediates with very short lifetimes. Computational quantum chemistry was used to assess the feasibility of these scenarios. Geometry optimizations and frequency calculations were performed at the B3LYP/6-31 + G(d,p) level of theory[18–22] using the Gaussian09 software suite.[23] Intrinsic reaction coordinate calculations were used to confirm the connectivity of transition state structures and minima on the potential energy surface.[24–27] Preliminary calculations performed in the gas phase are described below. 1,2-Dimethylaziridine was used for simplicity.

Without the benefit of polar solvent molecules, adduct **6** could not be located. Instead, a complex between **1** and CO_2 was found (Figure 1). This complex can rearrange through a concerted (2 + 2) cycloaddition for which the two bond-forming events occur very asynchronously. The free energy barrier for this process is predicted to be quite large, approximately 50 kcal/mol, suggesting that it will not occur in nonpolar environments. This reaction also has some characteristics of a pseudopericyclic reaction,[28,29] ie, the sigma bond and the orthogonal N lone pair are both involved. A stepwise mechanism in which a second molecule of aziridine attacks in the same step as CO_2 addition was also examined (**6** + **1** giving **7** in Scheme 2), but this pathway also has a high-predicted free energy barrier, 43 kcal/mol (see Supporting Information for details). In short, our computational results are not consistent with the observed reaction occurring in nonpolar environments. While additional

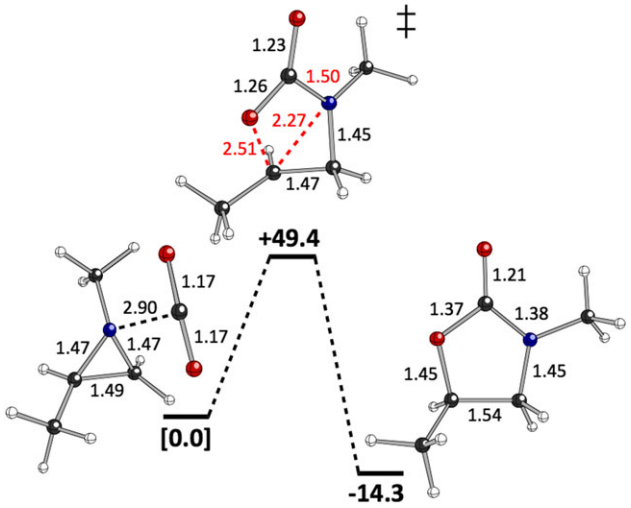


FIGURE 1 Stationary points involved in concerted addition of CO_2 to 1,2-dimethylaziridine. Selected distances are shown in Å, and relative energies are shown in kcal/mol. Note that the free energy barrier in dichlormethane (SMD-B3LYP/6-31 + G(d,p)) is predicted to be 33 kcal/mol

calculations that treat solvent effects can be pursued, our subsequent experiments (*vide infra*) suggest that a simple solvent effect is not responsible for the observed reactivity.

2.4 | Experiments with different solvents

To provide insights into whether or not the reactions involve polar transition state structures, reactivity in different solvents was examined. When aziridine **1** was subjected to 4 atm CO_2 at room temperature for 24 hours in different solvents, the results shown in Table 1 were obtained. The trend of the yield is consistent with the polarity/dielectric consstant of the solvents.[30] These results suggest that the reaction does indeed involve a rate-determining transition state structure that is more polar than the reactants.

2.5 | Kinetic study

To determine if the reaction follows the proposed stepwise mechanism, a determination of the rate law of the reaction with respect to aziridine concentration was attempted. All reactions were run in a thick-walled glass bottle and held at 4 atm pressure through a connection to a CO_2 tank. While we anticipate that the mechanism does display an intrinsic dependence on the partial pressure of CO_2, by holding the pressure, and thus, the concentration of CO_2 constant, any driving force due to CO_2 will be incorporated into the rate constant *k*. Therefore, we will be measuring the intrinsic driving force of the aziridine.[31,32]

The concentration of aziridine **1** and products **2 + 3** were monitored by GC-MS with hexamethylbenzene used as an internal standard (the concentration data are shown in the Tables S1-S3). Interestingly, the reaction profile shows that the rate of product formation and the rate of aziridine consumption are constant for the entire process. Thus, the reaction displays no sensitivity to the concentration of compound **1** (see Figures S3-S14).

Running the experiment in triplicate illustrated that the rate of conversion to the oxazolidinone is very reproducible for this particular batch of aziridine (Figures 2 and 3). In addition, the concentration of product matched the quantity expected by the measured quantity of aziridine **1** consumed. This confirms that the reactions display excellent mass balance with nearly all consumed aziridine being transformed to product (Figure 4).

TABLE 1 The effect of solvent polarity on the yield of the reaction of **1** and carbon dioxide (4 atm)

	Pentane	Toluene	Ether	THF	CH_2Cl_2
Dielectric constant	1.84	2.38	4.27	7.52	9.08
Oxazolidinones yield, %	Trace	6	7	18	32

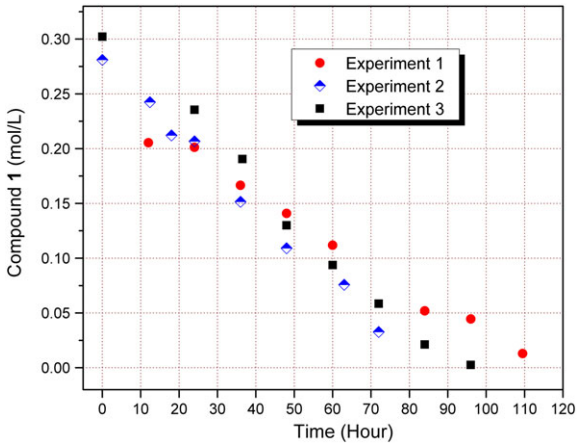


FIGURE 2 Overlaid plot of aziridine **1** concentrations vs time from experiments 1-3

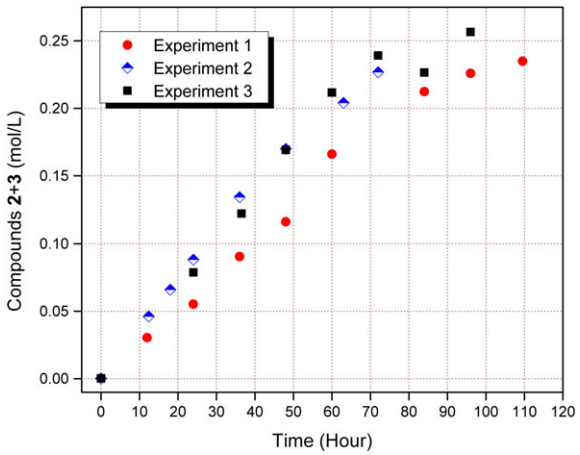


FIGURE 3 Overlaid plot of products **2 + 3** concentrations vs time from experiments 1-3

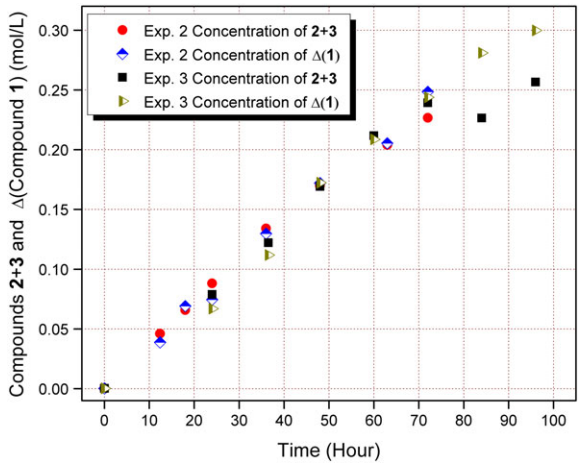


FIGURE 4 Overlaid plot of concentrations of products **2** + **3** from direct measurement and concentration of products **2** + **3** calculated from the fractional concentration of **1** from experiments 2 and 3 (from the data in Tables S2 and S3)

2.6 | Batches of aziridine 1 that did not react

1-Benzyl-2-methyl aziridine **1** is readily synthesized from 2-methylaziridine (90% pure) and butyllithium (1.6M in hexanes) to generate the aziridine anion followed by an S_N2 reaction with benzyl bromide (98% pure). For the work-up, the reaction mixture was washed several times with aqueous NH_4Cl and then dried with anhydrous K_2CO_3. It was discovered while performing the kinetic studies that some batches of newly synthesized aziridine **1** did not give any oxazolidinone product while others worked perfectly. For all the kinetics studies in the previous section, several reactive batches of aziridine **1** were combined to make a large reactive batch.

To determine if the purification somehow destroyed the reactive aziridine, one batch of **1** was synthesized and purified by silica gel chromatography using a 7:3 ratio of hexane : EtOAc as eluents. The purified aziridine **1** did not react with carbon dioxide even after 40 hours. A possibility is that the column chromatography may have done something to the aziridine and transformed it into an "unreactive aziridine." An NH_4I catalyst[13] was then added to this reaction of aziridine **1** and CO_2, and an almost quantitative yield of a mixture of oxazolidinones **2** + **3** was obtained. Therefore, this aziridine is not "spoiled" by the column.

Another possibility is an impurity in the starting material catalyzes the CO_2 insertion reaction. It is possible that when a sample of aziridine **1** is purified this catalyst is eliminated and the reaction does not work anymore. Another batch of aziridine was synthesized, purified, and subjected to reaction with carbon dioxide. However, in contrast to the previous case, this time the clean aziridine was still reactive with carbon dioxide. The NMR spectra of both purified aziridines were compared, and there are no differences (Figures S15 and S16). In addition, GC-MS and HPLC showed in both cases any trace impurity accounts for much less than 1 % of the starting material (Figure S17).

Additional batches of aziridine **1** were synthesized to determine, if in any of them, the amount of impurities was large enough to be observed spectroscopically. However, no impurity could be observed. All of these batches reacted with CO_2 in the presence of a salt catalyst, but in the absence of an added salt, many of these batches, even before purification, did not react with CO_2. The addition of 0.1 mL of water did not affect the reactivity, ie, those batches that reacted still reacted and those batches that did not react still did not react in the absence of an added salt catalyst.

It was suspected that the NH_4Cl used in the work-up step may catalyze the reaction. Reactive aziridine **1** was therefore washed with a large amount of water (3 × 25 mL water to wash 25-mL ether) to eliminate the salt. However, reactive **1** still gave nearly quantitative conversion after reacting with CO_2 for 24 hours.

To determine if the pH caused an unreactive aziridine to react and because NaOH is a stabilizer in the n-BuLi, to a reaction of **1** and CO_2 was added a 0.1 mL of NaOH solution or 0.1 mL of H_2SO_4 solution. Changing the pH also did not promote the reaction. (This result is consistent with our previous study,[13] in which adding trifluoroacetic acid had no effect on the rate of the reaction.)

The byproduct of the S_N2 reaction in the synthesis of aziridine **1** is LiBr. It is known that alkali halide salts catalyze the reaction of an aziridine and carbon dioxide,[12,13] and so it could be the amount of any residual LiBr that has caused the reaction of **1** and CO_2 to be inconsistent. To determine the amount of LiBr as an impurity in "reactive" and in "unreactive" aziridine **1**, as shown in Table 2, ICP-MS was used to measure the concentration of lithium and bromide ions.

There is no correlation between the concentration of lithium and the reactivity of aziridine **1**. Sample 2 has less Li^+ than sample 3, but sample 2 is "reactive" whereas sample 3 is "unreactive." Therefore, Li^+ is not a catalyst for the reaction. In contrast, there is a trend in the amount of bromide and the reactivity of aziridine **1**. In addition, note that the amount of bromide is much larger than the amount of lithium, so there is another source of Br^- in addition to LiBr.

To further investigate the reaction, a 50/50 mixture of a reactive batch of **1** and an unreactive batch of **1** was made.

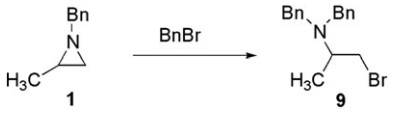
TABLE 2 Lithium and bromide concentrations in different samples of aziridine **1**

	Aziridine 1 + CO_2 Reaction	Concentration of Li^+, mmoles/L	Concentration of Br^-, mmoles/L
Sample 1	Active	12.5	413
Sample 2	Active	0.40	138
Sample 3	Inactive	0.69	44
Sample 4	Inactive	0.49	82

There are 3 possible outcomes from the reaction of this mixture with CO_2. If the product mixture consists of 50% oxazolinone and 50% aziridine, then there is something wrong with one batch of **1** and it does not show up spectroscopically. If the product mixture is 100% aziridine **1**, then there is something that inhibits the reaction. If the product mixture is 100% oxazolidinones **2 + 3**, then it supports the idea that there is a catalyst in some batches of aziridine that makes them reactive. When this catalyst is absent, the reaction does not work. The experimental result is that 100% of aziridine **1** converts to the oxazolidinones; however, the reaction took about twice as longer time to go to completion in comparison to the original reactive aziridine **1**.

To determine if the catalyst is stable after the reaction, the oxazolidinone product was mixed with "unreactive" aziridine **1**, and then subjected to CO_2. All of the aziridine converted to oxazolidinones, and thus, the catalyst persists after the reaction and stays reactive.

Until now, benzyl bromide (BnBr) was not considered as a catalyst or catalyst precursor because it has never been suggested in the literature that an alkyl halide can act as the catalyst or the precursor to the catalyst for the reaction of an aziridine with CO_2. In addition, NMR spectroscopy, HPLC, and GC-MS show that our starting aziridine is clean and contains no benzyl bromide. However, the possibility that BnBr reacts with aziridine **1** to give ring-opened amine **9** has not been ruled out (Scheme 3). An ammonium salt has been shown to be a good catalyst for the reaction of aziridine **1** with CO_2. If compound **9** picks up a proton either in the work-up or by deprotonating another molecule of **9** in an E2 reaction, then an ammonium salt can be generated.



SCHEME 3 Reaction of **1** with benzyl bromide

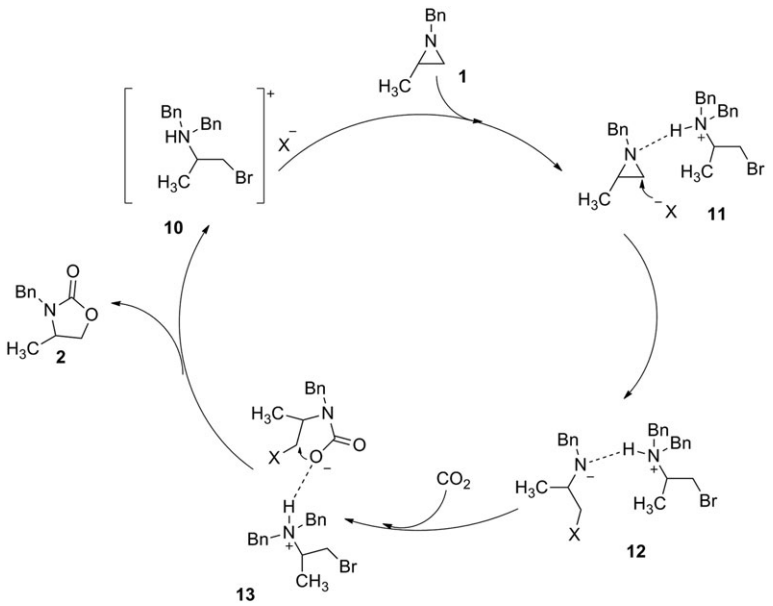
To obtain proof for this hypothetical catalyst, a synthesis of aziridine **1** using two equivalents of BnBr was set up. Then, this newly synthesized aziridine **1** was mixed with "unreactive" aziridine **1** and subjected to CO_2. All the starting material converted to products **2 + 3** after 12 hours. (Twelve hours is the time that the reaction of aziridine **1** with CO_2 and less than 1% of an ammonium salt is known to take.[13])

In an even more conclusive experiment, a catalytic amount of BnBr was added to "unreactive" aziridine **1** and then subjected to CO_2. After 12 hours, all of the starting material converted to oxazolidinones **2 + 3**. The BnBr was not observed in the NMR spectrum of the product (see Figures S18 and S19).

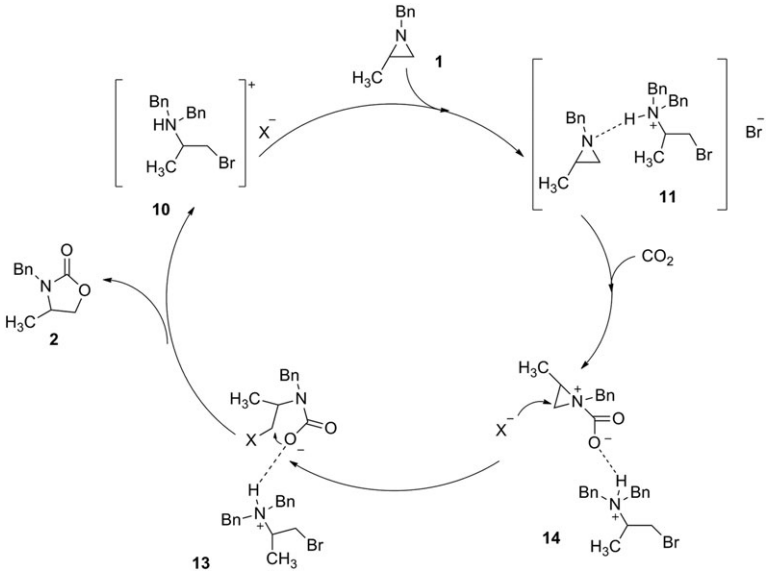
This reaction mixture was then injected into a high-resolution FT-mass spectrometer with electrospray ionization. As can be seen in Figure S20, peaks with a molecular formula consistent with compound **9** and consistent with the alkene from the E2 reaction discussed above were observed. Therefore, we believe that compound **9** and/or corresponding alkene catalyzes the conversion of aziridine **1** to oxazolidinones **2 + 3**.

On the basis of the proposed catalyst, the mechanism for the reaction using ammonium halide salts as the catalyst, and the fact that an amine is about 20 times more basic than an aziridine,[13] two possible mechanisms for oxazolidinone formation are proposed (Schemes 4 and 5).

In the first step in Scheme 4, aziridine **1** forms a hydrogen bonding with the catalyst to give complex **11**. A nucleophilic halide opens the aziridine ring to give intermediate **12.** A carbon dioxide adds to give intermediate **13.** Finally, product **2** is formed by ring closure**.** Alternatively, as shown in



SCHEME 4 Possible mechanism for the conversion of **1** to **2**



SCHEME 5 Second possible mechanism for the conversion of **1** to **2**

Scheme 5, complex **11** could add carbon dioxide first to give intermediate **14**. The halide then opens the ring to give intermediate **13**, and the cycle continues as in Scheme 4.

Both of the proposed mechanisms fit the observation that the reaction proceeds faster in the more polar solvents because all of the intermediates are charged species. The observed zero order with respect to aziridine **1** suggests that the rate controlling step does not involve the isolated aziridine. Instead, it is likely that we are observing saturation kinetics with the addition of CO_2 being the rate limiting step. In either possible mechanism, the large excess of carbon dioxide, held at constant pressure, masks any driving force that it may exert. This result does not allow us to distinguish between the two possible pathways involving either initial capture of CO_2 or ring opening by X^- from the catalyst (Schemes 4 or 5).

3 | CONCLUSION

The source of the erratic behavior in the reaction of a 2-alkyl azirdine and carbon dioxide has been explained by the *in situ* formation of an ammonium salt catalyst.[33] This catalyst is generated by the reaction of an aziridine and benzyl bromide in an S_N2 reaction. The catalyst allows the reaction to proceed in high yield with excellent regioselectivity.

Most importantly, our results suggest that precautions must be taken in investigating the reaction between an aziridine and carbon dioxide in the absence of an added catalyst to insure that there really is no catalyst present.

3.1 | Experimental procedures

These may be found in the Supporting Information.

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[33] The reviewers asked the question about whether our findings also apply to 2-aryl aziridines in addition to 2-alkyl aziridines. From our experience, 2-aryl aziridines react much more rapidly than 2-alkyl aziridines. In fact, there are a number of papers in the literature in which only 2-aryl react and 2-alkyl aziridines are stable. Thus, an even smaller amount of any catalyst would probably be needed for a 2-aryl aziridine reaction.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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