Lewis Acid Activation and Catalysis of Dialkylaminyl Radical Reactions

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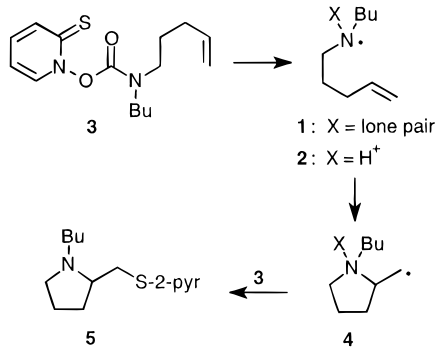
Lewis acid activation and catalysis of dialkylaminyl radical reactions is demonstrated both qualitatively and quantitatively. Cyclization of the *N*-butyl-4-pentenaminyl radical (**1**) in the presence of a wide range of Lewis acids was shown to be efficient with good to excellent yields of cyclic products obtained in reactions conducted even at −78 °C. Rate constants for fragmentation of the *N*-ethyl-2,2-diphenylethylaminyl radical (**6**), 6-*exo* cyclization of the *N*-methyl-6,6-diphenyl-5-hexenaminyl radical (**7**), and 5-*exo* cyclization of the *N*-methyl-5,5-diphenyl-4-pentenaminyl radical (**8**) in the presence of the Lewis acids $LiBF_4$, $MgBr_2$, and BF_3 were measured by laser flash photolysis (LFP) methods. The LFP studies demonstrated saturation kinetic behavior with respect to the Lewis acids. Equilibrium binding constants for the Lewis acids with the dialkylaminyl radicals and rate constants for reactions of the Lewis acid complexed dialkylaminyl radicals were obtained from nonlinear regression analysis of the observed rate constants.

Cyclizations of carbon-centered radicals have become one of the more important synthetic entries to five-membered carbocycles. Although related cyclizations of heteroatom-centered radicals to produce heterocycles are less well developed, nitrogen-centered radicals are now available from a variety of precursors, and pyrrolidine formations via nitrogen radical cyclizations are well documented.[1,2] Neutral aminyl radicals, the first formed species from most nitrogen radical precursors, are relatively unreactive, but it has long been known that protonation of aminyl radicals gives aminium cation radicals that are much more reactive. Recent direct kinetic studies of analogous dialkylaminyl radicals and dialkylaminium cation radicals show that intramolecular reactions of the protonated species are several orders of magnitude faster than those of the neutral counterparts.[3,4]

Aminyl radicals are also activated by complexation with Lewis acids[2,5] including such mild agents as $MgBr_2$[6] and $LiBF_4$,[5] and the use of Lewis acids as activating agents or catalysts instead of protic acids could offer considerable advantages in synthetic applications. In this work, we report evaluations of Lewis acid activation of a simple 5-*exo* aminyl radical cyclization and laser flash photolysis (LFP) kinetic studies of reactions of three dialkylaminyl radicals in the presence of Lewis acids. The qualitative studies show that a wide range of Lewis acids activate the aminyl radical, and the LFP results provide equilibrium binding constants and rate constants for reactions of the Lewis acid complexed aminyl radicals which can serve as basis reactions for kinetic scales of these species. Direct comparisons of the kinetics of the Lewis acid-complexed dialkylaminyl radical reactions with those of uncomplexed dialkylaminyl radicals and protonated dialkylaminium cation radicals are available from the results of this work and previous reports.

Scheme 1



Results

Product Studies. The 5-*exo* cyclization of the *N*-butyl-4-pentenaminyl radical (**1**) was studied under a variety of conditions. Radical **1** was produced in chain reactions of the PTOC[7] carbamate precursor **3**. Both **1** and its protonated counterpart, dialkylaminium cation radical **2**, can cyclize in a 5-*exo* manner to give pyrrolidinylmethyl radicals **4**. In the absence of other radicophiles, intermediates **4** react in a chain propagation step with **3** to give, ultimately, *N*-butyl-2-[(2-pyridylthio)-methyl]pyrrolidine (**5**) (Scheme 1).[8] Because the cyclization of neutral radical **1** is relatively slow, the yields of cyclic products often are low in the absence of an acid. The neutral acyclic radical **1** apparently does not react with the PTOC carbamate precursor, but low yields can result from radical−radical reactions (couplings and disproportionations), and the relative amounts of cyclization and radical−radical derived products will be a function of the rate of radical formation.

Precursor **3** was allowed to react in the presence of several Lewis acids at various temperatures. Reactions

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1997.

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(4) Musa, O. M.; Horner, J. H.; Shahin, H.; Newcomb, M. *J. Am. Chem. Soc.* **1996**, *118*, 3862−3868.
(5) Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493−6496.
(6) Dickinson, J. M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1990**, 434−436.
(7) The acronym PTOC derives from pyridine-2-thioneoxycarbonyl. PTOC carbamates as actually anhydrides of the thiohydroxamic acid and a carbamic acid.
(8) Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 3163−3165.

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Table 1. Yields of Product 5 from Reactions of 3 in the Presence of BF_3OEt_2

solvent	temp (°C)	[BF_3]	% yield
THF	−78	0	<4
		0.05	74
		0.10	98
		0.15	59
	−42	0.05	85
		0.10	80
		0.15	82
	0	0.012	22
		0.025	65
		0.05	81
		0.075	32
	25	0.01	14
		0.02	39
		0.03	46
		0.04	68
		0.05	98
CH_2Cl_2	−78	0.012	44
		0.025	69
		0.038	82
		0.05	97

Table 2. Yields of Product 5 from Reactions of 3 in the Presence of Titanium salts in CH_2Cl_2 at −78 °C

Lewis acid	concn (M)	% yield
Ti(O-*i*Pr)$_4$	0.025	>10
Ti(O-*i*Pr)$_3$Cl	0.012	34
	0.025	31
	0.038	28
	0.050	18
Ti(O-*i*Pr)$_2$Cl$_2$	0.012	60
	0.025	75
	0.038	10
	0.050	11
Ti(O-*i*Pr)Cl$_3$	0.012	30
	0.025	99
	0.05	81
$TiCl_4$	0.025	50

Table 3. Yields of Product 5 from Reactions of 3 in the Presence of Lewis Acids

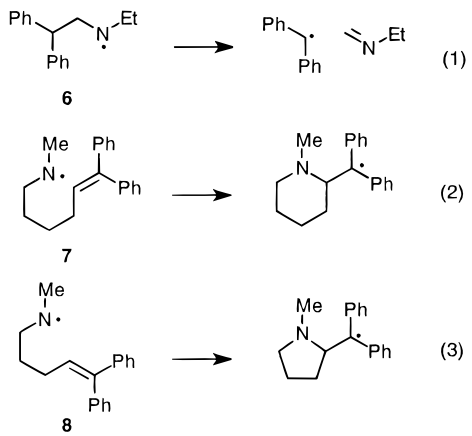
Lewis Acid	solvent	temp (°C)	concn (M)	% yield
none	THF	−78		<4
$MgBr_2$	THF	−78	0.012	69
			0.025	57
			0.050	38
$LiBF_4$	THF	22	0.075	57
	CH_3CN	22	0.050	18
	CH_2Cl_2	22	0.075	35
$AgBF_4$	THF	22	0.012	12
Et_2AlCl	THF	−78	0.03	20
	benzene	5	0.04	39
9-BBN-Br[a]	CH_2Cl_2	−78	0.025	27
			0.050	30
			0.10	41

[a] 9-Bromo-9-borabicyclo[3.3.1]nonane.

were initiated by irradiation with a 150 W tungsten filament bulb, and the reaction progress was monitored by TLC. After precursor **3** was depleted, the yields of product **5** were determined by GC. Tables 1−3 contain the results, some of which were previously communicated.[5]

Essentially all of the Lewis acids tested appeared to activate aminyl radical **1** toward cyclization, and catalytic behavior was apparent in several cases. Because the precursor, intermediate radicals, and products (and the solvent THF, when used) can complex with the Lewis acids, these results should be viewed qualitatively, but some general conclusions are possible. The most efficacious Lewis acids were BF_3 and titanium species of intermediate Lewis acidity. The activating effects of the

Scheme 2



salts $MgBr_2$ and $LiBF_4$ are noteworthy in that they represent quite mild conditions. In general, the yields of cyclic product **5** increased as the concentration of Lewis acid was increased, but high concentrations of Lewis acid were shown to reduce the yields of **5** in several cases. It is possible that the Lewis acids can interfere with the radical chain propagation step involving attack of intermediate cyclic radical **4** on the PTOC precursor by complexing with **3**. Alternatively, Lewis acid complexation by precursor **3** might further activate the already reactive acyl derivative toward nucleophilic attack that destroys **3**.

Kinetic Studies. In order to evaluate the Lewis acid activation in a quantitative sense, three dialkylaminyl radical reactions were studied by LFP. Radicals **6**−**8** were produced by photolysis of the corresponding PTOC carbamate precursors with 355 nm light from a Nd-YAG laser. Each of the radicals reacts to give a diphenylalkyl radical (Scheme 2) that is readily monitored by UV spectroscopy. The kinetics of reactions were followed by the same method as that previously used in kinetic studies of the neutral radicals[4] and their protonated counterparts.[3] The kinetics of the reactions of the neutral dialkylaminyl radicals at 20 °C are as follows: radical **6** fragments too slowly for accurate kinetic measurements ($k < 5 \times 10^3$ s^{-1}), radical **7** cyclizes with a rate constant of ca. 7×10^3 s^{-1}, and radical **8** cyclizes with a rate constant of 3.2×10^5 s^{-1}.[4]

Reactions of radicals **6**−**8** were studied in the presence of the Lewis acids BF_3, $LiBF_4$, and $MgBr_2$ in THF at 20 °C, and the cyclization of radical **8** in the presence of BF_3 was also studied at 4 °C. Accelerations of the fragmentation of **6** and cyclizations of **7** and **8** were obvious. The reactions demonstrated saturation kinetics expected for a rapid prior equilibrium between the uncomplexed dialkylaminyl radical and the Lewis acid followed by rate-limiting reaction of the Lewis acid complexed aminyl radical. Figures 1−3 show the results for fragmentation of radical **6** and cyclizations of radicals **7** and **8** at 20 °C.

For formation of a dialkylaminyl radical−Lewis acid complex (eq 4), the equilibrium constant for complex formation, K_C, is given in eq 5. The observed rate constant for formation of the diphenylalkyl radical product is given in eq 6 where k_x and F_x are, respectively, the rate constants for reaction and the mole fractions of the neutral aminyl radical (N) and the Lewis acid complex (C). Even at low concentrations of Lewis acids, the reactions occur essentially only from the complexed species, and the approximation in eq 7 applies. Substitution for F_C in eq 7 gives eq 8 where k_C is the rate constant

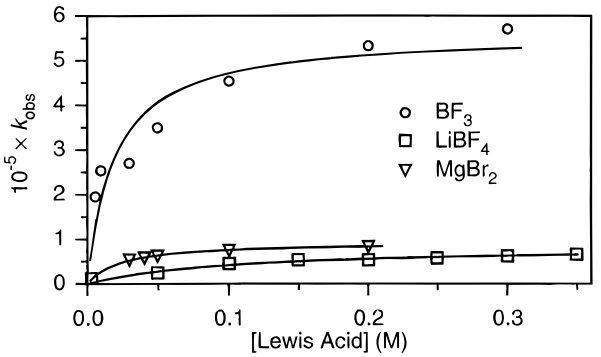


Figure 1. Observed rate constants for fragmentation of radical **6** in THF at 20 °C in the presence of Lewis acids. The symbols are the experimental rate constants, and the lines are the best fits from nonlinear regression analyses according to eq 8. For $LiBF_4$, the actual concentrations are twice the values listed on the axis.

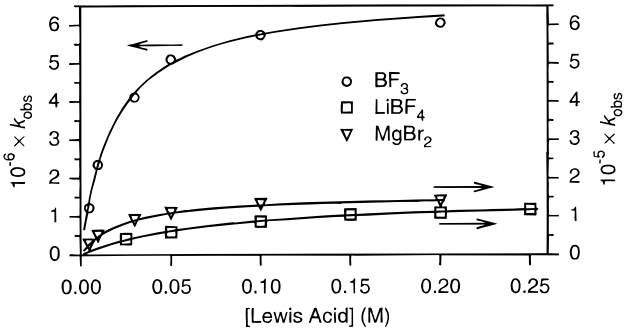


Figure 2. Observed rate constants for cyclization of radical **7** in THF at 20 °C in the presence of Lewis acids. See caption for Figure 1.

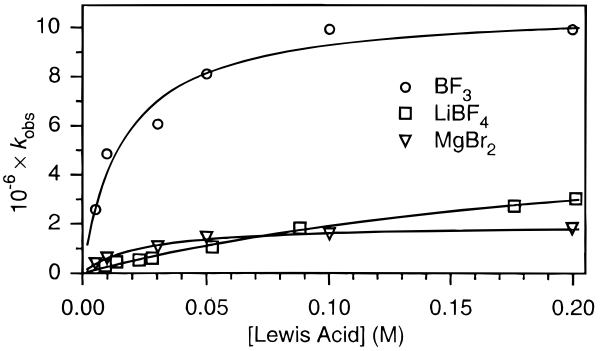


Figure 3. Observed rate constants for cyclization of radical **8** in THF at 20 °C in the presence of Lewis acids. The symbols are experimental rate constants, and the lines are fits from eq 8.

for reaction of the dialkylaminyl radical−Lewis acid complex and K_C is the equilibrium constant for complexation.

$$R_2N^{\bullet} + LA \rightleftarrows (R_2N^{\bullet}{-}LA) \quad (4)$$

$$K_C = [R_2N^{\bullet}{-}LA]/([R_2N^{\bullet}][LA]) \quad (5)$$

$$k_{obs} = k_N F_N + k_C F_C \quad (6)$$

$$k_{obs} = k_C F_C \quad (7)$$

$$k_{obs} = k_C K_C[LA]/(1 + K_C[LA]) \quad (8)$$

In the LFP experiments, the concentrations of the PTOC carbamate precursors were small ($< 3 \times 10^{-5}$ M), and any complexation between the Lewis acid and the precursors or products cannot affect the total amount of Lewis acid available. The rate constants for reaction of the complexed dialkylaminyl radicals and the equilibrium constants for complexation were solved by nonlinear regression analysis according to eq 8, and the results are given in Table 4. The results of the regression analyses for the reactions of radicals **6**−**8** are shown in Figures 1−3 as solid lines.

LFP kinetic studies also were conducted at varying temperatures with radical **7** and with radical **8** in the presence of BF_3. The observed rate constants are listed in Table 5. Due to the large equilibrium constant for complex formation with BF_3, the populations of complexed aminyl radicals predominated in all cases. For example, the smallest mole-fraction of complexed aminyl radical was in the low temperature studies with radical **8**; using an equilibrium binding constant of 40 M^{-1} and with the BF_3 concentration at 0.1 M, 80% of radical **8** would be in the form of the complex at 4 °C.

Using the weighted average equilibrium constant for BF_3 complexation at 20 °C of 56 M^{-1} (see Discussion) and the experimental equilibrium constant for BF_3 complexation at 4 °C of 40 M^{-1}, we estimated the equilibrium constant for complexation at all temperatures studied and calculated the mole-fraction of complexed species in each case. The experimental values of k_{obs} were then divided by the appropriate mole fraction to give the calculated rate constant for reaction of the complexed species, k_C, at each temperature; these values are also listed in Table 5. From the calculated values of k_C for reactions of the BF_3 complexes of radicals **7** and **8**, one computes the Arrhenius functions for these cyclizations given in eq 9 (for the BF_3 complex of radical **7**) and eq 10 (for the BF_3 complex of radical **8**) where errors are 2σ and R is in kcal/mol. One might note that the Arrhenius functions in eqs 9 and 10 are only slightly different than those one would obtain if the k_{obs} values were used or if the mole-fraction of complexed species was assumed to be constant and in the range of 0.9 at all temperatures.

$$\log (k_C\ \mathrm{s}) = (8.1 \pm 0.3) - (1.7 \pm 0.4)/2.3RT \quad (9)$$

$$\log (k_C\ \mathrm{s}) = (8.7 \pm 0.3) - (2.2 \pm 0.4)/2.3RT \quad (10)$$

As a check on the validity of the data treatment, one can compare the computed rate constants at 20 °C from eqs 9 and 10 with the rate constants determined at this temperature from the complete saturation kinetic study (Table 6 in Discussion). The two pairs of rate constants differ by 6% for radical **7** and 4% for radical **8**.

Discussion

Dialkylaminyl radical **1** provides an excellent test reaction for evaluation of Lewis acid activation. Radical **1** and related *N*-alkyl-4-pentenaminyl radicals have been produced from a variety of sources: thermolysis and photolysis of symmetrical tetrazenes;[9,10] radical chain reactions of *N*-chloroamines,[11] PTOC carbamates[8,12] and

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(10) Newcomb, M.; Burchill, M. T. *J. Am. Chem. Soc.* **1983**, *105*, 7759−7760.

(11) Stein, J.-L.; Stella, L.; Surzur, J.-M. *Tetrahedron Lett.* **1980**, *21*, 287−288 and references therein.

Table 4. Experimental Equilibrium Binding Constants and Rate Constants for Reactions of Dialkylaminyl Radicals in the Presence of Lewis Acids in THF at 20 °C[a]

	6		7		8	
acid	K_C	$10^{-4} \times k_C$	K_C	$10^{-4} \times k_C$	K_C	$10^{-4} \times k_C$
$LiBF_4$	4.9 ± 1.4	8.4 ± 0.8	6.8 ± 0.5	15.2 ± 0.4	4.0 ± 0.5	670 ± 50
$MgBr_2$	43 ± 1	9.3 ± 0.1	44.6 ± 1.5	15.7 ± 0.2	44 ± 2	199 ± 3
BF_3	53 ± 21	56 ± 5	55 ± 5	680 ± 16	61 ± 14	1080 ± 70
BF_3 (4 °C)[b]					40 ± 3.5	980 ± 30

[a] All uncertainties are 1σ. Equilibrium constants (K_C) are in units of M^{-1}, and rate constants (k_C) are in units of s^{-1}. [b] Data obtained at 4 °C.

Table 5. Rate Constants for Cyclizations of Radicals 7 and 8 in THF in the Presence of BF_3

radical	temp (°C)[a]	[BF_3] (M)	$10^{-6} \times k_{obs}$[b]	$10^{-6} \times k_C$[c]
7	0.0	0.2	5.4	6.1
	10.0		5.8	6.4
	20.0		6.0	6.6
	30.0		7.4	8.0
	40.0		8.3	8.9
	50.0		9.0	9.3
8	0.0	0.1	8.4	10.7
	1.5	0.2	8.4	9.5
	1.5	0.3	8.3	9.0
	8.0	0.2	9.2	10.3
	8.0	0.3	9.2	9.9
	10.0	0.1	9.6	11.8
	13.2	0.2	9.9	11.0
	13.2	0.3	9.8	10.5
	20.0	0.1	10.0	11.9
	30.0	0.1	12.3	14.3
	40.0	0.1	13.6	15.5
	50.0	0.1	15.9	17.8

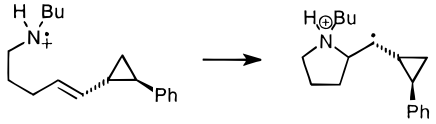
[a] ± 0.2 °C. [b] Observed rate constant in units of s^{-1} for reaction in the presence of BF_3. [c] Calculated rate constant in units of s^{-1}; see text.

other thiohydroxamate precursors,[13] and benzenesulfenamides[14,15] and related arenesulfenamides;[16] chemical[10] or electrochemical[17] oxidation of lithium amides; and ring openings of aziridines.[6,18] Surzur showed that protic acids and Lewis acids resulted in high yields of pyrrolidine products from **1**,[1] and a comparison of the reactivity of radical **1** and its protonated counterpart, aminium cation radical **2**, in the presence of various hydrogen atom transfer trapping agents has been reported.[12] Rate constants for cyclization of both aminyl radical **1** and aminium cation radical **2** are available from previously reported competitive trapping studies and recent direct kinetic studies.

From competition studies of the 5-*exo* cyclization of radical **1** versus trapping by Bu_3SnH, the rate constant for cyclization of **1** at 50 °C is 4.3×10^4 s^{-1}.[12,19] Assuming a log *A* value for cyclization of **1** of about 9.5, the rate constant for cyclization of **1** at 25 °C would be only 1.5×10^4 s^{-1}. Thus, one can readily rationalize modest yields of cyclic products formed from simple 4-pentenaminyl radicals such as **1**. Because radical−radical reactions will occur at the diffusion-controlled limit with spin statistical selection of 0.25 (a rate constant of about 5×10^9 M^{-1} s^{-1} in a low viscosity organic solvent at ambient temperature), the pseudo first-order rate constant for radical−radical reactions will be about 5×10^4 s^{-1} if the radical concentration reaches 1×10^{-5} M. The cyclization of radical **1** is only marginally fast enough to compete with radical−radical reactions under typical synthetic conditions.

Another feature that results in reduced yields of cyclic product from simple 4-pentenaminyl radicals is the reversibility of the cyclization reaction. Previously, our group reported that the cyclization of radical **1** was reversible.[12] Recently, Maxwell and Tsanaktsidis have claimed that our ring opening kinetic study could not be reproduced and that the cyclization reaction of **1** was not reversible.[16,20] Subsequently, we found that the results of Maxwell and Tsanaktsidis were artifacts apparently due to contamination of their radical precursor samples.[19] The equilibrium constant for cyclization of **1** is near unity,[19] and the product distributions from reactions of **1** reflect not only the rate constants for the unimolecular radical reactions but also those of the second order radical trapping reactions.

In contrast to the low reactivity of neutral dialkylaminyl radicals, protonated dialkylaminium cation radicals such as **2** (Scheme 1) react very efficiently in 5-*exo* cyclizations. Again, one can calculate an approximate rate constant for the unimolecular reaction. A competition study of cyclization of radical **2** in CH_3CN at 25 °C versus trapping by Bu_3SnH gave a ratio of rate constants of $k_{SnH}/k_c = 3$ M^{-1}.[12] On the basis of the reported rate constant for reaction of Ph_3SnH with dialkylaminium cation radicals at 25 °C in CH_3CN ($k = 2.4 \times 10^8$ M^{-1} s^{-1})[3] and with the assumption that Ph_3SnH should be about twice as reactive as Bu_3SnH (as it is in reactions with alkyl radicals[21]), the rate constant for cyclization of **2** at 25 °C is about 4×10^7 s^{-1}. This value is in good agreement with a recently reported directly measured rate constant, that for cyclization of radical **9** in CH_3CN at 10 °C, which is 1×10^8 s^{-1}.[22]



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The results in Tables 1−3 indicate that all of the Lewis acids tested resulted in acceleration of the 5-*exo* cycliza-

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(14) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275−1294 and references therein.
(15) Beckwith, A. L. J.; Maxwell, B. J.; Tsanaktsidis, J. *Aust. J. Chem.* **1991**, *44*, 1809−1812.
(16) Maxwell, B. J.; Tsanaktsidis, J. *J. Am. Chem. Soc.* **1996**, *118*, 4276−4283.
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(19) Newcomb, M.; Musa, O. M.; Martinez, F. N.; Horner, J. H. *J. Am. Chem. Soc.*, in press.
(20) Maxwell, B. J.; Tsanaktsidis, J. *J. Chem. Soc., Chem. Commun.* **1994**, 533−534.
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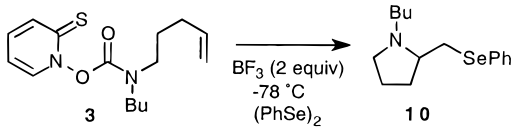
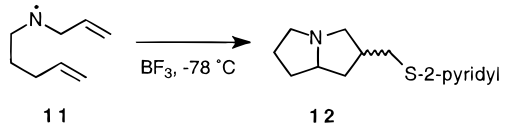
tion reaction of **1**. The excellent yields of cyclic product **5** obtained with BF_3 and various titanium species and the good yields of cyclic product found in the limited studies with other Lewis acids suggest that one can select from a wide range of aminyl radical activating agents. Nevertheless, we note that high Lewis acid concentrations were demonstrated to be deleterious to the overall yields of cyclic products in several cases.

We note that Lewis acid activation of dialkylaminyl radical cyclizations by BF_3 has been shown to be compatible with some other radical functionalization protocols. For example, when PTOC carbamate **3** was allowed to react in the presence of BF_3 and diphenyl diselenide, the phenylselenomethyl product **10** was obtained in 80% yield.[5] Similarly, the dialkylaminyl radical **11**, produced from its corresponding PTOC carbamate precursor, reacted in a tandem cyclization sequence to give, ultimately, pyrrolizidine **12** as a mixture of diastereomers in 70% yield.[5]





The LFP kinetic studies permit a quantitative evaluation of Lewis acid accelerations of dialkylaminyl radical reactions. The simultaneous solution of saturation kinetic data provides both the equilibrium (or pseudoequilibrium) binding constant for the first step in the reaction sequence and the rate constant for the second step, and these values are correlated. The three dialkylaminyl radicals **6**−**8** are similarly substituted about nitrogen, and the three apparent equilibrium constants for each particular Lewis acid were similar to one another. Therefore, we calculated the weighted average equilibrium constants for dialkylaminyl radical complexation by each Lewis acid at 20 °C and then used these values as constants in the regression analyses of k_{obs} to recalculate the rate constants of the reactions. The important point for such data treatment is that rapid equilibria for Lewis acid complexation must be established in all cases or else the apparent equilibrium constant from the initial regression analyses (listed in Table 4) will actually be the pseudoequilibrium constant described by eq 11 where k_f is the rate constant for formation of the complex, k_d is the rate constant for dissociation of the complex, and k_C is the rate constant for the radical reaction of the complex. If k_C was competitive with k_d for the fastest radical reaction, cyclization of radical **8**, then the apparent equilibrium constants for complexation of this radical resulting from the initial regression analyses would be smaller than those for radicals **6** and **7**; inspection of the data in Table 4 shows that they are not.

$$K_{app} = k_f/(k_d + k_C) \qquad (11)$$

The weighted average equilibrium constants for complexation in THF at 20 °C were as follows: (56 ± 5) M^{-1} for BF_3, (43.4 ± 0.9) M^{-1} for $MgBr_2$, and (5.3 ± 0.3) M^{-1} for $LiBF_4$. Regression analyses using these values as constants for K_C in eq 8 gave the rate constants listed in Table 6. For comparison purposes, we have included in Table 6 the rate constants for reactions of the uncomplexed dialkylaminyl radicals[4] and the protonated dialkylaminium cation radicals.[3]

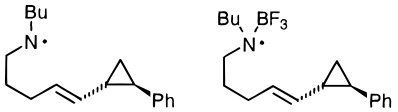
Table 6. Rate Constants for Reactions of Dialkylaminyl Radicals in THF at 20 °C in the Presence of Acids[a]

acid	$10^{-4} \times k_C$ for **6**	$10^{-4} \times k_C$ for **7**	$10^{-4} \times k_C$ for **8**
none[b]	<0.5	0.7	32
$LiBF_4$	8.1	16.5	560
$MgBr_2$	9.3	15.9	200
BF_3	56	677	1120
CF_3CO_2H[c]	2000	3800	1000000[d]

[a] Rate constants in units of s^{-1} calculated from eq 8 using weighted average values for K_C as constants. [b] Values from ref 4. [c] Values from ref 3; note that the dialkylaminium cation radical reactions are highly sensitive to solvent identity. [d] Rate-limiting protonation occurs; estimated value.

As in the case of the product studies with radical **1**, Lewis acid acceleration for reactions of **6**−**8** occurred for all three Lewis acids studied by LFP. The extent of activation by the Lewis acids correlated roughly for the three dialkylaminyl radical reactions, and the kinetic accelerations observed by LFP are consistent with the qualitative observations with radical **1**. BF_3 resulted in the greatest acceleration, and $LiBF_4$ and $MgBr_2$ gave similar accelerations.

The consistency in the values for the equilibrium constants for complexation by each Lewis acid with the three dialkylaminyl radicals **6**−**8** clearly suggests that these binding constants will also apply for other dialkylaminyl radicals. Another question to address is whether or not the catalytic effects of the Lewis acids observed for reactions of radicals **6**−**8** can be expected to be similar for other dialkylaminyl radical reactions. Some experimental evidence suggests that this will be the case for a given reaction type. For example, the qualitative results of the 5-*exo* cyclizations of radical **1** generally correspond to the quantitative results for the 5-*exo* cyclization of radical **8** in that BF_3 appeared to be more efficacious than $MgBr_2$ or $LiBF_4$ on the basis of the yields of **5** for reactions of **1** conducted under similar conditions. In a more quantitative evaluation, the rate constant for 5-*exo* cyclization of the neutral dialkylaminyl radical **13** at 20 °C is accelerated by about two orders of magnitude upon BF_3 complexation to give radical **14**,[19] an effect similar to the acceleration by BF_3 observed with **8**.

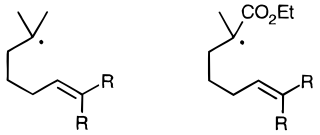


One point that deserves note is the relatively small kinetic accelerations observed in the 5-*exo* cyclizations of radical **8** in comparison to the 6-*exo* cyclizations of radical **7**. The neutral radical **8** cyclizes about 1.5 orders of magnitude faster than radical **7**, and, for the protonated analogs of **7** and **8**, the 5-*exo* cyclization is about 2.5 orders of magnitude faster than the 6-*exo* cyclization. Such differences in rate constants of 5-*exo* and 6-*exo* cyclizations of analogous radicals are typically found, and we have observed in several LFP studies of 5-*exo* and 6-*exo* cyclizations of terminal diphenylethene-containing radicals which are isostructural with **7** and **8** that the 5-*exo* cyclizations are about two orders of magnitude

faster than the corresponding 6-*exo* cyclizations.[3,4,23,24] One might rationalize that the cyclization kinetics of the $LiBF_4$ complexes of **7** and **8** are consistent with the kinetic behavior of other matched pairs, but the kinetics of the $MgBr_2$ and BF_3 complexes clearly are not. That the 5-*exo* cyclization of the BF_3 complex of **8** is only twice as fast as the 6-*exo* cyclization of the BF_3 complex of **7** is remarkable.

The unusual kinetic behavior of the BF_3 complex of **8** is apparent in the Arrhenius functions for cyclization of the BF_3 complexes of **7** and **8** (eqs 9, 10). Generally, the log *A* terms, the entropic terms, for 5-*exo* and 6-*exo* cyclizations of a matched pair of radicals are similar, and the E_a value for the 6-*exo* cyclization is greater than that for the 5-*exo* cyclization. However, the 5-*exo* cyclization of the BF_3 complex of **8** has a greater activation energy than the 6-*exo* cyclization of the complex of **7**. This suggests that the Lewis acid imposes a considerable steric barrier in the transition state of the 5-*exo* cyclization that is not present in the transition state of the 6-*exo* cyclization.

Elucidation of the origins of a barrier imposed by the Lewis acid BF_3 in the 5-*exo* cyclization reaction of **8** might require extensive computational work, but it is important to note that a kinetic barrier for 5-*exo* cyclization cannot be simply a function of a tertiary radical center *per se*. For example, the rate constants for 5-*exo* cyclizations of tertiary alkyl radicals **15** are similar to those of the corresponding secondary alkyl radicals.[21] On the other hand, the tertiary ethoxycarbonyl-substituted radicals **16** cyclize considerably less rapidly than the isostructural tertiary alkyl radicals **15** and the analogous secondary ethoxycarbonyl-substituted radicals.[24,25] We ascribed the slow reactions of tertiary radicals **16** to the planarity of the radical center which results in a steric interaction in the cyclization that is not present in a pyramidalized tertiary alkyl radical.[24]



15a: R = H **15b:** R = Ph **16a:** R = H **16b:** R = Ph

Another point that deserves comment involves the acceleration observed with $LiBF_4$. Anodic oxidation of lithium dialkylamides containing the 4-pentenaminyl moiety has been reported to give good to excellent yields of pyrrolidine products[17] in contrast to the modest yields typically observed when similar dialkylaminyl radicals are produced in chain reactions under neutral conditions. In the electrochemical reactions, which were run in THF, the supporting electrolyte was lithium perchlorate, and the lithium cation almost certainly served to catalyze the aminyl radical cyclizations.

One should note that the kinetic measurements reported in this work were performed in one solvent, THF. Whereas the kinetics of most radical reactions are relatively insensitive to solvent, those for reactions of dialkylaminium cation radicals are highly solvent sensitive.[3] Therefore, one should expect that the kinetics of reactions of Lewis acid complexes of aminyl radicals will also demonstrate considerable solvent sensitivity.

Finally, we comment on the utility of the LFP kinetic method for studies of Lewis acid effects in radical reactions, a topic of considerable current research interest. For example, focusing only on recent reports, Lewis acids have been employed to effect highly diastereoselective[26−35] and even enantioselective[36−39] radical reactions. In some cases, the Lewis acid might simply serve to control the conformation of a radical or molecule in the reaction and has little effect on the kinetics, but there is good evidence that Lewis acid catalysis is involved in selected cases.[26−30,37,38] The LFP method we employed in this work should be generally applicable for measuring both the binding constants and catalytic rate constants for the Lewis acids in these types of reactions because absolute kinetics are measured directly. An alternative approach, involving product yields from competing reactions, would be considerably more difficult to execute and less informative because the Lewis acid could affect the kinetics of both of the competing reactions.

Conclusion

Lewis acid catalysis of dialkylaminyl radical reactions is demonstrated both qualitatively and quantitatively by the studies reported here. The LFP kinetic method provides both equilibrium binding constants and catalytic rate constants for complexes of the aminyl radicals with Lewis acids. The degree of kinetic activation by the Lewis acids is much less than that observed upon protonation of dialkylaminyl radicals, but the accelerations in most cases are adequate for successful synthetic applications involving simple 4-pentenaminyl radical cyclizations. For example, the seemingly poor 6.2-fold acceleration observed in the 5-*exo* cyclization of radical **8** upon complexation with $MgBr_2$ suggests that the $MgBr_2$ complex of the simple 4-pentenaminyl radical **1** cyclizes with a rate constant of about 1×10^5 s^{-1} at ambient temperature; this rate constant is similar to that for the archetypal radical cyclization, 5-*exo* cyclization of the 5-hexenyl radical, one of the most important radical reactions from the perspective of organic synthesis.

Experimental Section

All Lewis acids with the exception of $MgBr_2$ were purchased from Aldrich Chemical Co. and used as received. Solutions

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of $MgBr_2$ were prepared by allowing dibromoethane to react with magnesium metal. The mixed titanium salts were prepared from appropriate amounts of $Ti(O\text{-}i\text{-}Pr)_4$ and $TiCl_4$. The PTOC carbamate **3** and the PTOC carbamate precursors to aminyl radicals **6**−**8** were prepared as previously reported.[3,12]

Product Studies. Solutions of PTOC carbamate **3** (0.05 M) and the appropriate Lewis acids were prepared under nitrogen in flasks shielded from light and equilibrated at the desired reaction temperature. Reactions were initiated by irradiation with a 150 W tungsten filament bulb placed ca. 0.6 m from the reaction vessels. Reaction progress was monitored by TLC. Upon consumption of **3**, the reaction mixtures were extracted with water, dried ($MgSO_4$), and analyzed by GC employing a predetermined response factor for the known product **5**.[12]

LFP Kinetic Studies. The method employed was the same as that previously used in kinetic studies of dialkylaminyl radicals and dialkylaminium cation radicals.[3,4] Samples of the appropriate PTOC carbamate[3] in THF in the presence of a Lewis acid were sparged with He and thermally equilibrated in a jacketed addition funnel. The samples were allowed to flow through a flow cell placed in a thermostated well in an Applied Photophysics LK50 kinetic spectrometer. Temperatures were measured with a thermocouple placed in the flowing stream approximately 1 cm above the irradiation zone. The samples were irradiated with a 7 ns pulse of 355 nm light from a Nd-YAG laser, and the absorbance at ca. 330 nm was monitored. For studies conducted with various concentrations of Lewis acids at 20 °C and 4 °C, the observed rate constants as a function of Lewis acid concentration were fit to eq 8 by nonlinear regression analysis to give the equilibrium binding constants and rate constants in Table 4.

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