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Published on Web 03/24/2006

Mechanism of Al^{III}-Catalyzed Transamidation of Unactivated Secondary Carboxamides

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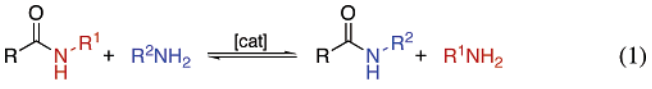
Abstract: The carbon−nitrogen bond of secondary carboxamides is generally thermodynamically and kinetically unreactive; however, we recently discovered that the trisamidoaluminum(III) dimer $Al_2(NMe_2)_6$ catalyzes facile transamidation between simple secondary carboxamides and primary amines under moderate conditions. The present report describes kinetic and spectroscopic studies that illuminate the mechanism of this unusual transformation. The catalytic reaction exhibits a bimolecular rate law with a first-order dependence on the Al^{III} and amine concentrations. No rate dependence on the carboxamide concentration is observed. Spectroscopic studies (^1H and ^{13}C NMR, FTIR) support a catalyst resting state that consists of a mixture of tris-(κ^2-amidate)aluminum(III) complexes. These results, together with the presence of a significant kinetic isotope effect when deuterated amine substrate (RND_2) is used, implicate a mechanism in which the amine undergoes preequilibrium coordination to aluminum and proton transfer to a κ^2-amidate ligand to yield an Al(κ^2-amidate)$_2$(κ^1-carboxamide)(NHR) complex, followed by rate-limiting intramolecular delivery of the amido ligand (NHR) to the neutral Al^{III}-activated κ^1-carboxamide. Noteworthy in this mechanism is the bifunctional character of Al^{III}, which is capable of activating both the amine nucleophile and the carboxamide electrophile in the reaction.

Introduction

The secondary carboxamide group is a fundamental component of biological and synthetic polymers (i.e., proteins and nylons) and constitutes a ubiquitous and important functional group in organic chemistry. Recent developments in dynamic covalent chemistry[1] suggest that facile amide exchange reactions would enable the synthesis of important new amide-based molecules and polyamide materials under equilibrium-controlled conditions. Toward this end, we have recently initiated efforts to identify catalysts that mediate efficient amide exchange reactions, including transamidation and amide metathesis (eqs 1 and 2).



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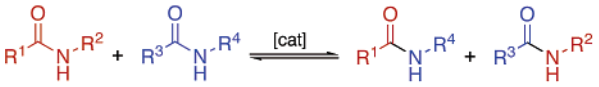

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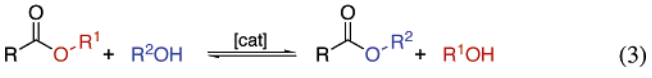

(3)

Transesterification (eq 3) is a relatively facile process that has been employed in numerous disciplines including organic synthesis, food science, and biodiesel applications.[2] These ester-alcohol exchange reactions can be promoted by acids, bases, nucleophilic catalysts, and metal alkoxides.[2,3] These reactions provide a powerful strategy for the manipulation of organic molecules that possess the carboxylic ester functional group. Catalysts for ester amidation have also been reported recently.[4] In contrast, examples of transamidation are scarce, and the limited synthetic applications to date generally consist of intramolecular reactions.[5] The difficulty of this reaction arises from the intrinsic strength of the amide C−N bond together with the presence of an acidic N−H bond in secondary amides. In a neutral aqueous solution, for example, hydrolysis of carboxylic esters proceeds more than 2 orders of magnitude faster than hydrolysis of carboxamides.[6]

Transamidation generally requires harsh conditions to cleave the chemically robust amide bond. For example, high temper-

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(3) For important recent leading references, see: (a) Stanton, M. G.; Gagné, M. R. *J. Am. Chem. Soc.* **1997**, *119*, 5075. (b) Stanton, M. G.; Allen, C. B.; Kissling, R. M.; Lincoln, A. L.; Gagné, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 5981. (c) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583. (d) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587.
(4) (a) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 10039. (b) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453.
(5) (a) Çalimsiz, S.; Lipton, M. A. *J. Org. Chem.* **2005,** *70*, 6218. (b) Alajarín, M.; Vidal, A.; Tovar, F. *Tetrahedron* **2005,** *61*, 1531. (c) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529. (d) Lasri, J.; González-Rosende, M. E.; Sepúlveda-Arques, J. *Org. Lett.* **2003**, *5*, 3851. (e) Langlois, N. *Tetrahedron Lett.* **2002**, *43*, 9531. (f) Bon, E.; Bigg, D. C. H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 4035. (g) Gotor, V.; Brieva, R.; González, C.; Rebolledo, F. *Tetrahedron* **1991**, *47*, 9207. (h) Zaragoza-Dörwald, F.; Von Kiedrowski, G. *Synthesis* **1988**, *11*, 917. (i) Crombie, L.; Jones, R. C. F.; Haigh, D. *Tetrahedron Lett.* **1986**, *27*, 5151. (j) Martin, R. B.; Parcell, A.; Hedrick, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 2406.
(6) Wolfenden, R.; Snider, M. J. *Acc. Chem. Res.* **2001**, *34*, 938.

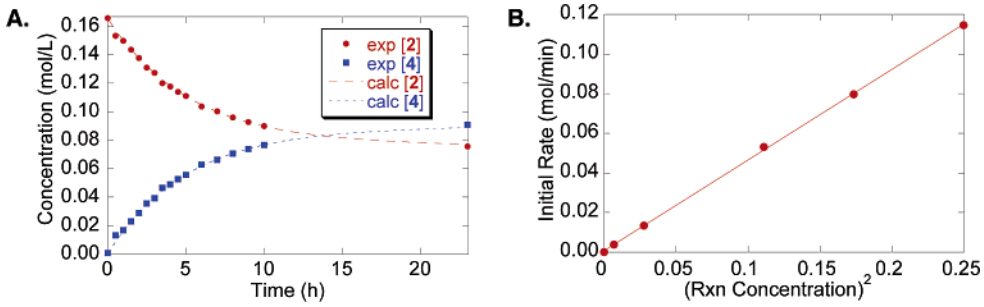


Figure 1. (A) Representative time-course for $Al_2(NMe_2)_6$-catalyzed transamidation between **2** and **3** (eq 4). The calculated curve fits reflect a nonlinear least-squares fit of the data to an equation associated with a bimolecular approach to equilibrium ($[A]_t = [A]_\infty + ([A]_0 - [A]_\infty)\, e^{-kt}$, $k = k_1 + k_{-1}$). Conditions: $[Al_2(NMe_2)_6] = 4.2$ mM, [carboxamide] = 0.17 M, [amine] = 0.17 M, 5 mL toluene, 90 °C. (B) Kinetic plot demonstrating a linear correlation between the rate and the square of the "reaction concentration" (linear least-squares curve fit). The "reaction concentration" (defined in the text) is arbitrarily assigned as the initial carboxamide concentration.

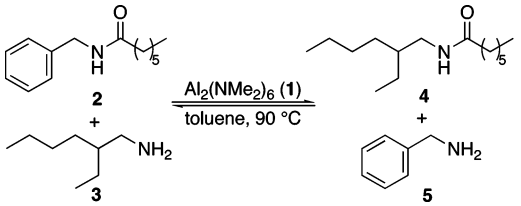
atures (>250 °C) have been employed to effect exchange in amide-containing polymers and polymer/amine mixtures.[7] A comparatively mild intermolecular transamidation has been achieved with stoichiometric or excess $AlCl_3$.[5f] Intramolecular examples have been reported that use stoichiometric $AlMe_3$ in combination with catalytic quantities of lanthanide reagents,[5a] and Brønsted acids are effective in intramolecular transamidation reactions that feature opening of a strained lactam ring.[5c]

We recently discovered that the homoleptic amidoaluminum complex $Al_2(NMe_2)_6$ catalyzes intermolecular transamidation between primary alkylamines and secondary carboxamides under relatively mild conditions.[8] Lewis acids, such as $Sc(OTf)_3$, promote thermodynamically favorable transamidation reactions between alkylamines and *N*-aryl carboxamides, but they are ineffective in the more difficult (and potentially more interesting) thermoneutral reactions between alkylamines and *N*-alkyl carboxamides. Alkali metal−amido reagents[9] (e.g., $LiN(SiMe_3)_2$) proved to be ineffective for both thermodynamically favorable and thermoneutral reactions because these basic reagents preferentially deprotonate secondary carboxamides without effecting transamidation.

In our initial report, we speculated that the ability of the amidoaluminum complex to promote thermoneutral transamidation might reflect a bifunctional mechanism. The aluminum center could serve both as a Lewis acid to enhance the electrophilicity of the carboxamide group and as a site for activation of the amine nucleophile via formation of an amidoaluminum fragment. To test this hypothesis and support future efforts to develop improved catalysts, we undertook a mechanistic investigation of the $Al_2(NMe_2)_6$-catalyzed transamidation involving primary alkylamines and secondary *N*-alkyl carboxamides. The results of this study, presented below, provide valuable insights into this unique equilibrium-controlled transformation and provide the basis for further development of this important class of reactions.

Results and Discussion

Kinetic Studies of Al^{III}-Catalyzed Transamidation. We initiated the study of $Al_2(NMe_2)_6$-promoted transamidation between primary alkylamines and secondary *N*-alkyl carboxamides by identifying a substrate pair that could be assayed readily by NMR spectroscopy and gas chromatography. The substrates *N*-benzylheptanamide (**2**) and 2-ethylhexylamine (**3**) (eq 4) proved suitable for this purpose. The combination of these substrates in a 1:1 ratio (0.17 M each) with 2.5 mol % $Al_2(NMe_2)_6$ in dry toluene at 90 °C results in transamidation, producing an equilibrium mixture of products **2**, **3**, **4**, and **5** in approximately 20 h (Figure 1A). Under these conditions, the final ratio of carboxamides, **2**:**4** = 1.2:1.0 based on GC analysis, confirms the near-thermoneutrality of the transamidation reaction. An identical product ratio is obtained if the reaction is performed in reverse, namely by initiating the reaction with the alternate pair of substrates, **4** and **5**. Formation of *N*,*N*-dimethylheptanamide from incorporation of the Me_2N- fragment of $Al_2(NMe_2)_6$ into the carboxamide was not detected by ^1H NMR spectroscopy or GC (see further analysis below).



(4)

The reaction time-course of eq 4, monitored by GC, exhibits well-behaved kinetics, and the data fit well to a calculated curve for a bimolecular approach to equilibrium (Figure 1A). A bimolecular rate law is supported further by the rate data obtained at different "reaction concentrations" (Figure 1B). (The "reaction concentration" was varied by changing the solvent volume while maintaining a constant absolute quantity of all reagents.) The initial rates exhibit a linear correlation with the *square* of the reaction concentration.

The origin of the bimolecular rate law was examined by evaluating the rate-dependence on each component of the reaction: $Al_2(NMe_2)_6$, amine, and carboxamide. The initial rate increases linearly with respect to $[Al_2(NMe_2)_6]$ over a range of 1−10 mol % of the dimer (i.e., 2−20 mol % [monomeric Al^{III}]) (Figure 2). Since the dimeric complex dissociates into monomeric Al^{III} species under the reaction conditions, as we elaborate below, the linear plot reflects a first-order dependence of the rate on the concentration of monomeric Al^{III} species.

(7) (a) Beste, L. F.; Houtz, R. C. *J. Polym. Sci.* **1952**, *8*, 395. (b) Ogata, N., *Makromol. Chem.* **1959,** *30*, 212. (c) Miller, I. K., *J. Polym. Sci., Part A: Polym. Chem.* **1976,** *14*, 1403. (d) McKinney, R. J. U.S. Patent 5,302,756, 1994. (e) McKinney, R. J. U.S. Patent 5,395,974, 1995.

(8) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003,** *125*, 3422.

(9) Hereafter, we avoid using the term "amide" in order to minimize confusion between organic "carboxamides" and metal-stabilized anionic "amido" groups (R_2N^-).

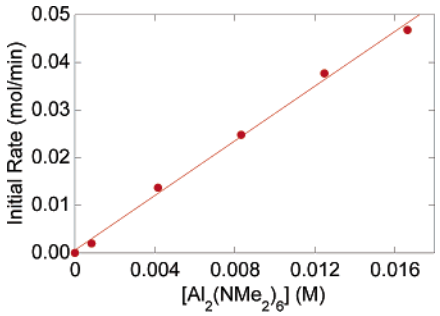


Figure 2. Dependence of the initial rate on catalyst concentration for the transamidation of carboxamide **2** with amine **3**. Initial rates, derived from monitoring the first 5% conversion, were determined by sampling [**2**] every 2 min. Conditions: [**2**] = [**3**] = 0.17 M, 5 mL toluene, 90 °C.

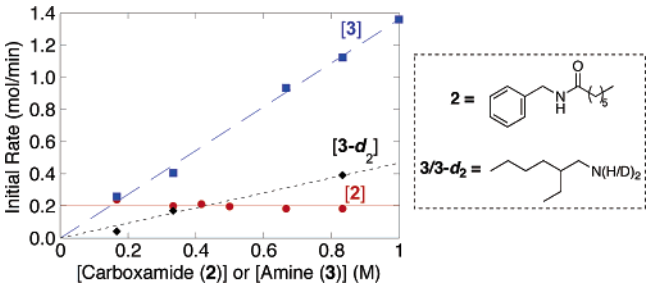


Figure 3. Initial-rate dependence on [**2**], [**3**], or [**3**-d_2] for the catalytic transamidation of **2** and **3** or **2**-d_1 and **3**-d_2. Initial rates, derived from monitoring the first 5% conversion, were determined by sampling [**2**] or [**2**-d_1] every 2 min. Conditions: [$Al_2(NMe_2)_6$] = 4.2 mM; [**2**], [**2**-d_1], [**3**] and [**3**-d_2] = 0.17 M.

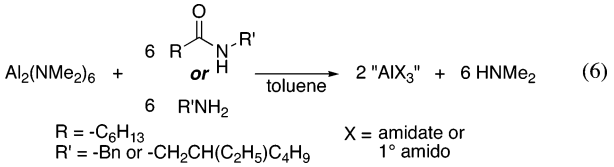
Initial rates were measured also at different concentrations of the substrates, carboxamide **2** and amine **3**, at 5 mol % [Al^{III}]. The rate exhibits a linear, first-order dependence on [amine], but no dependence on [carboxamide] (Figure 3, red circles and blue squares, respectively). The rate slows significantly if *N*-deuterated substrates, **2**-d_1 and **3**-d_2, are used in the reaction. The linear increase in the rate with respect to [**3**-d_2] (Figure 3, black diamonds) reveals a deuterium kinetic isotope effect of $k_H/k_D = 2.9$. (Proton exchange between the amine and carboxamide substrates under the reaction conditions prevents independent determination of isotope effects associated with the two different substrates. The lack of rate-dependence on [carboxamide], however, implies that the isotope effect arises solely from the deuterated amine.)

The kinetic data in Figures 2 and 3 support a simple bimolecular rate law (eq 5), consistent with the preliminary analysis of the reaction time-course data in Figure 1. The first-order dependence of the rate on [Al^{III}] and [amine] indicates these species participate in the turnover-limiting step. The substantial deuterium kinetic isotope effect indicates that proton transfer occurs in or before the turnover-limiting step.

$$\text{rate} = k[Al^{III}][RNH_2] \qquad (5)$$

Studies of Substrate Reactions with $Al_2(NMe_2)_6$. To gain additional insights into the catalytic mechanism, we spectroscopically probed fundamental reactions between the organic substrates and $Al_2(NMe_2)_3$. Further, we sought to characterize the catalyst resting state under the reaction conditions.

The independent addition of ≥6 equiv of primary amine **3** or **5** or carboxamide **2** or **4** to a toluene solution of $Al_2(NMe_2)_3$ at room temperature results in nearly quantitative formation of dimethylamine, as indicated by ^{1}H NMR spectroscopy (0.15 and 2.19 ppm for the N-*H* and N-CH_3 resonances, respectively)[10] (eq 6). The reaction of benzylamine (**5**) with $Al_2(NMe_2)_3$ generates a precipitate, presumably oligomeric amido- or imido-bridged Al^{III} aggregates, that remains insoluble even at 90 °C. The reaction solutions for each of the other substrates remain homogeneous. These observations suggest that Al^{III} prefers primary amido and amidate ligands over secondary amido ligands. Furthermore, the lack of Me_2N-Al^{III} fragments in the presence of the transamidation substrates provides an explanation for the absence of *N*,*N*-dimethylcarboxamide products under the catalytic reaction conditions.



(6)

The reaction of *N*-benzylcarboxamide **2** with $Al_2(NMe_2)_6$ was studied by FTIR spectroscopy using an in situ ZnSe ATR probe. Solution-IR spectra were acquired as the carboxamide was added via syringe pump to a solution of $Al_2(NMe_2)_6$ in toluene. Significant changes were observed in the spectra between 1300 and 1700 cm^{-1} (Figure S1). The presence of numerous overlapping bands hindered spectral deconvolution and detailed spectral assignment. Nevertheless, diagnostic IR bands associated with the formation and disappearance of intermediates were evident during the titration (Figures S1 and S2). Only after >3 equiv of **2** were added relative to [Al^{III}] did the carbonyl IR band of the free carboxamide (1674 cm^{-1}) become apparent in the spectrum. Similar insights were gained from ^{13}C NMR spectroscopic studies in which *N*-benzylcarboxamide **2** was titrated into a solution of $Al_2(NMe_2)_6$ in toluene-d_8. The chemical shifts of the carbonyl carbon atom at low concentrations of **2** are distinct from that of free carboxamide and consistent with formation of Al^{III}−amidate complexes (Figure 4). At a **2**:Al^{III} ratio of 1:1, two peaks are evident at 179.4 and 183.5 ppm. Although the precise identity of the complexes corresponding to these peaks is not known, neither of the peaks is associated with free carboxamide (171.8 ppm). At ratios of **2**:Al^{III} = 2:1 and 3:1, single (distinct) peaks are observed at 179.8 and 183.6 ppm, respectively. Finally, at ratios of **2**:Al^{III} > 3:1, two peaks are present, one of which is identical to that observed when **2**:Al^{III} = 3:1 (183.6 ppm), and the other corresponds to the free carboxamide.

In contrast to the ^{13}C NMR data, ^{1}H NMR spectra of mixtures of carboxamide and $Al_2(NMe_2)_6$ are rather complex because of the presence of numerous resonances arising from heptanoyl methylene groups in the carboxamide substrate and metal-amidate complexes (Figure S3). Nevertheless, distinct Ar-CH_2N- resonances can be identified for free carboxamide and aluminum-coordinated amidates in a relatively open region of the spectrum, at 4.25 and 3.90 ppm, respectively. The ^{1}H and ^{13}C NMR spectral assignments of the aluminum amidate complex formed when >3 equiv of **2** are present relative to [Al^{III}] are supported by gHMBC NMR spectra, which reveal a three-bond correlation between the C=O carbon atom and methylene protons of the benzyl group of the coordinated amidate (Figure S4).

(10) See Supporting Information for additional details.

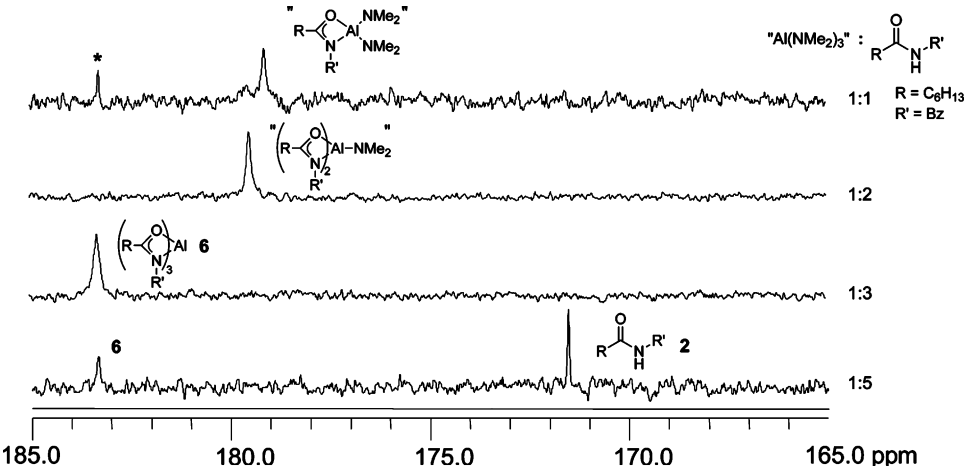
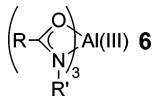
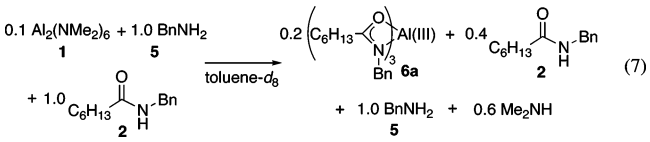


Figure 4. ^{13}C NMR spectra monitoring the changes that occur in the carbonyl region upon addition of *N*-benzylcarboxamide **2** to a solution of $Al_2(NMe_2)_6$ in toluene-d_8. The Al^{III}:carboxamide ratio present in each solution is indicated on the right-hand side of the spectra. [Note: ^{1}H NMR data (Figure S3) reveal that the peak labeled with an asterisk in spectrum for **2**:Al = 1:1 does not arise from the same complex as that present at **2**:Al ratios ≥ 3:1.]

Collectively, the FTIR and NMR spectroscopic data indicate that the secondary *N*-benzylcarboxamide, **2**, undergoes rapid and quantitative proton-coupled exchange with the dimethylamido ligands of $Al_2(NMe_2)_6$ to generate aluminum amidate complexes and free dimethylamine. Previous examples of Al^{III}−amidate complexes include both mononuclear and bridged-multinuclear structures, that possess alkyl groups or sterically encumbered phenoxides as ancillary ligands.[11,12] The amidate ligand generally adopts a κ^2 coordination mode in which both nitrogen and oxygen atoms bind to the metal center. The amidate may chelate a single Al^{III} center or bridge two different Al^{III} centers. On the basis of these literature precedents, together with the spectroscopic data described above, we propose that secondary carboxamides react with $Al_2(NMe_2)_6$ to produce a monomeric, pseudo-octahedral tris-amidate aluminum complex, $Al^{III}(\kappa^2$-amidate$)_3$, **6**. Several stereoisomers are possible for such structures; however, the spectroscopic data do not distinguish between them, if they are present. The monomeric nature of this complex is consistent with the presence of only one benzylic (ArCH_2N-) and one carbonyl (*C*═O) resonance in the ^{1}H and ^{13}C NMR spectra, respectively, for the aluminum−amidate complex present at **2**:Al^{III} ratios ≥3:1; multinuclear aggregates with both bridging and nonbridging amidates might be expected to exhibit multiple resonances.



To probe the relevance of the tris-amidate complex **6** to the transamidation reactions, we investigated the fate of $Al_2(NMe_2)_6$ with *both* amine and carboxamide substrates present. Ten mol % $Al_2(NMe_2)_6$ (i.e., 20 mol % Al^{III}) was added to a solution containing a 1:1 ratio of benzylamine (**5**) and *N*-benzylheptanamide (**2**) in toluene-d_8, and the resulting solution was examined by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum at room temperature reveals the presence of 0.2 equiv of the tris-*N*-benzylamidate **6a** (which consumes 0.6 equiv of **2**), 0.4 equiv of free carboxamide **2**, and 1.0 equiv of free benzylamine (eq 7). Nearly quantitative formation of dimethylamine is detected (0.6 equiv), although integration is complicated by the presence of overlapping resonances in the ^{1}H NMR spectrum. Upon heating the solution to 90 °C, no change is observed in this product ratio. The ^{13}C NMR spectrum of this solution confirms that **6a** and **2** are the sole carbonyl-containing products in solution. These results indicate that, in the presence of a mixture of excess primary amine and secondary carboxamide, Al^{III} exists primarily (>95%) as a monomer with three κ^2-amidate ligands.



(7)

NMR Spectroscopic Studies under Catalytic Conditions. To study the transamidation reaction mixture (eq 4) under catalytic conditions, ^{1}H NMR spectra were acquired for a reaction mixture consisting of 10 mol % $Al_2(NMe_2)_6$ (20 mol % Al^{III}) relative to *N*-benzylcarboxamide (**2**) and 2-ethylhexylamine (**3**) in toluene-d_8. A room-temperature spectrum reveals the presence of tris-*N*-benzylamidate complex **6a**, which consumes 60% of available **2** (cf. eq 7). Unreacted **2** (0.4 equiv) and amine **3** (1 equiv) are also present. Upon heating this solution to 90 °C, transamidation occurs, producing carboxamide **4** and benzylamine **5**. ^{1}H NMR spectra were acquired at 5-min intervals until the reaction reached equilibrium (Figure 5). Initially, **2** is the only carboxamide present in solution, and all of the Al^{III} is present as the tris-(*N*-benzylamidate)Al^{III} complex **6a**. As the reaction proceeds, the resonance associated with **6a** decays with concomitant growth of new resonances, attributed to new Al^{III}−amidate complexes **7a**, **7b**, and **6b**.

The individual resonances in each ^{1}H NMR spectrum were integrated in order to track the growth and/or decay of each species present in solution (Figure 6). The concentrations of amines **3** and **5** (open circles, Figure 6A) provide a direct indication of the reaction progress. The concentrations of free carboxamides **2** and **4** (filled triangles, Figures 6A) are

(11) (a) Kai, Y.; Yasuoka, N.; Kasai, N.; Kakudo, M. *J. Organomet. Chem.* **1971**, *32*, 165. (b) Huang, Y.-L.; Huang, B.-H.; Ko, B.-T.; Lin, C.-C. *J. Chem. Soc., Dalton Trans.* **2001**, 1359. (c) Huang, B.-H.; Yu, T.-L.; Huang, Y.-L.; Ko, B.-T.; Lin, C.-C. *Inorg. Chem.* **2002**, *41*, 2987.

(12) Power, M. B.; Bott, S. G.; Clark, D. L.; Atwood, J. L.; Barron, A. R. *Organometallics* **1990,** *9*, 3086.

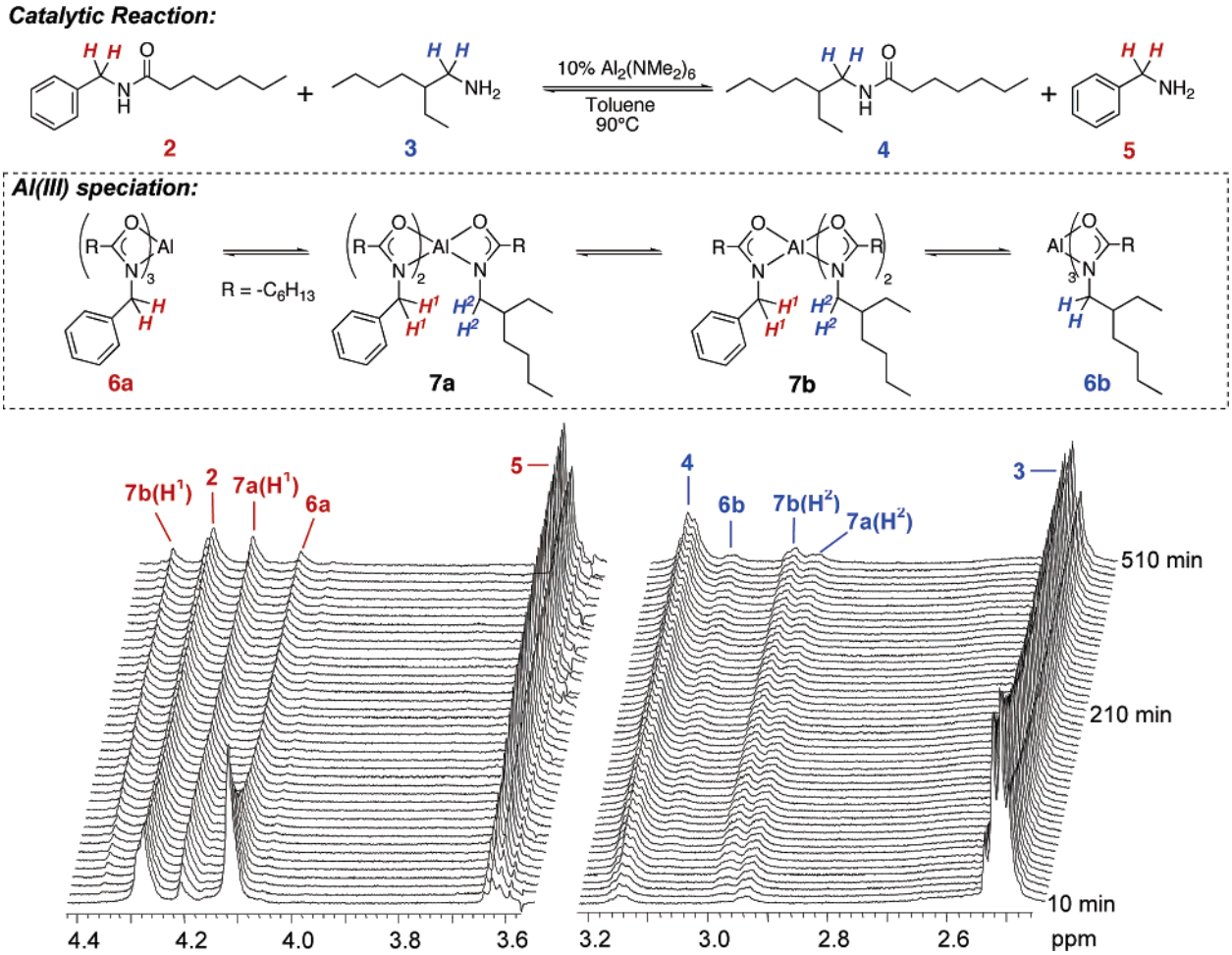


Figure 5. ^{1}H NMR spectral time-course for Al^{III}-catalyzed transamidation reaction between **2** and **3** (90 °C in toluene-d_8). Data were collected until the reaction reached equilibrium. The first spectrum was acquired 10 min after mixing, and additional spectra were acquired at 5-min intervals. The spectra display the diagnostic resonances of the CH_2 group adjacent to nitrogen in the amine and carboxamide reagents and products. The internal standard peak at 3.41 ppm (1,3,5-trimethoxybenzene) has been removed for clarity. Initial conditions: $[Al_2(NMe_2)_6] = 0.083$ M, $[\mathbf{2}] = [\mathbf{3}] = 0.17$ M.

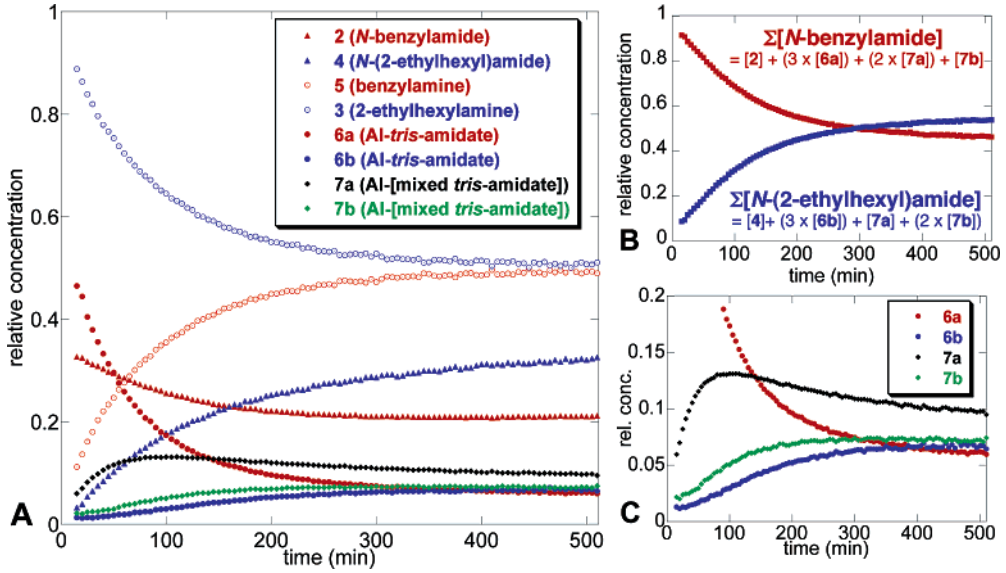
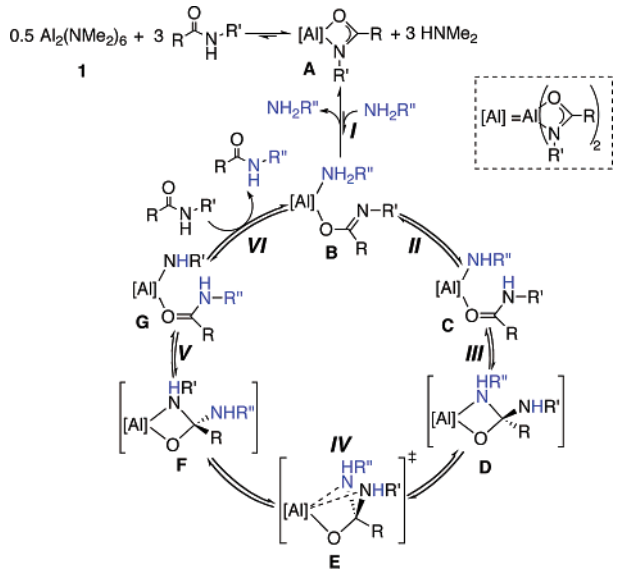


Figure 6. (A) Reaction time-course of the Al^{III}-catalyzed transamidation between **2** and **3** in toluene-d_8 at 90 °C. The concentrations of the species were determined by ^{1}H NMR spectroscopy, sampling every 5 min, with the initial time point at 10 min. Concentrations are plotted for amines **3** and **5**, carboxamides **2** and **4**, and the aluminum amidates **6a**, **6b**, **7a**, and **7b**. The concentrations of mixed Al^{III}−amidates **7a** and **7b** were determined from the weighted average of the two resonances associated with each amidate. Initial conditions: $[Al_2(NMe_2)_6] = 0.083$ M, $[\mathbf{2}] = [\mathbf{3}] = 0.17$ M. (B) Total carboxamide concentration present in the reaction, accounting for both free carboxamides and Al^{III}-coordinated amidates. (C) Expansion of the time-course data revealing the Al^{III}−amidate speciation during the reaction.

Scheme 1. Proposed Mechanism for Al^{III}-Catalyzed Transamidation



significantly lower than those of the amines because a large fraction (60%) coordinates to aluminum. Therefore, the concentrations of **2** and **4** must be combined with the concentrations of Al^{III}-coordinated carboxamides in **6a**, **6b**, **7a,** and **7b** to achieve an accurate depiction of the reaction progress (Figure 6B). The final equilibrium ratio of carboxamides detected in this ^{1}H NMR experiment (**2**:**4** = 1:1.2) is identical to that observed in the GC study (Figure 1A).

The equilibrium evolution of Al^{III}−amidate species follows the sequence **6a**→**7a**→**7b**→**6b** (Figure 6C). Complexes **6a** and **6b** have been prepared independently in solution and characterized by NMR spectroscopy (Figure S5), whereas the identities of **7a** and **7b** are inferred from the order in which they appear during the reaction course. The distribution of these four Al^{III}−amidate complexes at equilibrium deviates somewhat from a statistical ratio of **6a**:**7a**:**7b**:**6b** = 1:3:3:1. The observed ratio of 1.1:3.6:2.8:1.0 suggests that the *N*-benzylamidate anion has a somewhat higher affinity for Al^{III} relative to a proton than does the *N*-(2-ethylhexyl)amidate anion.

Proposed Catalytic Mechanism. The NMR spectroscopic studies described above provide strong evidence for a catalyst resting state consisting of an aluminum tris-amidate complex, such as **6**. To our knowledge, tris-amidate complexes of aluminum have not been characterized previously. ϵ-Caprolactam has been proposed to form a homoleptic tris-lactamate complex with Al^{III} upon reaction with $AlEt_3$; however, the complex was not isolated or characterized.[13] Well-defined examples of Al(κ^2-amidate) complexes bearing ancillary phenoxide and alkyl ligands have been reported previously by Barron[12] and Lin.[11] An Al(κ^2-amidate)$_3$ resting state accounts for the fact that variation of concentration of free carboxamide in solution has no effect on the rate (Figure 3) and that no [carboxamide] term appears in the rate law (eq 5).

On the basis of the mechanistic insights described above, including the rate law, deuterium kinetic isotope effect, and identity of the catalyst resting state, we propose the following catalytic mechanism (Scheme 1). The tris-amidate aluminum complex **A** enters the catalytic cycle via bimolecular reaction with a primary amine to form the amine adduct **B** (step I). Coordination of the amine to Al^{III} forces one of the amidate ligands to adopt a κ^1 binding mode. This preequilibrium step strongly favors the tris-amidate complex **A**. Proton transfer from the coordinated amine to the κ^1-amidate (step II) can account for the deuterium kinetic isotope effect and serves to activate both substrates. The anionic amido ligand is a better nucleophile than is a primary amine, and the electrophilicity of the neutral carboxamide is enhanced by virtue of its coordination to the Lewis acidic Al^{III} center. The tetrahedral intermediate **D** formed upon nucleophilic attack of the amido ligand on the coordinated carboxamide (step III) can either revert back to complex **C** or isomerize via coordination of the other nitrogen atom to Al^{III} to yield intermediate **F**. Subsequent breakdown of the new tetrahedral intermediate **F** (step V) and exchange of the neutral carboxamide ligand (step VI) completes the transamidation reaction. The inability to observe intermediates **B**−**G** spectroscopically and the unimolecular nature of steps II−V complicate efforts to probe this mechanism further. The precise identity of the turnover-limiting step is not known; however, the sizable kinetic isotope effect indicates that this step can occur no earlier than step II but may be as late as step IV (note that steps V and VI are approximately isoenergetic to steps III and II, respectively).

Implications of the Catalytic Mechanism. In our original catalyst screening study,[8] we tested three classes of metal complexes as potential transamidation catalysts: (1) Lewis acids, (2) alkali-metal−amido reagents, and (3) transition metal− and main group metal−amido complexes. Among the complexes tested, $Al_2(NMe_2)_6$ proved to be the best at promoting thermoneutral transamidation between primary alkylamines and secondary *N*-alkyl carboxamides. In the mechanism proposed above (Scheme 1), intermediate **C** plays a central role and is noteworthy because it embodies the bifunctional role of Al^{III} via activation of *both* the amine and carboxamide substrates. Lewis acids, such as $Sc(OTf)_3$, should be capable of electrophilic activation of the carboxamide, but the triflate anion is insufficiently basic to form a Sc−amido species. In contrast, alkali-metal amido species are quite basic. They will deprotonate the carboxamide N−H to yield a metal amidate complex analogous to the amidoaluminum complex **1** (cf. intermediate **A**, Scheme 1). However, alkali metal cations possess only a single positive charge and are relatively weak Lewis acids. Therefore, they are not effective at organizing multiple substrates in their coordination sphere and do not effect the bifunctional substrate activation mechanism proposed for Al^{III}.

This Al^{III}-catalyzed transamidation mechanism resembles mechanisms proposed for metalloenzyme-catalyzed hydrolysis reactions.[14] The metal cofactor in these enzymes often serves a bifunctional role, activating water via formation of a reactive M−OH fragment and activating the electrophilic substrate via coordination at the Lewis acidic metal center.

A critical challenge that must be overcome in these Al^{III}-catalyzed transamidation reactions is the high stability, and hence low reactivity, of the Al^{III}−amidate complex **A**. Attempts to destablize this Al^{III}−amidate interaction and achieve higher

(13) Konomi, T.; Tani, H. *J. Polym. Sci., Part A: Polym. Chem* **1971**, *9*, 325.

(14) See, for example: (a) Bertini, I.; Luchinat, C. In *Bioinorganic Chemistry*; Bertini, I., Gray, H. B., Lippard, S. J., Valentine, J. S., Eds.; University Science Books: Mill Valley, CA, 1994; p 37. (b) Parkin, G. *Chem. Rev.* **2004**, *104*, 699.

catalytic activity are currently being explored. The mechanistic insights gained from this study have prompted us to evaluate transamidation reactions between tertiary carboxamides and secondary amines. Tertiary carboxamides do not possess a N−H bond and, therefore, will not generate Al^{III}−amidate complexes. Preliminary studies suggest amidoaluminum complexes, such as **1**, are effective catalysts for these transmidation reactions.

Conclusion

The combined use of kinetic and spectroscopic studies has provided valuable insights into the mechanism of Al^{III}-catalyzed transamidations. The amidoaluminum complex $Al_2(NMe_2)_6$ was selected from catalyst-screening studies as an effective precatalyst.[8] Under catalytic conditions, $Al_2(NMe_2)_6$ reacts rapidly with secondary carboxamides to yield a tris-amidate−aluminum complex (**6)** that has been identified as the catalyst resting state. The reaction of **6** with a primary amine and subsequent proton transfer from amine to a coordinated amidate ligand are proposed to initiate the stepwise transamidation mechanism. The results of this study highlight the ability of an Al^{III} center to play a bifunctional role in the transamidation reaction, and the mechanistic insights are now being used to develop improved catalysts and target novel transformations of carboxamide-based molecules.

Acknowledgment. We are grateful to the NSF Collaborative Research in Chemistry program (Grant No. CHE-0404704) for financial support of this work.

Supporting Information Available: Experimental procedures and additional spectroscopic data, including FT-IR and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JA060331X