Atom efficient cyclotrimerization of dimethylcyanamide catalyzed by aluminium amide: a combined experimental and theoretical investigation†

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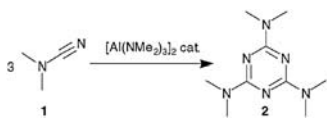
A novel method for the cyclotrimerization of dimethylcyanamide to form hexamethylmelamine has been developed using an aluminium amide catalyst; detailed DFT modelling of the catalytic cycle supports a triple insertion, nucleophilic ring closure, deinsertion mechanism.

Hexamethylmelamine (**2**) is a potent antitumour compound used in the treatment of ovarian cancer.[1] Additionally, various 1,3,5-triazine derivatives show significant pharmacological and herbicidal properties,[2] and can be used as polymer photostabilizers.[3] Consequently, this family of compounds has attracted considerable attention. Although **2** can be synthesized by the amination of cyanuric chloride with dimethylamine,[4] a simpler and atom economical synthesis can be envisaged through the cyclotrimerization of dimethylcyanamide (**1**) (eqn (1)).[5]



(1)

While there have been investigations into the cyclization of nitriles[6] and cyanamides,[7] carrying out these transformations in the absence of transition metal catalysts or harsh reagents presents a significant challenge. Several strong reagents have been found to catalyze the trimerization of dimethylcyanamide with variable degrees of success, including elemental sodium,[8] bis(trimethylsilyl)methyl lithium,[9] triflic anhydride,[10] and phenyl lithium.[11]

Neutral aluminium complexes are commonly used as Lewis acid catalysts in organic synthesis,[12] and aluminium amides are potential bifunctional catalysts, possessing a Lewis acidic Al(III) centre and activated nucleophilic amido groups. For example, aluminium amides have recently demonstrated notable activity as simple, mild, and inexpensive transamidation catalysts.[13] Reactions of group 13 amides and alkyls with unsaturated CN bonds, notably carbodiimide insertion[14] and nitrile insertion,[15] are not reported to be catalytic. These features led us to investigate aluminium amides as potential catalysts for the activation of cyanamides.

In the course of these investigations, we found that tris(dimethylamido)aluminium readily catalyzed the cyclotrimerization of dimethylcyanamide at room temperature. The addition of 4–5 mol% $[Al(NMe_2)_3]_2$ to a solution of dimethylcyanamide in hexane leads to the smooth formation of hexamethylmelamine, which can be easily isolated in excellent yield (86%). Intrigued by this reactivity, we undertook a computational study using Density Functional Theory (DFT)[16] in order to elucidate the mechanistic details of the transformation. Herein, we report both the synthetic and computational aspects of this remarkable example of main group catalysis.

Lewis acids, such as $SnCl_2$ and $La(OTf)_3$, are commonly used as catalysts for the cyclotrimerization of nitriles,[17] which led us to consider a simple mechanism where the aluminium amide acts only as a Lewis acid. In this mechanism, coordination of the nitrile function to the aluminium faciltates a [2 + 2] addition of a second equivalent of cyanamide, forming a diazine. A [4 + 2] cycloaddition of another equivalent cyanamide to this diazine gives **2**. However, the activation energy for the Lewis acid catalyzed [2 + 2] addition was prohibitively high (46.0 kcal mol^{-1}), indicating that this mechanism is not viable.

We have devised an alternative catalytic cycle for the cyclotrimerization initiated by insertion of dimethylcyanamide into the aluminium amide bond of the catalyst (Scheme 1). Two subsequent insertions of the cyanamide, followed by nucleophilic ring closure and an aromatizing de-insertion, provide the trimerization product, **2**.

The initial insertion requires the dissociation of the dimeric pre-catalyst into the active trivalent aluminium complex. The subsequent coordination of the nitrogen lone pair of the nitrile moiety to the formally empty aluminium p-orbital counterbalances much of the dissociation energy (10.6 kcal mol^{-1}), and significantly enhances the electrophilicity of the cyanamide (see Fig. 1). Furthermore, coordinated cyanamide is positioned for the insertion of the C≡N function into the aluminium amide bond, which has a calculated activation energy of only 15.2 kcal mol^{-1}, relative to the free precatalyst and dimethylcyanamide, **1**. The insertion occurs through the addition of aluminium amide to the nitrile triple bond *via* a four-centre transition state. The resulting trivalent aluminium intermediate (**5**) has a 150° C–N(guanidinate)–Al angle, indicating that the hybridization of the guanidinate nitrogen is between sp^2 and sp. Interestingly, the insertion product is

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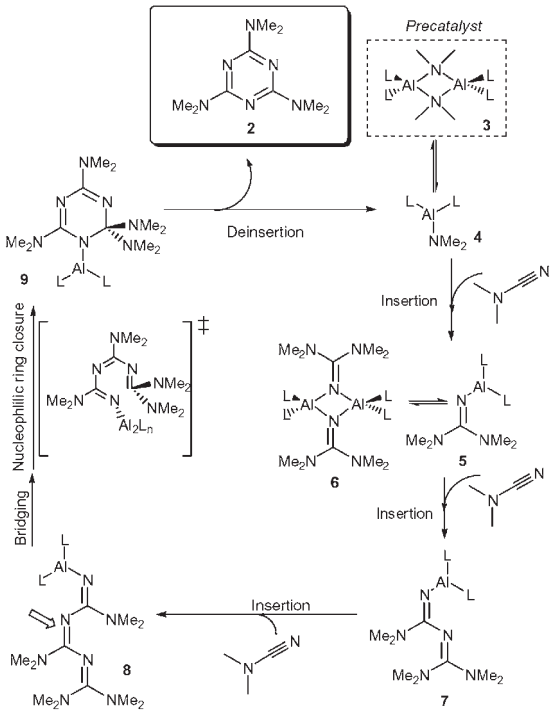


Scheme 1 Proposed catalytic cycle for the cyclotrimerization of dimethylcyanamide with tris(dimethylamide)aluminium catalyst. L = NMe_2 or other.

thermoneutral with respect to the starting materials and the dimeric catalyst, thus recovering the energetic penalty for dissociation of the aluminium amide precatalyst.

Experimental support for this step of the mechanism is provided though the stoichiometric reaction of the $[Al(NMe_2)_3]_2$ precatalyst and dimethylcyanamide. From this reaction, the dimerized form of **5**, $(Al(NMe_2)_2[NC(NMe_2)_2])_2$ (**6**), was isolated and characterized (Fig. 2).† Compound **6** is a competent catalyst in this cyclotrimerization reaction. This structure confirms that cyanamide undergoes facile insertion into an Al–N(amido) bond to form **5** and provides additional evidence for the bifunctional nature of the catalyst.

Although the first insertion product, **5**, may directly undergo further insertion as depicted in Scheme 1, it is likely that it will

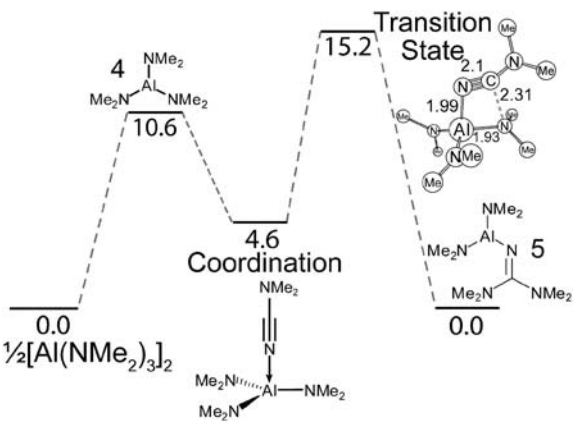


Fig. 1 Gibbs free energy reaction profile (kcal mol^{-1} with respect to the catalyst in the dimeric state and the free cyanamide) for the first insertion reaction.

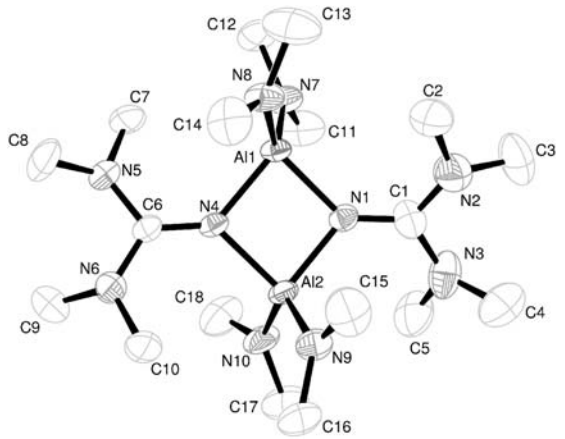
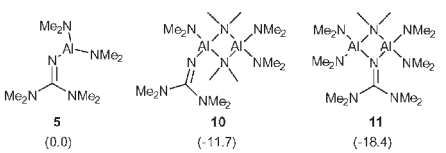


Fig. 2 Crystallographic molecular structure of **6** $[Al(NMe_2)_2\text{-}NC(NMe_2)_2]_2$.

form a stabilizing dinuclear Al species with a monomeric equivalent of the aluminium amide catalyst (**4**), which is putatively the most common trivalent aluminium complex *in situ*. Although it is possible to bridge through an amido ligand (**10**), the sp^2 hybridized nitrogen of the guanidinate is a more effective bridging ligand, so **11** is the more stable isomer (Scheme 2). All cyanamide insertion products likely form dinuclear guanidinate bridged complexes.

Two further cyanamide insertions are needed to generate a chain of sufficent length to cyclize and form the product. These insertions follow a mechanism analogous to the first insertion: dissociation of the dinuclear aluminium complex, coordination of cyanamide, the insertion transition state, formation of the three-coordinate guanidinate product, and then bridging with aluminium amide to form a dinuclear complex. The reaction energies for these steps are collected in Table 1. The coordination of cyanamide to the metal in the 2nd and 3rd insertions is somewhat weaker than in the first due to the strong π donation from the guanidinate to the metal, resulting in a more electron rich metal. In each case, insertion into the Al–N(guanidinate) bond is facile and the formation of the product is exergonic.

Once three insertions have occurred, cyclization is possible (**8** → **9** in Scheme 1). Our calculated reaction profile for the cyclization is shown in Fig. 3. Like intermediate **5**, intermediate **8** will form bridged dinuclear complexes with aluminium amide. While the guanidinate bridged species are more stable, species such as **12** (Fig. 3), in which the guanidinate group is terminal, are able to cyclize without requiring the energetically unfavourable dissociation of the dinuclear complex. The ring closure occurs through a nucleophilic attack by the guanidinate nitrogen on the π* orbital of the terminal guanidine C═N bond. The immediate product of the cyclization, **13**, has the aluminium internally coordinated to a *syn* dimethylamine group, facilitating



Scheme 2 Selected resting states of the first intermediate with Gibbs free energies (kcal mol^{-1}, with respect to **5** + ½$[Al(NMe_2)_3]_2$) in parentheses.

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Table 1 Relative free energies of insertion steps[a]

	Insertion 1	Insertion 2	Insertion 3
3-coordinate Al species	10.6 (**4**)	0.0 (**5**)	−6.5 (**7**)
Coordination with **1**	4.6	−1.1	−7.1
Transition state	15.2	9.2	4.5
Product	0.0 (**5**)	−6.5 (**7**)	−12.8 (**8**)
Bridging complex	−18.4 (**11**)	−25.0	−31.2

[a] All energies reported in kcal mol^{-1} relative to three units of dimethylcyanamide and $\frac{1}{2}$ unit of $[Al(NMe_2)_3]_2$.

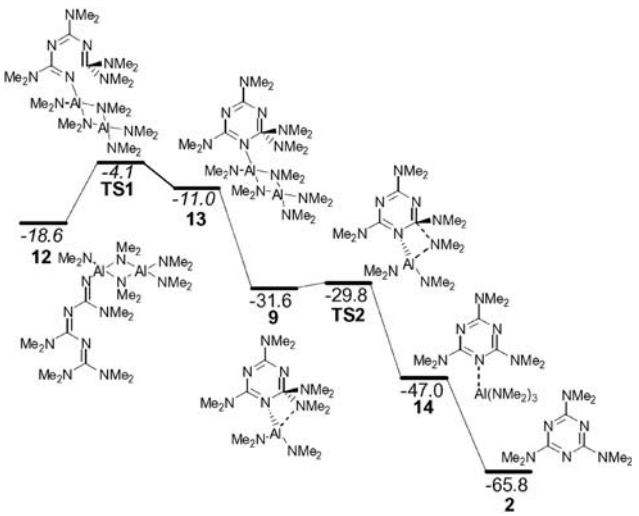

Fig. 3 Gibbs free energy reaction profile (kcal mol^{-1}) for the cyclization and de-insertion steps. All energies reported in kcal mol^{-1} relative to three units of dimethylcyanamide and $\frac{1}{2}$ unit of $[Al(NMe_2)_3]_2$.

the elimination of the catalyst through the dissociation of the dinuclear species, forming **9**. The catalytic cycle is completed with the facile transfer of an amido group to the aluminium (TS2) and by passing through **14**, in which the resultant aromatic melamine ring coordinates to aluminium amide through a nitrogen lone pair. The cyclization is thermodynamically driven by the formation of aromatic product **2**, which lies 47.0 kcal mol^{-1} lower in free energy than intermediate **12**. The overall trimerization reaction as shown in eqn (1) is exergonic by 65.8 kcal mol^{-1}.

It is notable that in order for the cyclization reaction to occur, the interior C=N bond of the third insertion product, **8**, must be *cis* with respect to the chain. (This bond is indicated with an arrow in structure **8** of Scheme 1.) Although our calculations show there is little preference for forming the *cis vs. trans* isomer, we also find that the *Z*/*E* isomerization has a remarkably small barrier of only 4.9 kcal mol^{-1}. Thus, if the *trans* isomer forms, it can easily isomerize to the *cis* product, **8**, thereby allowing for the cyclization.

We have found a main group catalyst, $[Al(NMe_2)_3]_2$, which accomplishes the cyclotrimerization of dimethylcyanamide, and have investigated the mechanistic details of the catalytic cycle with DFT calculations. A conventional mechanism where an aluminium centre simply serves as a Lewis acid was found to have a prohibitively high barrier. Our more detailed examination identified a much more facile mechanism, wherein three insertion reactions, followed by nucleophilic ring closure and de-insertion provides hexamethylmelamine (**2**). Facile *Z*/*E* isomerization of an internal imine allows the polymerized chain to adopt the necessary *cis* geometry for the ring closure. The ability of the ring closure step to occur while the aluminium is sequestered in a bridging complex allows the cyclization to occur more readily.

This reaction mechanism demonstrates it is possible to use established aluminium amide reactivity, such as nitrile insertion and amido group transfer, for the catalytic transformation of CN multiple bonds. As a result we are exploring approaches to novel 1,3,5-triazine heterocycles from the reactions of intermediates, such as **6**, with carbodiimides and isocyanates as well as continuing our investigations on the use of group 13 amides in the place of transition metal catalysts and harsh reagents for other reactions involving CN bonds. An analogous reaction mechanism may also be viable for other metal-amide catalyzed cyclotrimerizations.[9]

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