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Investigations providing a plausible mechanism in the hexamethyldisilazane-catalyzed trimerization of alkyl isocyanates

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ABSTRACT

Using HMDS as catalyst for the trimerization of isocyanates presents many advantages as the expected isocyanurate is not contaminated by the catalyst or other side-products resulting from its degradation. In addition, HMDS presents a low toxicity, and is compatible with industrial applications. This article describes the hexamethyldisilazane (HMDS)-catalyzed trimerization of octylisocyanate. Experimental investigations and mechanistic considerations indicate that the true catalyst of the trimerization is trimethylsilyloctylamine, which results from the preliminary condensation of HMDS with octylisocyanate.

1. Introduction

Isocyanates and polyisocyanates constitute a very important class of starting materials in many industrial applications, such as foams, elastomers, paints, surface coatings, and fibers.[1] Yet, the high toxicity of isocyanate constitutes a serious drawback for potential applications. Indeed, Bhopal disaster is by far, the most catastrophic accident in the history of chemical industry, and resulted from a leak of methyl isocyanate in the atmosphere.[2] Conversely, the atom efficiency is ideal when ureas or urethanes are synthesized from isocyanates and amines or alcohols as precursors, respectively. As no economically viable alternative to isocyanates has been discovered to date, different approaches for limiting the inherent toxicity of isocyanates were proposed. The major drawback of isocyanates dealing with its volatility, substitution of volatile monomers by higher molecular weight oligomers or derivatives was developed. Thus, urethane, biuret, carbodiimide, uretdione, and isocyanurate were proposed as low vapor pressure (non VOC) building blocks.[3] Among these oligomers, isocyanurates play an important role due to their stability and increased thermal resistance.[4] In addition, they were used as activators for the polymerization of ε-caprolactam,[5] as precursors in the preparation of flame-retardant materials for electrical devices,[6] in the preparation of copolymer resins[7] and more recently in organosilicon nanochemistry.[8]

Many catalysts, such as Lewis bases[9] (phosphines, carboxylates, ammonium salts, cyanates, carbamates, carbenes) or organometallic complexes[10] were employed for the trimerization of isocyanates. Nevertheless, very little information concerning the mechanism and the advantages/limitations of these approaches were reported. A noticeable exception concerns one recent report by Horváth et al. that described the mechanism of the phosphine-catalyzed trimerization of aryl isocyanates. In their study, they demonstrated that the initial step concerns the activation of the isocyanate by a nucleophilic attack of the phosphine on the electro-deficient isocyanate carbon atom affording a zwitterionic intermediate that was also proposed earlier by Verkade et al.[11]

As alkyl isocyanates generally exhibit a different behavior compared with the aryl analogues, and as they also constitute a very important class of industrial building blocks, we dedicated our attention towards the elucidation of the intrinsic mechanism of the hexamethyldisilazane (HMDS)-catalyzed cyclotrimerization of octylisocyanate ($C_8H_{17}NCO$). This catalyst presents potentially two

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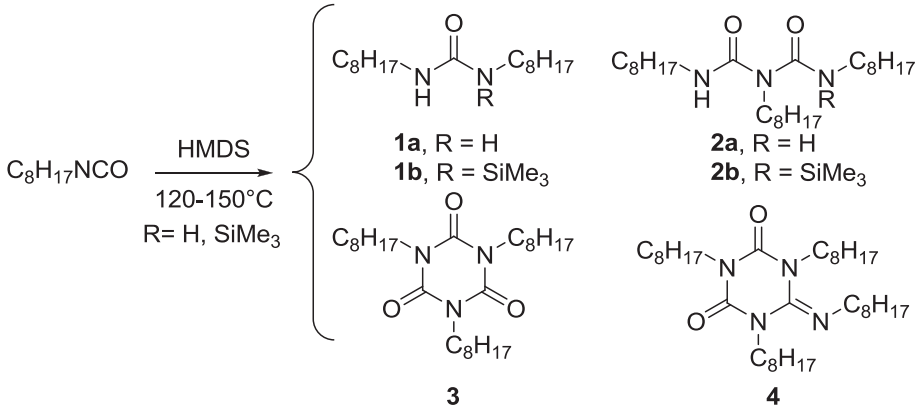
specific advantages: on the one hand it exhibits a relatively low toxicity and on the other hand it can be readily eliminated at the end of reaction due to its low boiling point compared to that of isocyanate oligomers. If this catalyst was claimed in several important patents,[12] to date very little is known concerning the mechanism of the catalysis. This lack of information is detrimental from both the academic and the industrial point of view. We believe that the mechanistic investigations disclosed in this paper will help improving the control and the optimization of such a complex process. The choice of octylisocyanate relies on its close similarity to the industrially relevant hexamethylenediisocyanate (HDI). Moreover, our choice is justified by its ease of handling and the fact that it affords easy-to-characterize low molecular weight products and by-products upon oligomerization.

2. Results and discussion

The solvent-free reaction between $C_8H_{17}NCO$ and different amounts of HMDS leads to a complex mixture of oligomers, such as dioctyl urea **1a**, octyltrimethylsilyl urea **1b**, biuret **2a**, trimethylsilyl biuret **2b**, isocyanurate **3**, iminotriazinedione **4**, etc.… impossible to analyze without the complete characterization of the pure products (Scheme 1).

Urea **1a** was prepared in quantitative yield by mixing directly octylisocyanate with an excess of octyl amine at room temperature. When the temperature was raised to 130 °C in the presence of octylisocyanate, **1a** was quantitatively converted into biuret **2a**. The syntheses of the low molecular weight oligomers (**3**–**5**) were also carried out. On a laboratory scale, we discovered that the easiest synthesis of isocyanurate **3** involved a catalytic amount (0.5 mol %) of trimethylsilanolate as catalyst. Use of such nucleophile as catalyst had already been claimed (but not described!) in several patents for the oligomerization of isocyanates.[13] Upon addition of trimethylsilanolate, trimerization of $C_8H_{17}NCO$ occurred readily in 1 h at room temperature and the expected isocyanurate was isolated in 83% yield. When the amount of Me_3SiONa was increased to 50% and the temperature raised to 60 °C, **3** was isolated in 94% yield. On the other hand, the preparation of the iminotrimer analogue **4** appeared more challenging. Even if it was reported that triphenylphosphine oxide catalyzes efficiently the trimerization of EtNCO and the formation of the corresponding iminotrimer,[14] in our hands, this procedure did not afford the expected iminotrimer **4** in decent yield. The major by-product of the reaction appeared to be the iminodimer **5** (10%). Actually, we found that the best catalyst for the formation of **4** was $Sn(acac)_2$. Using these conditions, after 3 h at 40 °C, the expected iminotrimer was isolated in 40% yield after purification by a silica-gel chromatography.

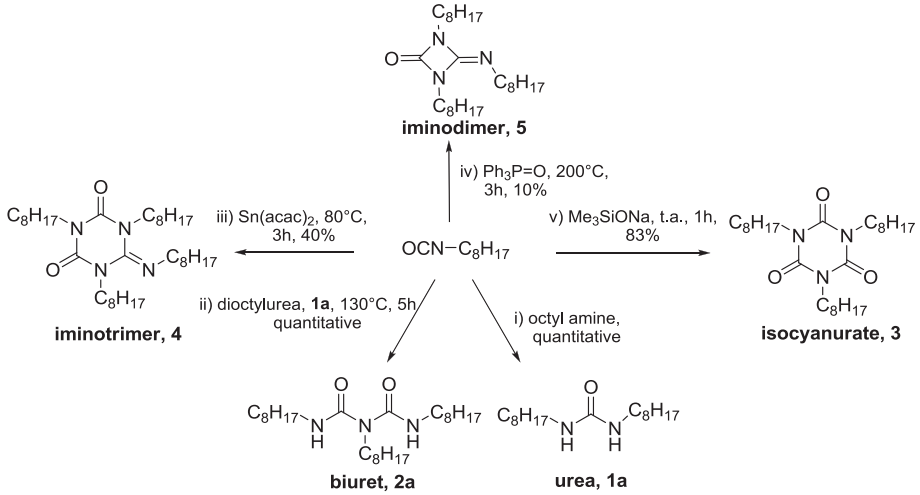


Scheme 1. Reaction between octylisocyanate and HMDS.

Accordingly, the first part of our work was devoted to the synthesis of the different products and by-products of the trimerization reaction. Inspired by methods described in the literature for alkyl or aryl isocyanates, we developed the synthesis of the intermediates using octylisocyanate as starting material (Scheme 2). Details concerning these syntheses are presented in the Experimental section.

Based on classical spectroscopic analyses, we unambiguously determined the structure of all isolated products. Thus, using the spectroscopic signatures of the pure products (Fig. 1), we could analyze the ^1H NMR spectrum of a complex reaction mixture.

Taking into account the formation of a complex mixture in the case of the HMDS-catalyzed oligomerization of octylisocyanate, we



Scheme 2. Synthesis of oligomerization products of octylisocyanate.

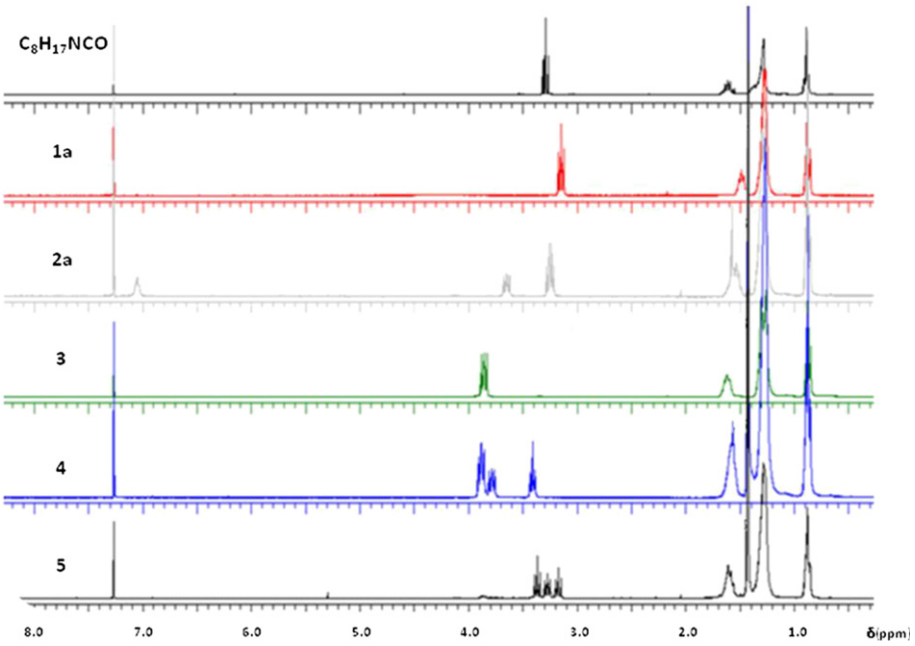
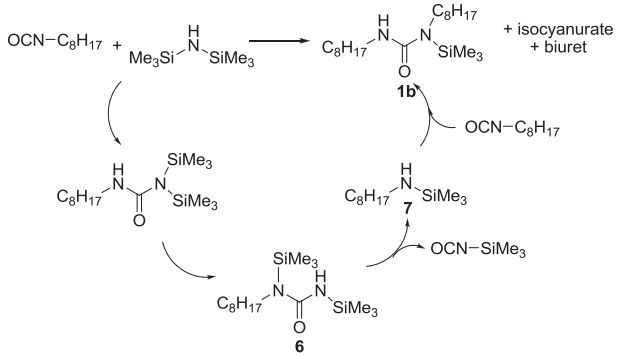


Fig. 1. ^{1}H NMR spectra of $C_8H_{17}NCO$ and the isolated pure products.

first carried out a reaction using a stoichiometric amount of HMDS in order to identify the first intermediates formed during this process. The reaction mixture was heated at 120 °C for 2 h before the temperature was increased to 150 °C for an additional 2 h. The progress of the reaction was monitored by analyses and NMR spectroscopy. After 4 h, the conversion was complete and we identified the octyltrimethylsilyl urea **1b** as the major product (>50% yield), and isocyanurate **3** and biuret **2a** as by-products (Scheme 3).



Scheme 3. Proposed reaction pathway for the reaction between stoichiometric amount of octylisocyanate and HMDS.

We explained the formation of **1b** by assuming that the reaction starts with the nucleophilic attack of HMDS on the electrophilic carbon atom of $C_8H_{17}NCO$ leading to the formation of *N*,*N*-bis(trimethylsilyl)octylurea. Then, the latter undergoes a TMS migration leading to the less hindered *N*,*N*′-bis(trimethylsilyl)octylurea, **6**. The driving force of this reaction can be attributed to the steric decongestion resulting from the migration of a TMS group. Such a mechanism was recently proposed by Cheng and Lu as the key step of the oligomerization of α amino acid *N*-carboxyanhydrides catalyzed by HMDS.[15]

Following, the transformation of **6** in trimethylsilyldioctylurea **1b**—the main product of the stoichiometric reaction—required the elimination of trimethylsilyl isocyanate. This hypothesis was confirmed by carrying the same reaction with argon flushing. Indeed, under these conditions, we analyzed the volatiles and detected the presence of trimethylsilyl isocyanate. This experiment clearly demonstrates that TMSNCO is a by-product in the reaction.

To determine the exact role of TMSNCO we carried out three additional 10% HMDS-catalyzed-oligomerizations of octylisocyanate in the presence of an excess TMSNCO (10, 25 or 100%, respectively). Two experimental procedures were tested: the first one in a double-necked round-bottom equipped with a condenser under argon atmosphere and the second one in a sealed tube. The results of this study are disclosed in Table 1.

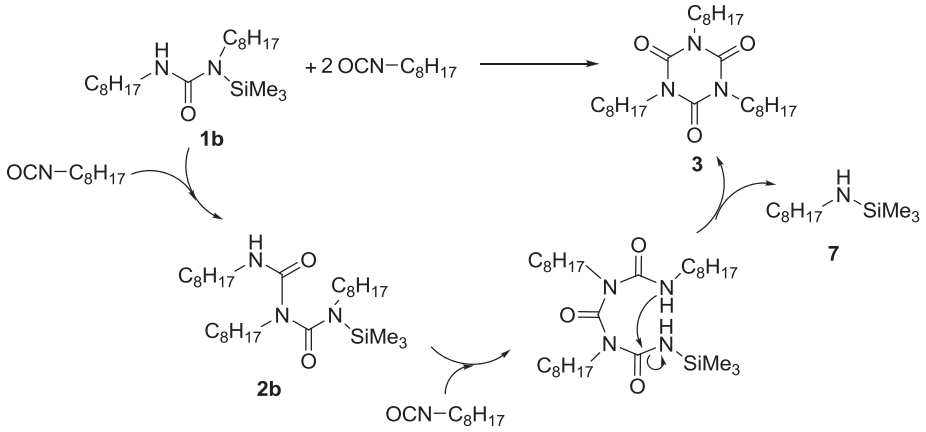
Table 1
Influence of TMSNCO

Entry	TMSNCO (%) added	Total conversion (%) after 4 h[a]	**3** (%) after 4 h[a]
1[b]	0	70	35
2[b]	10	66	34
3[c]	0	75	40
4[c]	10	60	32
5[c]	25	60	30
6[c]	100	50	18

[a] 2 h at 120° and 2 h at 150 °C.
[b] Open vessel.
[c] Reaction in sealed tube.

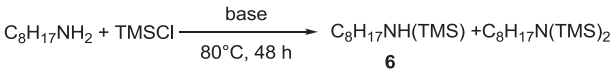
When the reaction was carried out in an open vessel (argon atmosphere), the addition of an excess TMSNCO did not influence the outcome of the reaction (Table 1, entries 1 and 2). This observation could be ascribed to the low boiling point (bp=90–92 °C) of TMSNCO, that is, rapidly evaporated from the reaction mixture. Conversely, when the reaction was performed in a sealed tube, the addition of TMSNCO clearly reduced the conversion of the starting material (Table 1, entries 4–6). Correlatively, the formation of the isocyanurate decreased. Therefore the key step—i.e., the formation of TMS-octyl amine **7** from **6** – hence elimination of TMSNCO should be considered as reversible.

The following step leading to the formation of the isocyanurate **3** was determined after the reaction between an excess of octylisocyanate with **1b** at 120–150 °C. These experimental conditions afforded the expected isocyanurate and the trimethylsilyl biuret **2b** intermediate. On the basis of these observations, we can propose the following mechanism for the formation of the symmetrical isocyanurate (Scheme 4).



Scheme 4. Formation of isocyanurate starting from the intermediate **1b**.

In parallel, in order to confirm the crucial role of **7**, we attempted to prepare the silylated amine **7** by reaction of octyl amine with TMSCl in the presence of a base (Scheme 5).



Scheme 5. Synthesis of trimethylsilyloctylamine.

Even though similar approaches were described in the literature,[16,17] neither the use of *n*-BuLi nor Et_3N as a base afforded the pure *N*-trimethylsilyloctylamine **6**. In our hands, an inseparable mixture of starting compound, mono- and disilylated amines was obtained. Upon careful distillation, it appeared that the expected mono-silylated amine undergoes a rapid trimethylsilyl migration that regenerates the starting material as well as the bis-silylated species. As we could not isolate the pure mono-silylated amine **6**, we reacted a 70:30 mixture of mono-silylated amine and disilylated amine analyses with a large excess of isocyanate. As expected, the isocyanurate **3** was obtained as the main product. Moreover, no traces of bis-silylated amine were observed at the end, indicating the fast dismutation of this product. This result undoubtedly strongly indicates that **6** constitutes the 'true catalyst' for the trimerization of $C_8H_{17}NCO$.

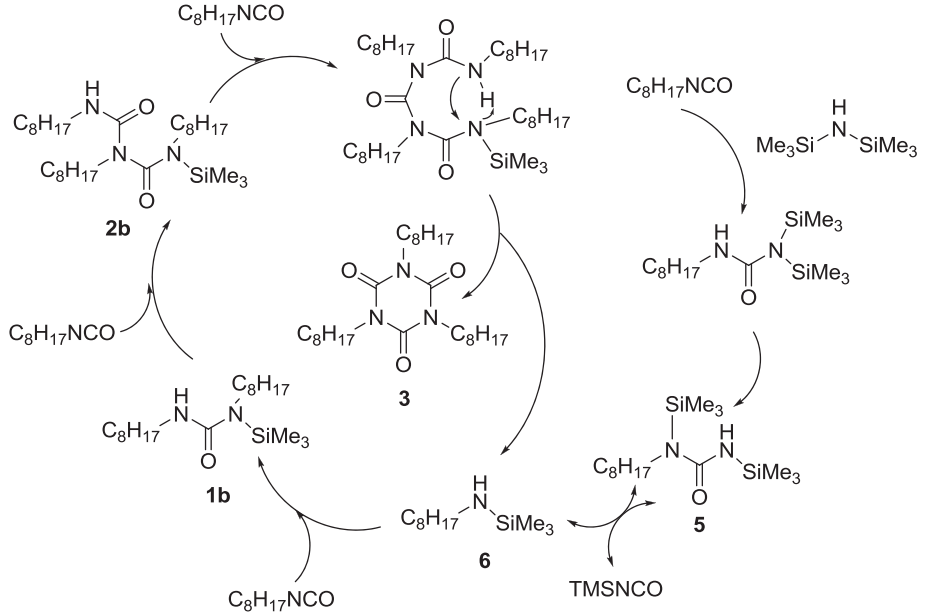
On the basis of the aforementioned results, we can propose the following mechanism for the HMDS-catalyzed cyclotrimerization of $C_8H_{17}NCO$ (Scheme 6).

The key point of the mechanism concerns the crucial role of the catalyst that does not only acts as a nucleophile but also was proved to be extremely active because the TMS group can migrate during the catalytic process. In that respect, this mechanism is very different from that described earlier by Horvárth and Richter in the case of the PPh_3-catalyzed trimerization of aromatic isocyanates. We believe that these new results will help designing new catalysts for a better control of industrially relevant reactions. Thus, HMDS appears as a powerful, relatively benign organocatalyst particularly suitable for the cyclotrimerization of aliphatic isocyanates.

3. Experimental part

3.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 300 and 75 MHz, respectively. The chemical shifts were



Scheme 6. Plausible mechanism for the HMDS-catalyzed trimerization of octylisocyanate.

recorded in δ relative to the residual solvent peaks at 7.26 (^{1}H) and 77.7 ppm (^{13}C), respectively.[18] MS analyses were carried out on a Thermofinnigan MAT 95 XL spectrometer located at the Centre Commun de Spectrométrie de masse de l'Université Claude Bernard Lyon1. TLC analyses were performed on silica-gel 60 F_{254}-coated aluminum sheets. Analytical data for compounds **1a** and **2a** are in agreement with the literature.[19,20]

3.2. Synthesis of urea 1a

Octylamine (1 equiv) was dissolved in CH_2Cl_2 (0.5 M) and cooled at 0 °C. Octylisocyanate (1 equiv) was added and the reaction mixture was allowed to warm to room temperature and stirred until the amine was totally consumed (TLC). The reaction mixture was filtered off, and the precipitate was collected and washed with cold CH_2Cl_2. After drying the expected urea was isolated in a quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, J=6.7 Hz, 6H, CH_3), 1.21 (m, 24H, CH_2), 1.42 (m, 4H, βCH_2), 3.07 (t, 4H, αCH_2), 5.69 (m, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.4, 24.1, 28.2, 30.8, 30.9, 31.8, 33.4 (CO signal missing). ESI MS (positive mode) m/z=284.35 (M^+).

3.3. Synthesis of biuret 2a

Dioctylurea **1a** (10 mmol, 1 equiv) and $C_8H_{17}NCO$ (12 mmol, 1.2 equiv) were mixed and reacted together in a sealed tube. After 15 min at 90 °C, the reaction mixture became clear. The reaction temperature was raised up to 130 °C and stirring was maintained for 20 h, until the urea was totally consumed (TLC monitoring). The yellowish reaction mixture was cooled to room temperature, and pentane was added. A white precipitate was filtered off, and the filtrate was evaporated to dryness affording the expected biuret **2a** as pale yellow oil in a quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79 (m, 9H, CH_3), 1.19–1.22 (m, 30H, CH_2), 1.47 (m, 6H, βCH_2), 3.27 (m, 4H, αCH_2), 3.64 (m, 2H, αCH_2), 6.99 (m, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 23.0, 27.4, 27.4, 29.3, 29.6, 29.66, 29.7, 30.0, 32.1, 41.1, 156.6.

3.4. Synthesis of *N*,*N*′,*N*″-trioctyl-1,3,5-triazine-triones, 3

At 0 °C, under Argon, Me_3SiONa (0.4 mmol, 0.4 mL of a 1 M solution in CH_2Cl_2) was slowly added over $C_8H_{17}NCO$ (20 mmol, 3.10 g). Upon stirring at room temperature, the solution becomes very viscous. After 48 h stirring, the reaction mixture was quenched with water and CH_2Cl_2 (20 mL) was added. The organic layers were washed with water (×3) and NaCl (×1). After drying with anhydrous $MgSO_4$, the crude product (oil) was purified by flash chromatography (cyclohexane/ethyl acetate=8/2) to give 2.9 g of pure product (Yield: 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.71 (m, 9H, CH_3), 1.10–1.15 (m, 30H, CH_2), 1.47 (m, 6H, βCH_2), 3.70 (t, 6H, J=7.6 Hz, αCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8, 21.3, 25.4, 26.5, 27.9, 30.4, 41.7, 52.1, 147.7. ESI-HRMS (positive mode) calculated for $C_{27}H_{52}N_3O_3$ ($M+H^+$) 466.4009; found 466.4026.

3.5. Synthesis of iminotrimer, 4

At room temperature, a sealed tube was charged with $C_8H_{17}NCO$ (15 mmol, 2.64 mL) and $Sn(acac)_2$ (1.5 mmol, 0.47g). After 45 min stirring at room temperature, the reaction mixture was heated to 80 °C. Immediately, a green precipitate appeared before the reaction mixture became reddish. Heating was maintained for 3 h. After, a 10:1 acetone/water mixture (15 mL) was added, inducing the formation of a precipitate that was filtered off. The filtrate was directly evaporated under vacuum affording a viscous orange oil that was purified over a silica-gel column chromatography. Using a mixture of cyclohexane/EtOAc 30:1 as eluent, the expected compound **4** (0.9 g, 40% yield) was eluted as the less polar product (R_f=0.55), before the isocyanurate 3 (R_f=0.42). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (m, 12H, CH_3), 1.28 (m, 40H, CH_2), 1.60 (m, 6H, βCH_2), 3.43 (t, 2H, J=6.5 Hz, αCH_2), 3.77–3.92 (m, 4+2H, αCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.41, 23.0, 27.0, 27.1, 27.3, 27.6, 29.5, 29.6–29.8, 31.9, 32.1, 32.2, 41.0, 44.0, 48.0, 53.8, 145.8, 160.1. ESI-HRMS (positive mode) calculated for $C_{35}H_{69}N_4O_2$ ($M+H^+$) 577.5421; found 577.5442.

3.6. Synthesis of iminodimer, 5

At room temperature, a sealed tube was charged with $C_8H_{17}NCO$ (15 mmol, 2.64 mL) and $O{=}PPh_3$ (1.5 mmol, 0.579 g). The reaction mixture was brought to 200 °C. When the reaction had reached 200 °C, small bubbles of CO_2 were evidenced in the reaction mixture and the reaction turned dark. After 12 h, the CO_2 bubbling had stopped and the reaction had become black. After cooling, the reaction mixture was directly poured on a silica-gel column chromatography and eluted with an increasing amount of AcOEt in cyclohexane. The iminodimer (157 mg, 10% yield) was isolated as the fourth spot, after elution of the iminotrimer **4**, di-iminotrimer, and the isocyanurate **3**. Two chromatography columns were required for isolating the almost pure iminodimer **5** (**4** and **5** display very similar polarities whatever the solvent). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (m, 12H, CH_3), 1.21 (m, 30H, CH_2), 1.55 (m, 6H, βCH_2), 3.10 (t, 2H, J=7.1 Hz, αCH_2), 3.20 (t, 2H, J=7.2 Hz, αCH_2), 3.32 (t, 2H, J=7.2 Hz, αCH_2). ESI-HRMS (positive mode) calculated for $C_{26}H_{52}N_3O$ ($M+H^+$) 422.4110; found 422.4103.

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