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Reaction of Metal Alkoxides with Lysine: Substitution of Alkoxide Ligands *vs.* Lactam Formation

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Summary. Reaction of $Ti(OEt)_4$ with lysine results in the formation of $Ti(OEt)_3$(lysinate), as previously reported. Contrary to that, $Al(O^sBu)_3$ only catalyzes the formation of 3-aminocaprolactam, and no substitution product was observed. The reaction of $Zr(OBu)_4$ with lysine at room temperature produced both 3-aminocaprolactam and $Zr(OBu)_3$(lysinate); the lysinate complex was not observed when the reaction was performed at elevated temperatures.

Keywords. Transition metals; Sol-gel processing; Amino acids; Coordination chemistry.

Introduction

Complexing ligands (*CL*) have often been reported in the sol-gel literature as chemical additives to moderate the reactivity of non-silicate metal alkoxides [1]. When a metal alkoxide $M(OR)_x$ is reacted, for example, with acetic acid or acetylacetone, part of the alkoxo ligands is substituted by acetate or acetylacetonate groups. A new molecular precursor $M(OR)_{x-y}(CL)_y$ is obtained with a different structure and a lower reactivity. Bidentate ligands (bridging or chelating), such as carboxylates, β-diketonates, phosphonates, sulfonates, *etc.*, are more strongly bonded than comparable monodentate ligands and are therefore less readily hydrolyzed than the remaining O*R* groups upon sol-gel processing. Such ligands are also suited to introduce organic functionalities into metal oxide-based hybrid materials [2]. The complexing ligand then has to be of the kind $(RO)_yM[CG–X–A]_x$, where *CG* represents the complexing group, *A* the functional organic group, and *X* an inert spacer. For example, an often used functional *CL* is methacrylate, where *A* is a polymerizable group.

Some time ago we reported that lysine is another type of functional *CL* that could be useful for coordinating metal ions or metal complexes to metal oxides *via*

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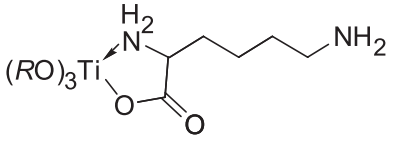


Fig. 1. Coordination of lysine to a Ti(O*R*)$_3$ moiety; for simplification, a monomeric formula is drawn to show the coordination mode of the aminocarboxylate ligand; the compound may actually be oligomeric due to bridging alkoxo ligands

sol-gel processing [3, 4]. While the α-amino carboxylate group of the lysinate ligand coordinates to the $M(OR)_x$ moiety as shown in Fig. 1 for Ti(O*R*)$_3$, the dangling ω-amino group is available to coordinate to other metal ions. The chelating coordination of the aminocarboxylate ligand to metal alkoxides was proven for [(*Et*O)$_3$Ti(glycinate)]$_2$ [3].

In this article we report that the reaction of lysine with metal alkoxides is not as general as it may have appeared previously, because the *Lewis* acidic alkoxides may also catalyze formation of the cyclic lactam.

Results and Discussion

We repeated first the previously [3, 4] reported reaction of Ti(OEt)$_4$ with lysine in ethanol both at room temperature and under heating to 80°C. Both reaction conditions led to the same results, which also reproduced our previous findings. Substantial shifts were observed in the ^{13}C (Table 1) and ^{1}H NMR spectra for the OCH$_2$ group of Ti–O*Et* groups, and the shift of the carbonyl carbon from 179.7 in lysine to 184.4 ppm in the product indicated the coordination of carboxylate group to the metal. The chemical shift of the methylene protons of the ε-carbon atom (–C*H*$_2$NH$_2$) in the reaction product were identical to that in lysine. The NMR spectra were thus fully consistent with the suggested composition, *viz.* Ti(O*Et*)$_3$(lysinate), with a coordinated α-amino carboxylate group and a dangling ω-amino group (Fig. 1). The integration of the ^{1}H NMR spectrum also supported the suggested composition.

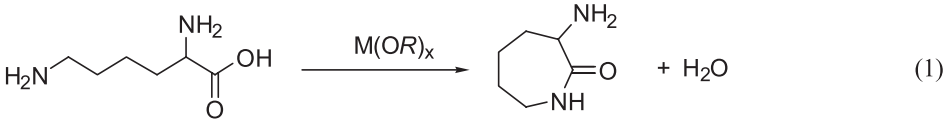
Table 1. ^{13}C NMR chemical shifts (δ/ppm) of *L*-lysine, *L*-3-amino-ε-caprolactam, Ti(O*Et*)$_3$(lysinate), and the reaction product between lysine and Al(O^s*Bu*)$_3$ (only lysinate moiety)

L-lysine (CD_3OD)	Ti(O*Et*)$_3$(lysinate) (CD_3OD)	3-amino-ε-caprolactam ($CDCl_3$)	Reaction product between lysine and Al(O^s*Bu*)$_3$[a] (CD_3OD)	Assignment
24.0, 30.9	24.5, 31.3	28.49, 29.09	29.8, 30.4	–*C*H$_2$*C*H$_2$CH$_2$NH$_{(2)}$
34.7	34.7	33.89	35.0	–*C*H$_2$CH(NH$_2$)–
41.4	41.7	41.88	42.7	–*C*H$_2$NH$_{(2)}$
57.0	57.0	53.93	54.5	–*C*H(NH$_2$)
179.7	184.5	179.68	180.9	–*C*(O)X

[a] The chemical shifts of the reaction product between lysine and Zr(O*Bu*)$_4$ were nearly identical (see Experimental)

The same reaction was performed with $Al(O^sBu)_3$ and $Zr(OBu)_4$ in their parent alcohols. Lysine dissolved when a suspension of one molar equivalent of lysine in a *s*-butanol solution of $Al(O^sBu)_3$ was heated to 80°C. Since lysine is not soluble in alcohols and did not react with $Al(O^sBu)_3$ at room temperature, some reaction must have occurred at elevated temperatures. After solvent removal, the reaction product was analyzed by NMR spectroscopy (^{13}C DEPT and 2D NMR). The chemical shifts of the butoxy groups were the same as in $Al(O^sBu)_3$. A careful analysis of the NMR signals of the lysinate moiety showed small but significant differences compared with the corresponding signals of $Ti(OEt)_3$(lysinate) as all carbon atoms of lysine were shifted (^{13}C NMR; see Table 1). Additionally, the protons of the ε-CH_2 group of lysine were now diastereotopic, which cannot be the case in a $(CH_2)_4NH_2$ chain. The CO band in the infrared spectrum was shifted from 1582 cm^{-1} in lysine to 1651 cm^{-1} (for comparison: 1644 cm^{-1} in $Ti(OEt)_3$(lysinate)). These data suggested a chemical transformation of lysine other than coordination to the metal alkoxide during the reaction with $Al(O^sBu)_3$. Comparison with an authentic sample proved that (alcohol soluble) 3-aminocaprolactam was formed. There were no indications for a substitution of butoxy groups, but we cannot exclude a weak coordination of the formed lactam to some aluminum oxo/alkoxo moiety.

3-Aminocaprolactam has been obtained from lysine with acid catalysts (*e.g.* treatment of lysine hydrochloride with aqueous HCl in MeOH [5]) under heating. Thus, $Al(O^sBu)_3$ reacts as a (*Lewis*) acidic catalyst for the lactam formation (Eq. 1). Another effect of the metal alkoxide may be the shift of the equilibrium in Eq. 1 due to reaction of the produced water with the alkoxide. Since only one equivalent of water is produced with the employed molar ratio, part of the AlO^sBu groups would still be present, as observed by NMR spectroscopy. It should be mentioned that alumina also catalyzes the formation of lactams from γ- or δ-amino acids [6].



(1)

When lysine was added to a solution of $Zr(OBu)_4$ in *n*-butanol, lysine already dissolved at room temperature. When the solution was then heated to 60–70°C, the reaction product had similar chemical shifts in the ^{13}C NMR spectrum as that of the reaction of lysine with $Al(O^sBu)_3$. Thus, 3-aminocaprolactam was also formed. However, when the reaction was performed at room temperature, the product mixture contained both the 3-aminocaprolactam and a zirconium compound with similar NMR data as $Ti(OEt)_3$(lysinate). It therefore appears that at room temperature two parallel reactions occur, *i.e.* lactam formation and substitution of an alkoxo ligand to give $Zr(OBu)_3$(lysinate). Since the latter compound was no longer observed after heating, the formation of the substitution product appears to be reversible.

Conclusions

We have previously shown that lysine can be used to introduce an aminoalkyl functionality into sol-gel materials, when reacted with titanium alkoxides. The

dangling ε-amino group was used to coordinate metal ions [3, 4]. The findings reported in the present paper lead to the conclusion that this approach is less general than we had optimistically anticipated. We have shown that formation of 3-aminocaprolactam, catalyzed by metal alkoxides, is the dominant reaction when aluminum or zirconium alkoxides are employed instead of titanium alkoxides. Although both reactions (substitution and lactam formation) were observed in the reaction with $Zr(OBu)_4$ in *n*-butanol at ambient temperature, the lactam is the only product at higher temperatures. This indicates that coordination of lysinate to the zirconium atom is an equilibrium in alcoholic solution.

There are two possible reasons why lactam formation may be favored for certain metal alkoxides. First, the *Lewis* acidity of the metal alkoxide may play a role. Second, since water is a by-product in the lactam formation, the reactivity of the metal alkoxide towards water (which is influenced by both the *Lewis* acidity and the coordination unsaturation) may also play a role. When metal alkoxides are employed that react more readily with water, lactam formation is favored due to the equilibrium shown in Eq. 1. It is known that $Al(OR)_3$ and $Zr(OR)_4$ are more reactive towards hydrolysis than $Ti(OR)_4$ (for a given group *R*).

Experimental

All operations were carried out in *Schlenk* tubes under an Ar atmosphere. The alkoxides and lysine were used as received.

Reaction of Ti(OEt)$_4$ with Lysine

An amount of 10 mmol of water-free *L*-lysine (1.51 g) was added to a solution of 10 mmol of $Ti(OEt)_4$ in 30 cm^3 of ethanol at room temperature. Although lysine is unsoluble in ethanol, it dissolved, and a clear light-yellow solution was formed. When any undissolved particles were present, they were filtered off. The reaction mixture was refluxed for 4–5 h. No visible changes were observed under heating. The solvent was removed *in vacuo* under light heating. The synthesis was also performed without heating. The reaction mixture was then left for 4–5 h at room temperature followed by removal of the solvent *in vacuo*. ^{13}C NMR (250 MHz, CD_3OD): $\delta = 18.7$, 25.6 (CH_3CH_2O–Ti), 24.5 (br) and 31.3 ($CH_2CH_2CH_2NH_2$), 34.7 (br, $CH_2CH(NH_2)COO$), 41.7 (CH_2–NH_2), 57.0 (br, $CH(NH_2)COO$), 58.6 (CH_2O–Ti), 184.5 (*C*OO) ppm.

Reaction of Al(O^{s}Bu)$_3$ with Lysine

An amount of 30 cm^3 of *s*-butanol and 10 mmol of lysine, 97% (1.51 g) was added to 10 mmol of $Al(O^sBu)_3$ (5.47 cm^3). The reaction mixture became transparent and light-yellow when heated under reflux for 4–5 h. After dissolution of lysine, some insoluble particles were sometimes present in the reaction mixture. In this case, the solution was filtered. The solvent was then removed *in vacuo*. A light-yellow powder was obtained and analyzed without further purification. ^{13}C NMR (250 MHz, CD_3OD): $\delta = 10.7$ (CH_3CH_2CHO–Al), 23.3 (CH_3CH–O–Al), 29.8 and 30.4 ($CH_2CH_2CH_2NH$), 33.1 (CH_2CHO–Al), 35.0 ($CH_2CH(NH_2)CONH$), 42.7 (CH_2NHCO), 54.5 ($CH(NH_2)CONH$), 70.2 (*C*H–O–Al), 180.8 (*C*(O)NH) ppm; 2D $^1H/^{13}C$ NMR (HMQC–GS, CD_3OD, 300 MHz): δ H/C = 0.93 – 3.65/9.4 (CH_3CH_2CHO–Al), 1.14/22.0 (CH_3CHO–Al), 3.22 and 3.32/41.4 (CH_2NHCO, diastereotopic), 1.8/53.9 ($CH(NH_2)CONH$), 0.93 – 3.65/68.9 (*C*H–O–Al) ppm; IR (KBr): $\bar{\nu} = 3461$ and 3293 (br, NH), 2930 and 2859 (CH), 1658 (CO) cm^{-1}.

Reaction of $Zr(OBu)_4$ with Lysine

An amount of 10 mmol of lysine (1.51 g) was added to a solution of 10 mmol of $Zr(OBu)_4$ in 30 cm^3 of *n*-butanol. Lysine dissolved already at room temperature under formation of a clear, light yellow solution. When the reaction mixture was heated to 60–80°C for 4–5 h, no visible changes were observed. The solvent was removed *in vacuo*. ^{13}C NMR (250 MHz, CD_3OD): $\delta = 14.5$ ($CH_3CH_2CH_2CH_2O$–Zr), 20.3 ($CH_3CH_2CH_2CH_2O$–Zr), 29.8 and 30.3 ($CH_2CH_2CH_2NHCO$), 35.0 ($CH_2CH(NH_2)$), 36.1 ($CH_3CH_2CH_2CH_2O$–Zr), 42.7 (CH_2NHCO), 54.5 ($CH(NH_2)$), 63.0 (CH_2O–Zr) ppm.

The synthesis was also performed without heating the solution. The reaction mixture was then left for 4–5 h at room temperature, and then the solvent was removed *in vacuo*. ^{13}C-NMR (250 MHz, CD_3OD): $\delta = 11.7$, 14.5 ($CH_3CH_2CH_2CH_2O$–Zr), 20.3 ($CH_3CH_2CH_2CH_2O$–Zr), 24.3 and 30.3 ($CH_2CH_2CH_2NH_2$), 25.2, 29.7, and 31.9 ($CH_2CH_2CH_2NH$), 35.0 ($CH_2CH(NH_2)$), 36.1 ($CH_3CH_2CH_2CH_2O$–Zr), 40.5 (CH_2NH_2), 42.7 (br, CH_2NH), 54.5 and 56.6 ($CH(NH_2)CONH$), 57.7 ($CH_2CH(NH_2)COO$), 63.0 and 69.4 (CH_2O–Zr) ppm.

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