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Communication

Reactions of α -amino acid-*N*-carboxyanhydrides (NCAs) with organometallic palladium(0) and platinum(0) compounds: structure of a metallated NCA product and its role in polypeptide synthesisAndrew A. Goodwin^a, Xianhui Bu^b, Timothy J. Deming^{c,*}^a Materials Research Laboratory, University of California, Santa Barbara, Santa Barbara, CA 93106, USA^b Department of Chemistry, University of California, Santa Barbara, Santa Barbara, CA 93106, USA^c Departments of Materials & Chemistry, University of California, Santa Barbara, Santa Barbara, CA 93106, USA

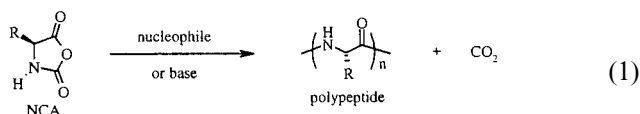
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Abstract

Pt(COD)₂ and two equivalents of PEt₃ were reacted with *L*-*tert*-leucine *N*-carboxyanhydride to yield the N–H oxidative addition product, H(PEt₃)₂PtNC(C(CH₃)₃)HC(O)OC(O) (**1**). The structure and identity of **1** were determined by X-ray crystallography. Pt(COD)₂ and two equivalents of PEt₃ were also reacted with *N*_α-carbobenzyloxy-*L*-phenylalanine NCA to yield the O–C₅ oxidative addition product, (PEt₃)₂PtC(O)C(CH₂C₆H₅)HN(C(O)OBn)C(O)O (**2**). When **1** was reacted with excess γ -benzyl-*L*-glutamate-*N*-carboxyanhydride (Glu NCA) in THF at room temperature, poly(γ -benzyl-*L*-glutamate) was formed in good yield, but with no control over polymer molecular weight. NMR studies showed that the *N*-carboxyanhydride ligand of **1** was responsible for polymerization initiation, which confirmed that metallated *N*-carboxyanhydrides, or ‘activated monomers’ are active, albeit inefficient, initiating species in NCA polymerizations. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Polypeptide; Platinum; Amino acid

Polypeptide materials are potentially useful for biomedical applications and for their ability to self-assemble into organized structures [1]. The chemical synthesis of polypeptides is most directly accomplished by the ring-opening polymerization of α -amino acid-*N*-carboxyanhydride (NCA) monomers (Eq. (1)) [2].

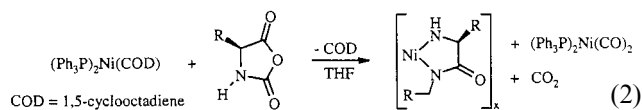


However, these polymerizations are often plagued by chain-breaking transfer and termination reactions that limit the utility of this chemistry [2]. For this reason, the mechanisms of NCA polymerization have long been under study to find ways to enhance control over chain growth in these reactions. These investigations, particularly of the reactions initiated by a strong base (e.g. sodium methoxide), have been severely hindered by the complexity of the polymerizations and difficulty in isolation of

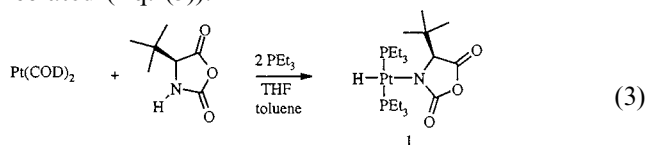
active intermediates [2,3]. One question in particular has concerned the existence and participation of metallated NCAs, or ‘activated monomers’, in base-initiated polymerizations [3]. We have pursued the development of new types of initiators for NCA polymerization to help address and solve these problems. We now report that platinum(0) oxidatively-adds across the N–H bond of an NCA to yield a metallated NCA platinum(II) hydride. Herein, we describe the synthesis and properties of this species, which also provides insight into the role of ‘activated monomers’ in base initiated NCA polymerizations.

We have been investigating the utility of low-valent transition metals as initiators for the controlled synthesis of polypeptides from NCA monomers. We have found that certain nickel(0) initiators are very effective at eliminating side reactions by in situ formation of amidonickelacycle propagating species [4]. These complexes are generated from initial oxidative-addition of nickel across the O–C₅ anhydride bond of an NCA followed by consumption of an additional NCA molecule (Eq. (2)) [5].

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We now report the reactivity of palladium and platinum with NCAs. When a variety of palladium(0) species were reacted with stoichiometric quantities of NCAs, the only isolable amino acid-containing products were polypeptides. In contrast to reactions with nickel(0), which also generated polymer, molecular weights of the palladium-generated polypeptides could not be controlled by monomer to initiator stoichiometry, and block copolypeptides could not be synthesized. Under most conditions, similar reactivity was observed with platinum(0) compounds, namely uncontrolled polypeptide formation. However, when sterically bulky *L*-*tert*-leucine NCA was added to $\text{Pt}(\text{COD})_2$ and two equivalents of PEt_3 , a stable addition product could be isolated (Eq. (3)).

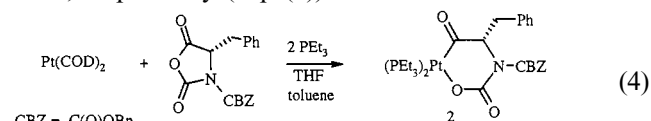


Full characterization of this compound, **1**, showed it to be the product of oxidative addition of platinum across the N–H bond of the NCA (Fig. 1) [6]. The geometry around platinum in **1** is square-planar with the phosphine ligands distorted toward the small hydride ligand, as usually observed for square platinum(II) hydrides

[7]. The Pt–N distances of 2.14–2.15 Å are typical for Pt–N single bonds [7], and the bonds and angles of the NCA ligand are only slightly distorted from those of parent NCAs [8]. The anhydride IR stretches of the NCA ligand were shifted to lower frequencies by ca. 65 cm^{-1} upon complex formation, indicating an increase in electron density in the group, which suggests considerable anionic character of the ligand.

The formation of **1** was unusual in light of the literature precedent for oxidative addition of platinum across the O–C anhydride bond of succinic anhydride [9]. It appears that with NCAs, the N–H bond is the more reactive site in the molecule toward platinum(0) [10]. Due to similarities in the polymerization chemistry of palladium and platinum, we believe that palladium also likely reacts at the N–H position of NCAs. We attempted to react $\text{Pt}(\text{COD})_2$ and two equivalents of PEt_3 with *L*-proline NCA, which lacks a hydrogen on nitrogen, in order to force addition across the anhydride bond. In this case, no reaction was observed after heating at 40°C for 3 days. Heating to higher temperatures only resulted in spontaneous polymerization of the NCA.

Determined to observe anhydride addition, we attempted the reaction of platinum with *N*_ε-carbobenzyl-oxy-*L*-phenylalanine NCA (CBZ-Phe NCA). This anhydride, which also lacks an acidic hydrogen, is unable to polymerize due to the electron-withdrawing CBZ group on nitrogen [11]. Reaction of CBZ-Phe NCA with $\text{Pt}(\text{COD})_2$ and two equivalents of PEt_3 at ambient temperature gave only a single platinum-containing product. IR analysis of the product showed the presence of three carbonyl bands at 1735, 1720, and 1624 cm^{-1} , which, after ^{13}C labeling experiments [12], could be assigned to the platinum(II) acyl, CBZ side chain carbonyl, and platinum(II) carbamate of the metallacycle **2**, respectively (Eq. (4)).



This and other characterization data [13] were consistent with oxidative addition of platinum across the O–C₅ bond of the anhydride: the same mode of addition as previously seen with nickel [5]. Thus, it appears that platinum can add NCAs across the anhydride linkage, but only in the strict absence of an N–H bond.

Isolation of the metallated NCA complex, **1**, gave us the opportunity to study its reactivity with additional NCA monomers. Deprotonated NCA molecules ('activated monomers') have long been hypothesized as intermediates in base-initiated NCA polymerizations [2]. In particular, they have been thought to be the active species in dialkylzinc and trialkylaluminum-initiated systems, although none of these intermediates has been

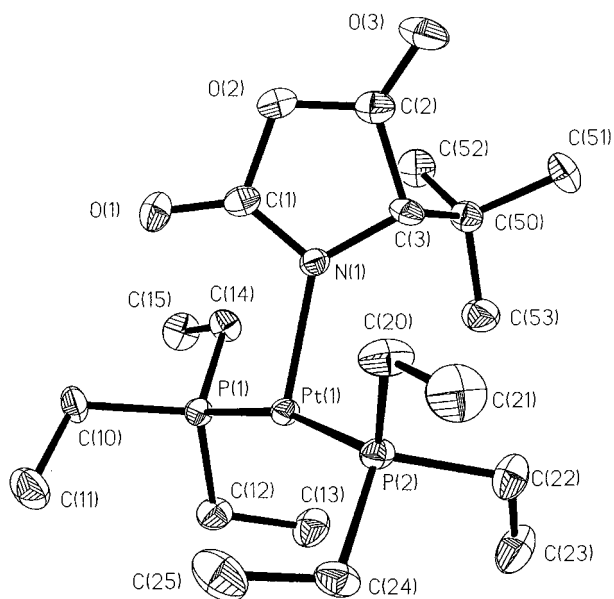
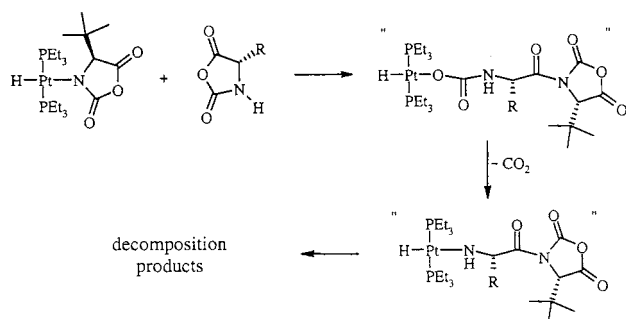


Fig. 1. Molecular structure of $\text{H}(\text{PEt}_3)_2\text{PtNC}(\text{C}(\text{CH}_3)_3)\text{HC}(\text{O})\text{OC}(\text{O})$ (**1**), showing the atom numbering scheme. Selected parameters: Pt–N(1) 2.154(3), N(1)–C(1) 1.324(4), N(1)–C(3) 1.471(4), O(2)–C(1) 1.454(4), O(2)–C(2) 1.352(4), C(2)–C(3) 1.530(5) Å, C(1)–N(1)–C(3) 109.9(3), P(1)–Pt–N(1) 95.87(8), P(2)–Pt–N(1) 97.84(8), and P(1)–Pt–P(2) 166.21(3) $^\circ$.



Scheme 1. Possible mechanism for reaction of **1** with additional NCA molecules.

either isolated or fully characterized [14]. Consequently, most of the proposed mechanisms regarding reactivity of metallated NCAs have been purely speculative [3]. We reasoned that reactivity studies with **1**, essentially an ‘activated monomer’ bound to platinum, would provide experimental verification of the participation of these intermediates in NCA polymerizations.

When **1** was reacted with 100 equivalents of γ -benzyl-L-glutamate-*N*-carboxyanhydride (Glu NCA) in THF at room temperature, poly(γ -benzyl-L-glutamate) was formed in good yields. Similar to our early experiments with palladium and platinum, there was no molecular-weight control in these polymerizations. ¹H-NMR analysis of reactions of **1** with ten equivalents of Glu NCA in THF-*d*₈ showed that only a small fraction of the platinum complex had reacted and that the hydridobis(triethylphosphine)platinum moiety of the reacting molecules remained intact [15]. This experiment showed that polymerization was initiated by the metallated NCA ligand, and not the hydride. Since **1** was unable to control NCA polymerizations, we surmised that metallated NCAs, at least those bound to platinum, form unstable propagating species in contrast to the robust amido–amidate chelates formed with nickel. This result may also serve to explain why most base and metal–alkyl-initiated NCA polymerizations allow little molecular-weight control and proceed through ill-defined intermediates. Assuming the metallated NCAs react as nucleophiles toward NCA monomers, the resulting products, platinum carbamates (Scheme 1), are expected to be unstable as they can lose CO₂ to form platinum amides, which are known to readily decompose through a variety of pathways [16].

In summary, we have reported a fully characterized platinum–NCA complex and have described its reaction chemistry with additional NCA monomers. The increased basicity of platinum(0), relative to nickel(0), resulted in a change of mechanism in its reactivity toward NCAs. This change caused formation of initiators similar to those found in strong-base-initiated NCA polymerizations, and allowed verification that metallated *N*-carboxyanhydrides, or ‘activated

monomers’ are active, albeit inefficient, initiating species in NCA polymerizations.

1. Supplementary material

Details of all reactions and polymerizations, experimental data for the structural analysis of **1**, and a table of intramolecular distances and angles (9 pages/PDF). Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 114213, for compound **1**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Acknowledgements

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- [6] Data for **1**: ¹H-NMR (C₆D₆): δ 3.58 (s, –NC(C(CH₃)₃)HC(O)OC(O), 1H), 2.10–1.15 (br m, –C(CH₃)₃– and –PCH₂CH₃, 21H), 1.15–0.75 (br m, –PCH₂CH₃, 18H), –18.0 (t + dt, Pt–H, 1H, *J*_{Pt–H} = 980 Hz, *J*_{P–H} = 16.7 Hz). IR (KBr): 2188 (ν (Pt–H), m), 1789 (ν (C=O), s), 1724 (ν (C=O), vs) cm^{–1}.
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- [12] The reaction of 2PEt_3 and $\text{Pt}(\text{COD})_2$ with $\text{CBZ-}^{13}\text{C}_5\text{-Phe NCA}$ under identical conditions gave a single platinum species with IR stretches of carbonyl bands at 1720, 1697, and 1624 cm^{-1} , which were assigned to the CBZ side chain carbonyl, platinum(II) ^{13}C -acyl, and platinum(II) carbamate of metallacycle **2**, respectively.
- [13] Data for **2**: $^1\text{H-NMR}$ ($\text{THF-}d_8$): δ 7.35–7.05 (br m, ArH, 10H), 5.10 (s, $\text{PhCH}_2\text{O-}$, 2H), 3.45 (t, $-\text{PhCH}_2\text{CH-}$, 1H), 2.12 (d, $\text{PhCH}_2\text{CH-}$, 2H), 1.82 (br m, $-\text{PCH}_2\text{CH}_3$, 12H), 1.09 (br m, $-\text{PCH}_2\text{CH}_3$, 18H). IR (C_7H_8): 1735 ($\nu(\text{Pt-C=O})$, vs), 1720 ($\nu(\text{C=O})$, CBZ, vs) cm^{-1} , 1624 ($\nu(\text{Pt-OC=O})$, vs).
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- [15] $^1\text{H-NMR}$ (C_6D_6): Compound **1**: δ –18.0 (t + dt, Pt–H, $J_{\text{Pt-H}} = 980\text{ Hz}$, $J_{\text{P-H}} = 16.7\text{ Hz}$); Compound **1** + Glu NCA: δ –16.8 (t + dt, Pt–H, $J_{\text{Pt-H}} = 980\text{ Hz}$, $J_{\text{P-H}} = 16.3\text{ Hz}$).
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