Amino Acid Derived Nickelacycles: Intermediates in Nickel-Mediated Polypeptide Synthesis

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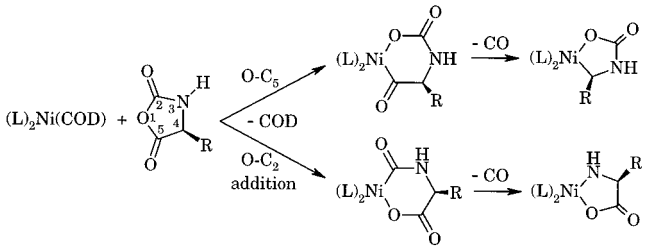
For years, the reaction chemistry of α-amino acid *N*-carboxyanhydrides (NCAs) has been under study since these molecules are potential precursors to sequence specific peptides, polypeptides, and other amino acid containing compounds.[1] NCAs are attractive peptide building blocks since they are readily prepared from amino acids and since they show no racemization at the chiral α-carbon either during preparation or in subsequent reactions.[2] Utilization of NCAs, however, has been limited because of their complicated reactivity and tendency to uncontrollably polymerize.[1] We have recently reported the living polymerization of NCAs and synthesis of block copolypeptides using nickel initiators.[3] We now report stoichiometric reactions where NCAs oxidatively add regioselectively to sources of zerovalent nickel to yield complexes which subsequently rearrange to unprecedented amido-amidate metallacycles. When complexed with donor ligands, the nickelacycles are efficient NCA polymerization initiators.

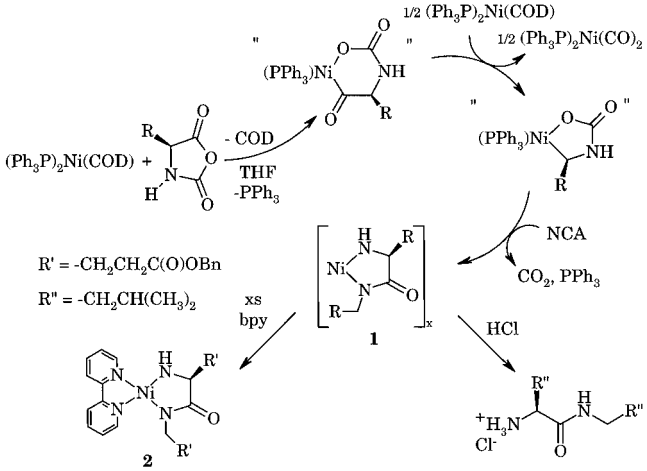
The oxidative addition of cyclic carboxylic acid anhydrides to nickel(0) was first reported by Uhlig and co-workers.[4] When succinic anhydride is added to $L_2Ni(COD)$[5] a six-membered acyl carboxylato nickelacycle is initially formed which decarbonylates above ambient temperature to form a stable five-membered alkyl carboxylato complex. With unsymmetric anhydrides, the regioselectivity of oxidative addition was found to vary with the donor ligand (L_2) and solvent.[6] When an NCA oxidatively adds to nickel(0) across the unsymmetric anhydride linkage, regioselectivity of addition is important in determining the nature and reactivity of the products. With both initial products, decarbonylation would be expected to be favored over decarboxylation due to the greater stability of the resulting five-membered metallacycles (Scheme 1).[4] We were interested in the addition of NCAs to nickel(0) because the resulting metal−amido or metal−carbamato complexes might prove useful as reactive, chiral synthetic intermediates.

When 2 equiv of PPh_3 and 1 equiv $Ni(COD)_2$ were reacted with 1 equiv of γ-benzyl-L-glutamate-*N*-carboxyanydride (Glu-NCA) in THF at room temperature, rapid consumption of the NCA was observed. From the golden brown solution, an alkane soluble brown oil and a THF soluble yellow powder were isolated. Analysis of the oil confirmed the presence of $(PPh_3)_2Ni(CO)_2$ [IR-(THF) ν(CO) = 2000, 1939 cm^{-1}][7] which was produced by the decarbonylation of an intermediate six-membered metallacycle followed by trapping of the carbon monoxide with $(PPh_3)_2Ni$-(COD). Infrared analysis of the yellow powder showed carbonyl

Scheme 1. Possible Anhydride Oxidative Addition Reactions between NCAs and Nickel(0) Complexes

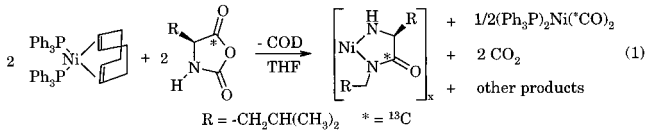


Scheme 2. Formation and Reactivity of **1** (Compounds in Quotations Were Not Isolated).



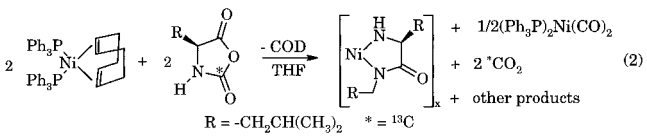
stretches at 1734 and 1577 cm^{-1} which were assigned, respectively, to the side-chain benzyl esters and amidate group of the chiral nickelacycle **1** (Scheme 2).

The structures and origins of these products were elucidated when [$^{13}C_5$]-L-leucine-*N*-carboxyanhydride was reacted with $(PPh_3)_2Ni(COD)$ in THF. An infrared spectrum of the crude reaction mixture showed a stretch at 1536 cm^{-1} for the [^{13}C]-amidate group [$^{13}C\{^1H\}$ NMR (THF-d_8) 182 ppm] as well as $(PPh_3)_2Ni(^{13}CO)_2$ stretches at 1954 and 1895 cm^{-1} [$^{13}C\{^1H\}$ NMR (THF-d_8) 202 ppm] which were isotopically shifted from the unlabeled compounds (eq 1). When [$^{13}C_2$]-L-leucine-*N*-carboxy-



(1)

anhydride was reacted with $(PPh_3)_2Ni(COD)$ in THF, analysis of the products showed exclusive formation of $(PPh_3)_2Ni(^{12}CO)_2$ [IR-(THF) ν(CO) = 2000, 1939 cm^{-1}] and the [^{12}C]amidate [IR(THF) ν(CO) = 1580 cm^{-1}] (eq 2). Since no mixed [^{13}C/^{12}C]products were observed, we concluded that oxidative addition was occurring exclusively at the C_5−O bond followed by decarbonylation and addition of a second NCA molecule to yield an amido amidate nickelacycle (Scheme 2).



(2)

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(5) L_2 = donor ligand(s); COD = 1,5-cyclooctadiene; bpy = 2,2′-bipyridyl.

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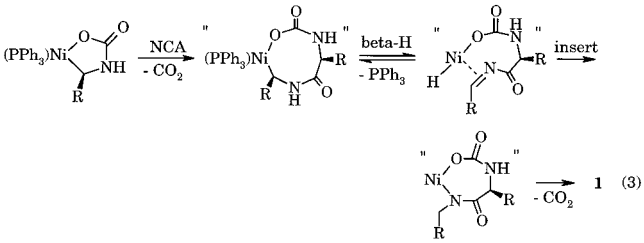
The transformation of the initial alkyl carbamate nickelacycle to the amido amidate might occur through a β-H elimination mediated ring contraction which would involve a hydridonickel carbamato imine intermediate (eq 3). Similar processes have been proposed for other metallacyclic ring contractions involving nickel.[8] Abstraction of the hydrogen from the N−H position is



(3)

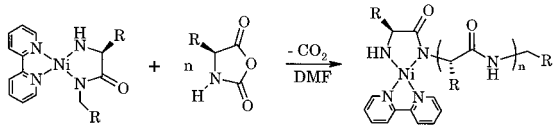
feasible considering puckering of the eight-membered ring in addition to precedent for reversible hydride insertion into metal−imine complexes.[9] The successful formation of an amido amidate with L-*tert*-butylglycine NCA[10] also supports β-H elimination at the N−H, rather than the C−H, position. The unusual stability of the final amido species is likely due to the rigidity of the metallacycle which prevents abstraction of a β-hydrogen.

The structure of these metallacyclic products was further confirmed by elemental analysis and acidolysis of the complexes. The product metallacycles contain no phosphine by elemental analysis and were found to consist of the empirical formula $[NiNHC(H)RC(O)NCH_2CHR]_x$. Osmotic molecular weight measurements in THF (ca. 7 mg/mL) showed that the complexes aggregate as dimers. Treatment of the metallacyclic complex derived from L-leucine NCA with HCl in THF gave only a single organic product. Analysis of this product by ^{1}H NMR spectroscopy and polarimetry, and comparison of the data with an authentic sample, showed it to be optically pure L-leucine isoamylamide hydrochloride (Scheme 2).[11]

When the donor ligands bound to the nickel(0) precursor were varied (e.g., alkyl phosphines, α,α'-diimines), the only products isolable from stoichiometric reactions with Glu-NCA in THF were some starting nickel(0) compound and poly(γ-benzyl-L-glutamate), PBLG. When 100 equiv of Glu-NCA was added to bpyNi(COD)[5] in DMF, all of the nickel precursor was consumed and PBLG was isolated in excellent yield (>95%) with narrow molecular weight distribution (M_n = 22 100, M_w/M_n = 1.15). We have shown that bpyNi(COD) initiates the living polymerization of NCAs.[3] It was suspected that bpyNi(COD) oxidatively adds Glu-NCA to form the active polymerization initiator in situ which then rapidly consumes the remainder of the monomer. To identify this active initiator, a series of experiments were performed where bpyNi(COD) was reacted with selectively ^{13}C-labeled NCA monomers.

To completely consume all the bpyNi(COD) in reactions with NCAs it was necessary to use at least a 5-fold excess of NCA monomer. BpyNi(COD) was reacted with 5 equiv of [$^{13}C_5$]-L-leucine-*N*-carboxyanhydride in THF. IR and $^{13}C\{^1H\}$ NMR analysis of the crude products verified the presence of bpyNi($^{13}CO)_2$ [IR(THF) $\nu(^{13}CO)$ = 1933, 1862 cm^{-1}; $^{13}C\{^1H\}$ NMR (DMF-d_7) 198 ppm], ^{13}C-labeled poly-L-leucine [IR (THF) 1613 cm^{-1} (νAmide I, vs); 1537 cm^{-1} (νAmide II, vs); $^{13}C\{^1H\}$ NMR (DMF-d_7) 177 ppm (bpyNiN(H)C(H)R^{13}C(O)N[CH(R)-^{13}C(O)NH]$_n$CH$_2$R)], and the labeled nickel−amidate endgroup [$^{13}C\{^1H\}$ NMR (DMF-d_7) 174 ppm (bpyNiN(H)C(H)R^{13}C(O)N-[CH(R)^{13}C(O)NH]$_n$CH$_2$R)]. The reaction with [$^{13}C_2$]-L-leucine-*N*-carboxyanhydride gave similar products, except for location of the ^{13}C label. We identified the presence of bpyNi($^{12}CO)_2$ [IR(THF) ν(CO) = 1978, 1904 cm^{-1}],[12] poly-L-leucine [IR (THF) 1653 cm^{-1} (νAmide I, vs); 1546 cm^{-1} (νAmide II, vs)],[13] as well as the [^{12}C]amidate endgroup [IR(THF) ν(CO) = 1577 cm^{-1}]. When the reaction was run in DMF-d_7, the presence of liberated $^{13}CO_2$ was also confirmed using $^{13}C\{^1H\}$ NMR [126 ppm (s, $^{13}CO_2$)].

All of these experiments were consistent with initial addition of the NCA to bpyNi(COD) across the C_5−O bond, analogous to the reactions using $(PPh_3)_2$Ni(COD). The primary influence of the ligands manifests itself in the reactivity of the resulting products. The ligand-free complex from the PPh_3 reaction was inert toward further reactivity with NCAs, while the bpy complex and complexes formed with other α,α'-diimines and alkyl phosphines were efficient NCA polymerization initiators. We were able to directly verify this phenomenon by synthesis of the reactive metallacycle intermediate formed in the bpyNi(COD)/NCA reactions. The stable metallacycle (**1**) was reacted with an excess of bpy in DMF to form the ligand adduct **2** (Scheme 2). Reaction of **2** with 100 equiv of Glu-NCA in DMF resulted in rapid polymer formation. The PBLG formed in this reaction was identical to that formed using bpyNi(COD) under otherwise identical conditions (M_n = 21 600, M_w/M_n = 1.09). The bpyNi-(COD)-mediated polymerizations of NCAs are therefore thought to proceed via amido-amidate nickelacycle active endgroups (eq 4). We are currently exploring other aspects of the chemistry of these metallacycles.



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Supporting Information Available: Details of all reactions and polymerizations (8 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(10) Amido amidate product: IR (THF) = 1578 cm^{-1} (νC═O).

(11) See the Supporting Information.

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