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Large-scale synthesis of α-amino acid-*N*-carboxyanhydrides

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ABSTRACT

Hetero- and homopolymers prepared from α-amino acid-*N*-carboxyanhydrides (NCAs) monomers are widely useful products. The preparation of pure NCA monomers has been extensively studied in the past. Purification methods including repeated crystallizations, extraction, and flash column chromatography have been devised. However, these methods are not easily amendable to large-scale NCA preparations. This article describes the synthesis of numerous highly purified NCAs on a >100 g scale using a simple filtration step through diatomaceous earth (celite). The resulting NCAs provided polyethylene glycol (PEG)–amino acid triblock polymers devoid of low-molecular-weight by-products that were routinely observed when unfiltered batches of NCAs were used. Also disclosed is the preparation of NCAs at ambient temperature. Traditionally, NCA reactions using a phosgene source are heated. This study shows these reactions can be driven by the slight exotherm that forms upon reagent mixing. This eliminates the need for an external heating source, simplifying large-scale reactions.

GRAPHICAL ABSTRACT

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Introduction

Beginning in 1906, Leuchs published his seminal work on the synthesis of α-amino acid-*N*-carboxyanhydrides (NCAs) and their application in polymerizations.[1] The original Leuchs method, and subsequent adaptations, react *N*-alkoxycarbonyl α-amino acids with a halogenating agent—such as $SOCl_2$, PBr_3, PCl_3, or α, α-dichloromethyl methyl ether—followed by thermal cyclization to produce the NCA and the corresponding alkyl halide.[2] A more direct route through treatment of underivatized amino acids with an excess of gaseous phosgene (carbonyl dichloride) was published by Farthing in 1950.[3] A simpler and safer extension of this work using a solution of phosgene in benzene was disseminated in

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Supplemental data (^{1}H NMR spectra of all compounds presented, along with literature references to further experimental details) can be accessed on the publisher's website.

1976,[4] which appears to be the basis for most contemporary NCA syntheses. Alternative methods treating amino acids with diphosgene (trichloromethyl chloroformate)[5] and triphosgene (bis(trichloromethyl) carbonate)[6] were also developed. Other synthetic routes include the treatment of *N*-carbobenzoxy-substituted amino acids with phosphorus pentachloride,[7] prebiotic approaches,[8] phosgene-free methods with diphenyl carbonate[9] or di-*tert*-butyltricarbonate,[10] and the nitrosation of *N*-carbamoyl amino acids with a mixture of nitric oxide/oxygen or sodium hypochlorite.[11] Employing these methods, more than 200 NCAs have been prepared to date from canonical and nonproteinogenic amino acids, as well as their derivatives.[2,12]

The ring-opening polymerization (ROP) of NCA monomers is a well-studied route to synthetic polypeptides and polypeptide hybrids that possess a broad range of useful physical properties.[13] A tremendous amount of work has been done to characterize the mechanism of these polymerizations, which either proceed through a normal amine mechanism (NOM) or activated monomer mechanism (AMM).[2,14] Improvements to reaction rates[15] and conditions,[16] in addition to the use of a variety of initiators, have also been extensively studied.[17] The combined efforts have created well-defined NCA-derived polymers with a broad range of molecular weights and narrow polydispersity. These polymers have found utility in asymmetric epoxidation[18] and biosensors,[19] but perhaps the most noteworthy application is to the biomedical fields—where siRNA delivery,[20] tissue engineering scaffolding,[21] liposome,[22] and micelle-based[23] drug delivery have all utilized NCA-derived polypeptides.

The successful application of NCAs requires the preparation of highly pure monomers free of electrophilic contaminants that can hinder or quench the polymerization. The majority of research in this field has centered on NCAs produced directly by phosgenation of amino acids—by far the most common synthetic route. The principal contaminants in these reactions are HCl and HCl salts of unreacted amino acids.[24] NCA polymerization initiated by chloride ions has been reported and thus should be eliminated.[25] Other possible contaminants are 2-isocyanatoacyl chlorides and *N*-chloroformyl amino acids—the former serving as an especially problematic electrophile for chain terminations.[26] The majority of NCAs are solids and thus typically purified by precipitation and crystallization protocols.[2] Solvents commonly used for crystallization are tetrahydrofuran (THF), ethyl acetate, and toluene—while conventional antisolvents include hexane, heptane, and petroleum ether. NCAs are commonly subjected to repeated crystallizations, often more than three times, in order to obtain the necessary purity. A high vacuum technique to repeatedly crystallize NCAs in a custom glassware apparatus has been developed.[27] Exceptionally pure NCAs can be achieved with this method, however, only on small scales. NCAs have also been purified via sublimation of the crude solid.[28] This procedure has had limited success and suffers from reduced yields due to thermal decomposition of the products. Another strategy to remove impurities is to successively wash an NCA reaction mixture with ice-cold water and 0.5% w/v $NaHCO_3$, followed by precipitation.[29] Time is critical, making scalability problematic, as this procedure must be carried out quickly to avoid undesired polymerization initiation by water. Rephosgenation is a strategy designed to specifically target unreacted amino acids–HCl salt contaminants. The crude reaction mixture is exposed to additional fresh phosgene with the hope of driving the reaction to completion.[24] Although this approach could reduce the amount of unreacted starting material, it can also increase the amount of other impurities. Flash column chromatography (FCC) with extensively dried silica gel has been demonstrated to remove many

common impurities and is especially attractive for low-melting solid or oil NCAs.[30] However, the purification is run under an atmosphere of nitrogen in a glovebox with anhydrous solvents, and is not amendable to large-scale NCA syntheses.

Our primary research focuses on the synthesis of triblock polymers consisting of a hydrophilic polyethylene (PEG) block,[31] an iron-glutamic hydroxamate stabilizing block, and a core block comprised of a mixture of D- and L-hydrophobic amino acids. Chemotherapeutics encapsulated in these triblock polymers have excellent pharmacokinetic properties accompanied by reduced toxicities.[23] Our work necessitates the large-scale synthesis of an assortment of NCAs devoid of impurities. We found it difficult to obtain the mandatory NCA purity, on a large scale, with the previously published methods. Although notable research on the large-scale synthesis of L-Leu NCA as been disclosed,[32] we wished to develop a more general procedure. The present study outlines the progress we have made towards this goal—including running the reaction at ambient temperature and simple solutions to workup issues.

Results and discussion

Large-scale NCA preparation

To manufacture our principal triblock polymers, in-house prepared[31] mPEG-NH_2 free-base is used to initiate the ROP of a mixture of D- and L-glutamic acid γ-benzyl ester NCAs or S-4-methoxybenzyl-L-cysteine NCA in a dichloromethane:*N,N*-dimethylacetamide (2:1, v/v) solvent mixture at room temperature.[23b] This living polymerization is continued by the addition of a mixture of hydrophobic NCAs selected from D-phenylalanine, *O*-acetyl-L-tyrosine, *O*-benzyl-L-tyrosine, and D-leucine to form the final block. Accordingly, these were the NCAs that we first began preparing on >100 g scale. After initially experimenting with phosgene in toluene and triphosgene, we elected to follow the general procedure of Katakai—which treats an amino acid–THF suspension with diphosgene.[5c] The originally procedure calls for the addition of activated charcoal to catalyze the in situ thermal decomposition of diphosgene to two equivalents of phosgene. However, we found this addition unnecessary and its presence only complicated the workup. We preferred the simplicity of using neat diphosgene, as it can be easily measured in a graduated cylinder before its addition to the reaction. Although we contemplated using another solvent or solvent combination, previous studies have shown the rate of the reaction is highest in THF, and its relatively low boiling point makes its removal facile. We were aware of the known side reactions between THF and HCl, but never found them to interfere with our NCA syntheses.[32c]

NCAs prepared in large quantities using the aforementioned procedure were used to prepare our triblock polymers. The polymerizations were monitored by gel permeation chromatography (GPC) for reaction progress and monodispersity. Interestingly, in some reactions, the formation of the desired triblock polymer was accompanied by a low-molecular-weight by-product (Fig. 1). This phenomenon was not observed in earlier, smaller scale NCA syntheses and polymerizations—this was a problem derived from large-scale NCA preparations. Immediately, one or more of the hydrophobic NCAs that make up the third block were suspected as the source of the problem since the low-molecular-weight by-product only appeared after their addition. Attempts were made to isolate the low-molecular-weight species via tangential flow filtration but a pure enough

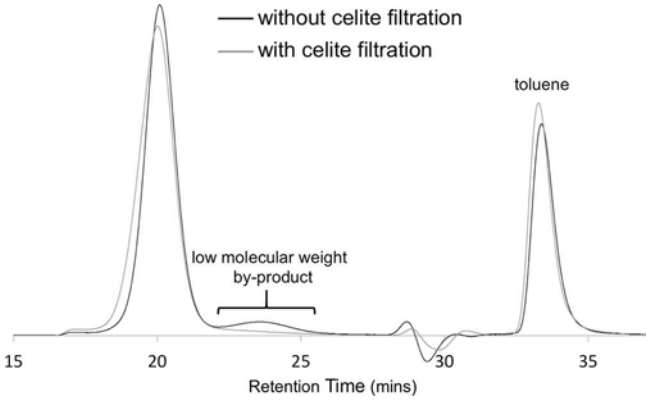

Figure 1. mPEG12 K-NH-*b*-*p*-[L-Cys(Mob)$_{10}$]-*b*-*p*-[L-Asp(OtBu)$_5$-*co*-D-Leu$_{15}$-*co*-L-Tyr(OBn)$_{20}$]-Ac triblock synthesized using NCAs prepared with and without celite filtration.

sample for accurate identification could not be isolated. High-performance liquid chromatography (HPLC) and NMR of the hydrophobic NCAs did not reveal any residual starting material or side products. However, melting points conflicting with literature values and slight insolubility in chlorinated solvents (e.g., DCM and $CHCl_3$) led us to suspect trace HCl contamination. Polymerizations initiated by chloride have been documented[25] and could explain the low-molecular-weight species observed by GPC.

As previously discussed, many innovative methods have been developed to remove contaminant HCl, including liquid–liquid extraction, and flash column chromatography (FCC). Unfortunately, these strategies are impractical and unsuitable for large-scale synthesis. Olefin-containing HCl scavengers including (−)-α-pinene and (+)-limonene have been used in NCA preparations in the past.[32c] We found the addition of these cyclic monoterpenes complicated the workup for many of the NCAs by hindering product precipitation. We experimented with propylene oxide as an alternative HCl scavenger,[33] but did not find any benefit to its inclusion. HCl removal by filtration was left as the most appropriate option for large-scale synthesis. Crude NCA mixtures have been filtered through activated charcoal embedded with silver oxide to serve as a chloride scavenger,[34] but diatomaceous earth (celite) was selected as a cheaper and simpler option.[29] HCl solubility is higher in THF than in chlorinated solvents, and thus filtration of the initial reaction mixture was not suitable.[2] Therefore, after the removal of THF, the crude reaction solid was combined with dichloromethane (DCM) and stirred before filtering through a bed of celite. The clear filtrate was concentrated and precipitated from THF–heptane. For added assurance, the crude reaction mixture can be directly precipitated with heptane, and then filtered as a DCM suspension before a second THF–heptane precipitation.

To gauge the effectiveness of the celite filtration workup, L-Tyr(OBn) NCAs prepared with and without filtration were subjected to proton-induced x-ray emission (PIXE) analysis, which provides simultaneous analysis of 72 inorganic elements from sodium to uranium. The results showed celite filtration reduced the chlorine content from 733 to 115 ppm (Table 1). PIXE analysis also detected measurable quantities of calcium, iron, and zinc—the latter two most likely originating from galvanized steel tubing or containers used in the industrial production of the amino acid. Celite filtration reduced these elements below their detection limit. The two L-Tyr(OBn) NCA lots were used in the preparation of

Table 1. PIXE analysis of L-Tyr(OBn) NCA with and without celite filtration.

Celite filtration	Cl (ppm)	Ca (ppm)	Fe (ppm)	Zn (ppm)
No	733	6.0	3.5	2.9
Yes	115	—[a]	—[a]	—[a]

[a]Below detection limit (95% conf.).

a triblock polymer, specifically, mPEG12 K-NH-*b*-*p*-[L-Cys(Mob)$_{10}$]-*b*-*p*-[L-Asp(OtBu)$_5$-*co*-D-Leu$_{15}$-*co*-L-Tyr(OBn)$_{20}$]-Ac. The triblock derived from the unfiltered NCAs was beset by 8.1% of the low-molecular-weight by-product, while the celite-filtered triblock had none (Fig. 1).

A total of 12 NCAs were prepared on a large scale employing the celite filtration protocol (Table 2). Subsequent triblock polymers prepared from these NCAs were devoid of the low-molecular-weight by-products observed without the filtration. The simple addition of a celite filtration step dramatically improved the quality of the NCA products.

As an aside, NCA reactions are typically monitored visually; when the reaction goes clear, it is assumed that all of the starting material has been converted to product. We found it advantageous to monitor by miniworkup and ^{1}H NMR. We noticed that depending on the particular vendor we received our amino acids from, some reactions would be complete by NMR but would not be totally clear, or vice versa. For clarification, PIXE analysis was run on two lots of D-phenylalanine amino acid—one that produced a clear reaction and one that did not (both reactions were complete by NMR). The latter contained higher levels of phosphorus, chlorine, iron, and copper (Table 3). It is most likely that phosphate and transition metal-chloride salts were used in the manufacture of the D-phenylalanine amino acid. However, working up the two reactions utilizing the celite filtration method produced identical high-quality NCAs. Although visual reaction monitoring is facile and convenient, NMR analysis should also be employed for reassurance.

Table 2. α-Amino acid-*N*-carboxyanhydrides prepared with celite filtration.

Amino acid	Diphosgene equiv.	Reaction time (min)	Product amount (g)	Isolated yield (%)
L-Asp(OtBu)	0.6	15	76.8	77.7
D-Asp(OBn)	0.6	15	152	97.2
L-Asp(OBn)	0.6	15	122	97.9
L-Cys(Mob)	0.6	30	74.4	87.0
D-Glu(OBn)	0.6	60	122	89.4
L-Glu(OBn)	0.6	60	101	82.9
D-Leu	0.6	45	102	78.1
D-Phe	0.6	90	135	89.7
D-Tyr(OAc)	1	120	119	95.5
L-Tyr(OAc)	1	180	154	88.4
D-Tyr(OBn)	0.6	60	84.8	95.1
L-Tyr(OBn)	0.6	120	135	93.3

Table 3. PIXE analysis of d-phenylalanine amino acids.

D-Phe AA	P (ppm)	Cl (ppm)	Ca (ppm)	Fe (ppm)	Cu (ppm)
Clear reaction	—[a]	67	6.7	—[a]	—[a]
Nonclear reaction	46	120	—[a]	19	6.9

[a]Below detection limit (95% conf.).

Table 4. NCAs prepared at ambient temperature.

Amino acid	Diphosgene equiv.	Exotherm (°C)	Reaction time (h)	Product amount (g)	Isolated yield (%)
L-Asp(OtBu)	0.6	38	2	59.0	91.5
L-Cha	1	26	72	31.2	67.7
L-Glu(OBn)	1	40	4	148	93.7
L-Leu	0.8	41	22	61.0	78.3
D-Nle	1	38	0.75	26.8	92.0
D-Phe	1	42	1.5	81.3	79.8
L-Thr(OtBu)	1	42	4	9.88	71.7
L-Trp	1	35	2.5	11.6	99.0
L-Trp(CHO)[a]	1	—[b]	49	33.9	97.1
L-Tyr(OAc)	1	36	22	45.5	93.5

[a]Used as its HCl salt.
[b]Internal reaction temperature did not rise from ambient (23 °C).

Ambient temperature reactions

NCA synthesis with an amino acid and a phosgene source are traditionally performed at 50–60 °C. During exploratory work with L-tryptophan, an interesting observation was made. The reaction solubilized in less than one minute, however, ^{1}H NMR analysis revealed the reaction was only ~75% complete. This gives more credibility to the philosophy of monitoring these reactions by NMR rather than visual inspection. When the reaction was left unheated, an exotherm up to 35 °C was observed and the reaction was complete in 2.5 h. Thus, a series of amino acids were reacted with diphosgene, without external heating, and each reaction did indeed go to completion (Table 4). The temperature of the reactions were carefully monitored, with some reaching over 40 °C. In most cases, one equivalent of diphosgene was used to keep the reaction times within practical limits. The majority of the reactions were complete in less than 24 h—the exceptions being the L-cyclohexylalanine and N^{in}-formyl-L-tryptophan-HCl salt that took 72 and 49 h, respectively. Not surprisingly, these were the two reactions with the lowest exotherm. L-Tyr(OtBu) NCA was also prepared with the hope that the lower temperature would prevent hydrolysis of the protection group. Unfortunately, between 20–40% loss of the *tert*-butyl group was observed. It appears, at least for the NCAs screened, that heating the reaction is not necessary and only serves to increase rate. It may be advantageous for large-scale NCA reactions to be performed at ambient temperature to avoid the often-troublesome heating of sizable reaction vessels. In many instances, the isolated yields obtained for the unheated reactions were higher than their heated reaction equivalents.

Conclusion

In summary, we have shown that the synthesis of NCAs benefit from a celite filtration step during the workup. This method is easily adaptable to large-scale (>100 g) syntheses—something that previous purification methods fail to address—and does not require specialized glassware, repeated crystallizations, or a glovebox. The highly purified NCAs obtained from this technique produced polymers free of low-molecular-weight by-products observed when NCAs were prepared on a large scale without the filtration. We also demonstrated that NCAs prepared from the reaction of an amino acid and diphosgene do not require an external heating source. The exotherm of the reaction is enough to drive these reactions to completion within practical time limits. This approach

can be advantageous for syntheses that require the troublesome heating of sizable reaction vessels.

Experimental

Materials and methods

Trichloromethyl chloroformate (diphosgene) was obtained from Oakwood Chemical. *Caution! Trichloromethyl chloroformate is extremely toxic and should only be used after all the necessary precautions and safeguards are in place*. All amino acids were purchased from Bachem with the following exceptions: L-cyclohexylalanine and N^{in}-formyl-L-tryptophan were purchased from Chem-Impex; L-leucine was purchased from Advanced ChemTech; *O*-benzyl-D-tyrosine was purchased from Ark Pharm; L-tryptophan was purchased from Acros; and D-phenylalanine was purchased from Creosalus. Anhydrous tetrahydrofuran (THF; OptiDry, FisherPak) and dichloromethane (DCM; HPLC grade) were purchased from Fisher Scientific and dried via passage through an Mbraun MB-SPS encapsulated solvent purification system prior to use. Heptane (technical grade) was purchased from Fisher Scientific. Diatomaceous earth (Celte S) was obtained from Sigma Aldrich and dried in an oven at ~150 °C for at least 24 h before use. Gel-permeation chromatography (GPC) measurements were carried out using a Waters 515 isocratic pump connected in series to a Waters guard column (200 Å, 6 × 40 mm, 6 µm), two Ultrahydrogel 250 columns (7.8 × 300 mm, 6 µm), an Ultrahydrogel 500 column (7.8 × 300 mm, 10 µm), a Waters 2487 UV detector, a Wyatt Dawn Heleos light scattering detector, and a Wyatt Optilab rEX refractive index detector. A H_2O/CH_3CN (60:40, v/v, with 0.1% TFA) mixture used as the eluent at a flow rate of 0.7 mL/min at 35.5 °C. Proton-induced x-ray emission (PIXE) was performed by Elemental Analysis, Inc. (Lexington, KY, USA). ^{1}H NMR spectra were measured with a Varian VNMRS 400-MHz spectrometer.

General procedure for synthesis of NCAs

A two-necked, round-bottomed flask was charged with the requisite amino acid (1 eq.) and dried under high vacuum at ~30–40 mTorr for >36 h to remove as much residual moisture as possible. The reaction flask was equipped with a reflux condenser topped with a dual-connection glass adapter, with one end connected to a nitrogen source and the other vented to the top of the fume hood (to properly exhaust the HCl vapors generated). Depending on the reaction scale, either a magnetic stir bar or mechanical paddle stirrer was inserted. Anhydrous THF was added to give an amino acid concentration of 0.4–0.5 M. To the resulting heavy suspension was added neat diphosgene (0.6–1.0 eq.; see Tables 2 and 4) in one portion. The reaction was carefully warmed to 55 °C with an oil bath or left to stir at ambient temperature. The reaction was considered complete when all the solids in the reaction dissolved and ^{1}H NMR analysis of a vacuum-dried 0.3-mL aliquot indicated complete conversion to the product. Once at ambient temperature, the reaction mixture was transferred to a clean and dry round-bottomed flask, and concentrated on a rotary evaporator with the water bath maintained between 25 and 30 °C. Fresh anhydrous THF (~6–8 mL/g of amino acid) was added to dissolve the material before reconcentrating. The crude product was dissolved in a minimal amount of THF

(~4–6 mL/g of amino acid) and transferred to a large precipitation container. Under a blanket of nitrogen, with vigorous mechanical stirring, heptane (6–8 × crude volume) was added over 10–30 min to precipitate. The resulting solid was collected by vacuum filtration, washed with additional heptane (1–2 × crude volume), and dried in a vacuum oven at room temperature overnight. Anhydrous DCM (~8–10 mL/g NCA) was added to the material and stirred for 15–30 min under nitrogen in order to dissolve as much of the crude material as possible. Oven-dried celite with a bed height of 2–4 cm was prepared in a sintered glass Buchner funnel, topped with a Whatman glass microfiber filter, and rinsed with anhydrous DCM before use (taking care to avoid cracks in the bed). The DCM-NCA suspension was filtered through the celite bed and then rinsed through with additional anhydrous DCM (3–5 mL/g of NCA). The clear filtrate was concentrated on a rotary evaporator with the water bath maintained at 25–30 °C. Anhydrous THF (~6–8 mL/g of NCA) was added to dissolve the product before reconcentrating. The material was dissolved in a minimal amount of THF (~4–6 mL/g of NCA), precipitated with heptane (6–8 × crude volume), and collected/dried using the same method as described for the first precipitation. The final product was packaged under either nitrogen or argon in a container that was then sealed in a FoodSaver heat-seal vacuum bag and stored at − 78 °C until use.

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