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Communication

Synthesis of the unnatural amino acid N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine: A novel organometallic nuclease

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ABSTRACT

The synthesis of a new unnatural amino acid, N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine, was achieved by coupling a ferroceneacetic acid molecule onto the side chain amine of a lysine. The structure of the compound provides options for incorporation of the molecule into peptides or large proteins. In addition, N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine exhibits nuclease activity. It is expected that incorporation of this ferrocenyl amino acid into any nucleic acid-binding protein will endow the protein with nuclease capability.

1. Introduction

The field of bioorganometallic chemistry focuses on the discovery and synthesis of organometallic compounds that possess novel biological activities. In particular, ferrocenyl compounds have been developed for a wide range of applications in the biological, medicinal, and pharmaceutical disciplines [1–3]. Ferrocene is a neutral, stable organometallic compound that readily undergoes a reversible one electron-oxidation to form the ferricenium radical cation [4]. These characteristics led to the design of ferrocenyl derivatives that function as highly sensitive detectors of biomolecules or as reporters of protein activity [5].

A multitude of recent studies have produced ferrocenyl conjugates with amino acids and end-labeled ferrocenyl di- and tripeptides with each demonstrating distinctive electrical, structural, and medicinal properties [6–10]. Reports of incorporating unnatural ferrocene amino acids into internal sites of peptides [11,12], are more rare due to the incompatibility of organometallic compounds with multiple rounds of traditional solid phase peptide synthesis (SPPS). A few ferrocenyl derivatives have been directly coupled onto the free lysine or cysteine side chains of proteins to serve as electroactive probes [13], but the incorporation of unnatural ferrocenyl amino acids into larger proteins at unique positions remains unrealized. Hence, the use of ferrocenyl compounds to extensively investigate or modify protein function has been limited.

The work presented here reflects our goal to incorporate unnatural ferrocene amino acids into a nucleic acid-binding protein at specific sites to confer nucleolytic activity. Previous protein nucleases were constructed with inorganic transition metal complexes that cleave the nucleic acid backbone upon binding directly to the nucleic acid or by generating a diffusible reactive species in the vicinity of the backbone [14–16]. However, derivatives of ferrocene have also been reported to cleave DNA [17]. Therefore, a nucleic acid binding protein containing a ferrocene moiety could serve to determine the specific interactions that occur within a protein-nucleic acid complex. Towards this objective, the synthesis of N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine, **1**, was devised. The synthetic strategy used to prepare this new conjugate offers flexibility for introduction into either peptides or proteins. In addition, N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine exhibits the ability to cleave DNA. Therefore, our ferrocenyl amino acid can be further developed as a novel chemical nuclease to investigate protein–nucleic acid interactions.

2. Results and discussion

2.1. Synthesis of N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine conjugate

The synthesis (Scheme 1) begins with the preparation of N^{α}-(1,1-dimethylethoxy-carbonyl)-L-lysine-*tert*-butyl ester (**3**) in two steps starting from a N^{α}-*t*Boc-N^{ε}-(carbobenzyloxy)-L-lysine (**2**): a coupling reaction to protect the carboxyl group followed by removal of the Cbz group from the ε-amino group of the lysine side chain. An overall yield of 70% was realized. Coupling of the free

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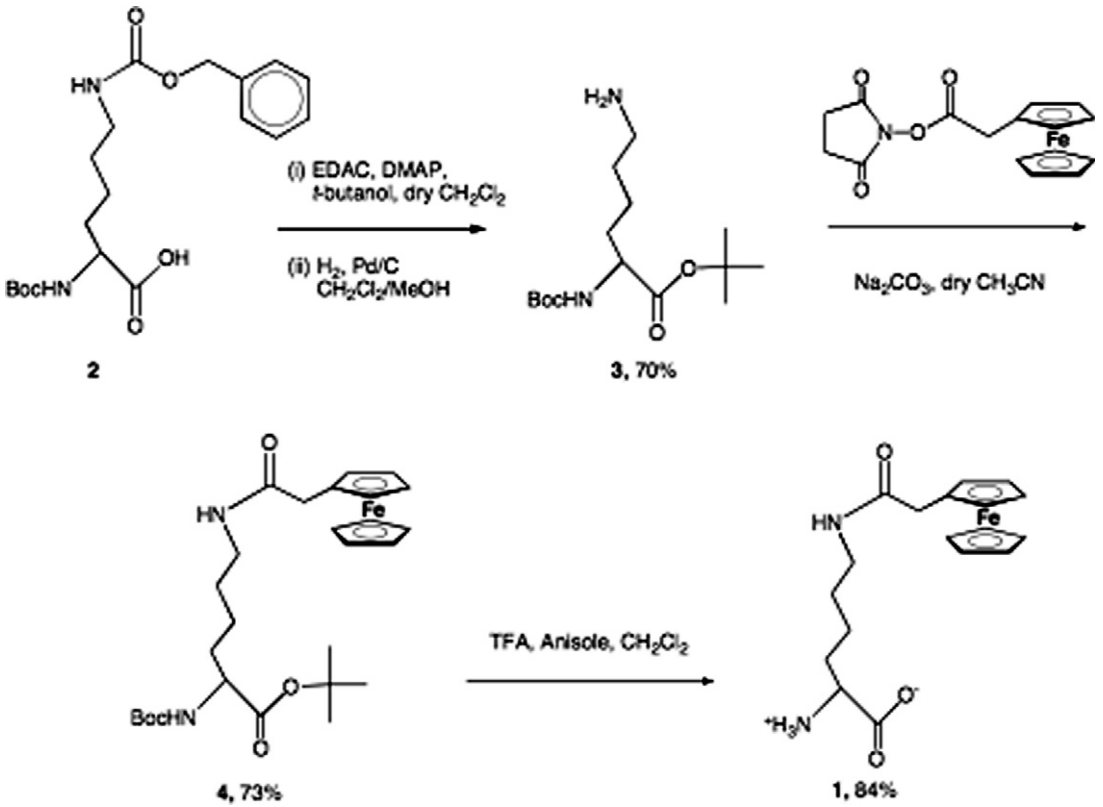

Scheme 1. Synthesis of N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine, **1**.

ε-amino group of **3** with the succinimido ester of ferroceneacetic acid results in a stable amide bond that attaches the ferrocene substituent onto the lysine side chain to produce compound **4** in a 73% yield. Attempts to form an amide bond between **3** and ferrocene carboxaldehyde using an oxidative amidation approach [18] failed, most likely due to the oxidation of the ferrocene moiety and the bulky *tert*-butyl protecting groups on **3**. However, both of these protecting groups can be simultaneously and easily removed with TFA in a single deprotection step. This final step generated **1**, a new ferrocenyl amino acid that exhibits chemical nuclease activity. Spectral analyses of the synthetic products confirm their structure and the reaction yields are comparable to those reported for the synthesis of similar ferrocene-amino acid compounds [7,11]. Isolation of the final compound required reverse phase chromatography on a solid phase extraction column with an elution gradient of 10–25% acetonitrile in water.

The alpha amino group of **1** can be modified with a Boc or Fmoc group for incorporation into a small peptide using solid phase peptide synthesis [19,20]. Alternatively, the N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine can be readily modified for incorporation into larger nucleic acid-binding (or any other) proteins via *in vitro* translation using chemically misacylated suppressor tRNA molecules [21]. This is accomplished by re-protecting the alpha amino group with a 6-nitroveratryl-oxycarbonyl (NVOC) substituent and converting the carboxyl group into a cyanomethyl ester to facilitate coupling of the conjugate onto a hybrid dinucleotide molecule [22]. After subsequent addition of the modified ferrocenyl amino acid onto the suppressor tRNA, the NVOC group can be easily removed with light [23]. Incorporation of this molecule into a broader range of proteins will enhance research avenues in the field of bioorganometallic chemistry. Future applications include electrochemical studies of the activity of enzymes and electron transporting proteins and endowing nucleic acid-binding proteins with nucleolytic capability to explore the structure of nucleic acid–protein complexes.

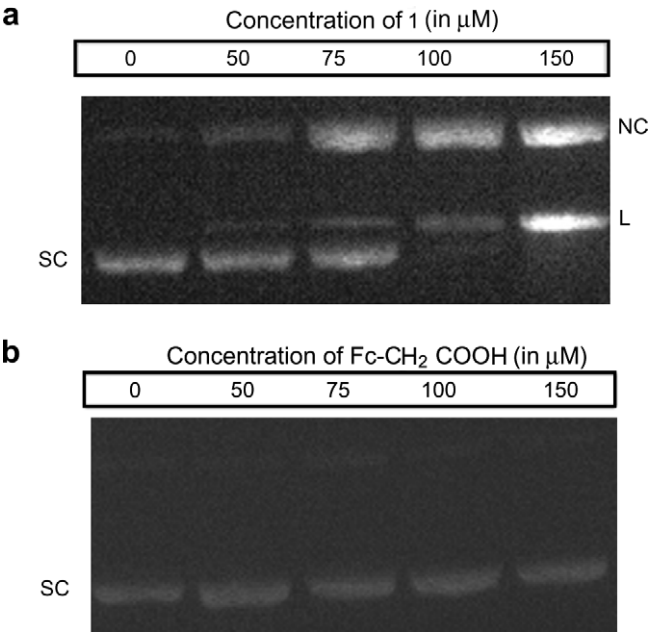

Fig. 1. DNA cleavage assays. A 20 μl reaction containing pUC19 DNA, (1.0 μg, 75 μM bp) was incubated with 0–150 μM of 1 (**a**) or ferrocene acetic acid (**b**) at 25 °C for 16 h. Separation of supercoiled (SC), nicked circular (NC), and linear (L) forms of pUC19 DNA in each reaction was accomplished by agarose (1%) gel electrophoresis.

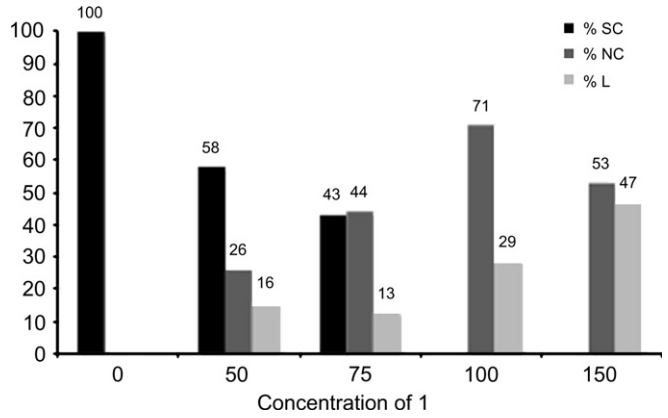

Fig. 2. Analysis of DNA cleavage products produced by N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine. Quantification of supercoiled (SC), nicked circular (NC), and linear (L) forms of pUC19 DNA generated by **1** in DNA cleavage assays (Fig. 1a) was performed using ImageAide Band Matching Analysis Software (Spectronics Corporation).

2.2. DNA cleavage studies

The ability of N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine to cleave DNA was assessed by incubation of the conjugate with supercoiled pUC19 DNA. It is apparent that the redox-active center of the ferrocene moiety in **1** is capable of significant nuclease activity, since substantial reduction of the supercoiled (SC) DNA form was observed in its presence (Fig. 1a). The conjugate afforded predominately circular nicked DNA (single strand cleavage) at low concentrations, but production of the linear form (double strand cleavage) also increased up to 47% at higher concentrations of **1** (Fig. 2). Based on the structure of our conjugate, the increase in the linear form is most likely a result of two single strand breaks on complementary strands of the DNA rather than a direct double strand cleavage pathway as seen for inorganic diiron complexes [24,25]. In contrast, no DNA cleavage was observed in assays with ferroceneacetic acid (Fig. 1b). While ferrocene itself does not cleave DNA, the ferricenium cation (oxidized form, Fe^{3+} ion present) and other ferrocene derivatives containing a positive charge do exhibit single-strand DNA cleavage [8,17]. Unlike ferroceneacetic acid, our ferrocenyl compound contains a lysine zwitterion whose free amine group may bring the redox center of the ferrocene moiety into close proximity of the negatively charged DNA backbone. It is also possible that the lysine substituent coupled to the ferrocenyl group in **1** increases the conversion to or stabilizes the formation of the ferricenium cation. Investigations are continuing to determine the mechanism and specificity of the nuclease activity exhibited by our novel organometallic amino acid.

3. Conclusion

In summary, an efficient synthetic route has been designed to produce N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine using common reagents and straightforward reactions with high yield. This unnatural ferrocenyl amino acid is suitable for incorporation into peptides or proteins through different downstream synthetic strategies. Our initial studies indicate that N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine can cleave DNA effectively and experiments to determine the specificity and mechanism of this nucleolytic activity are ongoing. The structure and activity of this compound will be further developed to investigate the proficiency of this novel ferrocenyl chemical nuclease.

4. Experimental

All reagents and solvents were obtained from Sigma–Aldrich or ACROS. TLC was performed on silica gel/ UV 254 (0.25 mm thick) or on Alltech C18 reverse phase Prep Plates. Flash and gravity column chromatography were performed with 6 nm silica gel, 200–425 or 70–230 mesh, respectively. IR analysis was performed on a Nicolet Fourier Transform IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DX 300 instrument and mass spectroscopy (FAB+) data was obtained on a JEOL JMS-AX505HA mass spectrometer. HPLC analysis was accomplished using a Rainin HPXL solvent delivery system (isocratic, 6:4 water–acetonitrile, rate: 1 ml/min) equipped with an Econosil C18 column (25 × 4.6 mm, 5 m) and a Rainin Dynamax UV-1 detector (λ = 225 nm). LC–MS was conducted using a Waters Alliance LC with a photodiode array detector interfaced with a JEOL JMS-AX505HA mass spectrometer at the University of Notre Dame Mass Spectrometry Facility.

4.1. General procedure for the synthesis of N^{α}-(1,1-dimethylethoxycarbonyl)-L-lysine-tert-butyl ester (**3**)

N^{α}-*t*Boc-N^{ε}-(carbobenzyloxy)-L-lysine (**2**, 3.986 g, 10.5 mmol), 4-dimethyl-aminopyridine (DMAP, 786 mg, 6.4 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDAC, 4.191 g, 21.9 mmol) were dissolved in dry CH_2Cl_2 (10 ml) before addition of dry *tert*-butyl alcohol (12 ml, 121.4 mmol). The mixture was stirred at 25 °C for 16 h under argon, diluted with 60 ml of CH_2Cl_2, washed with 100 ml of each water and saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to a yellow viscous oil. The crude product was purified by flash silica gel chromatography using acetone–hexanes (1:1). Fractions containing the N^{α}-*t*Boc-N^{ε}-(carbobenzyloxy)-L-lysine-*tert*-butyl ester [R_f 0.78 in acetone–hexanes (1:1)] were collectively concentrated into a yellow oil that was suspended in 20 ml of CH_3OH–CH_2Cl_2 (1:1) along with palladium-activated carbon (0.55 g, 5.2 mmol). The mixture was stirred under hydrogen gas for 90 min. Catalyst was removed by vacuum filtration. The filtrate was concentrated to a clear oil and subjected to flash silica gel chromatography: mixture was loaded and washed with CH_2Cl_2 before the product was eluted with CH_3OH–CH_2Cl_2 (7:3) and concentrated to afford compound **3**, a yellow viscous oil (2.25 g, 70%). R_f = 0.00 (acetone–hexanes 1:1). FT-IR (neat): 3364, 2978, 1711, 1500, 1392, 1367, 1154 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 1.46 (s, 9H), 1.24–1.63 (m, 6H), 4.2 (m, 1H), 5.2 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 155.4, 79.8, 78.0, 54.5, 40.8, 32.0, 30.5, 28.9, 28.0, 27.5, 21.4.

4.2. General procedure for the synthesis of N^{α}-(1,1-dimethylethoxycarbonyl)-N^{ε}-(ferrocene-1-acetyl)-L-lysine-tert-butyl ester (**4**)

To a solution of ferrocene acetic acid (347 mg, 1.42 mmol) dissolved in dry CH_2Cl_2 (8 ml) was added *N*-hydroxysuccinimide (163 mg, 1.42 mmol) and DCC (293 mg, 1.42 mmol). The reddish-brown reaction mixture was stirred under argon for 50 min, diluted with 25 ml of CH_2Cl_2 and filtered under vacuum. The filtrate was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to a dark, red-orange residue. This acetylferrocene-*N*-hydroxy-succinimido ester (1.42 mmol assumed) was then suspended in dry CH_3CN (5 ml) along with **3** (470 mg, 1.56 mmol) and Na_2CO_3 (181 mg, 1.70 mmol). The cloudy red mixture was stirred under argon for 90 min, concentrated under vacuum, dissolved in 50 ml of CH_2Cl_2 and washed with equal volumes of 0.5 M sodium ascorbate, water, and saturated NaCl. The organic layer was dried over anhydrous Na_2SO_4 and reduced to a sticky dark red-orange residue by rotary evaporation. The crude residue was purified by gravity silica gel column chromatography using step gradients (50 ml each) of 20%, 25%, and 30% acetone in hexanes. Fractions containing pure product were concentrated to a viscous, yellow-orange oil of com-

pound **4** (749 mg, 73%). $R_f = 0.90$ (acetone–hexanes 1:1). FT-IR (neat): 3320, 3094, 2978, 1713, 1652, 1530, 1392, 1367, 1153, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta = 1.25–1.67$ (m, 6H), 1.41 (s, 9H), 1.43 (s, 9H), 3.14 (m, 2H), 3.27 (s, 2H), 4.10 (br, 5H), 4.12 (m, 4H), 5.00 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 171.8$, 170.9, 155.4, 81.8, 81.0, 79.6, 69.1, 68.9, 68.5, 53.7, 39.1, 37.9, 32.5, 31.0, 29.0, 28.3, 28.0, 22.4. MS (FAB+) m/z $[M+H]^+$ calcd for $C_{27}H_{40}N_2O_5Fe$: 528; found: 528.

4.3. General procedure for the synthesis of N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine (**1**)

N^{α}-(1,1-Dimethylethoxycarbonyl)-N^{ε}-(ferrocene-1-acetyl)-L-lysine-*tert*-butyl ester (**4**, 269 mg, 0.51 mmol) and anisole (0.117 ml, 1.07 mmol) were dissolved in dry CH_2Cl_2 (2.5 ml) and cooled in an ice bath. A 0.50 ml aliquot (6.49 mmol) of trifluoroacetic acid (TFA) was slowly introduced into the flask and after stirring for 5 min, the dark green mixture was warmed to room temperature. After addition of another 0.80 ml (10.4 mmol) of TFA, the mixture was stirred for 3–4 h. Excess TFA was removed under vacuum leaving a thick, dark green residue that was applied to a flash silica gel column and washed with acetone–hexanes (6:4). The product was eluted with 3% triethylamine in methanol and concentrated under reduced pressure. The sample was further purified using reversed phase chromatography on a solid phase extraction column with a gradient of 10-25% acetonitrile in water. Fractions containing pure product were detected by HPLC in 6:4 water–acetonitrile ($\lambda = 225$ nm) and lyophilized to yield **1** as a yellow-orange solid (96% pure, 159 mg, 84%). $R_f = 0.47$ [reverse phase TLC: CH_3CN-50 mM sodium acetate pH 4.5 (4:6)]. IR (Nujol mull): 3300, 2871, 2724, 1628, 1525, 1203, 1171, 1104 cm^{-1}. ^1H NMR (DMSO-d_6) $\delta = 1.14–1.44$ (m, 6H), 3.10 (m, 2H), 3.28 (br, 2H), 3.99 (s, 1H), 4.08 (m, 5H), 4.12 (m, 4H), 7.48 (br, 1H), 7.85 (br, 1H). HPLC-MS (FAB+) m/z $[M+H]^+$ calcd for $C_{18}H_{24}N_2O_3Fe$: 373.3; found: 373.5.

4.4. DNA cleavage experiments

DNA cleavage assays (20 μl) contained 1.0 μg of pUC19 vector DNA (New England Biolabs, 75 μM bp) along with increasing concentrations (0–150 μM) of **1** or ferroceneacetic acid (Sigma) dissolved in 10% DMSO in 10 mM Tris–HCl, pH 8.0. After incubation for 16 h at 25 °C, the cleavage products of each reaction were separated by gel electrophoresis (1% agarose, 0.5 μg/ml ethidium bromide) in 0.5 × TBE buffer at 90 V for 90 min, visualized by UV light, and captured on a digital image. The intensity of each band was measured using ImageAide Band Matching software (Spectronics Corporation) in order to calculate the percentage of each DNA form generated during a reaction. An appropriate correction factor was applied to compensate for the low affinity of supercoiled (SC) DNA in comparison to the nicked circular (NC) and linear (L) forms of DNA [26].

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