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N′-Alkylated Guanidiniocarbonyl Pyrroles: New Receptors for Amino Acid Recognition in Water

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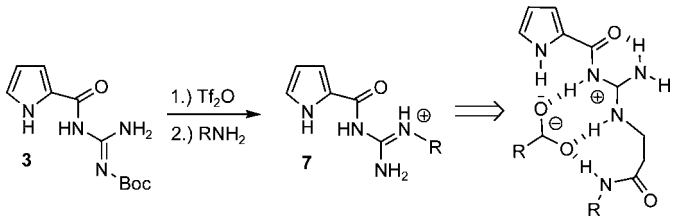
ABSTRACT



N′-Substituted guanidiniocarbonyl pyrroles 7 were synthesized for the first time by activation of a Boc-protected guanidiniocarbonyl pyrrole 3 with triflic anhydride and subsequent reaction with a primary amine. These guanidinium cations are efficient receptors for the complexation of amino acid carboxylates even in water (K_{assoc} > 10^3 M^{-1}) as could be shown by UV titration studies.

We have recently introduced a new de novo designed binding motif for carboxylates, the guanidiniocarbonyl pyrroles **1**, which strongly bind carboxylates even in aqueous solvents through a combination of ion pairing and multiple hydrogen bonds (Figure 1).[1] Due to the increased acidity of the acyl guanidinium moiety and the additional H-bonds, these complexes are much stronger than those of simple guanidinium cations, which only form stable ion pairs in organic solvents of low polarity such as chloroform or acetonitrile.[2] This recognition motif has already found versatile use in various fields of supramolecular[3] and bioorganic chemistry.[4] However, in complexes with such guanidiniocarbonyl pyrroles, so far only one side of the carboxylate substrate is used for binding interactions with the receptor. The other side of the substrate is still completely free and only exposed to the solvent. Additional binding interactions to this backside of the substrate by a side chain attached to the N′ of the guanidiniocarbonyl pyrrole could therefore help to further increase the complex stability and also to increase the selectivity of the recognition event with respect to the bound carboxylate. We were therefore interested in the synthesis of N′-substituted guanidiniocarbonyl pyrroles of type **2** and the study of their binding properties (Figure 1).

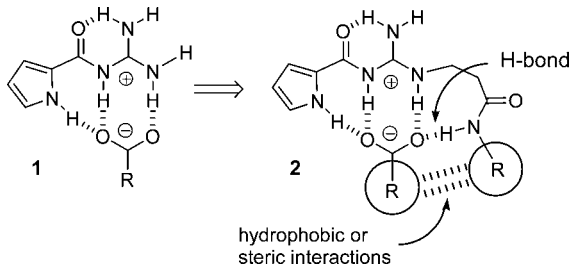


Figure 1. Additional binding interactions in complexes between N′-substituted guanidiniocarbonyl pyrroles **2** and carboxylates should alter their stability and selectivity compared to the unsubstituted guanidiniocarbonyl pyrrole **1**.

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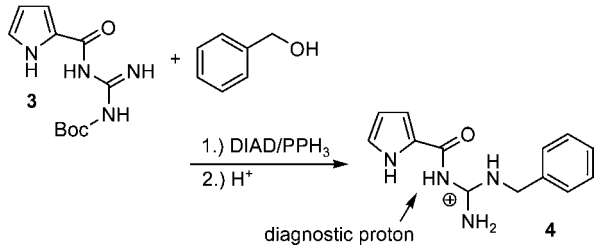
Due to the low reactivity of pyrrole carboxylic acid derivatives, most of the standard procedures reported in the literature for the preparation of N′-alkylated guanidines,[5] such as the use of 1*H*-pyrazole-1-Boc-carboxamidine[6] or Boc-activated thioureas,[5e] do not work for pyrroles as it was not possible to obtain the corresponding N-acylated pyrrole derivatives in decent yields.

According to work by Kozikowski, di-Boc- or di-Cbz-guanidine can be alkylated with alcohols using a Mitsunobu protocol.[7] However, the mono-Boc-protected acyl guanidine **3**, also a diacylated guanidine, only reacted with reactive alcohols such as benzyl but no aliphatic alcohols. The reaction of **3** with benzyl alcohol and DIAD/PPH_3 in THF provided a single substitution product **4** in 83% yield (Scheme 1), whereas aliphatic alcohols such as propanol or

Scheme 1. Synthesis of N′-Substituted Guanidiniocarbonyl Pyrroles via a Mitsunobu Protocol



3-hydroxy propanoic acid did not react at all even at elevated temperatures. Obviously, the reactivity of the guanidiniocarbonyl pyrrole **3** is greatly reduced compared to the di-Boc-guanidine used by Kozikowski.

That the alkylation with benzyl alcohol indeed gave the desired N′-substituted isomer **4** as the only product and not the N-substituted isomer, with the benzyl group attached to the amide NH, could be shown by NMR after removal of the tBoc protecting group with TFA in CH_2Cl_2. The ^{1}H NMR spectrum clearly shows a signal for the guanidinium amide NH^a at $\delta = 11.1$, and two separate signals with a relative intensity of 1:2 for the guanidinium NH^b and NH^c protons at $\delta = 9.5$ and $\delta = 8.9$, respectively (Figure 2). For the N-substituted isomer, the spectrum would not show the guanidinium amide NH^a at $\delta = 11.1$ any more but—due to fast exchange processes—only one broad signal for the four guanidinium NH_2 protons at $\delta \approx 8-9$ with an intensity of 4. In principle, the Mitsunobu reaction is hence a useful way to prepare *N*′-alkyl-substituted guanidiniocarbonyl pyrroles but only for reactive alcohols.

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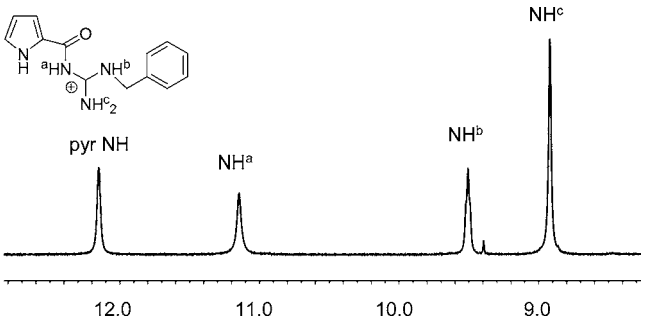
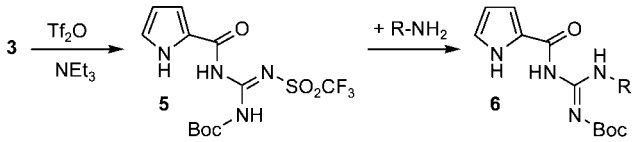
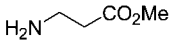
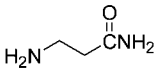
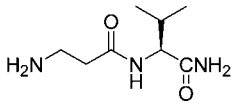


Figure 2. Part of the ^{1}H NMR of **4** indicating the N,N′ substitution pattern of the guandinium moiety.

We finally succeeded to prepare the desired *N*′-alkyl-substituted derivatives by using a *N*′-Boc-*N*″-triflyl guanidiniocarbonyl pyrrole **5** as the guanidinylation reagent.[8] Reaction of mono-Boc-guanidiniocarbonyl pyrrole **3** with triflic anhydride in the presence of NEt_3 in CH_2Cl_2 gave the corresponding triflyl guanidiniocarbonyl pyrrole **5**, which can be further reacted without isolation with a primary amine to give the desired N′-substituted guanidiniocarbonyl pyrroles **6** in good overall yields (Scheme 2).[9] Even deactivated

Scheme 2. Synthesis of N′-Substituted Guanidiniocarbonyl Pyrroles via Triflyl Activated Derivatives



R-NH_2	yield %
butyl amine	46
benzyl amine	39
aniline	13
tert.-butyl amine	-
	80
	67
	63

amines, such as aniline, do react but only with modest yields. This reaction is, however, limited to unhindered primary amines. Secondary amines or highly sterically hindered primary amines such as *tert*-butylamine do not react under these conditions.

To find out whether the corresponding N′-substituted guandiniocarbonyl pyrrole cations **7**, obtained as their chloride salts after removal of the Boc-protecting group in **6** with HCl, are indeed efficient receptors for the complexation of amino acid carboxylates in aqueous solvents, we

investigated the complexation properties of a first example, the valine-derived receptor **8**, using UV-titration studies (Figure 3). Aliquots of the substrate were added to a solution

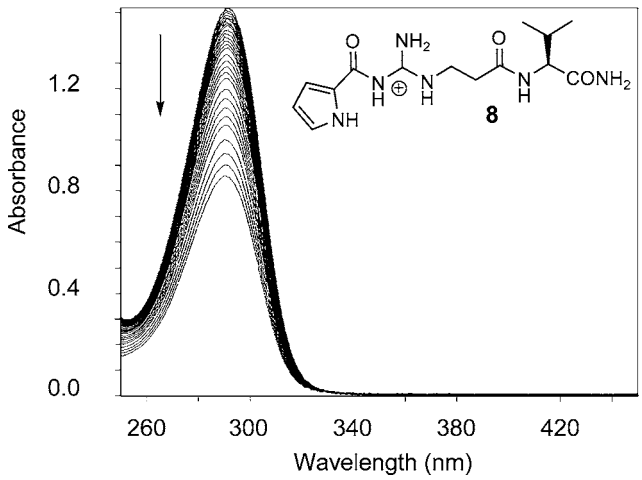


Figure 3. UV titration data for the binding of valine to **8** in water.

of the receptor in water (bis-tris-buffer, 3 mM at pH = 6.1, $[\text{receptor}]_o = 8 \times 10^{-5}$ M, $[\text{substrate}]_o = 2 \times 10^{-3}$ M). Changes in the UV spectrum of the receptor were recorded and used to determine the binding constants as the absorbance of the pyrrole moiety at $\lambda = 290$ nm decreases upon complex formation. Analysis of the data was performed using the Specfit/32 software program from Spectrum Software Associates using nonlinear least-squares fitting with a 1:1 association model.[10]

These preliminary binding studies show that the N′-substituted guanidiniocarbonyl pyrrole **8** indeed strongly binds amino acid carboxylates even in aqueous buffer solution with association constants of $K_{assoc} \geq 10^3$ M^{-1}. Furthermore, the complex stability seems to depend on the nature of the amino acid side chain. Valine is bound nearly two times better than alanine ($K_{assoc} = 1750$ and 1000 M^{-1}, respectively). As the unsubstituted guanidiniocarbonyl pyrrole cation **1** does not discriminate between these two amino acids, this indicates that interactions with the additional sidearm attached to N′ are probably responsible for the different complex stabilities.

According to molecular mechanic calculations (Macromodel V 8.0, Amber* force field, GB/SA water solvation treatment)[11] the stronger binding of valine could reflect favorable hydrophobic interactions between the two isopropyl side chains in the aqueous solvent (Figure 4): The carboxylate of the amino acid forms an ion pair with the guandinium moiety with additional H-bonds from the pyrrole NH and the side chain amides to the carboxylate. This places the two alkyl side chains opposite to each other allowing for hydrophobic and/or steric interactions. A detailed study of the complexation properties of this new receptor class concerning the complex structure and the substrate selectivity is currently under investigation.

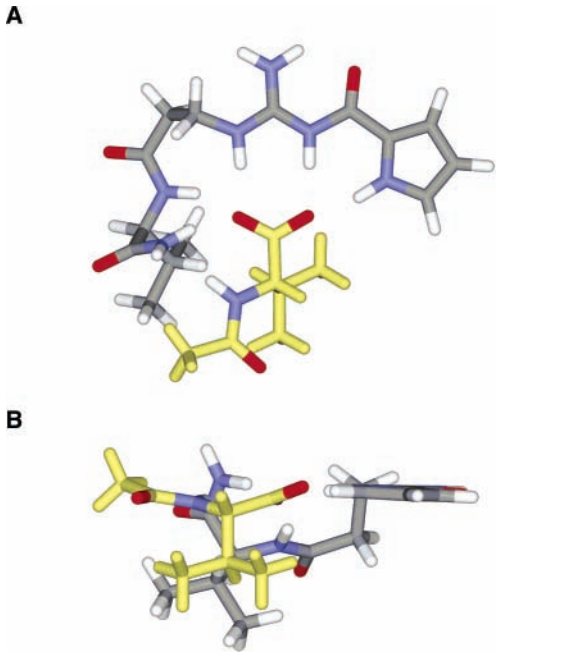


Figure 4. Proposed structure for the complex between **8** (gray) and valine (yellow) based on molecular mechanics calculations (A, top view; B, side view).

In conclusion, we have presented here for the first time the successful synthesis of N′-substituted guanidiniocarbonyl pyrroles **7**. As preliminary binding data show, this new receptor class efficiently binds amino acid carboxylates even in water. Through a further variation of the side chain the development of highly selective receptors for the recognition of amino acids in water should be possible. Furthermore, a second side chain attached at position 5 of the pyrrole, as in our previous guanidiniocarbonyl pyrroles of type **1**, should lead to tweezer receptors with even more advanced complexation properties.

Acknowledgment. This work was supported by the Deutschen Forschungsgemeinschaft (SCHM 1501/2-2) and the Fonds der Chemischen Industrie.

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(9) **Typical Reaction Protocol.** A solution of **3** (252 mg, 1 mmol, 1 equiv) and NEt_3 (208 μl, 1.5 mmol, 1.5 equiv) in dry CH_2Cl_2 (5 mL) was cooled to −78 °C under nitrogen atmosphere. Triflic anhydride (200 μl, 1.2 mmol, 1.2 equiv) was added dropwise within 10 min. After complete addition, the mixture was stirred for 0.5 h and was then allowed to warm to room temperature over 2 h. Five drops of water and a solution of β-alanine methyl carboxylate hydrochloride (168 mg, 1.2 mmol, 1.2 equiv) with NEt_3 (208 μl, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred overnight and then washed with saturated sodium carbonate and brine. After removal of the solvent, the crude product was purified by flash chromatography on silica gel using ethyl acetate/hexane (1/1.6 with 1% NEt_3) to yield **6** as pale yellow crystals (270 mg, 80% yield).

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